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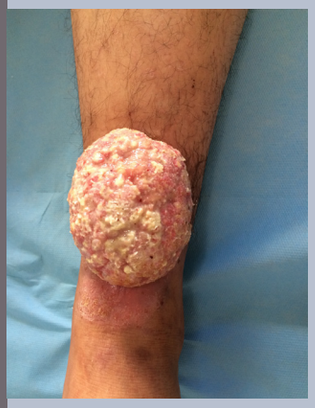

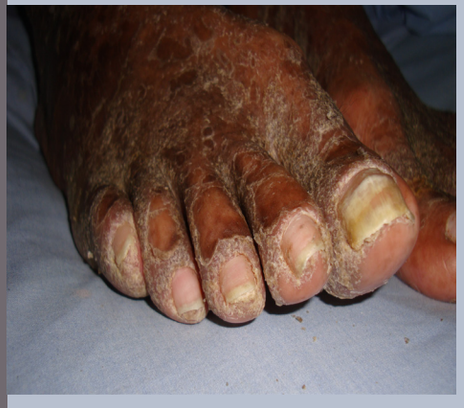

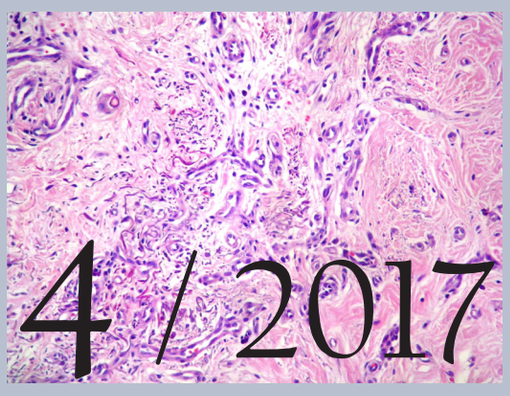

Editorial Pages

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Original Article

Effect of vitamin E isoforms on the primary intention skin wound healing of diabetic rats

Bijo Elsy[1], Aijaz Ahmed Khan[1], Veena Maheshwari[2]

[1]Department of Anatomy, JN Medical College, Aligarh Muslim University, Aligarh, India , [2]Department of Pathology, JN Medical College, Aligarh Muslim University, Aligarh, India

Corresponding author: Dr. Bijo Elsy, E-mail: bijobaby22@yahoo.com

ABSTRACT

Introduction: Impaired wound healing events is a common complication in diabetes. One of the effective nutritional antioxidant on skin wound healing is vitamin E which contains saturated tocopherol and unsaturated tocotrienol forms. This present study is designed to explore the effect of different vitamin E isoforms on stitched skin wound in both healthy and diabetic rats. **Materials and Methods:** Forty eight albino rats were divided into eight groups; healthy control, diabetic control, healthy treated (d-α-tocopherol, d-δ-TRF and co-administrated) and diabetic treated (d-α-tocopherol, d-δ-TRF and co-administrated). Diabetes was induced through single subcutaneous injection of alloxan at the dose of 100 mg/kg. Treated groups were administered d-a-tocopherol (200 mg/kg), d-δ-TRF (200 mg/kg) and co-administration (100 mg/kg of these two compounds each) orally and daily for three weeks. A horizontal skin incision was made on right mid-thigh region at 2.95 ± 0.17cm in length and wound was closed with an absorbable suture. **Results:** Histopathological and histomorphological results at the end of 3rd week revealed that the d-δ-TRF treated groups promote the regeneration and reorganization of epidermal and dermal components in healing of primary intention more effectively than the d-α-tocopherol and co-administrated groups. **Conclusion:** It is concluded that among different vitamin E isoforms the d-δ-TRF appears to be a more effective nutritional antioxidant on skin wound healing in both healthy and diabetics.

Key words: Antioxidant; d-a-tocopherol; d-δ-TRF; Diabetes; Rats; Skin; Wound

INTRODUCTION

In diabetes the free radicals impair the normal wound healing by damaging keratinocyte, endothelial cells, capillary permeability and collagen metabolism [1]. Oxidative stress induces cellular dysfunction and retards angiogenesis and the healing process [2]. Thus, elimination of reactive oxygen species (ROS) is an important strategy to improve the healing of wounds in diabetes mellitus patients [3].

The unsaturated tocotrienol forms of vitamin E are more potent antioxidants [4] and suppress ROS production more efficiently than most active saturated tocopherol forms [5,6]. Each isoforms of vitamin E have different biological activities towards free radicals [7]. In addition tocotrienol possess antidiabetic and anticancer properties as well [8]. Interestingly, the antitumor activity of tocotrienols is not dependent on its antioxidant activity [9,10].The highly biopotent γ and δ- tocotrienols may play a physiological role in modulating normal cell growth, function and remodeling. These compounds inhibit tumor growth without harming normal tissues [11-14].

Sutures enhance wound closure and promote healing. Sutures initially provide the mechanical strength to seal the wound and protect it from pathogens [15]. Available studies [16,17] revealed that topically applied vitamin E does not help in improving the cosmetic appearance of scars or its failure to reduce postoperative scar formation. In a 10 days study [18] it has shown that topical tocopherol treatment enhances the rate of secondary skin wound closure in streptozotocin-induced diabetic rat.

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According to Zaini et al [19], the tocotrienol-rich fraction (TRF) treatment accelerate the wound contraction rate, enhance the reepithelialization, the regeneration process and stimulate the granulation tissue formation in deep partial-thickness burn wounds. In another study [20] it was revealed that the supplementation of TRF at 200 mg/kg was able to improve wound healing in type 1 induced diabetic rat.

Our previous studies [21-23] explain the effect of different vitamin E isoforms via single and co-administrations on secondary skin wound healing and from these studies it was concluded that the d-δ-TRF treated group showed comparatively faster recovery and regeneration of epidermal and dermal components than other treated and control groups.

At present all available data on vitamin E application on skin wound healing either topical application on primary intention of healing or oral administration on secondary intention of healing. To our knowledge, so far no information is available on oral administration of vitamin E isoforms on primary intention type of skin wound healing. Hence the present study was attempted to explore the effect of oral administration of different isoforms of vitamin E on the basis of histopathological characteristics and histomorphological measurements of incised skin wounds in both healthy and diabetic rats closed with absorbable suture in experimental surgery.

MATERIALS AND METHODS

Forty eight albino rats of either sex each weighing 230-320g was obtained from central animal house of JN medical college, AMU, Aligarh. The study has been approved by Institutional Animal Ethical Committee (No. 8937/2014).

This present study followed the same method as described in our previous studies [21,22] of animal care, induction of diabetes, monitoring of blood sugar level, surgical procedure, tissue sample collections and fixation.

Experimental Groups, Route and Dosage of Treatment

Total forty eight animals were divided into eight groups having six rats in each group: (1) healthy control- HC; (2) diabetic control- DC; (3) healthy d-α-tocopherol treated- HPT and (4) diabetic d-α-tocopherol treated- DPT; (5) healthy d-δ-TRF treated- HTT and (6) diabetic d-δ-TRF treated – DTT; (7) healthy d-a-tocopherol and d-δ-TRF treated- HXT and (8) diabetic d-α-tocopherol and d-δ-TRF treated- DXT.

The d-α-tocopherol treated groups were received 200mg/kg d-α-Tocopherol (Myra e capsule [Vitamin E] manufactured by PT Daya- Baria laboratoria Tbk, Indonesia; Imported and packed by United laboratories, Inc, 66 United St, Philippines). The d-δ-TRF treated groups were received 200mg/kg d-δ-TRF (Unique E Tocotrienol, tocopherol free, 90% δ and 10% γ tocotrienols, AC Grace Company, P.O Box 570, Big Sandy, TX 75755, USA). The co-administrated groups were received 100mg/kg of d-α-tocopherol and d-δ-TRF each.

All treated groups were supplemented vitamin E isoforms (d-a-tocopherol and d-δ-TRF) daily for three weeks by oral administration.

Surgical Procedure

All animals received general anesthesia via inhalation of ether. Horizontal skin incision was made on the shaved right mid-thigh region at 2.95 ± 0.17cm in length. Skin were closed with 3-0 Vicryl (2metric–NW2401) absorbable sterilized surgical needled suture USP (synthetic; braided coated polyglactin 910 violet; from Ethicon, manufactured in India by Johnson and Johnson Ltd, Aurangabad). Povidone-iodine solution (antisepsis) was applied on the wound and 0.5 ml Voveran (analgesic) and 2 mg single shot of Gentamycin (antibiotic) were also injected simultaneously.

Sample Collection and Fixation of Tissue

On completion of three weeks animals were sacrificed under deep ether anesthesia and then excised the healed parts of skin with adjacent area. The excised tissues were immersion-fixed in 10% neutral buffered formalin

Macroscopic Examination

The macroscopic changes in the wound healing stages were observed and recorded photographically on 1st, 7th, 14th & 21st day of creation of wounds.

Histopathology and Histomorphometry

Fixed tissue samples were processed for light microscopical studies. The 5m thick paraffin sections were stained with Haematoxylin & Eosin (H&E),

Masson's Trichrome (MT) and Aldehyde Fuchsin with Fast Green (AF with FG).

In histomorphometry the measurements of epidermal and neoepidermal thickness were performed on the H & E and MT stained sections by using software Motic images plus version 2.0.

Statistical Analysis

Histomorphological measurements were statistically evaluated and the significance calculated by using one way 'ANOVA' followed by Tukeys test. All the results were expressed as mean ± SD and $P < 0.05$ was considered as statistically significant.

RESULTS

Body Weight and Blood Sugar Level

Weight and blood sugar levels of all animals in each group were monitored at weekly intervals and results were reported in previous studies [21-23].

Macroscopic Observations

On 3rd week scar were not formed in any groups by morphological examination on stitched skin wounds and better wound healing was observed in all treated groups especially in d-δ-TRF treated group showed almost complete healing as compared to control groups (Fig. 1).

Microscopic Observations

Histomorphometry

In treated groups the mean values of neoepidermis were significantly thicker ($P<0.01$) than the corresponding epidermal border thickness which in the order of d-δ-TRF> co-administrated> d-α-tocopherol groups as compared to control groups (Fig. 2).

Reepithelialization

Complete reepithelialization was noticed in all groups (controls and treated). On 3rd weeks, all groups were showed interdigitations but well defined interdigitations at dermoepidermal junction appeared on the entire length of neoepidermis were seen only in treated groups (Fig. 3).

Cellular components

On 3rd week more cellularity were observed in control groups as compared to all treated groups. Among different treated groups reduced cellularity were seen in d-δ-TRF treated group than d-a-tocopherol and co-administrated treated groups (Fig. 4).

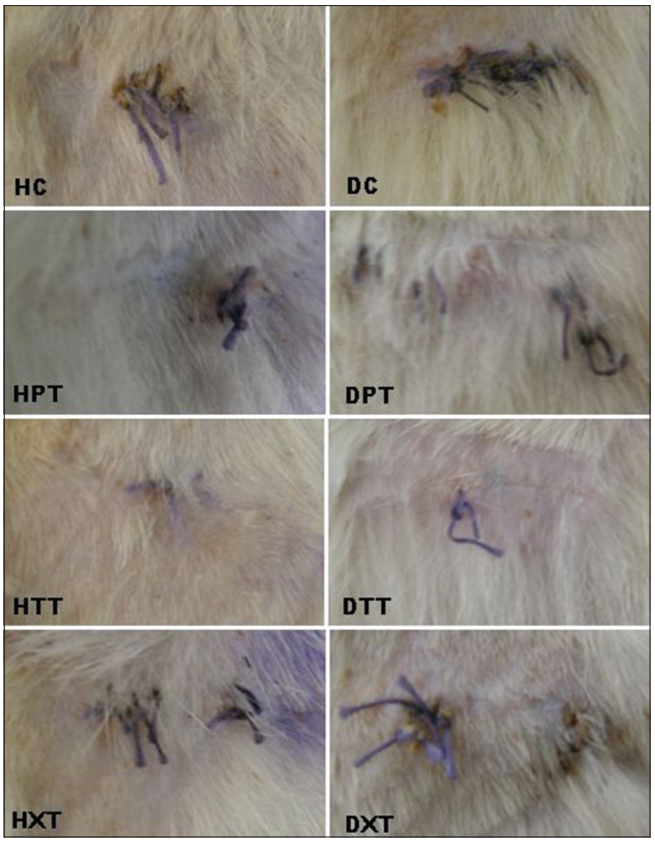

Figure 1: Photographs showing skin wounds of all groups on 3rd week. The d-δ-TRF treated group showed almost complete healing and all other treated groups have shown better healing as compared to control groups.

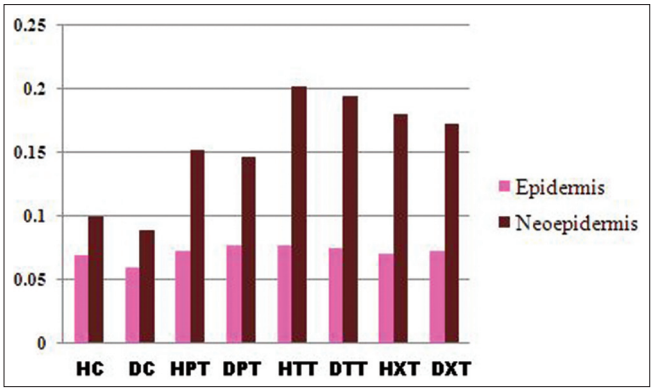

Figure 2: Border & neoepidermal thickness (mm; Mean ± SD) at the end of 3rd week. In all treated groups the mean values of neoepidermis were significantly thicker ($P<0.01$) than the corresponding epidermal border thickness as compared to control groups.

Neovascularization

Reduced vascularity was observed in all treated groups. In HC has shown more vertically oriented blood capillaries whereas in DC blood capillaries were swollen (Fig. 3).

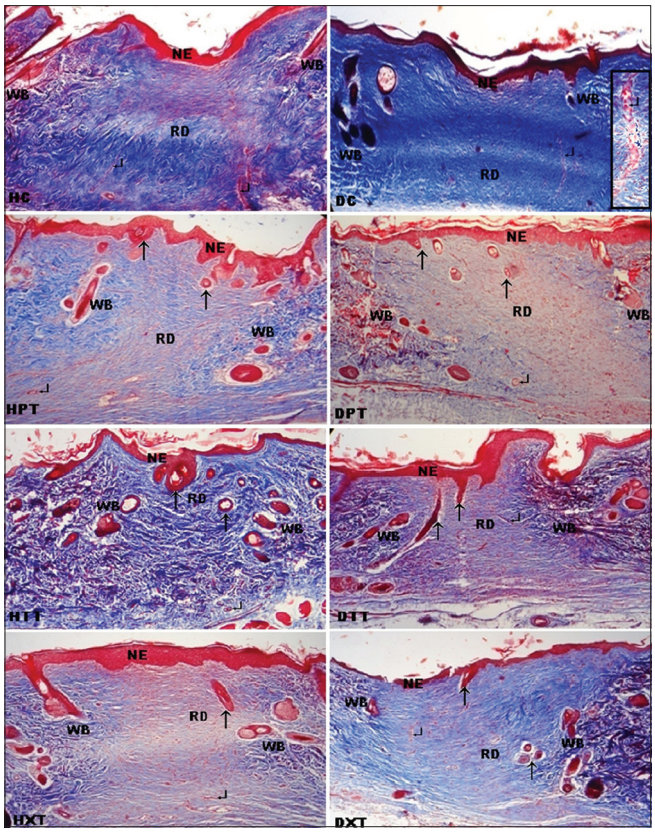

Figure 3: Representative images of MT stained sections on 3rd weeks, showing collagen fibres (Blue colour) in the regenerating dermis (RD), interdigitations, ↑: Hair follicles with hair and sebaceous glands, NE: Neoepidermis, WB: Wound Borders, ⌟: Blood capillaries in all groups at initial magnification x100 and in DC inset⌟: Swollen blood capillary at initial magnification x400.

Matrix remodeling and skin appendages

On 3rd weeks, in all treated groups the collagen fibres in the regenerated dermis were mostly horizontally arranged and compactly interwoven especially in HTT most of the collagen fibres were matured but these fibres were more thickened which form fibrosis in control groups (Fig. 3).

Well defined elastin fibres were seen in the area of regenerating dermis and nearby this area in all treated groups and reappearance of these fibres in the order of d-δ-TRF> co-administrated> d-α-tocopherol groups. Whereas in control groups these fibres were seen only at wound margins (Fig. 5).

At the end of study period, more hair follicles with hairs and sebaceous glands were observed in regenerating dermis and neoepidermis of all treated groups which in the order of d-δ-TRF>d-α-tocopherol> co-administrated groups. But in control groups these features were restricted at the wound margins (Figs 3 and 4).

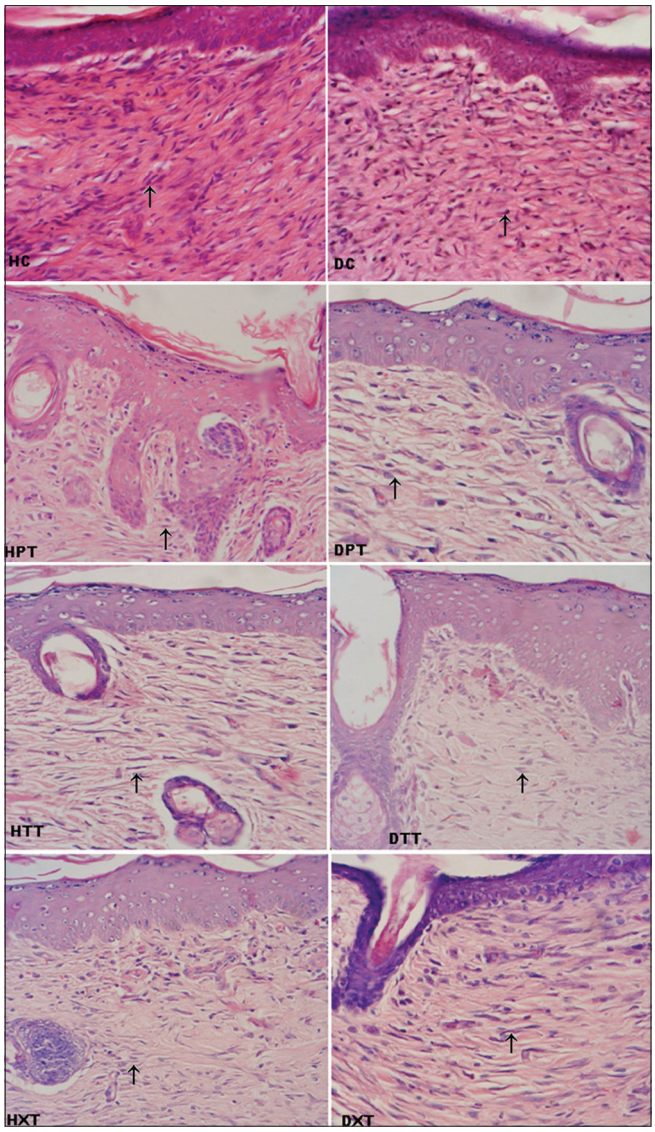

Figure 4: Representative images of H & E stained sections on 3rd weeks, ↑: Showing more cellularity in regenerating dermis of control groups than all treated groups and presence of hair follicles with hair and sebaceous glands in all treated groups at initial magnification x400.

DISCUSSION

Impeded wound healing is now a well-known phenomenon in both experimental and clinical diabetes [24]. Hyperglycemia is known to cause increased production of free radicals and insufficiencies in the antioxidant system [25]. The antioxidants have the ability to reduce the diabetic complications by arresting free radical-induced damage [26]. Vitamin E is a family of essential micronutrients [27] and its one of the most popular applications are in the treatment of burns, surgical scars and wounds [28].

Macroscopic examinations healing wounds on 3rd week revealed that scar was not formed in any

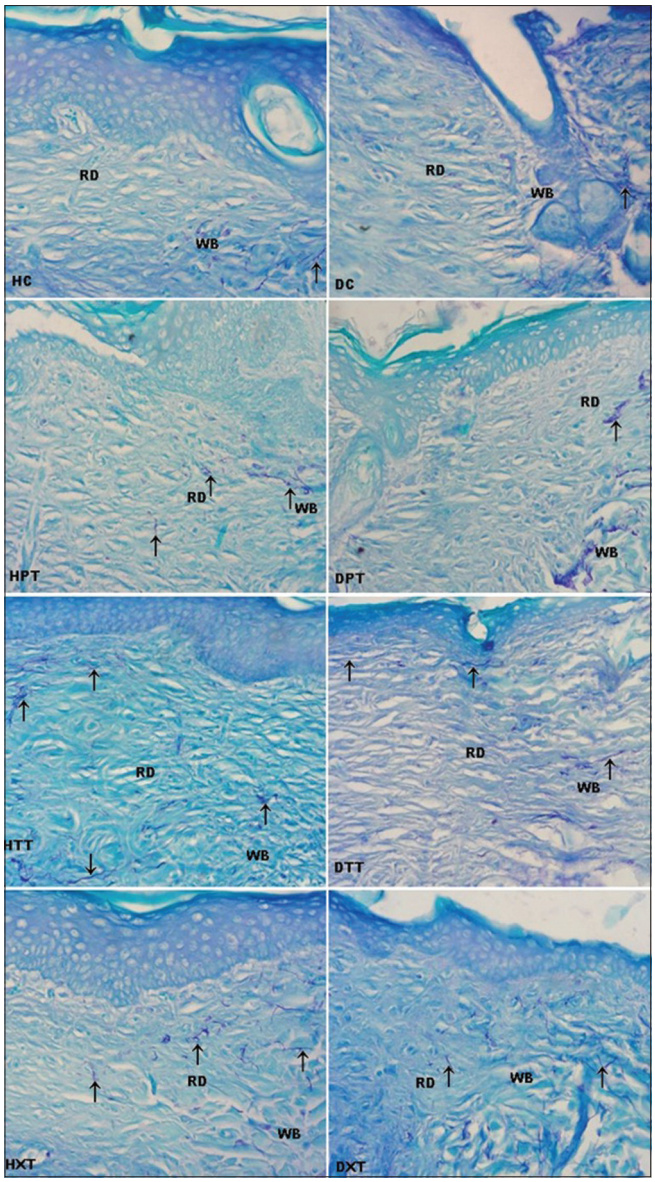

Figure 5: Representative images of AF with FG stained sections on 3rd weeks, showing elastin fibres arrangement. Arrows (→) pointing the presence of elastin fibres (violet colour) WB: wound borders; RD: regenerating dermis, initial magnification x400.

groups. However, a better and faster wound healing was observed in d-δ-TRF treated group followed by d-α-tocopherol treated and co-administrated groups as compared to control groups.

Good marker for superficial changes in the wound is the epidermal thickness [29]. The mean values of histomorphological measurement in the present study showed that on 3rd week in d-δ-TRF group the neoepidermal thickness was remarkably higher than the corresponding border epidermal thickness compared to all other groups. But in co-administrated groups it was thicker than the respective border epidermis of d-α-tocopherol and control groups.

The histopathological observations have shown complete reepithelialization and interdigitations in all groups. But well defined interdigitations on the entire length of neoepidermis appeared only in treated groups. The interdigitations at dermoepidermal junction are known to provide both physical and trophic support. Therefore, the neoepidermis in treated groups has obviously more capacity to resist the possibility of desquamations [21-23].

Presence of more fibroblasts in the granulation tissues is an indicator of dermal regeneration [24] but reduced cellularity indicates that the dermal components are in advanced stages of remodeling [30]. On 3rd weeks cellular components were more in control groups whereas these features were reduced in d-δ-TRF group than d-a-tocopherol and co-administrated groups. These results suggest that the dermal regeneration process was slow in control groups but the three weeks d-δ-TRF supplementation boost the early dermal regeneration as compared to d-α-tocopherol supplementation and co-administration.

Well-structured capillary vessels with absence of hemorrhage are the characteristic feature of neovascularization [24]. More vertically oriented capillary vessels that run towards the epithelial surface were seen in HC whereas in DC blood capillaries were swollen. Reduced vascularity in the reparative tissue is an indictor of dermal remodeling [30]. This finding is supported by the present study as it indicated that the numbers of blood capillary vessels were reduced in all treated groups. These results were also in agreement with our previous studies [21-23].

The collagen fibres are mainly found in the papillary and reticular layers of the dermis and they provide both mechanical and structural integrity to the dermis [31]. At the end of study period, in both control groups the collagen fibres were thicker in the scar tissue. In all treated groups collagen fibres were horizontally placed and compactly interwoven and in addition to these features in HTT most of the collagen fibres were mature, a feature similar to our previous studies [21-23] on secondary skin wound healing. The horizontal alignment of collagen fibres suggests a better tissue remodeling [32].

Tough the elastin is a minor component of the dermis it has an important function in providing the elasticity of the skin [33]. Well defined elastin fibres were seen in the regenerating dermis and its nearby area in all treated groups, plenty of these fibres reappeared in d-δ-TRF treated group followed by co-administrated group compared to d-α-tocopherol treated group. But in control groups these fibres were observed only at wound margins. Same observations were found in our previous studies [21-23] of secondary skin wound healing. Presence of elastin fibres in the healing wound indicates final stages of matrix remodeling [34].

Presence of epidermal appendages such as hair follicles and sebaceous glands in the regenerating dermis and neoepidermis indicate the faster healing and quicker remodeling of wound matrix [32]. At the end of study period, more hair follicles with hairs and sebaceous glands were observed in all treated groups whereas these features were restricted at wound margins in control groups. This study is in agreement with our previous studies [21-23] that among different isoforms of vitamin E, the d-δ-TRF has potency to accelerate the matrix remodeling more effectively than d-α-tocopherol and co-administration of both these isoforms. In matrix remodeling the d-α-tocopherol treated group had shown better results than co-administrated groups.

CONCLUSION

Based on histopathological and histomorphological results it is concluded that the d-δ-TRF accelerates the regeneration and reorganization of epidermal and dermal components in healing of primary intention more effectively than the d-α-tocopherol and co-administration. Therefore among these different vitamin E isoforms the oral administration of d-δ-TRF is a most potent nutritional adjuvant on incisional skin wound healing in both healthy and diabetics.

ACKNOWLEDGEMENTS

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Original Article

Therapeutic potential of d-δ-tocotrienol rich fraction on excisional skin wounds in diabetic rats

Bijo Elsy[1], Aijaz Ahmed Khan[1], Veena Maheshwari[2]

[1]Department of Anatomy, JN Medical College, Aligarh Muslim University, Aligarh, India, [2]Department of Pathology, JN Medical College, Aligarh Muslim University, Aligarh, India

Corresponding author: Bijo Elsy, E-mail: bijobaby22@yahoo.com

ABSTRACT

Introduction: Long-standing hyperglycemia in addition to many of its associated complications also hampers normal wound healing which may be further aggravated in the presence of infection and oxidative stress. Therefore, antioxidant supplementation appears to be strategically relevant for wound healing. This study is designed to explore the therapeutic potential of d-δ-tocotrienol rich fraction (d-δ-TRF) on skin wound healing in both healthy and diabetic rats. **Materials and Methods:** Diabetes was induced through single subcutaneous injection of alloxan at the dose of 100 mg/kg at hip region. 24 albino rats were divided into four groups; healthy control, diabetic control, healthy treated and diabetic treated. d-δ-TRF was administered to treated groups (200 mg/kg), orally, daily for 3 weeks. Full thickness excisional skin wounds were. Wound area was studied by assessing the morphological, histomorphological and histological features at weekly intervals and biochemical analyses were performed at the end of 3rd week. **Results:** The findings of present study revealed that d-δ-TRF accelerated the skin wound healing by means of early regeneration of both epidermal and dermal components; enhancement of serum protein synthesis, improvement of antioxidant status, maintenance of glycemic condition and controlling serum creatinine levels in diabetic rats. **Conclusion:** It is concluded that d-δ-TRF has significant therapeutic potency on the healing of skin wounds in both healthy and diabetics.

Key words: Antioxidant; d-δ-Tocotrienol; Diabetes; Rat; Skin; Wounds

INTRODUCTION

In diabetes wound healing is delayed due to hyperglycemia, infections and oxidative stress [1]. Hyperglycemia is known to causes increased production of free radicals and insufficiencies in the antioxidant system [2]. Excess reactive oxygen species (ROS) is secreted in the inflammatory phase of wound healing by neutrophils and macrophages [3]. Both non-enzymatic antioxidants (e.g., glutathione, vitamin C, vitamin E) and enzymatic antioxidants (e.g., SOD, GPX, PRDX, and catalase) are involved in the fine tuning of ROS level [4]. And an optimal ROS level is distinctive for each step of wound healing [5].

The antioxidants have ability to reduce the diabetes complications by arresting free radical-induced damage [6]. Vitamin E has both saturated (tocopherols) and unsaturated (tocotrienols) forms and is an effective antioxidant. Free-radical scavenging effects of tocotrienols appear superior because of their better distribution in the fatty layers of the cell membrane [7].

Tocotrienols are believed to possess antioxidant, antidiabetic, anti-inflammatory, anticancer, immunostimulating, cardioprotective, neuroprotective, hepatoprotective and nephroprotective properties [8]. Interestingly, the antitumor activity of tocotrienols is not dependent on its antioxidant activity [9,10]. The highly biopotent γ and δ- tocotrienols may play a physiological role in modulating normal mammary gland growth, function and remodeling. Nevertheless anticancer effects on mammary tumor cells by applying these compounds did not display any adverse effect on normal mammary epithelial cell growth [11-13].

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The tocotrienol-rich fraction (TRF) of palm oil consists of 25% α -tocopherol and 75% tocotrienol [14]. The concentrations of different constituents of palm oil-derived-TRF per gram are α-tocopherol at 171.1 mg, α-tocotrienol at 190.4 mg, β-tocotrienol 36.0 mg, γ-tocotrienol 211.2 mg and δ-tocotrienol 150 mg [15]. Therefore, TRF being an excellent antioxidant has been effectively used as a nutritional supplement due to its potential therapeutic benefits [16].

In deep partial-thickness burn wounds, the TRF treatment has been shown to accelerate the wound contraction rate, enhance the reepithelialization, the regeneration process and stimulate the granulation tissue formation [14]. According to Musalmah et al [17], supplementation of TRF at 200 mg/kg was able to improved wound healing in type 1 induced diabetic rat.

Data related to the effects of specific tocotrienol isoforms treatment on skin wound healing are scarce. The available very limited studies mainly focused on wound healing effects of TRF [14,17]. Since TRF contain different vitamin E isoforms, it was not possible to determine which isoforms was specifically responsible to promotes skin wound healing. Hence the present study is focused to assess the therapeutic antioxidant potency of d-δ-TRF on full thickness excisional skin wound healing in healthy and diabetic rats by using histological, histomorphological and biochemical parameters.

MATERIALS AND METHODS

Twenty four albino rats of either sex each weighing 230-320g were obtained from central animal house of JN medical college, AMU, Aligarh. The study was approved by Institutional Animal Ethical Committee (No. 8937/2014). Prior to commencement of the experiments, animals were acclimatized to the new environmental condition for a period of one week. They were kept in a well ventilated room and maintained on a standard pellet diet and water [18].

Induction of Diabetes

Diabetes was induced to the diabetic group after deprivation of food for 4 hours, followed by single subcutaneous injection (hip region) of alloxan (100 mg/kg; Alloxan monohydrate from Sigma-Aldrich). Food and water were provided after one hour of injection. Blood was obtained via tail vein for monitoring sugar level by using Glucometer (Dr Morepen gluco one) on the 4th day of alloxan injection. Animals with blood sugar level at 250 mg/dl and above were selected as diabetic for this study. Weight and blood sugar levels of all animals in each group were monitored at weekly intervals [18].

Experimental Groups, Route and Dosage of Treatment

Animals were divided into four groups having 6 rats in each group: (1) healthy control- HC; (2) diabetic control- DC; (3) healthy d-δ-TRF treated- HTT and (4) diabetic d-δ-TRF treated - DTT (200 mg/kg body weight, orally, daily for 3 weeks. Unique E Tocotrienol, tocopherol free, 90% δ and 10% γ tocotrienols, AC Grace Company, P.O Box 570, Big Sandy, TX 75755, USA). Orally supplemented tocotrienol was rapidly taken up by the skin [19]. Dosage of d-δ- tocotrienol rich fraction (200 mg/kg body weight) was based on previous studies of TRF [15,17,20].

Surgical Procedure

All animals received general anesthesia via inhalation of ether and after that, the dorsal surface of thoracic region was shaved and antisepsis was performed over the shaved area. Full thickness excisional skin wounds of 8.5 ± 0.48 mm diameter (an area equivalent to 46.74 ± 0.32 mm^2) was made on pinched skin fold of shaved area. Type and size of wound model were very akin to the murine excisional wound model described earlier [21]. Povidone-iodine solution (antisepsis) was applied on the wound and 0.5 ml Voveran (analgesic) and 2 mg single shot of Gentamycin (antibiotic) were also injected simultaneously [18].

Sample Collection and Fixation of Tissue

On completion of 3 weeks animals were sacrificed under deep ether anesthesia and then excised the healed parts of skin with adjacent area. The excised tissues were immersion-fixed in 10% neutral buffered formalin. Blood samples were collected into sterilized vials by direct puncture of heart at the time of sacrifice. Samples were allowed to clot, centrifuged at 2500 rpm for 30 min, the serum was separated and stored in vials and used to assay all biochemical parameters [18].

Macroscopic Examination

The macroscopic changes in the wound healing sequence of events were observed and recorded photographically on 1st, 7th, 14th & 21st day of creation of wounds.

Histopathology & Histomorphometry

Fixed tissue samples were processed for light microscopical studies. The 5 μm thick sections were stained with Haematoxylin & Eosin (H & E), Masson's Trichrome (MT), Aldehyde Fuchsin with Fast Green (AF with FG) and PicroSirus Red with Fast Green (PSR with FG).

Histomorphometry was performed on both H & E and MT stained sections. While H & E sections were used for measuring the Global Healing Index (GHI), MT stained sections were used for estimation of Global Remodeling Index (GRI). Histological features under x 4 objective lens of trinocular microscope (Olympus, BX40; Japan) were recorded by digital camera (Sony 18.2 MP, Japan) and measurements were made by using software Motic image version 2.0. Measurements related to epidermal thickness and calculation of healing indices were based on the mathematical model for healing and remodeling matrix [22].

Biochemical Estimation & Analysis

a. All lipid profiles, serum creatinine and serum total protein content were carried out by using Avantor Benesphera™ clinical chemistry Analyzer C61.
b. *Enzymatic antioxidant*
Serum catalase was assayed by colorimetery as described [23]. The light absorbance of the sample was determined at 620 nm.
c. *Non-invasive biomarker (oxidative stress parameter)*
Serum total antioxidant capacity (TAC) was evaluated using ferric reducing antioxidant power (FRAP) assay [24]. The absorbance of sample was measured at 620 nm using photo colorimeter.

Statistical Analysis

All the data were statistically evaluated and the significance calculated using one way 'ANOVA' followed by Tukeys test. All the results were expressed as mean ± SD and $P < 0.05$ was considered as statistically significant. Student t test was used for comparing the blood sugar level in DTT group before and after supplementation of d-δ-TRF ($P < 0.0001$).

RESULT

Body weight and Blood Sugar Level

Weight and blood sugar levels of all animals in each group were monitored at weekly intervals. Mean body weight in DC showed slight weight reduction whereas in all other groups (HC, HTT& DTT) remained stable at the end of study period (Table 1). Mean blood sugar levels of healthy groups (HC & HTT) remained within normal limits. In DTT the mean blood sugar level was significantly ($P<0.0001$) reduced after 3 weeks supplementation of d-δ-TRF while in DC showed > 500 mg/dl throughout the experimental period (Table 2).

Macroscopic Observations

In treated groups remarkable progressive changes in the size of wound area were observed at the end of 14th day compared to control groups (Fig. 1).

Microscopic Observations

Histomorphometry

In all groups the neoepidermis was developed at the end of 2nd week. However, in treated groups the mean values of neoepidermis were significantly thicker ($P<0.01$) than the corresponding epidermal border thickness on 2nd and 3rd weeks (Table 3). During the study period in treated groups the GHI and GRI were significantly higher ($P<0.01$) compared to control groups (Figs 2 and 3).

Reepithelialization

Complete reepithelialization was noticed in all the groups (controls and treated). On 2nd and 3rd weeks, in treated groups well defined interdigitations at dermoepidermal junction appeared on the entire length of neoepidermis (Figs 4, 5a and 7). On 2nd weeks in HC poorly defined interdigitations at wound margins while in DC absence of interdigitations (Fig. 4). On 3rd weeks

Table 1: Body weights (g) of the animals of all groups during the period of study

Groups	Day 0	Day 7	Day 14	Day 21
HC	270±35.59	266.67±15.28	283.33±20.82	290±21.60
DC	277.5±25	247.5±17.08	235±23.80	227.5±22.17
HTT	270±26.46	266±14.26	272.5±17.07	285±20.82
DTT	271.25±20.97	251.25±20.5	265±23.80	275±20.82

Note the mean body weight in DC showed slight weight reduction while all other groups remained stable at the end of study period

Table 2: Blood sugar (mg/dl) level of the animals of all groups during the period of study

Groups	Day 0	Day 7	Day 14	Day 21
HC	146±28.21	124±19.98	160.67±18.01	167±17.06
DC	540.25±47.12	553±39.42	574.25±30.20	578±34.73
HTT	150±35.36	170±30.53	117.5±21.92	134.67±29.69
DTT	574.71±33.74	406.25±1.31	286.75±19.96	195±31.10

Note that the mean blood sugar levels of healthy groups (HC & HTT) remained within normal limits. In DTT group the mean blood sugar level was significantly ($P<0.0001$) reduced after 3 weeks treatment while in DC showed > 500 mg/dl throughout the experimental period

in control groups these features were restricted to only at the wound margins (Fig. 5a and 7).

Cellular components

At the end of study period, the granulation tissue consists of mainly fibroblasts in all groups. The fibroblasts appeared oval or spindle shaped and scattered in HC. In DC these cells were mainly stellate whereas in treated groups spindle shaped cells lie parallel to the neoepidermis. More cellularity was observed in control groups as compared to treated groups (Fig. 6).

Table 3: Border & neoepidermal thickness (mm; Mean ± SD) at the end of 2nd & 3rd week

Groups	2 weeks		3 weeks	
	Border epidermis	Neoepidermis	Border epidermis	Neoepidermis
HC	0.078±0.018	0.109±0.013	0.075±0.014	0.115±0.014
DC	0.058±0.017	0.075±0.025	0.061±0.013	0.092±0.043
HTT	0.093±0.017	0.248±0.035	0.089±0.013	0.222±0.031
DTT	0.088±0.014	0.237±0.038	0.068±0.012	0.192±0.026

Note that the neoepidermal thickness in treated groups (HTT & DTT) is thicker than that of their respective epidermal border thickness on 2nd and 3rd weeks

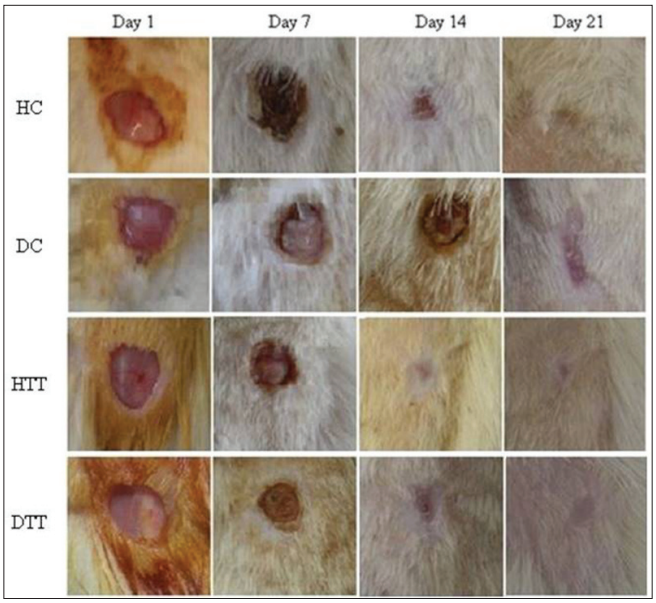

Figure 1: Photographs showing skin wounds of different groups at weekly intervals. Note that on 14th day an observable change in the size of the wound area in treated groups.

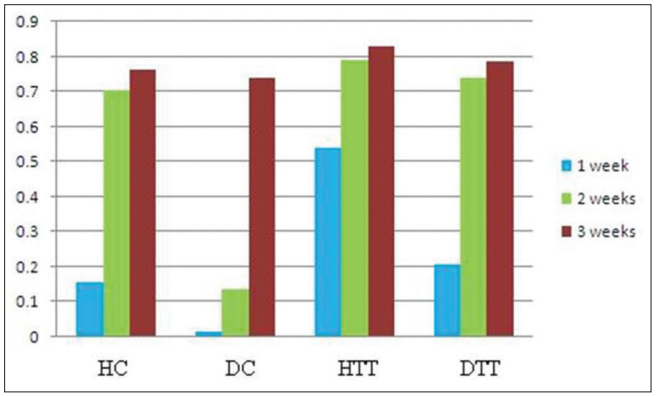

Figure 2: Weekly mean values (in mm) of Global Healing Index (GHI).

Neovascularization

In treated groups, well formed vertically oriented blood capillaries appeared by the end of 2nd week while they appeared late in HC by the end 3rd week. Swollen capillaries and extravasation of blood cells were seen in DC granulation tissue on 3rd weeks whereas in treated groups less number of vessels was observed on 3rd weeks (Figs 5a and 5b).

Matrix remodeling and Skin appendages

On 2nd and 3rd weeks, in treated groups the collagen fibres in the regenerated dermis were mostly horizontally arranged and compactly interwoven but these fibres were more obliquely placed in HC on 3rd weeks. In DC on 2nd weeks collagen fibres were arranged as wavy pattern and on 3rd weeks these fibres were poorly interlaced in the suprahypodermal area (Figs 4, 5a and 7).

The elastin fibres in control groups were found in the wound margins while in the treated groups these fibres

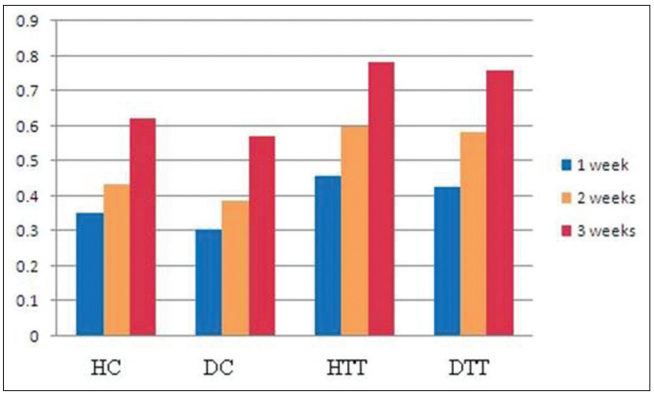

Figure 3: Weekly mean values of Global Remodeling Index (GRI).

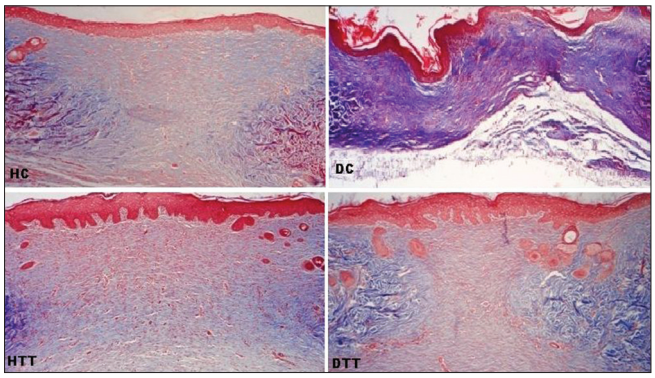

Figure 4: Representative images of MT stained sections on 2nd weeks, showing presence of interdigitations and hair follicles at initial magnification x100.

were noticed in one step advanced stage and newly formed smaller fibrils were diffusely arranged in the regenerating dermis on 3rd weeks (Fig. 8).

On 2nd weeks, in control groups the hair follicles were confined to wound margins while in treated groups hair follicles were notice almost in the central part of the wound (Fig. 4). At the end of study period, in treated groups hair follicles and sebaceous glands were in advance stage into the regenerating dermis and newly formed hairs found within the hair follicles and neoepidermal surface. In control groups hair follicles and sebaceous glands remained only at the wound margins (Figs 6 and 7).

Biochemical Analysis

Lipid profiles

Total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) in DC were significantly higher ((P<0.01) compared to DTT. Whereas high density lipoprotein (HDL) in DC showed significantly lower (P<0.01) compared to DTT (Table 4).

Serum creatinine level and serum total protein content

Serum creatinine level in DC were significantly higher ((P<0.01) compared to all other groups. Serum total protein content in treated groups (HTT & DTT) showed significantly higher (P<0.01) compared to control groups (HC & DC) (Table 5).

Enzymatic antioxidant and oxidative stress parameter

Serum catalase activity and total antioxidant capacity in treated groups (HTT & DTT) exhibited significantly higher (P<0.01, P<0.05) compared to control groups (HC & DC). These analyses values in DC showed significantly lower (P<0.05) compared to HC group (Table 5).

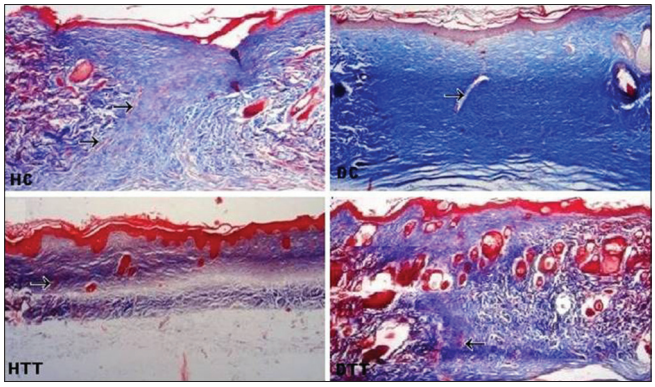

Figure 5a: Representative images of MT stained sections on 3rd weeks, showing collagen fibres arrangements and interdigitations. Arrows (→) pointing the presence of capillary vessels at initial magnification x100.

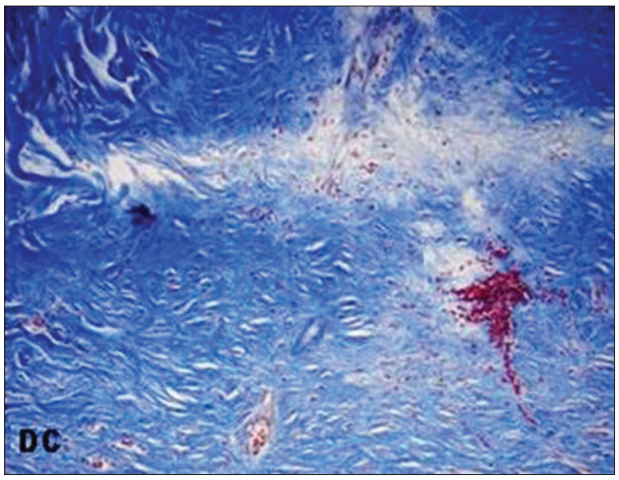

Figure 5b: Representative images of MT stained sections on 3rd weeks DC showing the presence of swollen capillaries and extravasation of blood cells in the regenerating dermis at initial magnification x400.

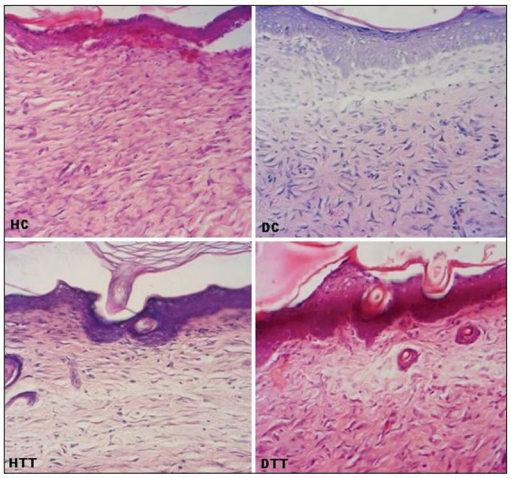

Figure 6: Representative images of H & E stained sections on 3rd weeks, showing arrangement of cells and presence of hairs at initial magnification x400.

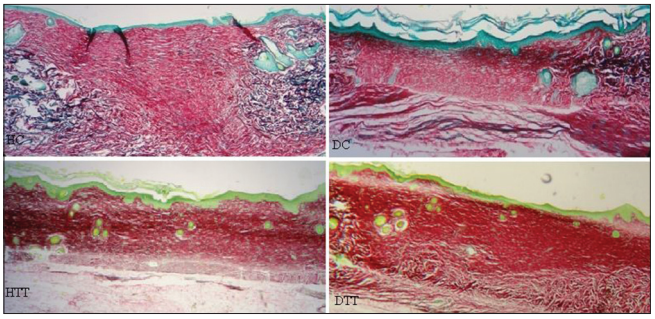

Figure 7: Representative images of PSR with FG stained sections on 3rd weeks, showing collagen fibres arrangement, interdigitations and hairs within the hair follicles at initial magnification x100.

Table 4: Effects of d-δ-TRF supplementation on lipid profiles (Mean ± SD)

	Lipid profiles				
Groups	**Total cholesterol (mg/dl)**	**HDL (mg/dl)**	**LDL (mg/dl)**	**VLDL (mg/dl)**	**Triglycerides (mg/dl)**
HC	45.66±0.83	15.28±0.22	13.56±0.19	16.82±0.42	101.75±4.60
DC	54.30±1.19	11.05±0.21	18.02±0.09	25.23±0.89	171.15±11.53
HTT	45.82±0.42	17.08±0.10	12.84±0.11	15.90±0.21	101.25±1.48
DTT	46.46±0.29	16.98±0.16	13.15±0.05	16.33±0.08	110.6±0.42

Note that in DC mean values of TC, TG, LDL, VLDL were significantly higher ((P<0.01) and HDL significantly lower (P<0.01) compared to DTT

Table 5: Effects of d-δ-TRF supplementation on biochemical parameters (Mean ± SD)

	Serum analyses			
Groups	**Creatinine (mg/dl)**	**Total protein (g/dl)**	**Catalase (u/ml)***	**TAC (mmol/L)**
HC	0.425±0.010	5.05±0.07	0.0672±0.004	1285.5±67.18
DC	0.790±0.022	4.5±0.14	0.0438±0.005	1000±67.88
HTT	0.430±0.013	5.85±0.08	0.156±0.006	2063.3±72.89
DTT	0.441±0.020	5.5±0.01	0.105±0.007	1888.3±72.78

Note that all biochemical parameters reveal significantly less in DC compared to all other groups (P<0.05). Catalase (u/ml)*u-mmols of H_2O_2 utilised/mt

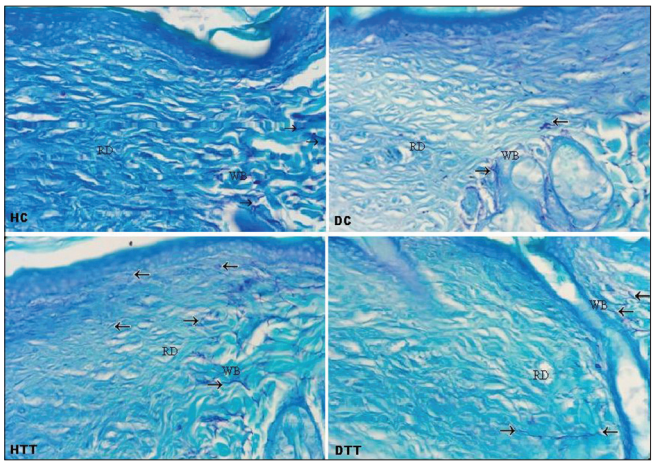

Figure 8: Representative images of AF with FG stained sections on 3rd weeks, showing elastin fibres arrangement. Arrows (→) pointing the presence of elastin fibres (violet colour) WB: wound borders; RD: regenerating dermis, initial magnification x400.

DISCUSSION

Impaired wound healing is a well-documented phenomenon in both experimental and clinical diabetes [25]. Free radicals impair the normal wound healing by damaging keratinocyte, endothelial cells, capillary permeability and collagen metabolism [26]. Oxidative stress induces cellular dysfunction and retards angiogenesis and the healing process [27]. Thus, elimination of ROS is an important strategy to improve the healing of wounds in diabetes mellitus patients [28]. The unsaturated isoforms of vitamin E e.g., tocotrienols possess excellent antioxidant activity and suppress ROS production more efficiently than saturated forms e.g., tocopherols [29].

In the present study, in DC reduced mean body weight at the end of experimental period but in DTT these were stable throughout experimental period. These findings are in agreement with related study [20] whose had demonstrated that, diabetic group without TRF supplementation showed significantly lower body weight than that of diabetic rat treated with TRF for 4 weeks.

While oral administration of d-δ-TRF for 3 weeks in DTT revealed reduced mean blood sugar level and in DC showed hyperglycemic state throughout the study period. These results correlate with other study [30] showing that the tocotrienol supplementation significantly increased the insulin levels and reduced the blood glucose in diabetic induced rats in dose dependent manner.

Macroscopic observation of healing wounds revealed remarkable changes in the wound size in treated groups even on14th day, suggestive of faster recovery in the treated groups. The reepithelialization in epidermis is widely accepted to be one of the major processes in wound healing that ensures successful repair [31- 33]. Basal keratinocytes from both the wound edge and epidermal appendages such as hair follicles, sweat glands and sebaceous glands constitute the main sources for cells responsible for the reepithelialization [34].

Thickness of the epidermis is a good indicator for the superficial changes in the wound [22]. The mean values of histomorphological measurement in the present study showed that although the neoepidermis regenerated during the 2nd weeks in all groups, in treated groups the neoepidermal thickness was remarkably higher than the border epidermal thickness at the end of 2nd and 3rd weeks.

The global healing and remodeling indices (GHI and GRI) are used to measure the different stages of skin wound healing and its progress Lemo et al [22]. In cases of stronger wound remodeling the GRI can go up to 1. The mean values of GHI and GRI in the present study were high compared to control groups, indicating the positive therapeutic effects of d-δ-TRF in both healthy and diabetics.

Progression of wound healing revealed that while complete reepithelialization took 3 weeks in control group it took only two weeks in the treated group suggesting that d-δ-TRF promotes wound healing.

The interdigitations at dermoepidermal junction are known to provide both physical and trophic support. In treated groups well developed interdigitations appeared on entire length of neoepidermis on 2nd weeks and were well defined than those in the control groups on 3rd weeks. Therefore, the neoepidermis in treated groups has more capacity to resist the possibility of desquamations.

Dermal regeneration has been characterized by granulation tissue rich in fibroblasts, generally oriented parallel to the epidermal layer [25]. On 3rd weeks cellular components were more in control groups than treated groups. The fibroblasts were oval or spindle shaped and scattered in HC whereas in DC these cells were mainly stellate shaped, indicating incomplete dermal regeneration. In treated groups spindle shaped fibroblast lie parallel to the neoepidermis, suggesting that the d-δ-TRF supplementation helps the complete dermal regeneration.

Neovascularization is characterized by well-structured capillary vessels and absence of hemorrhage [25]. Numerous, well formed vertically oriented capillary vessels that run towards the epithelial surface were seen by the end of 3rd week in HC on whereas in treated groups these were observed by the end of 2nd week thus indicating an early and good neovascularization in the treated group. Swollen capillaries and extravasation of blood cells were seen in DC granulation tissue even on 3rd week, pointing towards its poor and delayed neovascularization. As remodeling progresses, there is a gradual reduction in the cellularity and vascularity of the reparative tissue [35]. This finding is supported by the present study as it indicated that the numbers of capillary vessels were reduced in treated groups on 3rd weeks.

The collagen fibres are mainly found in the papillary and reticular layers of the dermis and they provide both mechanical and structural integrity to the dermis [36]. In early phase of healing the collagen fibres in dermis revealed different orientation and packing density. On 2nd weeks collagen fibres were arranged as wavy pattern in DC. At the end of study period, in HC more fibres were obliquely placed while in DC the suprahypodermal area consists of poorly interlaced collagen fibres. In treated groups these fibres were horizontally placed and compactly interwoven and this horizontal alignment of collagen fibres indicates a better tissue remodeling [37].

Tough the elastin is a minor component of the dermis it has an important function in providing the elasticity of the skin [38]. At the end of experimental period, in control groups the elastin fibres appeared at the wound margins. In treated groups these structure were noticed one step advanced stage and newly formed smaller fibrils were diffusely arranged in the regenerating dermis. Presence of elastin fibres in the healing wound indicates final stages of matrix remodeling [39].

At the end of study period, in control groups hair follicles and sebaceous glands remained only at the wound margins. In treated groups hair follicles and sebaceous glands were in advance stage and had their made their presence into the regenerating dermis and even newly formed hairs were found within the hair follicles and on the neoepidermal surface, which indicated a faster healing and quicker remodeling of the wound matrix [37].

The predictors of cardiovascular complications in diabetes are believed to be dyslipidemia and hyperglycemia [40-43]. The present data indicated that mean values of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels were higher and high density lipoprotein (HDL) level lower in DC, indicating significant dyslipidemia in untreated diabetic rats [44]. The lower mean values of TC, TG, LDL and VLDL levels and high HDL level were recorded in DTT after 3 weeks treatments. This result is in agreement with related study [45].

The serum creatinine level is known to be a significant marker of diabetic nephropathy. Our result showed the serum creatinine level was higher in DC than all other groups and almost similar observation has been shown in the STZ-induced diabetic rat [44]. In DTT these level were improved after 3 weeks treatment and similar to the level of healthy groups (HC & HTT). The abnormally high level of serum creatinine was consistent with the impaired kidney function [46].

The total protein content is also known to be an indicator for the protein level and cellular proliferation of the wound tissue [47]. The result of present study also indicates that the d-δ-TRF treatment enhances protein synthesis in treated groups and its level lower in DC, which is in agreement with [44] who found that diabetic rats showed lower serum total protein level and when treated with vitamin E its level improves significantly.

Catalase is a preventive antioxidant which inhibits the initial production of free radicals. When H_2O_2 is generated in large quantities, the enzyme catalase is also used for its removal [48]. The present study showed that the serum catalase activity was lower in DC. Many other studies [49,50] stated that the catalase activity had decreased in plasma, liver and kidney of diabetic control rats. The decreased catalase activity in plasma and tissues of STZ-diabetic rats may be due to its increased utilization for scavenging the toxic products of lipid peroxidation or due to decreased availability of H_2O_2 [49]. Vitamin E treatment has been shown to normalize the catalase activity in the control group [50]. The result of present study revealed that d-δ-TRF supplementation enhances the serum catalase activity in treated groups.

Antioxidant capacity of plasma is the primary measure and marker to evaluate the status and potential of oxidative stress in the body [51]. Total antioxidant capacity has been shown to be significantly reduced in plasma and liver homogenate FRAP of diabetic rats compared to control animals [52-54]. The observation of present work with significantly lower ($P<0.05$) serum FRAP level in diabetic control compared to healthy control is in agreement with the findings of above mentioned workers. In treated groups, after 3 weeks supplementation with d-δ-TRF revealed the improved serum antioxidant capacity.

CONCLUSION

Based on findings of the present study it is concluded that d-δ-TRF promotes skin wound healing in both healthy and diabetic rats and thus indicative of its strong therapeutic potential in future in the management of skin wounds.

ACKNOWLEDGEMENTS

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Abbreviations

AF with FG: Aldehyde Fuchsin with Fast Green; DC: Diabetic Control; DTT: Diabetic d-δ-tocotrienol rich fraction treated; FRAP: Ferric Reducing Antioxidant Power; GHI: Global Healing Index; GRI: Global Remodeling Index; HC: Healthy Control; H&E: Haematoxylin & Eosin; HTT: Healthy d-δ-tocotrienol rich fraction treated; MT: Masson's Trichrome; TAC: Total Antioxidant Capacity; PSR with FG: Picro Sirus Red with Fast Green.

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Our Dermatology Online

Original Article

Decreased arylesterase activity and increased total oxidative status in rosacea

Sertac Sener[1], Fadime Kilinc[1], Ayse Akbas[1], Ahmet Metin[2], Suzan Demir Pektas[3], Salim Neselioglu[4], Ozcan Erel[4]

[1]Dermatology Clinic, Ataturk Training and Research Hospital, Ankara, Turkey, [2]Department of Dermatology, Yildirim Beyazit University Medical Faculty, Ankara, Turkey, [3]Department of Dermatology, Aydın State Hospital, Aydın, Turkey, [4]Department of Biochemistry, Yildirim Beyazit University Medical Faculty, Ankara, Turkey

Corresponding author: Sertac Sener, MD, E-mail: sertacsnr@yahoo.com

ABSTRACT

Background: Rosacea is an inflammatory skin disease of face. In recent years, it is revealed that imbalance is significant in oxidant/antioxidant system in pathophysiology. **Objective:** In this study, the role of oxidative stress on rosacea was investigated. **Methods:** 34 rosacea patients and 33 healthy control cases between 18 and 70 years old are included in the study. In all the cases, serum lipids, Paraoxonase1 (PON1), stimulated Paraoxonase1 (stPON1), Arylesterase (ARES), Total Oxidant Status (TOS) and Total Antioxidant Status (TAS) levels are measured. **Results:** ARES levels were significantly lower and TOS levels were significantly higher in the patient group ($p<0,001$). Oxidative Stress Index (OSI) was found to be shifted towards the oxidative side in the patient group ($p<0,001$). **Conclusion:** This situation shows that oxidative stress may have a role in the rosacea pathophysiology.

Key word: Arylesterase; Rosacea, Oxidative stress; Total antioxidant capacity; Total oxidant status

INTRODUCTION

Rosacea is a chronic, inflammatory disease with exacerbations. The disease affecting the capillary vessels and pilosebaceous unit, is characterized by midfascial erythema, telangiectasia, papules and pustules [1]. It is known four subtypes [2] as erythematotelangiectatic (type I), papulopustular (II), phimatous (III) and ocular rosacea (IV). Pathophysiological mechanism is associated with inflammation triggered with ultraviolet (uv) radiation, vascular changes, microorganisms or oxidative tissue damage [3]. Researches have revealed that imbalance in oxidant/antioxidant system is an important factor in rosacea. In rosacea patients, high serum peroxide level and low tissue superoxide dismutase (SOD) activity were shown [4,5]. Skin biopsy samples were taken from the rosacea patients and the healthy controls. Reactive oxygen species (ROS) and SOD levels were determined. In rosacea lesions, there was a higher ROS activity and a lower SOD level when compared to the controls [6]. The inhibition of ROS activity in neutrophils with various topical and systemic drugs used in the treatment of rosacea supports the "oxidative stress phenomenon" hypothesis [7-9]. On the other hand, PON1 is an enzyme having antioxidant and anti-inflammatory activity and it was found that serum PON1 levels decreased in rosacea [10].

In the studies performed till now, generally oxidant and antioxidant molecules were measured separately. In this study, we evaluated TOS and TAS and investigated whether oxidative stress had a role in rosacea or not.

MATERIAL AND METHOD

The planned prospective controlled study was accepted by the ethics committee of our hospital. All the cases had signed the informed consent form and their approvals were taken.

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Thirtyfour rosacea patients and 33 healthy controls were included in the study. None of the cases was using any drugs, alcohol or tobacco and they had no additional diseases. The patients were divided in subtypes by using The National Rosacea Society classification [2]. Nine patients was evaluated as subtype I, 16 patients as subtype II and 9 patients as subtype III. In addition to the skin lesions, 7 patients having eye involvement were also noted.

The serum PON, stPON, ARES, TAS, TOS, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) levels were measured and OSI was calculated in all cases. TOS and TAS levels were determined by using new automatic colorimetric measurement methods [11,12]. TOS results were calibrated and expressed as micrometer hydrogen peroxide equivalent per liter ($\mu MH_2O_2Eq/L$). TAS results were shown as (mmolTroloxEq/L). OSI (arbitrary unit) was calculated according to the TOS/TAS X 100 formula. PON and ARES activities were measured by using commercial kits and the results were recorded as kU/L.

RESULTS

Thirty four rosacea patients (13 males) with an average age of 47,41 ± 8,84 and 33 healthy cases (16 males) with an average age of 47,76 ± 10,57 were included in the study. There was no significant difference between the groups in terms of age and gender (p>0.05).

ARES levels were significantly lower and TOS levels were significantly higher in the patient group (p<0,001). OSI was found to be shifted towards the oxidative side in the patient group (p<0,001). The results are shown in the Table 1.

Also serum TG levels were significantly higher in the patient group (Z=2.051, p<0,05). The serum PON, stPON, TAS, TC, LDL and HDL levels did not show a statistically significant difference between the groups (p>0,05).

A positive correlation was found between TAS and TG levels in the patient and control groups (r=0.647 and r=0.667, respectively; p<0.001). No significant relation was found between oxidative stress (TAS, TOS, OSI) levels and age, rosacea subtype, disease duration or eye involvement.

Table 1: Laboratory findings of the rosacea patients and the healthy controls

Measurement	Patients	Controls	Statistics test	P
TG	117.00 (69.25)[1]	96.00 (54.00)	Z=2.051	0.040*
TC	208.74±43.22[2]	192.09±39.27	t=1.648	0.104
HDL	47.14±9.90	48.52±11.96	t=-0.517	0.607
LDL	129.17±27.54	121.66±31.93	t=1.032	0.306
PON1	176.00 (234.00)	213.00 (130.00)	Z=1.079	0.281
ARES	195.00 (66.00)	292.00 (22.50)	Z=6.842	0.001*
STPON1	378.50 (436.50)	345.00 (241.00)	Z=0.414	0.679
TAS	2.15 (0.42)	2.21 (0.27)	Z=1.198	0.231
TOS	10.80±2.64	8.79±1.89	t=3.570	0.001*
OSI	0.05±0.01	0.04±0.01	t=3.518	0.001*

[1]median (IQR); [2]mean±sd, TC: Total cholesterol, TG: triglycerid, HDL: high density lipoprotein, LDL: low density lipoprotein, PON: paroxonase, STPON: stimulated PON, ARES: arylesterase, TOS: total oxidant status, TAS: total antioxydant status, OSI: oxydative stress index. The normally distrubuted variables are reported as mean±standard deviation (mean±sd) and compared with independent samples t-test and non-normally distrubuted variables are reported as interquartile-ranges (IQR) (median) and compared with Mann-Whitney U test
*statistically significant

DISCUSSION

In this study, we have evaluated the effect of oxidative stress in rosacea patients. Independent from the rosacea subtypes, TOS levels were increased in the patients' group. ARES activity was lower and triglyceride (TG) levels were significantly higher in the patients' group as well.

Vascular and inflammatory factors play role in the pathophysiology of rosacea [3,13]. Inflammation is related to the oxidative processes of proteins and lipids. ROS damages the activation of natural defense system, changes the lipid balance and stimulates the inflammatory mediators such as cytokines [14]. Activated inflammatory cells, especially neutrophils, provide ROS release in rosacea. On the other hand, uv radiation cause ROS production on the skin and it is an important factor aggravating rosacea. As a result, these free oxygen radicals cause oxidation of lipids and lipoproteins [15-18].

The study of Baz et al. have showed that rozacea is an oxidative stress situation. They found increased ROS activity and decreased antioxidant potential due to high malondialdehyde levels [19].

PON1 is an antioxidant and anti-inflammatory enzyme associated with HDL and it has PON, ARES and dyazoxonase activities. This enzyme prevents the oxidation of serum lipoproteins and the accumulation of hydrolyzed lipid peroxide. The oxidative medium caused by the free radicals and peroxides oxidizes

the sulfhydryl groups of PON and ARES enzymes, and PON1 enzyme activity decreases [20,21]. In other words, when the medium is oxidated more, PON and ARES enzyme activities decrease leading to a diminished antioxidant capacity. Various studies showed decreased PON1 activity in systemic diseases including metabolic syndrome, atherosclerosis, diabetes mellitus and in various skin diseases such as psoriasis, recurrent aphtous stomatitis [22-25]. Takcı et al. reported that PON1 activity (PON and ARES) is lower and serum lipid hydroxyperoxide levels are higher in rosacea patients indicating increased oxidative stress in rosacea [10].

Up to now, different oxidant and antioxidant molecules in rosacea has been investigated. However separate measurements of these molecules require complex and expensive methods. Also they may cause false results due to the additive effect. Our TOS measurement method shows the global effect of numerous oxidants and also our TAS measurements reflect the total effect of various antioxidants in the organism. These methods are rapid, cheap, easy and reliable. It has also been shown by this method that oxidative stress was increased in vitiligo, aphtous stomatitis, psoriasis and seborrheic dermatitis [22,26-28].

Although TAS level is not statistically different from the control group, this study suggests inflammation-related TOS level increases and ARES activity decreases in rosacea. Besides, OSI which is the essential indicator of oxidative stress shifts towards the oxidative stress side. In fact human body is a dynamic system. Despite the attacks of free radicals, every metabolic process in the organism is in relation with other processes in order to maintain the oxidant/antioxidant balance [18]. In our study, the increase in oxidation observed in rosacea patients possibly decreased the antioxidant ARES enzyme activity. However no significant decrease occurred in the PON1 levels and TAS.

CONCLUSION

This study suggests that oxidative stress contributes to the rosacea pathophysiology. TOS and TAS levels measurement is a reliable method to determine oxidative stress in rosacea.

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Our Dermatology Online

Original Article

Pattern of patch test reactivity among patients with clinical diagnosis of contact dermatitis: A hospital-based study

Sudip Parajuli[1], Vikash Paudel[2], Upama Paudel[1], Dinesh Binod Pokhrel[1]

[1]Department of Dermatology and Venereology, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal, [2]Department of Dermatology and Venereology, National Medical College, Birgunj, Nepal

Corresponding author: Dr. Sudip Parajuli, E-mail: sudipparajuli@gmail.com

ABSTRACT

Introduction: The patterns of positive patch test in Nepal have not been defined so far. The aim of this study was to describe the patterns of patch test reactivity in suspected Allergic Contact Dermatitis (ACD) patients. **Methods:** This was a hospital based retrospective study performed to investigate patch test reactivity in patients with ACD from April, 2016 through October, 2016. The data of patients who underwent patch test during this period were extracted and analyzed. **Results:** A total of 35 patients were included in the study. Nineteen (54.3%) tested positive to either one or more allergens. Among them, 17 (89.4%) reacted positively to a single allergen. The following patterns of positives were seen: nickel sulfate, 5 (26.3%), fragrance mix 3 (15.7%), and parthenium 3 (15.7%). Cobalt sulfate, formaldehyde, potassium dichromate, benzocaine, nitrofurazone, chlorocresol each was positive in single patient. Majority of the patients were housewives (22.6%) followed by students and officers (13% each), farmers (10%), health care workers (9.7%), wet work (6.5%) and others (20). Less than half (45%) of the hand eczema showed positive patch test. Similarly,40% of the patient of scattered generalized dermatitis showed reactivity to parthenium, nickel sulfate and multiple antigens. **Conclusions:** The most common allergens identified were nickel sulfate, fragrance mix and parthenium. Since, there is no well defined contact allergen in the Nepalese community, so patch test kits developed elsewhere might not have been beneficial and calls for need of large scale investigation to identify the local allergens.

Key words: Allergic contact dermatitis; Nickel sulfate; Patch tests

INTRODUCTION

Skin diseases are the common and significant cause of morbidity in Nepal. Among them, eczemas are the commonest with high prevalence of allergic contact dermatitis (ACD) [1]. Because of diversity in genetic, environment, topography and occupation of Nepalese population, these factors may also influence the exposure patterns and could be responsible for the variations in the patterns of skin reactivity. Patch test is the gold standard test for allergic contact dermatitis despite the fact that 10% to 15% of normal healthy individuals may react to one or more allergens. Over 3000 chemicals are known to cause ACD but, fortunately, only a small number of these chemicals are responsible for symptoms in the majority of cases [2]. The knowledge about the common allergens and a comprehensive history of the patient's exposure will be valuable for selecting the test panels for patch testing. The culprit antigens and the patch test patterns are not defined so far in Nepal. The aim of this study was to describe the patterns of patch test reactivity amongst suspected allergic contact dermatitis in Nepalese population visiting Tribhuvan University Teaching Hospital.

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METHODS

This was a hospital based retrospective study performed to investigate pattern of patch test reactivity among patients with clinical diagnosis of contact dermatitis in outpatient department at Department of Dermatology and Venereology, Tribhuvan University Teaching Hospital, Kathmandu from April, 2016 through October, 2016. It is a referral hospital for the patients from various parts of Nepal.There were thirty five patients with suspected ACD who underwent patch test with 20 antigens of the Indian Standard series approved by contact and occupational dermatitis forum of India(CODFI) during this period. The test panel consisted of following antigens: Vaseline (as control), Wood alcohol, Peru balsam, formaldehyde, Mercaptobenzothiozole, Potassium bichromate, Nickel Sulfate, Cobalt sulfate, Colophony, Epoxy resin, Paraben mix, Paraphenylene diamine, Parthenium, Neomycin, Benzocaine, Chlorocresol, Fragrance mix, Thiuram mix, Nitrofurazone, and Black rubber mix. The test panel was applied on healthy skin of upper back which was free of lesions that might interfere with the interpretation of the results. The patients were instructed to wear patch for 48 hours and to avoid contact with water, sun exposure and sweating. The results were read after 48 hours, and then again at 72 hours and 96hours after application of patch. The interpretation of the results were done using recommendations of the International Contact Dermatitis Research Group (ICDRG). The demographic and clinical profile along with results of patch tests of all these patients were extracted and filled in preformed pro forma. These data were entered in SPSS-20 software for statistical analysis.

RESULTS

There were 35 patients with the clinical diagnosis of ACD who underwent patch test during this period. Out of 35 patients suspected to have ACD, 19 (54.3%) individuals tested positive to either one or more allergens; these included 10 males with a mean age of 35.3 years and 9 females with a mean age of 44.6 years. Among the 19 patients, 17 (89.4%) reacted positively to a single allergen. A female preponderance was evident among the patients with ACD, 20 (57.2%) females compared to 15 (42.8%) males, however patch test positivity was more in male than female (52% vs 48%).

Majority of the patients were housewives (22.6%) followed by students and officers (13% each), farmers (10%), health care workers (9.7%), wet work (6.5%) and others (20).

Among them, 11 (31.4%) patients presented with hand eczema only where as 7 (20%) had both hand and foot eczema. Other presentations were foot eczema (8.6%), scattered generalized dermatitis (28.6%), eczema localized to pubic region (5.7%), and eyelid eczema (5.7%). Fig. 1 shows the pattern of patch test reactivity among the patients with ACD.

Among the positive results, nickel sulfate (5,26 - 2%) was found to be the most frequently reacting allergen. Other positive results were seen with fragrance mix (3,15 - 7%) and parthenium (3,15 - 7%). Cobalt sulphate, formaldehyde, potassium dichromate, benzocaine, nitrofurazone, chlorocresol each was positive in single (5.2%) patient. Reactivity against the rest of the panel was not remarkable.

Out of all hand eczema cases, less than half (45%) showed positive patch test which included fragrance mix (2), chlorocresol (1), nitrofurazone (1) and nickel sulphate (1) whereas foot eczema had reactivity with potassium dichromate only. Similarly, 6(60%) of the patient of scattered generalized dermatitis did not show reactivity with any of the antigens, comprising positive reaction in each patient only with parthenium, nickel sulphate and multiple antigens.

Twenty three (65.7%) patients were from the capital city, Kathmandu. History of atopy was present in 17.1% of the patients.

DISCUSSION

In Nepal, skin problems are the one of the most common causes of medical consultations with contact dermatitis leading the group. Overall, around half the patients presenting with clinical diagnosis of allergic contact dermatitis tested positive to the patch test allergen. In one of the studies done by Alomgren A et al. [3], 46.4% of the patient had tested positive to patch test allergen similar to that seen in our study. This study had addressed the need of development of local allergen for diagnosis of majority of contact dermatitis cases. Nickel sulfate was found to be the most frequently reacting patch test allergen in this study. Similar findings were noted in other studies [4]. Because of the presence of nickel in a large variety

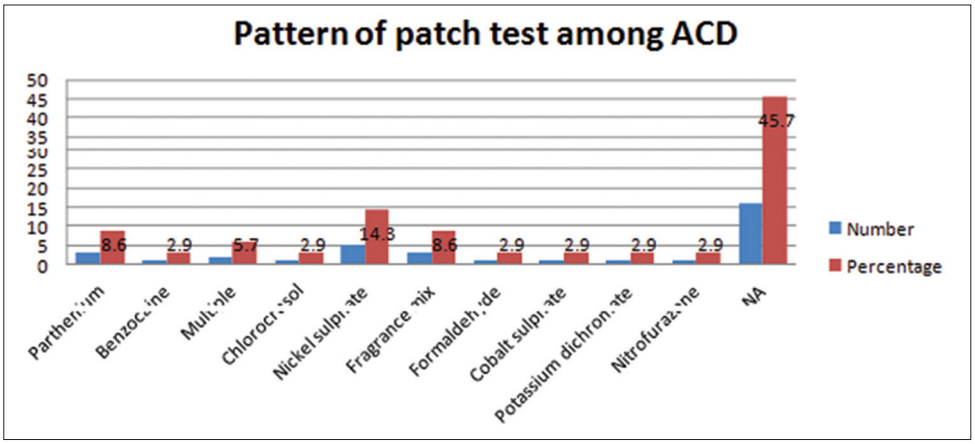

Figure 1: Pattern of patch test among suspected clinical Allergic Contact Dermatitis.

of products it is very difficult to avoid contact with nickel and this is probably the main reason for the high incidence of nickel allergy.

Parthenium and fragrance mix were the second among the most common allergens and majority of patients with scattered generalized dermatitis did not showed positivity with the known antigens. *Parthenium hysterophorus* has been reported as alien invasive agricultural and environmental problem in Nepal and has been reported since 1967 with rapid expansion in last 20 years [5]. In India, *Parthenium hysterophorus* has been reported as one of the important cause of airborne contact dermatitis [6]. This further indicates that in future, we might see many more cases of Parthenium dermatitis, as the population gets sensitized to this plant. In addition to Parthenium, Fragrance mix was found to be common allergen which might indicate a majority of our population getting sensitized to cosmetic products containing fragrance mix.

Out of 20 allergens tested in these 35 patients, 12 antigens were found to be negative in all of these cases. This raises a question about the value of the patch test in our context; however, a further large scale study will be needed to validate this observation.

Females were more prone to develop ACD (i.e. 57.1%) as majority were housewives (20%) and they were more exposed to household activities, farming, wet works than the males. This female predominance was justified in one of the multicentre studies by Bhattarai S et al. [7] done in Nepal in patients with hand eczema.

This small scale study gives an overview of contact allergens in different forms of contact dermatitis in our set up. Further studies on patch test with large number of patients done for regional or specific clinical cases of allergic contact dermatitis will be needed in future to define the exact contact allergens in Nepal and their relevance in our local context.

CONCLUSIONS

Although the patients are exposed to multiple of allergens in day to day life, there is still no well defined contact allergen that causes ACD in our society. Furthermore, the patch test kits developed else-where could not be beneficial in our context as the exposure of the allergen might be different. Although the present study examined a relatively small number of patients, it does however, reveal a pattern of sensitization by contact allergens that this study population was exposed to. The results observed in this small study indicate that there is need for a systematic large scale investigation to identify the local allergens for formulation of policies directed towards avoidance of exposure to the allergens to reduce morbidity.

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Our Dermatology Online

Original Article

The benign tumours of skin adnexal diagnosed in ouagadougou: Histopathological and epidemiological profile

Aimé Sosthène Ouédraogo[1,2], Norbert W Ramdé[1,2], Muriel Sidnoma Ouédraogo[2,3], Lamien-Sanou Assita[1,2], Franck A. H. A Ido[1], Ibrahim Savadogo[4], Souleymane Ouattara[5], Olga Mélanie Lompo[1,2]

[1]Department of Pathology, Yalgado Ouédraogo University Teaching Hospital of Ouagadougou, Burkina Faso, [2]University of Ouaga 1 Pr Joseph KI-ZERBO, Burkina Faso, [3]Division of Dermatology and Venerology, Yalgado Ouédraogo University Teaching Hospital of Ouagadougou, Burkina Faso, [4]Department of Pathology Regional Hospital of Ouahigouya, Burkina Faso, [5]Department of Pathology, Blaise Compaoré University Teaching Hospital Burkina Faso

Corresponding author: Dr. Aimé Sosthène Ouédraogo, E-mail: sostheneaime@yahoo.fr

ABSTRACT

Introduction: The tumours of skin adnexal are rare and very often benign. Because of their large diversity they caused some diagnose and classification problems. They are tumours of ten mixed up with other skin tumours. The objective of this study was to study the histopathological and epidemiological profile of the benign skin adnexal tumours in Ouagadougou and to classify them according to the differenciation type in order to well know them and improve their treatment. **Methodology:** We conducted a retrospective study on the period of sixteen years going from 1st January 1998 to 31 December 2013. This study interested all cases of benign skin adnexal tumours histologically confirmed (diagnosed) in the three pathology laboratories of the Ouagadougou town. **Results**: We collected sixty cases of skin adnexal tumours on the total of 763 cases of skin tumours representing 7.8%. The benign tumours represented 86 % of the adnexal tumour cases. These tumours were occurred in the relatively young age and were preferentially located on the head (cephalic) extremity. On the histological plan, the hair follicle tumours were more frequent (42.5%) followed by sweat gland tumours (30.5%) and sebaceous gland tumours (27%). **Conclusion**: The annex tumours are majoritary benign occurring often on the head extremity and dominated by the hair follicle tumours.

Key words: Tumours (tumors); Skin adnexal; Histology; Ouagadougou

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Original Article

Les tumeurs bénignes des annexes cutanées diagnostiquées à ouagadougou: Profil épidémiologique et histopathologique

Aimé Sosthène Ouédraogo[1,2], Norbert W Ramdé[1,2], Muriel Sidnoma Ouédraogo[2,3], Lamien-Sanou Assita[1,2], Franck A H A Ido[1], Ibrahim Savadogo[4], Souleymane Ouattara[5], Olga Mélanie Lompo[1,2]

[1]Department of Pathology, Yalgado Ouédraogo University Teaching Hospital of Ouagadougou, Burkina Faso, [2]University of Ouaga 1 Pr Joseph KI-ZERBO, Burkina Faso, [3]Division of Dermatology and Venerology, Yalgado Ouédraogo University Teaching Hospital of Ouagadougou, Burkina Faso, [4]Department of Pathology Regional Hospital of Ouahigouya, Burkina Faso, [5]Department of Pathology, Blaise Compaoré University Teaching Hospital Burkina Faso

Corresponding author: Dr. Aimé Sosthène Ouédraogo, E-mail: sostheneaime@yahoo.fr

RESUME

Introduction: Les tumeurs des annexes de la peau sont rares et très souvent bénignes. Elles posent du fait de leur grande diversité des problèmes de diagnostic et de classification. Ce sont des tumeurs souvent confondues avec d'autres tumeurs cutanées. Cette étude avait pour but d'étudier le profil épidémiologique et histopathologique des tumeurs bénignes des annexes cutanées à Ouagadougou et de les classifier en fonction du type de différenciation afin de mieux les connaître et d'améliorer leur prise en charge. **Méthodologie**: Nous avons mené d'une étude rétrospective sur seize ans, allant du 1er Janvier 1998 au 31 Décembre 2013. Cette étude a intéressé tous les cas de tumeurs bénignes des annexes de la peau histologiquement confirmées dans les trois laboratoires d'anatomie pathologique de la ville de Ouagadougou. **Résultats**: Nous avons colligé soixante cas de tumeurs des annexes cutanées sur 763 cas de tumeurs cutanées soit 7,8%. Les tumeurs bénignes constituaient 86,7% des cas de tumeurs annexielles. Ces tumeurs survenaient à un âge relativement jeune et étaient localisées préférentiellement sur l'extrémité céphalique. Sur le plan histologique, les tumeurs pilaires étaient les plus fréquentes (42,5%), suivies des tumeurs sudorales (30,5%) et des tumeurs sébacées (27%). **Conclusion**: Les tumeurs annexielles sont majoritairement bénignes, survenant souvent sur l'extrémité céphalique et dominées par les tumeurs pilaires.

Mots clés: Tumeurs; Annexes cutanées; Histologie; Ouagadougou

INTRODUCTION

Les tumeurs annexielles cutanées sont des tumeurs développées à partir des annexes de la peau à savoir les follicules pileux, les glandes sébacées et les glandes sudorales. Ce sont des tumeurs le plus souvent bénignes [1]. La grande diversité des types histologiques pose parfois des difficultés diagnostiques et de classification. La littérature sur les aspects histologiques de ces tumeurs au Burkina Faso, est rarissime. Nous avons entrepris cette étude dont le but est d'étudier les particularités histopathologiques de ces tumeurs, de les classifier en fonction du type de différenciation afin de permettre leur meilleur connaissance.

MATÉRIELS ET MÉTHODES

Nous avons mené une étude rétrospective sur une période de 16 années consécutives, allant du 1er janvier 1998 au 31 décembre 2013. Nous avons analysé tous les diagnostics histologiques de tumeurs annexielles cutanées posés dans les trois laboratoires d'anatomie pathologique de la ville de Ouagadougou. Ces

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laboratoires étaient les seuls en activité au Burkina Faso durant la période étudiée. Ils recevaient des prélèvements de patients provenant de toutes les régions du pays. Ont été retenus tous les comptes-rendus d'examen anatomo-pathologique concernant les patients de tout sexe et de tout âge.

Tous les prélèvements analysés dans les trois laboratoires ont été fixés par du formol tamponné à 10%. Après inclusion en paraffine, coupes de 2 à 4 microns et étalement sur lames, les pièces ont été colorées à l'hématéine et éosine. Le safran était ajouté en fonction de sa disponibilité dans le laboratoire.

Les tumeurs annexielles ont été réparties en trois grands groupes: un premier groupe constitué des tumeurs à différenciation sudorale; un deuxième groupe rassemblant les tumeurs à différenciation sébacée; le troisième groupe était constitué des tumeurs à différenciation pilaire. Nous avons analysé les informations sociodémographiques des patients concernés, les localisations tumorales, et les données histologiques.

RÉSULTATS

Fréquence Globale

Au cours de la période d'étude, nous avons colligé 763 cas de tumeurs cutanées dont 60 cas de tumeurs annexielles représentant 7,8% de l'ensemble des tumeurs de la peau.

Parmi les 763 cas de tumeurs cutanées, 262 (34,3%) étaient bénignes et 501 (65,7%) malignes.

Les tumeurs annexielles bénignes avec 52 cas représentaient 19,8% des tumeurs bénignes cutanées.

Les tumeurs annexielles cutanées étaient constituées de 86,7% de tumeurs bénignes et 13,3% de tumeurs malignes.

Les Types Histologiques

Le tableau suivant montre la répartition des tumeurs bénignes des annexes cutanées selon la différenciation et le type histologique (Tableau 1 – 7).

Nous avons observé 2 cas d'adénomes tubulo-papillaire chez deux adultes de 20 et 30 ans localisés au membre supérieur et au tronc, 1 cas d'hidradénome tubulo-papillifère chez un adulte de 20 ans localisé au membre

Tableau 1 : Répartition des tumeurs bénignes selon le type histologique (n=52)

Type de differentiation	Type histologique	Effectif	Pourcentage (%)
Pilaire	Pilomatricome	09	17,3
	Kyste trichilemmal proliférant	07	13,5
	Trichoépithéliome	06	11,5
n=22 (42, 3%)			
Sébacée	Hamartome verruco-sébacé	08	15,4
	Adénome sébacé	03	5,8
n=14 (27%)	Hyperplasie sébacée	03	5,8
Sudorale	Porome eccrine classique	06	11,6
	Hidradénome nodulaire	03	5,8
	Syringome	02	3,8
eccrine	Cystadénome eccrine	01	1,9
n=12 (23%)			
Sudorale	Adénome tubulo-papillaire apocrine	02	3,8
	Syringocystadénome papillifère	01	1,9
apocrine	Hidradénome tubulo-papillifère	01	1,9
n=04 (7, 7%)			
Total		52	100,0

Tumeurs bénignes pilaires

L'âge

inférieur et 1 cas syringo-cystadénome papillifère chez un adulte de 40 ans localisé au membre supérieur.

DISCUSSION

Les tumeurs des annexes cutanées sont relativement rares. Cette étude a retrouvé une fréquence de 7,8% de l'ensemble des tumeurs cutanées. Ce constat est partagé par d'autres auteurs africains et dans le monde [1,2]. En effet Samaïla au Nigéria [1] a retrouvé dans sa série une fréquence de 0,9%. Ce sont des tumeurs à majorité bénignes. Dans notre étude, les tumeurs bénignes ont représenté 86,7% et les tumeurs malignes 13,3%. Samaïla, Radhika et col, Rajalakshm et col ont retrouvé respectivement, 88,5%, 77,14% et 90,48% de tumeurs bénignes contre 11,5%, 22,63% et 9,52% de tumeurs malignes dans leurs séries [1,3,4].

Les tumeurs des annexes cutanées sont des tumeurs rencontrées chez des sujets relativement jeunes [1,5]. La moyenne d'âge était de 39,75 ans. Samaïla retrouvait une moyenne d'âge de 33 ans [1].

Ces tumeurs se localisaient préférentiellement sur l'extrémité céphalique et les membres. En effet, la

Tableau 2 : Répartition des tumeurs bénignes pilaires en fonction de l'âge des patients (n=22)

Tranche d'âge (années)	Pilomatricome	Kyste trichilemmal proliférant	Trichoépithéliome	Total
<=10	01	00	00	01
[20-30]	02	02	02	06
[30-40]	04	01	02	07
[40-50]	01	02	01	04
[50-60]	00	01	01	02
[60-70]	00	01	00	01
[70-80]	01	00	00	01
Total	09	07	06	22

Le siège

Tableau 3 : Répartition des tumeurs bénignes pilaires en fonction du siège (n=22)

Siège anatomique	Pilomatricome	Kyste trichilemmal proliférant	Trichoépithéliome	Total
Tête et cou	06	05	05	16
Tronc	01	01	00	02
Membres supérieurs	01	01	01	03
Membres inférieurs	01	00	00	01
Total	09	07	06	22

Tumeurs bénignes sébacées

L'âge

Tableau 4: Répartition des tumeurs bénignes sébacées en fonction de l'âge des patients (n=14)

Tranche d'âge (années)	Hamartome verruco-sébacé	Adénome sébacé	Hyperplasie sébacée	Total
<=10	01	00	00	01
[10-20]	01	01	00	02
[20-30]	01	00	01	02
[30-40]	02	01	01	04
[40-50]	01	01	01	03
[50-60]	01	00	00	01
[60-70]	01	00	00	01
Total	08	03	03	14

Le siège

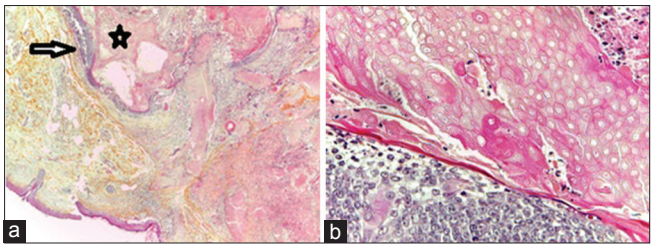

Figure 1: Pilomatricome Coloration HES. (a) G 40 Prolifération montrant une double cytologie constituée de cellules basophiles (flèche) et de cellules fantômes (étoile) séparées par une zone de transition (b) G100 Fort grossissement montrant les détails cytologiques et la zone de transition.
Source : Service d'anatomie pathologique/Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU YO)

tête et le cou étaient les principales localisations des tumeurs pilaires et sèbacées. C'est un constat partagé par d'autres auteurs dont Samaïla (46%), Sharma (64,28%), Rajalakshm (10 localisations sur l'extrémité céphalique sur 21) [1,3-5]. Il s'agit en effet de zones anatomiquement riches en structures pilo-sébacées. Les tumeurs sudorales ont plus tendance à se localiser au niveau des extrémités et du tronc.

Les tumeurs à différenciation pilaire bénignes étaient les plus fréquentes; et dominées par le pilomatricome. Celui-ci représentait 17,3% des tumeurs bénignes des annexes. Ce type histologique était également le plus représenté dans l'étude de Song et col [6]. Il s'agit d'une tumeur d'origine matricielle fréquente et facilement reconnaissable qui a la particularité unique d'aboutir à des cellules fantômes correspondant à une tentative abortive de produire une tige pilaire [5] (Fig. 1a). Cette tumeur a été décrite pour la première fois sous le nom " d'épithélioma momifié de Malherbe " en 1880 par Dr Chenantals Malherbe [7]. Elle se rencontre à tout âge mais 40% sont observés avant l'âge de 20 ans [8]. La grande majorité siège au niveau de l'extrémité céphalique (tête et cou) mais quelques-uns sont localisés sur les membres supérieurs et rarement le tronc [5].

Sur le plan histologique, on observe une prolifération dermique de plusieurs massifs de cellules, avec alternance de cellules fantômes anucléées réalisant un syncytium dont on voit très bien les membranes et de cellules matricielles très fortement basophiles, de petite taille à noyau central hyperchromatique (Fig. 1b). L'aspect pathognomonique est l'existence d'une zone de transition entre les cellules fantômes et les cellules basophiles [5].

C'est une tumeur bénigne pouvant subir des poussées de croissance très inquiétantes, surtout au départ, ou entraîner une réaction inflammatoire avec des douleurs. L'exérèse est curatrice [5].

Tableau 5: Répartition des tumeurs bénignes sébacées en fonction du siège (n=14)

Siège anatomique	Hamartome verruco-sebacé	Adénome sebacé	Hyperplasie sébacée	Total
Tête et cou	06	03	03	12
Tronc	01	00	00	01
Membres inférieurs	01	00	00	01
Total	08	03	03	14

Tumeurs bénignes sudorales

Les tumeurs bénignes eccrines en fonction de l'âge

Tableau 6: Répartition des tumeurs bénignes sudorales eccrines en fonction de l'âge (n=12)

Type histologique	[20-30]	[30-40]	[40-50]	[50-60]	[60-70]	Total
Porome eccrine classique	00	03	01	01	01	06
Hidradénome nodulaire	01	01	00	01	00	03
Syringome	02	00	00	00	00	02
Cystadénome eccrine	00	01	00	00	00	01
Total	03	05	01	02	01	12

Les tumeurs bénignes sudorales eccrines selon le siège

Tableau 7 : Répartition des tumeurs bénignes sudorales eccrines selon le siège (n=12)

Siège anatomique	Porome eccrine classique	Hidradénome nodulaire	Syringome	Cystadénome eccrine	Total
Tête et cou	02	00	01	01	04
Tronc	01	03	00	00	04
Membres inférieurs	03	00	00	00	03
Membres supérieurs	00	00	01	00	01
Total	07	03	02	01	12

Les tumeurs bénignes sudorales apocrines selon l'âge et le siège

Les tumeurs bénignes sudorales étaient le deuxième groupe le plus rencontré. On distinguait les tumeurs eccrines et apocrines. Les tumeurs eccrines étaient les plus fréquentes localisées au niveau de l'extrémité céphalique mais aussi au niveau du tronc et des membres. Dans les séries de Samaïla, Rajalakshm et Sharma, ces tumeurs étaient les plus fréquentes [1-3]. Dans notre série, le porome eccrine classique était le type histologique prédominant. Il fait partie du groupe des poromes et est développé à partir des kératinocytes bordant le trajet intra épidermique du canal sudoripare eccrine. Il a été décrit pour la première fois en 1956 par Pinkus et col [9]. Il s'observe chez l'adulte à partir de la trentaine et siège le plus souvent au niveau des membres inférieurs ou au niveau des extrémités en particularité les régions palmo-plantaires [5]. La tumeur apparaît sous la forme d'une lésion saillante, bien limitée, à surface érythémateuse et parfois un peu suintante, attirant l'attention à l'examen clinique [5,10]. Sur le plan histologique, la tumeur est faite de grandes travées de petites cellules rondes formant des nappes très homogènes connectées à l'épiderme et descendant dans le derme moyen et profond (Fig. 2a). Il n'y a pas d'atypies cytologiques. On observe parfois de petits canaux (Fig. 2b) tantôt réduits à une lumière sans bordure, tantôt limités par un petit groupe de cellules porales avec ou sans cuticule éosinophile [5].

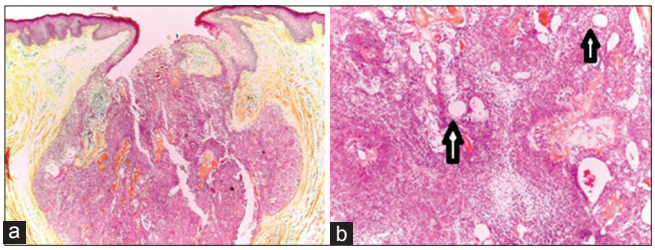

Figure 2 : Porome eccrine Coloration HES. (a) G 40 Prolifération en travées formant des nappes homogènes connectées à l'épiderme et s'enfonçant dans le derme moyen et profond, (b) G 100 Détail au fort grossissement montrant les formations canalaires au sein de la proliférationv(flèches).
Source : Service d'anatomie pathologique/Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU YO)

Ces tumeurs doivent être excisées en totalité car les porocarcinomes surviennent dans près de la moitié des cas sur des poromes eccrines préexistants [5]. Le traitement est chirurgical.

Le troisième grand groupe est constitué des tumeurs bénignes à différenciation sébacée. Ces tumeurs viennent également au troisième rang dans la série de Rajalakshm et au deuxième rang dans la série de Samaïla et Sharma [1-3]. L'hamartome verruco-sébacé était prédominant suivi de l'adénome sébacé. L'hamartome verruco-sébacé est plus une malformation, qu'un processus tumoral. C'est le plus complexe des

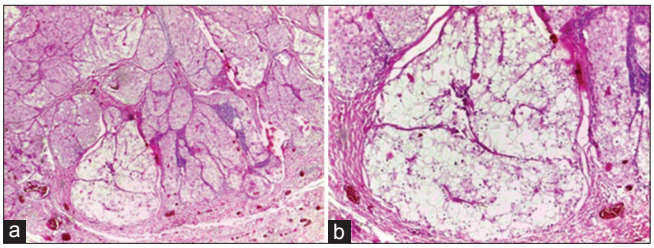

Figure N°3 : Adénome sébacé Coloration HE (a) G 40 Prolifération réalisant de volumineux lobules sébacés associant en quantité variable des sébocytes matures et immatures (b) G100 Détail au fort grossissement montrant un volumineux lobule sébacé constitué de sébocytes matures.
Source : Service d'anatomie pathologique/Centre Hospitalier Universitaire Yalgado Ouédraogo (CHU YO)

hamartomes cutanés comprenant des éléments sébacés, glandulaires, pilaires et épidermiques. La grande majorité est localisée sur l'extrémité céphalique (visage, cuir chevelu). Il en existe au niveau du cou, du thorax et plus rarement des membres [5].

L'aspect histologique évolue de la période néonatale à l'adolescence. En effet, à la période néo natale, on observe de volumineuses glandes sébacées superficielles ne semblant pas appendues à une structure folliculaire normale. On observe en surface un aspect lisse et une simple acanthose sans papillomatose ni hyperkératose. A la période de l'adolescence, l'aspect est verruqueux avec une acanthose endophytique qui rappelle une tumeur infundibulaire [5].

L'adénome sébacé est une tumeur bénigne localisée préférentiellement sur les zones riches en glandes sébacées (visage et cou) [5]. Il ne reproduit pas la structure normale de la glande, mais est fait de volumineux lobules sébacés associant en quantité variable des sébocytes matures et immatures (Figs. 3a et 3b). Les raisons esthétiques et fonctionnelles motivent l'exérèse de ces lésions. La transformation carcinomateuse est rare [5].

CONCLUSION

Les tumeurs des annexes de la peau sont rares, très souvent bénignes et localisées sur l'extrémité céphalique. Les raisons esthétiques et parfois fonctionnelles motivent l'exérèse de ces lésions. Cette exérèse dans la plupart des cas est curatrice. Certaines de ces tumeurs bénignes ont un potentiel de dégénérescence maligne d'où la nécessité d'une exérèse suivie d'un examen anatomopathologique.

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Our Dermatology Online

Brief Report

The rediscovery of the Redwood orpiment and a cocktail of plants macerates containing arbutin to defeat the Arribas-Silvestre's syndrome in a bien agée upper class lady

Lorenzo Martini

University of Siena, Department of Pharmaceutical Biotechnologies, Via A. Moro 2, 53100 Siena, Italy

Corresponding author: Lorenzo Martini, M.Sc. E-mail: martinil163@libero.it

ABSTRACT

The Arribas-Silvestre's syndrome is a sort of photodermatitis induced especially in elder (especially women) when they use to put pure essences or fragrances directly onto their skin, take some medicaments and expose to sun rays periodically. The black spots are irreversible and are aesthetically unpleasant. Generally people tend to renounce to treat this disease, since it seems no remedy is available and strongest lotions or emulsions containing 2-5% of hydroquinone are banished and anyway perilous. Here I herald a simplest method using on alternate days an ancient orpiment to abrade black spots and a mix of herb macerates containing arbutin, apt to bleach the original brownish or black maculae.Results are amazing.

Key words: Arribas-Silvestre's syndrome, photodermatitis, fragrances, arbutin, Felix von Luschan's chromatic scale

INTRODUCTION

Several factors can make human skin sensitive to UV rays, including having an inherited tendency to photosensitivity, taking certain medications, or being exposed to plants in the Apiaceae or Umbelliferae family, including weeds and edible plants, such as hogweed, cowbane, carrot, parsnip, dill, fennel, celery, and anise [1-6].

Photodermatitis can have several causes, including:

- Diseases, such as lupus or eczema, that also make skin sensitive to light,
- Genetic or metabolic factors (inherited diseases or conditions, such as pellagra, caused by lack of niacin and vitamin B-3),
- Diseases, such as polymorphic light eruptions, characterized by sensitivity to sunlight,
- Reactions to chemicals and medications,
- Skin reactions to sun rays and chemical substances can give raise to acute or chronic diseases, but especially they can be provoked by allergens or toxic elements.

For instance

Antibiotics, such as tetracycline and sulfonamides, antifungals, such as griseofulvin, coal tar derivatives and psoralens, used topically for psoriasis, retinoids, such as tretinoin and medications containing retinoic acid, used for acne, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy agents, sulfonylureas, oral medications used for diabetes, antimalarial drugs, such as quinine and other medications, used to treat malaria, diuretics, antidepressants, such as the tricyclics, used for depression, antipsychotics, such as phenothiazines, anti-anxiety medications, such as benzodiazepines may all induce direct toxic effects, that yield to acute or on going (idest acute or chronic) photodermatities and these agents are to be considered toxic substances.

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Meanwhile fragrances, sunscreens with PABA, industrial cleaners that contain salicylanilide and Concrete of Lavender may induce allergic effects, that yield to acute or on going (idest acute or chronic) photodermatities.

The irreversible skin spots evoked by fragrances, especially musk, ambrette, lemon oil, coumarins and methylcoumarins are designed under the name of Arribas-Silvestre's syndrome.

The aforesaid maculae remain throughout the entire life and are so difficult to be removed and polished, so that the man or woman who have them, is forced to renounce progressively to whichever remedy to attempt to clear his/her skin.

This case report deals of an old lady, even if fashionable, debonnaire and bien agée one, who has been putting some drops behind her ears of pure bergamot oil and other fragrances (rose églantine or civet) since very long time and presented skin spots almost remarkable, with fastidious itch and sometimes, when exposed to sun rays or during windy days, scared and pustulous maculae.

We have rediscovered the very first orpiment proposed by Dr. Redwood in 1857 [6], apt to abrade all the skin where amounts of melanin are deposited.

The recipe consists in 7% of barium sulphide in rice starch and glycerine to be gently scrubbed onto the spots.

The operation of scrubbing the orpiment must be repeated periodically, almost three times during a week, in order to have a polished skin, that must anyway clarified by the usage of a mix of selected mix of bleaching agents.

The bleaching agents are not but herbs that contain high percentages of arbutin [7,8], that when in contact with the sweat of the skin, drives to hydroquinone.

The extracts of the herbs are:
- Pyrus malus peel extract,
- Arctostaphylos uva ursi leaf extract,
- Schisandra chinensis callus extract,
- and glycolic macerate of cranberry leaves.

All these extracts are dispersed in palm oil and the mix has to be shake before usage.

The mix of bleaching agents must be very soft and delicate with regards to the abraded skin and so the dynamics of treatments should follow the following schedule:

First the scrubbing by the aids of the orpiment (3 minutes) the night before to go to bed, thus the use of the lotion containing the bleaching agents, at the successive morning, one day of rest and after again for 6 times and so for two entire weeks.

The double treatment (use of the orpiment and after some hours the employ of the lotion) must be applied on alternate days for 14 days, and so the total applications result [7].

MATERIALS AND METHODS

We behind her ears, she was not capable to clear for years.

We gave her the Redwood's orpiment she had to scrub gently for three minutes the night before to go to bed, on alternate days and We consigned to her even the mix of glycolic extracts to bleach the "thesaurismosis" onto her skin, treatment she had to carry out the morning after.

We prayed the volunteer not to take benzodiazepines (she commonly used to take to sleep) and NSAIDs, since one week before the beginning of the treatment and to avoid the sun rays during the daylight.

Effectively we have had the chance of having 2 weeks of rain and clouds, that permitted to make our experimentations.

The entire duration of the alternate treatments was of 14 days.

After this day, skin turned out clear and safe, smooth and velvety.

Here follows the Felix von Luschan's chromatic scale [8,9] (Fig. 1) and in the successive Table I refer, it is possible to notice how the values decreases day after day.

It is supposed that an old lady presents a coloured face skin that necessitates a pigmented blush that visagistes call "Rachel", that correspond to number 8.

Skin spots caused by the Arribas-Silvestre's syndrome in my case correspond to the number 29.

We repeat that the applications are only 7 in 14 days.

Table 1: The von Luschan's values scored at alternate day, during treatment with Redwood's orpiment and the mix of herbs containing arbutin

Initial chromatic score	After 1st day	After 3rd day	After 5th day	After 7th day	After 9th day	After 11st day	After 13rd day
29	27	25	21	19	16	13	9

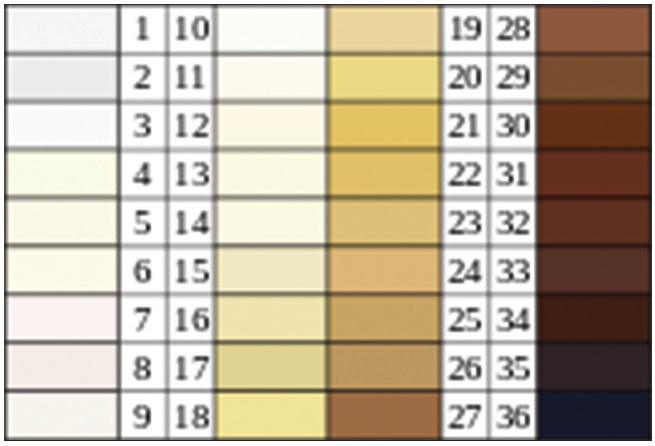

Figure 1: Felix von Luschan's chromatic scale.

RESULTS

In Table I the values of the decrease of the colour of the F.van Luschan's scale are plotted, considering the day of treatment.

These values overlook concerns of generic skin chromatism but keeps indeed on account the fact that old people generally present a skin sometimes yellowish or greyish.

CONCLUSIONS

It is not really possible to define a statistical behaviour of the lowering of the intensity of the amount of melanin, during the entire treatment, even if the results are quite satisfactory.

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Our Dermatology Online

Brief Report

Is it justifiable to assert that clinical lycanthropy may be correlated to porphyria cutanea tarda?

Lorenzo Martini

Department of Pharmaceutical Biotechnologies, University of Siena, Via A. Moro 2, 53100 Siena, Italy

Corresponding author: Lorenzo Martini, M.Sc., E-mail: martinil163@libero.it

ABSTRACT

Scope of this study is to demonstrate an old theory expressed in 1963, when Illis (Guy's Hospital in London) established a correlation between the clinical lycanthropy and congenital porphyria cutanea tarda. We had the fortune to live in a village where they say a lycanthrope lives too and is accustomed to hid himself at home for the 3 days when on the full moon, when he becomes (and behaves as) a werewolf. Werewolves like to walk around before dawn craving for water and since We love to walk very early in the morning (as philosopher Emanuel Kant used to do), We have had this chance to encounter this mysterious man, who is a normal man with a regular lifestyle according to lunar cycle. He presents a very pale face with scares and blisters and generally when somebody asks him about this cutaneous manifestations he says he detests sun and light and his skin reacts by this way. We attempted to treat this individual by a pomade containing rutin, diosmin,Centella asiatica,niacinamide and escin. Results are encouraging as well.

Key words: Diosmin; Escin; Clinical lycanthropy; Werewolves; RAL scale

INTRODUCTION

Some modern researchers have tried to explain the reports of werewolf behaviour with recognised medical conditions, for instance Dr Lee Illis of Guy's Hospital in London wrote a paper in 1963 entitled "On Porphyria and the Aetiology of Werewolves", in which he argues that historical accounts on werewolves could have in fact been referring to victims of congenital porphyria, (especially porphyria cutanea tarda) stating how the symptoms of photosensitivity, reddish teeth and psychosis could have been grounds for accusing a sufferer of being a werewolf [1].

Porphyria cutanea tarda (commonly referred to as PCT) is recognized as the most prevalent subtype of porphyritic diseases [2].

The disease is characterized by onycholysis and blistering of the skin in areas that receive higher levels of exposure to sunlight. The primary cause of this disorder is a deficiency of uroporphyrinogen decarboxylase (UROD), a cytosolic enzyme that is a step in the enzymatic pathway that leads to the synthesis of heme. While a deficiency in this enzyme is the direct cause leading to this disorder, there are a number of both genetic and environmental risk factors that are associated with PCT [3].

Typically, patients who are ultimately diagnosed with PCT first seek treatment following the development of photosensitivities in the form of blisters and erosions on commonly exposed areas of the skin. This is usually observed in the face, hands, forearms, and lower legs. It heals slowly and with scarring.

Widespread beliefs that lycanthropy was due to medical conditions go back to the second century, when the Alexandrian physician Paulus Aegineta attributed lycanthropy to melancholy or anyway to an excess of black bile. In 1563, a Lutheran physician named Johann Weyer wrote that werewolves suffered from an imbalance in their melancholic humour and exhibited the physical symptoms of paleness, "a dry tongue and a great thirst" as well as sunken, dim and dry eyes. Even King James VI in his 1597 treatise

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Daemonologie does not blame werewolf behaviour on delusions created by the Devil but as an excess of melancholy as the culprit which causes some men to believe that they are wolves and to counterfeit the actions of these animals. The perception of a link between mental illness and animalistic behaviour can be traced throughout the history of folklore from many different countries.

This is however argued against by Woodward [4], who points out how mythological werewolves were almost invariably portrayed as resembling true wolves, and that their human forms were rarely physically conspicuous as porphyria victims. Others have pointed out the possibility of historical werewolves having been sufferers of hypertrichosis, a hereditary condition manifesting itself in excessive hair growth. However, Woodward dismissed the possibility, as the rarity of the disease ruled it out from happening on a large scale, as werewolf cases were in medieval Europe. Similarly Woodward suggested rabies as the origin of werewolf beliefs, claiming remarkable similarities between the symptoms of that disease and some of the legends. Woodward focused on the idea that being bitten by a werewolf could result in the victim turning into one, which suggested the idea of a transmittable disease like rabies. However, the idea that lycanthropy could be transmitted in this way is not part of the original myths and legends and only appears in relatively recent beliefs. Lycanthropy can also be met with as the main content of a delusion, for example, the case of a woman has been reported who during episodes of acute psychosis complained of becoming four different species of animals [5].

Legend has it that werewolves spend most their time in human form but then, on the full moon, transform into a giant man-eating wolf with no human conscience. The werewolf usually turns back into a human at sunrise, with no recollection of their wolfish activities [6].

Lycanthropy, the clinical name given to werewolves in fiction, is actually a real medical term referring to someone who is under the delusion that they are a wolf.

Some medical theories concerning the origin of werewolves were explored in the book "Why do Men have Nipples?" by Billy Goldberg and Mark Leyner. One of these is once again based around porphyria, the same disease with links to the vampire myth. Some sufferers of cutaneous porphyria exhibit the canine "fang" look caused by the erosion of the gums. Also, following exposure to light, the healing blisters on sufferers' skin often grow a fine layer of hair.

The authors also speculate that the disease congenital hypertrichosis universalis could be a cause of the werewolf myth as this also causes excessive hair growth across the whole body. However, this disease is extremely rare so may not be prevalent enough to have bred such a popular myth.

Someone suffers too from congenital hypertrichosis universalis.

MATERIALS AND METHODS

In this study We have made up my mind to assume Dr Illis' concern for true, that is that manifestations of werewolves' behaviours are connected to a type of congenital and hereditary porphyria cutanea tarda.

We have had the fortune to encounter a real lycanthrope in the village I live and I may assert that for all the three days of the full moon, this subject shows his face bloody and full of reddish and inflamed capillaries, beyond the reddish teeth and other symptoms (I have had the chance to meet him when he is in this acute phase, before dawn).

But generally his face is pale, because he is forced to hid it underneath a huge broad-brimmed hat (a darkish Pamela), and his skin is full of mild pinkish scares, and he uses generally to apply corticosteroids and barium sulphate pomades to camouflage this phenomenon, and this fact let me to speculate on the fact he suffers from porphyria cutanea tarda.

We have recruited this "lycanthrope", a young man (36-years-old).

In the village we live everybody knows about his malaise, even everybody pretends not to know it, since thinks it is a mere legend and a stupid myth.

We have to stress We had the chance to meet periodically and exactly during the time of the full moon, (generally three days and nights) the person (the so-called werewolf), in the morning early, when he is trying to escape from his house (his hiding place) at dawn, looking for wells and fountains.

It must be remembered that We love to walk around very early in the morning, before dawn.

When there is no full moon, We meet him always at the same café very early in the morning and his face is quite clear and presenting scares, blisters and pimples, and his eyes are limpid and luminous: he does never remember that during the 3-4 days of full moon he had behaved as a real lycantrhrope, even he asserts he felt his face burning like fire and needed absolutely water to drink, even if he has always preferred to stay at home, hidden and asking for some days off work.

He is a distinct and cultured man and is conscious of his periodical malaise and really desires to cure it and for this decided to use my treatment and undergo the experimentations We suggested to him, consisting in spreading a special cream the same evening when full moon had to raise and to apply it every 6 hours for 3-4 days of full moon.

The cream We gave to the volunteer contains, besides certain common excipients:
Rutin
Diosmin
Rosa moschata seed oil
Niacinamide
Centella asiatica extract
Escin

In extraordinary high percentages.

We prayed him to escape from his cache before dawn, when on the full moon, promising him a huge pitcher of chilled mineral water, and We had the chance to observe the change of colour of his face, under the same street-lamp at the same hour, when using the emulsion We had given to him previously.

It is well known that niacinamide is a strongest vasoconstrictor and even all the other ingredients do are.

To determine the degree of the nuance of red the face of the lycanthrope assumed day during the lunar cycle I have chosen the RAL, that is a colour matching system used in Europe that is created and administrated by the German RAL gGmbH (RAL non-profit LLC), which is a subsidiary of the German RAL Institute. In colloquial speech RAL refers to the RAL Classic system, mainly used for powder coatings.

The numeration starts from the highest value to up, to the lowest and so the lightest red is number 3023 and the most intense red is 3000.

In Table 1 We all the values scored for the nuances of red are plotted.

Commonly experts use only the last 2 digits, for instance; 23 for pinkish and 03 for ruby red.

The 15 digits are justified by the fact that We considered even the face colour the evening before the full moon, and so each cycle comprehends 5 numbers.

RESULTS

If the evening before the advent of the full moon the colour of his face was 00-01, the day after (at the first dawn), the colour was 11-12, while the second day (at the second dawn) the nuance was 13-14 and finally at the third day (at dawn) the nuance was decisively 22-23.

I deem that are diosmin and rutin to play a suggestive impulse to lighten the "rubor" that covers the lycanthrope's face.

But it is important to add that the synergy created by the insertion in formula of Centella asiatica extract, niacinamide and escin is fundamental to achieve a complete vasoconstition.

Table I: The RAL scale of colours

RAL 3000	Feuerrot	Flame red
RAL 3001	Signalrot	Signal red
RAL 3002	Karminrot	Carmine red
RAL 3003	Rubinrot	Ruby red
RAL 3004	Purpurrot	Purple red
RAL 3005	Weinrot	Wine red
RAL 3006	Schwarzrot	Black red
RAL 3007	Oxidrot	Oxide red
RAL 3008	Braunrot	Brown red
RAL 3009	Beigerot	Beige red
RAL 3010	Tomatenrot	Tomato red
RAL 3011	Altrosa	Antique pink
RAL 3012	Hellrosa	Light pink
RAL 3013	Korallenrot	Coral red
RAL 3014	Rosé	Rose
RAL 3015	Erdbeerrot	Strawberry red
RAL 3016	Lachsrot	Salmon pink
RAL 3017	Leuchtrot	Luminous red
RAL 3018	Leuchthellrot	Luminous bright red
RAL 3019	Himbeerrot	Raspberry red
RAL 3020	Reinrot	Pure red
RAL 3021	Orientrot	Orient red
RAL 3022	Perlrubinrot	Pearl ruby red
RAL 3023	Perlrosa	Pearl pink

CONCLUSIONS

High concentrations of vasocostricting agents, that are commonly inserted in cosmetic formulations in subliminal percentages, may exert splendid results even in extreme cases like clinical lycanthropy.

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Our Dermatology Online

Case Report

A case of pemphigus foliaceus and pustular psoriasis with a brief review of literature

Darjani Abbas[1], Rafiei Rana[1], Mesbah Alireza[2], Shafaei Sareh[1], Rafiee Behnam[3]

[1]Skin Research Center, Guilan University of Medical Sciences, Razi Hospital, SardareJangal Street, Rasht, Iran, [2]Razi Pathobiology, Rasht, Iran, [3]Research Intern. University of Texas, MD Anderson Cancer Center 1515 Holcombe blvd. B4.4512, Houston, TX, 77030, USA

Corresponding author: Rafiei Rana, MD, E-mail: rafieirana@yahoo.com

ABSTRACT

Rarely pemphigus foliaceus could be associated with generalized pustular psoriasis. A 66-year-old woman with diffuse flaccid bullae and erosions of pemphigus foliaceus underwent two sessions of pulse therapy of corticosteroid and oral prednisolone during the interval time. Two weeks after the second session of pulse therapy with improvement of the lesions, during tapered dosage of oral prednisolone, facial annular erythematous lesions appeared and were superimposed by generalized pustular eruptions. Skin biopsy of pustular lesions showed pustular psoriasis so intramuscular methotrexate was added. Two years later, during decreasing dosage of methotrexate and prednisolone, she had eruptive recurrence of pustules and flaccid bullae associated with erythroderma and fever which were controlled with increasing dosage of corticosteroid and starting oral retinoid. These hypotheses may explain co-occurring pemphigus foliaceus and pustular psoriasis: decreasing dosage of corticosteroid, interleukin-8 overproduction in keratinocytes and increased activity of plasminogen activator in skin lesions.

Key words: Pemphigus foliaceus; pustular psoriasis; immunobullous disease

INTRODUCTION

Pemphigus foliaceus (PF) is an autoimmune bullous disease (AIBD) which is presented by superficial flaccid blisters, erosions, scales and crusts on the seborrheic areas of the face and trunk without mucosal involvement [1]. Pathologically, PF is characterized by granular layer acantholysis with acantholytic cells and intraepidermal deposition of Immunoglobulin G (IgG) and complement component 3 (C3) on immunofluorescent studies as a result of antibody production against desmoglein 1, a component of desmosome [2]. Although psoriasis and AIBD are classified as different diseases, PF coexistent with psoriasis vulgaris has been reported in a few cases [3], but association with pustular psoriasis has been very rare [4,5].

Micro-environmental factors could be able to induce concurrent autoimmune phenomenon in an individual patient [3]. Herein, we report a case of PF and generalized pustular psoriasis (GPP).

CASE REPORT

First Admission

In 2014, a 64-year-old woman with diffuse flaccid superficial bullae and erosions from 2 months ago was admitted to our hospital. In physical examination there were extensive bullae, erosions, scales and crusts on the scalp, face, trunk and limbs with no typical pre-existing psoriasis lesions. Nikolsky sign was positive. Mucosal surfaces were intact. Onychomycosis in toe nails with no pitting or oil spot was detected. In past medical history she had a hysterectomy 20 years ago and hyperlipidemia which was under control with atorvastatin (20mg daily). There was no history of psoriasis or bullous diseases in her family.

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Biochemical and hematologic laboratory evaluations were within normal limits. Biopsy of the bullous lesion and perilesional area was made. Biopsy samples showed subcorneal cleft with acantholytic cells and intercellular deposition of IgG and C3 (Fig. 1a-c) in direct immunofluorescent (DIF) studies which confirmed the diagnosis of PF. Indirect immunofluorescent (IIF) studies were not performed.

According to the extensity and severity of her disease, two sessions of pulse therapy with corticosteroid (1 gr intravenous methyl prednisolone daily for three consecutive days) with one month interval and oral prednisolone 60mg daily in the interval time were administered. Bullous lesions were controlled after one month, so oral prednisolone dosage was decreased to 50 mg daily but after two weeks, facial annular erythematous lesions (Fig. 2a) appeared which were followed by generalized pustular eruptions associated with fever, burning and pruritus. Tzanck smear, potassium hydroxide examination and microbial culture of new lesions were non-remarkable. In new laboratory evaluations there were elevated erythrocyte sedimentation rate (ESR: 67) and leukocytosis with neutrophilia. Serum levels of calcium, zinc, albumin and antinuclear antibody (ANA) were within normal limits. Blood and urine cultures were negative. Again biopsy was made from new pustular lesions which showed mild spongiosis with subcorneal neutrophilic pustules without acantholytic cells or eosinophilic infiltration (Fig. 3a and b). DIF studies of perilesional area of new pustules were non-remarkable, therefore diagnosis of generalized pustular psoriasis (GPP) was proposed and intramuscular methotrexate (MTX) (12.5mg weekly) with oral folic acid (1 mg six days per week) were added to corticosteroid therapy. After two weeks pustular lesions were controlled so she was discharged from the hospital, her medications were tapered and she was followed in the outpatient clinic for two years. She had gradually become chushingoid (facial puffiness and weight gain), hypertensive and depressed, so hydrochlorothiazide, captopril, nitrocontin and alprazolam were added to her medications.

Second Admission

Two years later in 2016, about two weeks after changing intramuscular MTX (5mg per week) to oral MTX (7.5mg per week) and tapering oral prednisolone to 10mg daily; she had recurrence of pustules, flaccid bullae, crusted and exudative lesions (Fig. 2b and c) which were followed by erythroderma, fever and malaise, so she was admitted to the hospital again. In new laboratory evaluations, significant findings were: anemia (Hemoglobin: 11, Mean corpuscular volume: 87) with

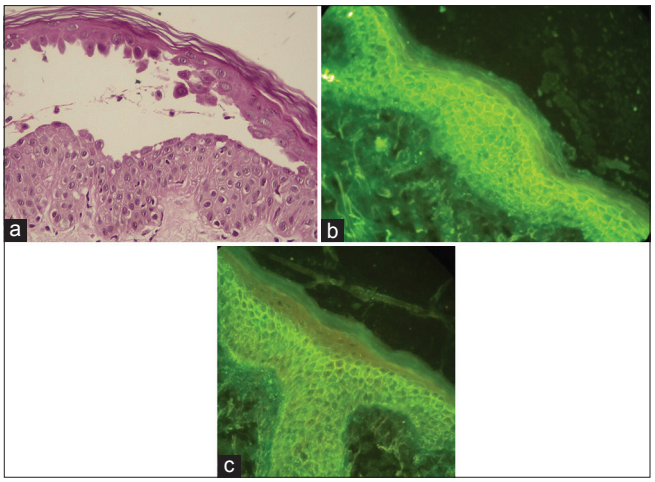

Figure 1: (a) Acantholysis of the upper epidermis with acantholytic cells [Hematoxylin-eosin, original magnification × 400]; (b and c) Direct Immunofluorescent staining on the perilesional tissue demonstrated intercellular IgG and C3 depositions. (Original magnification ×200).

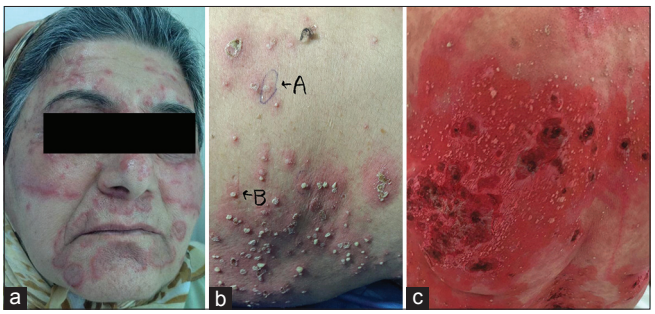

Figure 2: (a) Facial annular erythematous lesions before pustular eruptions. (b) Disseminated bullous (arrow A) and pustular lesions (arrow B) on the back. (c) Crusted lesions on the back which have been stained with eosin.

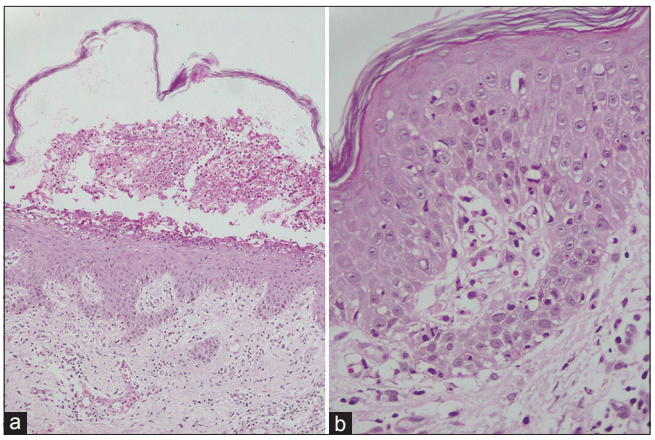

Figure 3: a) Subcorneal pustules; b) Transmigration of the neutrophils associated with dermal telangiectasia. (H&E, original magnification: (a) ×100, (b) ×400).

normal iron profile), leukocytosis with neutrophilia, raised ESR (ESR: 42), positive C-reactive protein (CRP: 3+), hypoalbuminemia with total serum calcium concentration of 7mg/dl, leukocyturia with nitrite positivity in urine analysis.

Culture of exudative lesions revealed Methicillin-resistant Staphylococcus aureus, but urine and blood culture were negative. Serum levels of sodium, potassium, zinc and magnesium were within normal limits. Imaging findings (chest X-ray and abdominopelvic ultrasound) were no remarkable.

Parenteral hydrocortisone (150mg daily) and antibiotics (ceftazidim 2gr daily + clindamycin 1800 mg daily) were administered. Supportive cares for erythroderma and fever were done and MTX was discontinued. Her lesions were controlled after two weeks and oral prednisolone 50mg with oral retinoid (acitretin 25mg daily) was administered.

DISCUSSION

Our case initially had only bullous lesions which clinically and pathologically were diagnosed as PF but after decreasing the dosage of corticosteroid, she showed annular erythema and pustules with systemic symptoms, so the most probable diagnosis was PF superimposed by GPP.

Although rarely PF could be associated with GPP; interestingly we found case reports that PF has initially manifested as neutrophilic pustules but in those cases, pathologic changes and DIF studies of the pustules confirmed PF not GPP [1,5,6]. In our patient pustular lesions had no pathologic criteria of PF and were preceded by annular erythema, so she was not a case of pustular PF.

Psoriasis could be associated with AIBD especially bullous pemphigoid but coexistence of psoriasis with PF has been reported rarely. Patients with pustular psoriasis have been more prone to develop AIBD than other types of psoriasis. The onset of pustular psoriasis has been simultaneous, before or after the onset of AIBD [7]. Coincidence of PF and annular pustular psoriasis has been reported only in a few cases [4,5]. Our patient initially had annular lesions on the face which were superimposed by generalized eruptive pustular lesions with systemic symptoms, so we considered the diagnosis of PF and GPP.

This association has been explained by multiple hypotheses including: Common pathogenic pathway, common human leukocyte antigen (HLA) type in either diseases, treatment complications or just a simple coincidence [3,7-9].

Most authors have believed that it is more than a coincidence. We have found following comments about these co-occurrences in the literature:

- There has been significant decreased suppressor activity in psoriasis disease which results in increasing production of autoantibodies against skin antigens [9]
- Plasminogen activator which has a major role in the induction of acantholysis has been increased in psoriatic lesions [8,9]
- HLA-DR4 haplotype is a common HLA type in both diseases [8]
- IgG autoantibodies could be able to induce Interleukin-8 (IL8) expression in keratinocytes; IL-8 has an important role in the production of neutrophilic pustules [4]
- Corticosteroids which have been used for treatment of AIBD could be a trigger for pustular psoriasis [7] on the other hand phototherapy for psoriasis may be a trigger to produce endogenous pemphigus autoantibodies [3,10]; in addition heat and ultra violet (UV) radiation are exacerbating factors in PF [2]. Also interleukin-1 (IL-1) is a proinflammatory cytokine which has a major role in AIBD, psoriasis and UV damage [7]
- Enalapril or penicillamin intake, topical dithranol or salicylic acid, transient hypo zincemia and potential infectious foci, all have been incriminated in previous case reports [5,11].

We think that in our case, probable triggering factors for GPP include: tapered dosage of the corticosteroid, unknown transient electrolyte imbalance during pulse therapy with corticosteroid, captopril intake and skin infection.

In previous case reports corticosteroids plus ciclosporin, dapsone, MTX or acitretin have been used with moderate improvement and some recurrences during dosage tapering [2,4,5].

In conclusion; although PF and GPP are considered as completely separate diseases, this case and similar cases confirm that there is a pathogenetic linkage in these autoimmune diseases.

Abbreviations

Autoimmune bullous disease: (AIBD)
Pemphigus foliaceus: (PF)
Generalized pustular psoriasis: (GPP)
Direct immunofluorescent: (DIF)
Indirect immunofluorescent: (IIF)
Antinuclear antibody: (ANA)
Methotrexate: (MTX)
Human leukocyte antigen: (HLA)
Interleukin-8: (IL8)
Ultra violet: (UV)
Interleukin-1: (IL-1).

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Our Dermatology Online

Case Report

Plakophilin 4 and ARVCF expression in a bullous cutaneous drug reaction

Ana Maria Abreu Velez[1], David J. Cohen[2], Michael S. Howard[1]

[1]Georgia Dermatopathology Associates, Atlanta, Georgia USA, [2]Dermatologic Surgery Specialists, PC, Macon, Georgia, USA

Corresponding author: Ana Maria Abreu Velez, E-mail: abreuvelez@yahoo.com

ABSTRACT

The subepidermal vesiculobullous disorders include a wide variety of pathogenically unrelated entities, which share the formation of clefts or bullae. A 59 year old female presented with a sudden eruption of pruritic skin vesicles and blisters on several areas of her body. The patient was taking multiple medications. We decided to test for the expression of p0071 and ARVCF because they are linked with tight, adherens, and occludens cell junctions in the epidermis and the dermis, and study if these molecules participate in the bullae formation. Skin biopsies were taken from lesional skin and were tested by hematoxylin and eosin(H&E) staining, as well as via immunohistochemistry (IHC) and direct immunofluorescence(DIF) using multiple antibodies. ARVCF and p0071 were overexpressed in the epidermis, and in dermal cell junctions around the blisters along with ribosomal protein S6-pS240, Factor XIIIa, CD15, CD45, multiple immunoglobulins, complement, fibrinogen and HLA-DP, DQ, DR antigen. All these molecules were also overexpressed around dermal vessels, eccrine glands and in neurovascular cell junctions below the blister. A normal control did not display the overexpression. Drug reactions may cause blisters; regional cell junctions may be altered, as demonstrated by overexpression of ARVCF and p0071. The overexpression likely contributes to passage of immunologic cells and formation of edema, directly contributing to blister formation.

Key words: Subepidermal blisters; Drug reactions; Plakophilin 4; ARVCF

INTRODUCTION

Drug eruptions often present with blisters [1,2]. Sometimes these blisters present when patients are taking multiple medications. Little is known about cell junction alterations and their putative roles in drug reactions. Here we described an interesting case, suggesting involvement of altered cell junctions in blister formation.

CASE REPORT

Here we present a 59 year old female, who presented with a sudden eruption of pruritic skin vesicles and blisters. The patient was taking NitroQuick® 0.4 mgs/day, Phentanyl 75® mg/day, ProAir HFA 90® mgs/day, Tetracycline 500 mg/day, Vectical® 3 mcg and Pamelor® 50 mg/day (for medical depression and some breathing difficulties). Skin biopsies were taken for hematoxylin and eosin (H&E) staining, for direct immunofluorescence (DIF) and for immunohistochemical (IHC) staining; their processing was performed as previously described [2]. The pathology results demonstrated a subepidermal blister due to a drug reaction, and the patient was evaluated to determine which medication was causing the reaction. The patient was provided with Phenergan®50 mgs/day, and Olux E® topical foam with improvement.

We utilized normal skin samples from breast reduction surgery as controls. For the DIF, we utilized standard panel antibodies as previously described [2]. In addition to these, we utilized a polyclonal antibody to Armadillo Repeat Gene Deleted in Velo-Cardio-Facial syndrome (ARVCF) (source guinea pig and tested in human and bovine, Catalog No. GP155, dilution 1:20; from Progen Biotechnik, Heidelberg, Germany); as its secondary, we utilized goat anti-guinea pig IgG (H&L), conjugated

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with Alexa 555 (2 mg/ml; 0.5ml) from Invitrogen (Carlsbad, California, USA), Catalog No. A.21435. We also utilized anti-p0071 (mouse monoclonal multi-epitope cocktail, Catalog No. 641166) from Progen and as its secondary, a Texas red conjugated goat anti-mouse IgG, at a 1:50 dilution (Invitrogen, Catalog No. T862).

We further utilized polyclonal rabbit anti-human myeloperoxidase, monoclonal mouse anti-human antibodies to cyclo-oxygenase 2 (COX-2), anti-human HLA-DP, DQ, DR antigen, CD4, CD8, CD15, CD45; ribosomal protein S6-pS240/phosphorylation site specific (Ribo), and Factor XIIIA(all from Novocastra/Leica, Buffalo Grove, Illinois, USA).

The H&E staining demonstrated a subepidermal blister, with partial re-epithelialization of the blister base. Within the blister lumen, no significant cellular infiltrate was seen (Fig. 1a, red arrow, 100X). Dermal papillary festoons were observed; within the dermis, a mild, superficial, perivascular infiltrate of lymphocytes, histiocytes, neutrophils and occasional eosinophils was identified. DIF displayed IgG (+++, on focal cell junctions in the epidermis and dermis; no classic intercellular staining between epidermal keratinocytes was seen); IgE (+, focal dermal positivity); Complement/C1q (+, linear at the dermal/epidermal junction and on c-ANCAS); Complement/C3 (+, focal linear at the base membrane zone (BMZ), and focally on dermal neural structures); Lambda light chains (+, focal cell junctions in the dermis); albumin (+++, focal cell junctions in the epidermis and dermis) and fibrinogen (+++, neurovascular structures). ARVCF was overexpressed throughout the dermis (++++); p0071 was overexpressed in the epidermis ++++), as well as on blood vessels near eccrine glands and on material excreted through eccrine glands (++++). Our normal skin controls displayed p0071 (+), and ARVCF (+), stains. The other immunoglobulin, complement and inflammatory cell markers were negative.

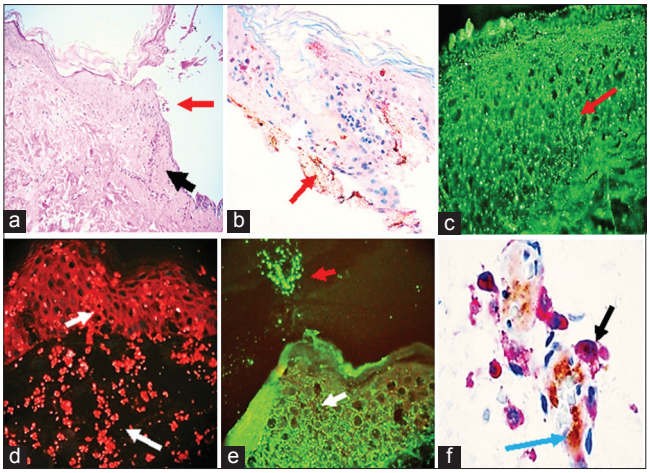

Figure 1: (a) H&E staining shows a subepidermal blister base(red arrow); the black arrow shows the lymphohistiocytic infiltrate around upper dermal vessels (100X). (b) Double IHC staining, showing positive staining for CD15 (brown staining) and COX-2(red staining) near the epidermis (red arrow). (c)DIF using FITC conjugated anti-human fibrinogen antibodies shows positive dot pattern staining in several epidermal cell junctions (antigens of unknown nature; yellow staining; red arrow). (d) DIF showing overexpression of p0071 in the neurovascular net around eccrine gland ducts. Notably, p0071 seems to be reactive to material extruded though the eccrine ducts. The epidermis also showed positive staining for p0071 (red staining; white arrows). (e) DIF using FITC conjugated anti-human fibrinogen antibody, and showing a detail of the reactive material extruded through an eccrine gland acrosyringium (green/yellow staining; red arrow). The white arrow highlights reactivity on epidermal cell junctions. (f) Double IHC staining, showing positivity around upper dermal blood vessels for Factor XIIIa (brown staining; blue arrow), in proximity to CD45 (red staining; black arrow).

Our IHC results demonstrated strong reactivity with Factor XIIIa in cells around the dermal blood vessels. HLA-DP, DQ, DR antigen was also very positive around these vessels (Fig. 1). The inflammatory infiltrate around the vessels was also positive for CD45; this staining highlighted fragmented lymphocytes. Both CD4 and CD68 were negative, and only few cells were positive for CD8 and COX-2 around the dermal blood vessels. Ribo was positive on epidermal cells surrounding the blisters. Some CD15 positive cells were noted around the blisters, and around upper dermal blood vessels.

DISCUSSION

Blistering drug eruptions are common, possibly due to an aging population and the increased number of medications that many patients are utilizing; the overall drug reaction patterns seem to be more complex than previously described [1-2]. Many drug reactions may involve excretions of drug breakdown products through the sweat glands, as shown in this case via overexpression of p0071, ARVCF and other markers [3]. Here, we detected reactivity with secondary intracellular cell signaling molecules (Ribo), as well as immunoglobulins, complement, and CD15 to epidermal and dermal antigens. Notably, p0071 is a plakophilin and a member of the p120 (ctn) family of armadillo-related proteins [4]. Here we demonstrated overexpression of p0071 and ARVCF;

these molecules are linked with tight, adherens, and occludens cell junctions. We hypothesize that edema and inflammatory cells penetrate the blister through altered cell junctions [3] ARVCF and p0071 molecules are also present in in the cells junctions of the vessels and nerves.

We speculate that the drug reaction elicits inflammation, facilitating the passage of cells as well as serum from adjacent vessels that are overexpressing HLA-DR,DP,DQ antigen. We speculate that additional cells, present in the dermis before initiation of the drug reaction are also involved. In our case, such a constellation of events and cells staining positive for Factor XIIIa, CD15 and CD45 were likely involved in the pathologic process as well as some drug metabolites excreting through the acrosyringia of eccrine glands.

Excretion of material by eccrine glands has previously been described by others in drug reactions [3]. We have previously described increased expression of p0071 in another drug reaction [2]; we speculate that both p0071 and ARVCF not only play roles in maintaining tissue integrity and cell adhesion, but also have putative roles in cell signaling and may help inflammatory mediators to move through cell junctions, as shown by the overexpression of these two molecules. We noted a CD8 T cell response and intensification of HLA-DP, DQ, DR antigen, COX-2 and Ribo expression in the lesion, suggesting not only a non-specific immune response(COX-2), but also a more specific immune response with antigen presentation through the HLA-DP,DQ,DR and T cell interactions; secondary cell signaling is likely occurring via Ribo. These features may explain why some people who have experienced one drug reaction are prone to present with additional drug reactions (possibly due to an immune memory response). In our case ARVCF was overexpressed throughout the dermis. It is known that ARVCF binds to the PDZ-domain of zonula occludens ZO-1 and ZO-2 tight junction proteins [5].

Our findings may explain the dot-like reactivity seen in both the dermis and the epidermis with p0071 and ARVCF as a response against likely cell junctions, suggesting that, at least in this case, the drugs acted as triggering factor(s). Specifically, epitopes on cells junctions and/or other molecules were presented as putative antigens through the HLA-DP,DQ,DR overexpression. p0071 has been described as a protein with dual localization in adherens junctions and desmosomes, depending on the cell type examined; here we clearly see an extrusion of p0071 (possibly part of damaged adherens junctions, extruded by the immune response through eccrine sweat glands; see Fig. 1).

In summary, we observed strong reactivity to epidermal and dermal cell junctions in a drug reaction via DIF and IHC. Drug reactions may cause blisters; here, we demonstrated cell junction marker expression for p0071/plakophilin and ARVCF. The overexpression of these markers may in turn contribute to passage of immunologic cells and edema in blister formation, as well as drug metabolite excretion through acrosyringia of eccrine glands. Few publications in the medical literature have described p0071 and ARVCF expression in cutaneous drug reactions.

Abbreviations

Basement membrane zone (BMZ), direct immunofluorescence (DIF), immunohistochemistry (IHC), hematoxylin and eosin staining (H&E), armadillo repeat gene deleted in velo-cardiofacial syndrome (ARVCF), tight junctions (TJs), adherens junctions (AJs), ribosomal protein S6-pS240/phosphorylation site specific (Ribo), cyclo-oxygenase 2 (COX-2), 4',6-diamidino-2-phenylindole (DAPI).

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Our Dermatology Online

Case Report

Fixed drug eruption induced by *Moringa oleifera* leaf extracts - A case report

Fatai Olatunde Olanrewaju, Olaniyi Onayemi, Olayinka Abimbola Olasode, Muphy Mufutau Oripelaye

Department of Dermatology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-ife, Osun state, Nigeria

Corresponding author: Dr. Fatai Olatunde Olanrewaju, E-mail: docjufat@yahoo.com

ABSTRACT

Fixed drug eruption (FDE) is a commonly encounter cutaneous drug reaction at the dermatology clinics. The diagnosis is made when a characteristic lesion occurred repeatedly at the same site following re-exposure to the precipitating agent. We are presenting Moringa oleifera as a cause of FDE in a 55 year old man making the plant part of the growing list of implicating agents causing FDE. The mechanism by which it causes the lesion may not be completely understood but may probably be due to high sulphur content in the leaf extracts. The sulphur may serve as hapten and activate CD 8+ effector/memory T- cell leading to generation of proinflammatory cytokines such as interferon-gamma which causes tissue damage.

Key words: *Moringa oleifera*; Fixed drug eruption; Sulphur

INTRODUCTION

The natural origin and supposed safety of alternative medicine in form of herbal medication have made them to gain wide acceptability throughout the world. *Moringa oleifera* has been of particular interest as evidence by its increasing cultivation and use especially in Nigeria in the past one decade. Despite increased use, not much has been said about the adverse reactions especially cutaneous side effects following consumption of its different parts- leaves, pods, beans, back and roots. We are reporting a rare case of fixed drug eruption (FDE) following consumption of aqueous leaf extract of *Moringa oleifera*. We suggest that attending dermatologist be aware and have high index of suspicion of *Moringa oleifera* as a cause of FDE while making a diagnosis most especially in those that developed FDE while taken herbal preparations.

Moringa oleifera belong to the genus Moringa and Moringaceae family and is the commonest of the thirteen species [1]. The plant is native to northern India but has become naturalized and widely cultivated in West Africa [2,3].

M. oleifera is known by many indigenous names such as horseradish tree, benzolive, drumstick tree, kelor, merango, mlonge, mulangay,saijhan and sajna [4]. In Nigeria, the plant is recognized by the Hausa as zogale, Fulani as kabije, Yoruba as Igi-iyanu and Igbo as Okwe-oyibo [5]. Many therapeutic effects like antibiotic, anticancer, antioxidant, antihypertensive has been attributed to this wonder plant [5,6]. The documented dermatological uses include improvement in wound healing, reduce wrinkle, improves acne vulgaris and psoriasis, the seed oil as an emollients, hair conditioner and antifungal properties [6]. The plant has been demonstrated to have inhibitory effect on Trichophyton rubrum and Trichophyton mentagrophytes [7,8].

Moringa oleifera leaf extracts contain significant amount of important nutrient such as carbohydrates, lipids and proteins in form of essential amino acids, vitamins A, B and C, minerals like potassium, calcium, iron, zinc, phosphorus and sulphur. The

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sulphur content per 100g of leaves can be as high as 137mg and 870mg for fresh and dried leaves respectively [9,10].

CASE REPORT

A 55 year old Nigerian man presented at the dermatology clinic complaining of recurrent dark spots on his trunk, arm, forearm and thigh for 1 year (Figs. 1–4). The dark spots usually reappeared on the same sites and occasionally new ones appeared at different sites. They usually began with itching, erythema and sometimes vesicles at the center of the lesions. It eventually subsided within 2-3 weeks to leave annular hyperpigmented patches. He has had several episodes in the past one year prior to presentation with worsening of symptoms following each repeated episodes of which no attributable etiology was found by the patient.

Skin examination revealed multiple annular hyperpigmented (Figs. 1 and 2), edematous patches (Fig. 4) and plaques 2-4 cm in diameter with erythematous edges (Fig. 1), on the chest, arm, forearm and thigh. The buccal mucosal were spared. The provisional diagnosis of fixed drug eruption was made at the first clinic visit but the offending agent could not be ascertain having denied oral intake of any common medication known to induced FDE. The patient however claimed to first noticed the lesions in the past one year when he started taken water based leaf extract of *Moringa oleifera* as blood detoxifying agent. He was subsequently counseled to meticulously lookout for these cutaneous lesions when taking any medications. The patient presented two weeks later with reappearance of similar lesions and

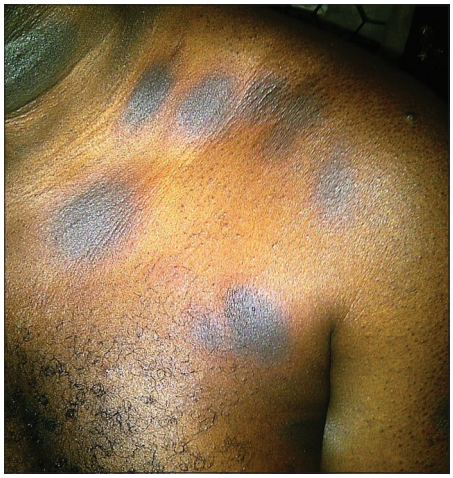

Figure 1: Hyperpigmented fixed drug eruption with erythematous edge on the left shoulder region.

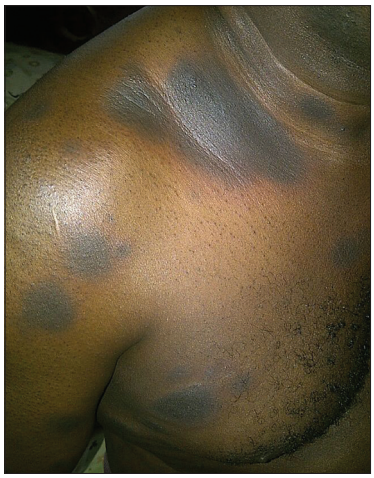

Figure 2: Hyperpigmented fixed drug eruption patch on the right shoulder region.

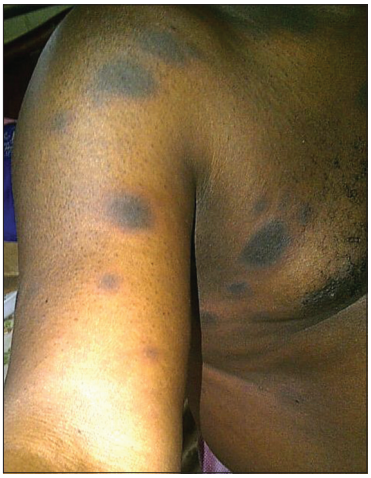

Figure 3: Hyperpigmented fixed drug eruption on the right arm.

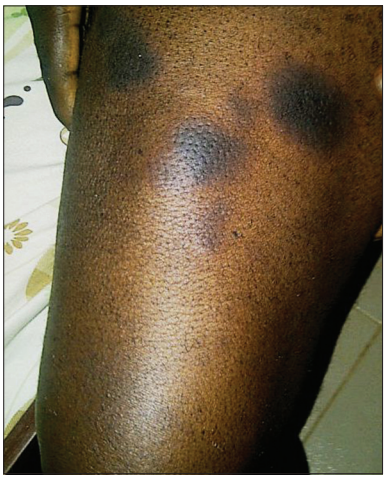

Figure 4: Urticaric and hyperpigmented fixed drug eruption on the right thigh.

deeper hyperpigmentation of the pre-existing patches following oral consumption of freshly prepared leaf extract of *Moringa oleifera*. This confirmed our initial diagnosis of fixed drug eruption and the implicating agent. There was no significant finding on systemic review and no constitutional symptoms such as fever, malaise, nausea and vomiting. The complete blood count and other biochemical parameters were all within normal physiological range. The diagnosis of FDE is usually made clinically, other useful tests required in establishing diagnosis of FDE include patch test on affected skin, drug challenge and biopsy of lesional skin. Patient was counseled to stop consumption of *Moringa oleifera* and was treated with antihistamine and topical steroid with resolution of symptoms but the post-inflammatory hyperpigmentation remained. He has been on follow up with no appearance of the lesion in the past two years since he stopped consumption of *Moringa oleifera*.

DISCUSSION

Fixed drug eruption is the term used to describe the appearance of skin lesions on precisely the same site(s) each time the incriminating drug is administered. Brocq first coined the term fixed drug eruption in 1894 but the entity was earlier described in 1889 by Bourns when he noticed the characteristic skin reactions to antipyrine [11].

FDE has been reported by many authors to be caused by increasing list of different agents including antibiotics, anticonvulsants, analgesics and herbal medications. The plant leaf extract have high sulphur content which probably serve as hapten to induce FDE [9,10]. The clinical diagnosis of fixed drug eruption is made by taking a careful history to elicit the fact that a drug, over-the-counter medications has been taken and when a characteristic adverse cutaneous drug reaction appear at the same site(s) upon repeated exposure to the offending agent. Among the commonest agents reported to cause FDE are sulphonamides and non-steroidal anti-inflammatory drugs (NSAID) [12]. The sites and appearances can be different and any part of the skin or mucous membrane can be affected. The precipitating agent or drug can have predilections for specific sites [13]. Tetracycline tends to cause FDE on the glans penis, sulphonamides cause lesions on any part of the body and NSAID such as aspirin usually affects the trunk and limbs [12]. The lesion of FDE may present as targetoid, bullous/vesicular, hyperpigmented, nonpigmented or urticaric, migrating, linear, eczematous or generalized.

The mechanism by which medications cause FDE is not completely understood, however the condition is thought to be due to delayed (type IV) hypersensitivity reactions [14]. Excessive activation of intraepidermal $CD8^+$ effector/memory T-cells which are resident in FDE lesions are said to be very important and sufficient enough in the pathogenesis and reactivation of lesions. The CD8+ T-cells propagate tissue damage by releasing pro-inflammatory cytokines such as interferon-gamma and tumor necrosis factor-alpha [15]. To confirm diagnosis re-challenge test can be undertaking cautiously in order to avoid extensive bullous lesion such as Steven-Johnson syndrome and toxic epidermal necrolysis.

CONCLUSION

Moringa oleifera consumption has increased in recent time for different reasons. FDE is a rare adverse cutaneous side effect of the plant and physicians need to be aware of this side effect. We report a rare case of FDE following consumption of aqueous extract of *Moringa oleifera* leaves. We recommend that physicians should be on the lookout for this side effect when taking history from patients with FDE.

Abreviations

FDE: Fixed Drug Eruption; NSAID: Non-Steroidal Anti-inflammatory Drugs.

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Our Dermatology Online

Case Report

Generalized livedo reticularis like eruption induced by trimethoprim/sulfamethoxazole: A case report with concomitant myelosuppression

Pinar Incel Uysal[1], Basak Yalcin[1], Onder Bozdogan[2]

[1]Dermatology Department, Ankara Numune Training and Research Hospital, Ankara, Turkey, [2]Pathology Department, Ankara Numune Training and Research Hospital, Ankara, Turkey

Corresponding author: Dr. Pinar Incel Uysal, E-mail: pinarincel@hotmail.com

ABSTRACT

Livedo reticularis is a reticular discoloration of the skin because of the vascular anatomy of the skin. The condition most commonly affects the legs. Drug induced livedo reticularis which is an acknowledged side effect of amantadine, tends to be widespread, asymptomatic, benign rash. There are also reports of livedoid eruption induced with drugs including dapsone, imatinibe, gefitinibe. We describe a case of livedo reticularis like eruption and haemotological toxicity with trimetophrim-sulfamethoxazole. The purpose of this report is to remind clinicians of this rare, benign side effect of the common prescribed medication.

Key words: Livedoid eruption; Skin rash; Trimetophrim-Sulfamethoxazole

INTRODUCTION

Livedo reticularis is a network like livedoid eruption which commonly occurs after physical exposure such as cold. Drug induced livedo reticularis is a very rare manifestation. In the literature there are reports that were associated with drugs including amantadine, dapsone, imatinibe, rasagiline [1-5]. These reactions usually show benign course and resolve without complication after discontinuation of the causative drug.

TMP-SMX is commonly used antimicrobial drug which has a wide range of adverse effects. Severe liver failure, skin rash, early onset bone morrow changes are included in idiosyncratic reactions. Skin rash is a common adverse effect. Although the majority of these are mild and self-limited reactions, there are reports about life threatening skin eruptions such as DRESS, toxic epidermal necrolysis triggered by TMP-SMX [6].

We describe 31-year-old female with pancytopenia and generalized livedoid reticularis which have occurred after introduction of trimetophrim-sulfamethoxazole (TMP-SMX). The rash and bone morrow suppression disappeared after withdrawal of the drug.

CASE REPORT

A 31-year-old woman with acute otitis media presented with widespread eruption for 4 days. She was prescribed TMP-SMX for acute otitis media a week before the occurrence of the eruption. At initial presentation, her main complaint was slightly burning sense of the eruption. She did not give any history of joint symptoms, fever, malaise, thrombotic episodes and abortus. Family history was unremarkable. The rash was not cold induced. The skin examination revealed general reticular livedoid eruption more intense on the proximal part of lower extremities (Fig. 1a) and upper parts of trunk (Fig. 2a). Oral and genital mucosa, nails and scalp were not involved. Lymph nodes were not enlarged. Other systemic examinations were normal. She was not taking any medication except TMP-SMX for otitis media. TMP-SMX therapy was discontinued.

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Punch biopsy specimen was obtained from left thigh and an extensive laboratory tests for the causes of livedo reticularis was performed. Leukocytopenia (2.5 $\times 10^3$ leukocytes), mild thrombocytopenia (133 $\times 10^3$ thrombocytes), anemia (Hb, 11 g/dl; Htc, 35.9%) were observed in the blood count. Peripheral blood smear revealed hypochromic microcytic red cells without cell atypia. Abnormal biochemical parameters were as follows: ESR, 22 mm/h; ASO, 235 IU/ml, Fe, 19 μg/dl. Urine analysis was normal. Comprehensive metabolic profile, protein C and S, lupus anticoagulant, antithrombin III, antiphospholipid antibodies, cryoglubulines, antinuclear antibodies, complement levels, rheumatoid factor, coagulation studies were normal. HIV and VDRL serology tests were negative. Local moisturizers and topical steroids were prescribed. Patient was consulted with haematology. Haematological abnormalities were associated with TMP-SMX use. Iron supplement was started with the diagnosis of iron deficiency anemia. Histological examination showed chronic lymphocytic inflammatory cell infiltrate along with a few eosinophiles and marked edema in the dermis (Fig. 3).

The patient was asked to come for follow-up every week. The rash and myelosuppression were persisted for the first week. Her blood parameters (WBC, 4.8x$10^3/\mu$L; PLT, 195x$10^3/\mu$L) increased 2 weeks after the discontinuation of drug. Slight increase of haemoglobin level (Hb, 11. 8g/dl) was achieved at third week control. Gradual resolution of the eruption was observed over the next month (Figs 1b - 2b).

DISCUSSION

TMP-SMX which is one of the oldest antimicrobial agents inhibits sequential steps in the synthesis of tetrahydrofolic acid. Thrombocytopenia and leucopenia are the most common hematologic side effects due to TMP-SMX. On the other hand wide range of haematological toxicities have been described [7]. These toxities are more common in adults. Thrombocytopenia, leukocytopenia and iron deficiency anemia were present in our case. Her clinic was not critic. Two weeks after discontinuation of the drug, increased levels of the white blood cells and platelets were achieved.

Skin rashes are one of the most common side effects of TMP-SMX. Even though majority of these reactions are mild, diffuse, morbilliform reactions, serious reactions

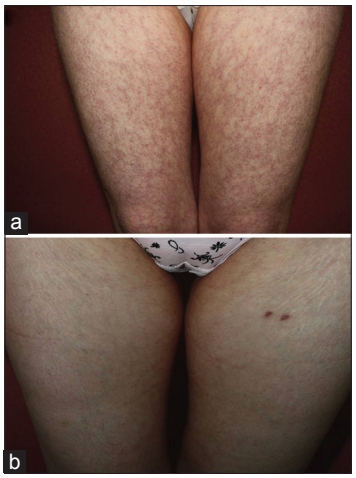

Figure 1: Marked livedo reticularis on the thighs of the patient at initial presentation (a). Improvement of the eruption after discontinuation TMP-SMX (b).

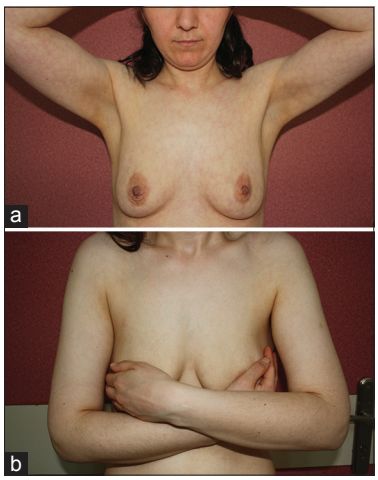

Figure 2: Reticular eruption on the trunk (a). Complete clearance of the lesions at 1-month follow-up (b).

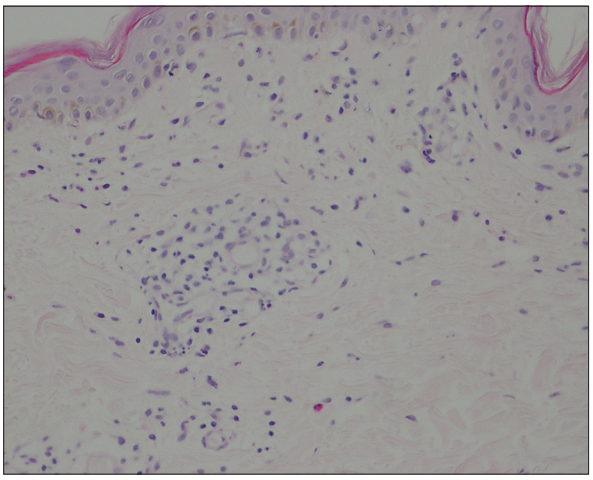

Figure 3: Nonspecific inflammatory infiltration including a few eosinophils and edema in the dermis. Original magnification, x200, H&E.

have occurred. Our patient has used TMP-SMX for a week preceding the eruption. The abrupt onset of the condition after TMP-SMX therapy suggested us a causal relationship between the drug and rash. However we performed other laboratory tests with the aim of investigating and excluding potential cause of the livedo reticularis. Similarly some other reports in the literature, histopathology did not yield diagnosis in our patient. Nonspesific histopathological changes without vasculitis were observed in most of the cases of drug induced livedo reticularis like as in our case [3,5,8]. Our case presented easily recognizable clinical picture of livedo reticularis. Nevertheless, because of nonspecific microscopical findings without any clue of the condition, a diagnosis of livedo reticularis-like eruption secondary to TMP-SMX was made. Based on uncomplicated clinic and subtle subjective symptoms of our patient we did not consider any systemic therapy. Two weeks after cessation the medication, partial improvement of the discoloration was observed. At fourth week of the initial examination, rash was disappeared completely. However re-challenge was not attempted because of the relapse risk of drug induced bone morrow toxicity. In patients with livedo reticularis or racemosa identifying the underlying cause is important for management. Although it is not fully understood, it is believed that Amantadine -a well known causative agent for livedo reticularis- leads to cathecolamine depletion [8,9]. Recently, it has been reported that there are similar cases induced with some agents such as gefitinibe, imatinibe, dapsone, rasagiline [3-5,10].

CONCLUSION

This case, to our knowledge, is the first report relating TMP-SMX to livedo reticularis like eruption. Rash with mild hematologic toxicity was another interesting aspect of our case. As it is understood from some reports in literature the exact mechanism leading this widespread eruption with vascular origin is unknown for today. Obviously drug induced reticular eruptions need more understanding. In conclusion, in view of wide use of TMP-SMX, we want to underlie this mild, rare adverse cutaneous reaction.

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Our Dermatology Online

Case Report

A cutaneous rash with mixed gell coombs allergic features, sclerodermoid changes and status post previous therapy

Ana Maria Abreu Velez[1], Josepha Devaro[2], Michael S. Howard[1]

[1]Georgia Dermatopathology Associates, Atlanta, Georgia, USA, [2]Coastal Dermatology, Savannah, Georgia, USA

Corresponding author: Ana Maria Abreu Velez, E-mail: abreuvelez@yahoo.com

ABSTRACT

Allergies and autoimmune diseases may both be considered hyper-immune responses, where the body's immune system becomes supercharged and attacks or responds to inappropriate antigens. We describe a skin rash with a mixed allergic and autoimmune host response. A 65 year old female consulted her dermatologist for a pruritic rash. The patient had taken many medications without improvement of the rash, and lived in an area affected by environmental spills; other patients had presented with similar rashes concurrently. A clinical evaluation was performed, and skin biopsies were obtained for hematoxylin and eosin (H&E) examination, as well as for immunohistochemical (IHC) and direct immunofluorescence (DIF) studies. The H&E review revealed a mild, superficial, perivascular dermal infiltrate of lymphocytes, histiocytes, mast cells and eosinophils. Dermal sclerodermoid alterations were also noted. A mild peripheral blood eosinophilia was found; cutaneous IHC staining revealed staining for anti-HLA-DP, DQ, DR antigen and Complement/C5b-9/MAC, in the areas of the perivascular infiltrate and the sclerodermoid changes. The DIF confirmed these findings. Our case is characterized by a mixed allergic/autoimmune reaction, which did not fit exclusively into any single Gell Coombs immune response category.

Key words: Shotgun therapy; Skin rash; Gell coombs classification of allergic reactions; Clorox®

INTRODUCTION

One of the major problems that health personnel face when evaluating skin rashes is prior "shotgun" therapy; specifically, often patients take multiple medications to address the initial rash, and thus are exposed to multiple putative allergens. Additionally, patients are often seen by several health providers that before the initial rash is properly diagnosed.

Evaluating skin rashes may also be difficult in areas subject to environmental toxins, especially when several patients in a limited geographic area present simultaneously with skin rashes. Under these conditions, initial diagnoses considered often include allergies (seasonal and/or due to specific antigens including pollen, dust or others) [1-4]. Contact dermatitis is also part of the initial differential diagnosis. Here we present a very unusual cutaneous rash case, with a combined immune response.

CASE REPORT

A 65 year old female resident of Savannah, Georgia visited the dermatologist with a history of six months of a recurrent, itchy rash manifested as papules on her arms, back, chest, and legs. The patient stated the lesions started after she cleaned several trailers, using strong detergents and Clorox®. She denied constitutional symptoms, or gastrointestinal complaints. The patient owned multiple dogs, cats, horses, goats and a donkey. Prior to presentation, the patient had been previously seen by both immunologists and dermatologists for the rash, and had been evaluated for insect bites and/or skin infections; all previous evaluations were negative. The physical examination revealed papules on the patient's arms, back, chest and legs. Similar cases had been concurrently reported to local health authorities in the geographic area, and local environmental toxin contamination had been previously documented.

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The patient received Pyrmethamine® cream, three separate bursts of oral steroids, Keflex,® Augmentin,® and Ivermectin tablets repeated for 10 days with no improvement. Most of her blood workup was normal electrolyte panel, hepatic function testing, BUN, creatinine, TSH, and ANAs). A complete blood count showed a mild eosinophila (9 with a normal range of 0-7). A Prednisone taper was given as well as Atarax,® Zyrtec® 10 mgs, and Benadryl 25 mgs at bed time. A RAST test was negative. Heavy metal panels for her blood and urine were also negative (testing for arsenic, cadmium, lead and mercury). Tissue transglutaminase (TTG) antibody, IgA and anti-IgA anti-endomysium antibodies were negative. Skin biopsies for hematoxylin and eosin (H&E) staining, for immunohistochemistry (IHC) and for direct immunofluorescence (DIF) were taken.

No patient identifiers were recorded, and our research was conducted following medical guidelines of non-disclosure. Lesional skin was biopsied and studied utilizing hematoxylin and eosin (H&E) staining, as well as via IHC, and direct immunofluorescence; all techniques were performed as previously described [5,6].

Microscopic Description

Examination of the H&E tissue sections demonstrated a histologically normal epidermis. Within the dermis, a mild, superficial, perivascular infiltrate of lymphocytes, histiocytes, mast cells and occasional eosinophils was seen. Dermal sclerodermoid alterations were also noted. A mild, superficial, perivascular dermatitis with an additional sclerodermoid component was diagnosed (Fig. 1).

DIF

The DIF examination revealed IgG (+++, diffuse dermal matrix fibers); IgA, IgM, IgD, IgD and IgE (+, focal within dermal hair shafts); Complement/C1q (++, diffuse dermal matrix fibers, piloerector basement membrane and focal within hair follicles); Complement/C3(focal spotty positivity at BMZ, and on neurovascular supplies into hair follicles); Kappa light chains (++, diffuse dermal matrix fibers in the central dermis); Lambda light chains (++, diffuse dermal matrix fibers and dermal nerves); albumin (++, dermal perivascular) and fibrinogen (++, diffuse dermal matrix fibers, focal dermal perivascular, on piloerector muscles and on dermal nerves) (Fig. 1).

IHC

Our IHC staining revealed positive strong staining with anti-HLA DP, DQ, DR antigen throughout the neurovascular dermal plexus, as well as on vessels around eccrine sweat glands (Fig. 1). Complement/C5b-9/MAC was positive around hair follicles and sebaceous glands, throughout the neurovascular plexus and in the areas of sclerodermoid changes seen by H&E review. CD45 positive cells were seen around the upper and middle dermal blood vessels, and around vessels supplying eccrine gland ducts and neurovascular packages in the dermis (Fig. 1) Staining for CD3 and CD8 was mildly positive around the superficial dermal blood vessels. Dermal staining for CD20 was negative. Factor XIIIa staining was positive around the sclerodermoid areas, and around dermal blood vessels. Staining for CD68 was positive around dermal blood vessels, piloerector muscles, and in the sclerodermoid areas (Fig. 1). Staining for CD1a was positive in the areas of the dermis below the inflamed vessels.

DISCUSSION

We present a case of a skin rash with sclerodermoid changes, and an allergic-like immune response in a geographic area where similar, concurrent cases were seen in other patients. An eosinophilia-myalgia syndrome secondary to L-tryptophan-containing products or toxic oils was considered in the differential diagnosis [7]. The serum and skin biopsy eosinophilia, and the IgE detected by DIF indicated an allergic component. However, the dermal sclerodermoid alterations, combined with the positive HLA-DR, DP, DQ antigen and Complement/C5b-9/MAC IHC staining suggested antigen presentation via a likely environmental trigger component. Heavy metal testing displayed negative results. The significant exposure to Clorox may represent a primary sensitizing factor in the case.

The RAST tests currently on the market do not contain many of the allergens a patient may be exposed to. Our patient had significant contact with Clorox,® and animals; she was also likely exposed to environmental toxins, given her geographic location. Often environmental spills are not reported to the authorities; the observed neural reactivity and sclerodermoid changes in the skin suggest a possible toxin exposure.

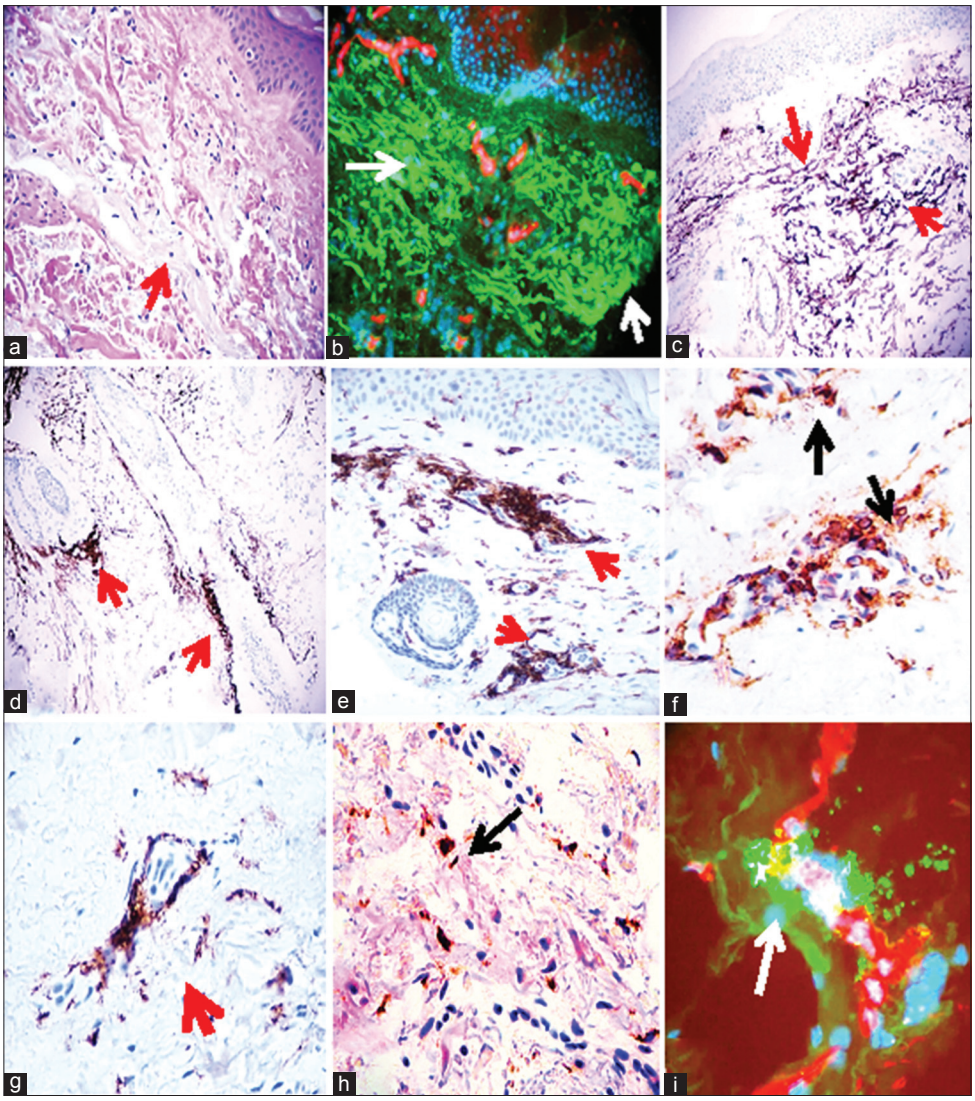

Figure 1: (a) H&E staining demonstrates dermal edema and solar damage (100X, red arrow). (b) DIF using FITC conjugated IgG antibody, and showing positive staining on dermal collagen fiber (green staining; white arrows) (100X). Cell nuclei are counterstained with DAPI in blue; the red staining represents Texas red conjugated *Ulex* antibody on dermal blood vessels. (c) IHC staining shows positive Complement/C5b-9 stain (brown staining; red arrows), in the same areas of the abnormal dermal fibers seen by H&E. In (d) IHC staining for Complement/C5b-9 against the hair follicles and sebaceous glands, and in (e) against the vessel s(brown staining; red arrows). (f) Double IHC staining showing positive HLA-DR, DP, DQ antigen staining (brown) colocalizing with von Willembrand factor staining (red), around the upper dermal inflamed vessels (black arrows) (400X). (g) IHC staining showing positive CD45 staining around dermal blood vessels and nerves (brown staining; red arrow). (h) IHC double staining using CD68 (brown staining; black arrow) and Factor XIIIa (pink/purple), showing positivity to the vessels and also to extracellular structures. (i) DIF using FITC conjugated anti-human IgD antibody showing positive staining on dermal neurovascular structures (green staining; white arrow).

The histopathologic and immunodermatologic findings of this patient did not fit exclusively into a single diagnostic category (e.g., contact dermatitis, allergic dermatitis, drug eruption), and sclerodermoid changes were also noted. In similar cases, we recommend evaluating the patient for possible heavy metal and toxins in blood, hair and/or nail tissue, especially when other people in the patient's community are presenting with similar clinical findings. Complement/C5b-9 IHC staining was positive in several areas of the skin, and could be detected in early and late stages of some sclerodermoid conditions triggered by organic solvents, silica or other agents (and not detected via heavy metal panels or RAST testing) [8,9].

In complex rash cases, another complicating diagnostic factor is previous treatment by multiple healthcare providers. Often, multiple medications are prescribed when a causative diagnosis is not established; the medications then may complicate discovery of the true cause of the disease. We recommend a complete clinical examination before initiation of any therapy, prescribing antihistamines to address pruritus while working to achieve an accurate diagnosis.

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Abbreviations and Acronyms

Immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF, IIF), hematoxylin and eosin (H&E), basement membrane zone (BMZ), fluorescein isothiocyanate (FITC), 4',6-diamidino-2-phenylindole (DAPI).

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Our Dermatology Online

Case Report

Pigmented contact dermatitis to p-paraphenylenediamine in a textile factory worker

Mrinal Gupta

Treatwell Skin Centre, Opp Science College, Canal Road, Jammu, J & K, India

Corresponding author: Dr. Mrinal Gupta, E-mail: drmrinalgupta@yahoo.com

ABSTRACT

Pigmented contact dermatitis (PCD) is a noneczematous variant of contact dermatitis, characterized clinically by hyperpigmentation with little or no signs of dermatitis. The commonly implicated agents causing PCD include cosmetics like fragrances, lipsticks and kumkum, preservatives, optical whiteners, benzyl salicylate and metallic compounds like nickel sulphate and nickel oxide. We present a case of PCD in a 45-year old textile factory worker, who presented with gradually progressive asymptomatic hyperpigmentation of the face which started after he started working in a textile factory. Patch test revealed sensitization to *p*-Paraphenylenediamine, thereby confirming the diagnosis of PCD to *p*-Paraphenylenediamine.

Key words: Pigmented contact dermatitis; *p*-Paraphenylenediamine; occupational dermatosis; pigmented cosmetic dermatitis; textiles

INTRODUCTION

Pigmented contact dermatitis (PCD) is a noneczematous variant of contact dermatitis, characterized clinically by hyperpigmentation with little or no signs of dermatitis. PCD has been found to be caused by a large number of agents with the most commonly implicated ones being cosmetics like fragrances, lipsticks and kumkum, preservatives, optical whiteners, benzyl salicylate, minoxidil and metallic compounds like nickel sulphate, chromium hydroxide and nickel oxide [1]. Herein, we present a case of PCD in a 45-year old textile factory worker, who presented with gradually progressive asymptomatic hyperpigmentation of the face which started after he started working in a textile factory.

CASE REPORT

A 45-year-old man presented with a three year history of worsening non-pruritic pigmentation over the face. The pigmentation started over the forehead and over the period of time involved the whole face but remained asymptomatic throughout. The patient correlated the onset of lesions with his change in job, when he started working in a textile factory where he was engaged in the job of textile packing. There was no history of any similar lesions prior to that and the patient gave no history of any drug intake or hair dye use but the patient was using regular toiletries like cold creams and soap. He had no personal or family history of atopy or any similar condition in the family members. On examination, there were hyperpigmented patches, symmetrically distributed over her forehead and cheeks with relative sparing of the nose and the malar prominences (Fig. 1). Nails, mucosae, hair and rest of cutaneous examination was normal. Systemic examination and routine laboratory investigations revealed no abnormality.

Differential diagnoses considered included pigmented contact dermatitis and melasma. The clinical appearance and the patient's age were considered less typical for melasma.

Patch tests were performed with Indian standard series, cosmetic series and the patient's own products using Finn Chambers, and were read after 48 and 72 hours.

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The patch test showed positive (2+) reaction to *p*-Paraphenylenediamine (PPD)(Fig. 2). Other allergens and patient's own products showed negative response.

On the basis of history, clinical examination and patch test, a diagnosis of PCD to PPD was made. The patient was advised a change in job profile which he refused and was started on topical 4% hydroquinone cream at night with sunscreens during daytime. After three months of therapy, there was only a mild improvement in symptoms.

DISCUSSION

The term "pigmented contact dermatitis" was coined by Osmundsen in 1970, who described an epidemic of melanosis in Copenhagen which was due to contact dermatitis caused by an optical whitener present in a washing powder [2]. A large number of chemicals with a similar tendency to induce PCD have been identified in the subsequent years. The exact mechanism by which these chemicals induce pigmentation is unknown but it has been postulated that these agents produce a cytolytic type of type IV allergy mainly at the basal layer of the epidermis that results in pigmentary incontinence [3].

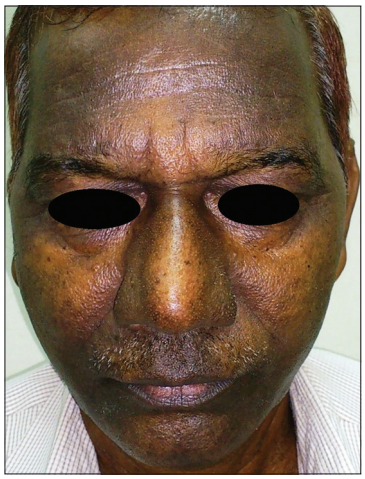

Figure 1: Hyperpigmented patches on the temporal, forehead and zygomatic areas, with sparing of the nose and malar prominences.

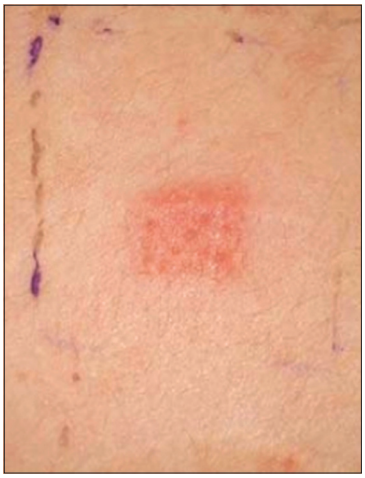

Figure 2: Patch test positive reaction to PPD.

Clinically, PCD manifests as reticulate reddish brown or slate grey pigmentation without any signs of preceding inflammation like itching, erythema or scaling. PCD usually occurs due to direct contact with the allergens and the sites coming in contact with the causative agents are commonly affected with face being the most commonly involved site. Diagnosis is mainly done on clinical examination but patch test has been found useful in confirmation of the diagnosis [1]. Patch testing should be carried out with standard series, cosmetic series, fragrance series and the personal products of the patients as it helps in identification of the causative agent. In an Israeli study, 26 patients with PCD were subjected to patch test and the most commonly identified allergens were nickel sulphate, fragrance mix and potassium dichromate [4].

PPD, an arylamine derivative first described by Hoffmann in 1863, is one of the most commonly implicated agents causing contact sensitivity. It is a commonly used coloring agent and is present in hair dyes, dyes for henna tattoos, textiles, leather and fur, and black rubbers. Being a member of 1,4-substituted benzenes, it cross-reacts with para-amino benzoic acid (PABA), sulphonamides, para-amino salicylic acid, ester anesthetics, thiazides, sesquiterpene-lactone mix, and azo dyes [5]. The reported prevalence of positive patch test reactions to PPD among dermatitis patients is 4.4% in Asia, 4.1% in Europe, 6.0% in North America, and 11.5% in India. The most common clinical presentations of PPD sensitivity include contact dermatitis localized to sites of contact or photoexposed skin, periorbital dermatitis, airborne contact dermatitis, hand dermatitis and pigmented contact dermatitis [6].

Contact sensitivity from PPD is becoming a prevalent health problem. Strict regulations are required to regulate its concentration in various products. As it is used in a large number of industries, it can pose a risk for various occupational groups as well as the general public. There needs to be a continued awareness among

the factory workers as well as the general population of the potential risk of PPD, especially in darker skin types where the pigmentary changes can be quite marked.

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Our Dermatology Online

Case Report

Lupus erythematosus panniculitis

Alizade Narges[1], Rafiei Rana[1], Mesbah Alireza[2], Naji Rad Sara[3]

[1]Department of Dermatology, Skin Research Center, Guilan University of Medical Sciences, Razi Hospital, Rasht, Iran, [2]Department of Pathology, Skin Research Center, Guilan University of Medical Sciences, Razi Hospital, Sardare Jangal Street, Rasht, Iran, [3]Department of Internal Medicine, Internal Medicine Resident, Nassau University Medical Center, New York, USA

Corresponding author: Dr. Rafiei Rana, E-mail: rafieirana2@gmail.com

ABSTRACT

Lupus erythematosus panniculitis is a rare type of chronic cutaneous lupus erythematosus which is histopathologically characterized by a lobular panniculitis. We present a 43-year-old woman with an indurated painful plaque on her right flank from 3 years ago. She mentioned a previous blunt trauma to this site. Microscopic examination revealed a predominant lobular panniculitis with lymphoid follicle formation, hyaline fat necrosis, membranocystic changes and mucin deposition. She was treated with oral hydroxychloroquine with moderate improvement. An indurated subcutaneous painful plaque could be the presenting feature of lupus panniculitis and we should evaluate systemic involvement in these patients.

Key words: Lupus panniculitis; Lobular panniculitis; Lymphoid follicle

INTRODUCTION

Lupus erythematosus panniculitis (LEP) is a subtype of cutaneous lupus erythematosus which is also named lupus erythematosus profundus. Histopathologically, LEP could be characterized by epidermal changes similar to discoid lupus erythematosus (DLE) and a periseptal or lobular panniculitis [1,2].

Lymphoid follicle formation, dermal mucin deposition, hyaline fat necrosis and fibrosclerosis are other characteristic features which have been reported [2,3]. LEP usually presents by subcutaneous nodules, indurated plaques or ulcerations which involves face, proximal extremities and breast [1,3,4].

CASE PRESENTATION

We report a 43-year-old woman who developed an indurated painful pigmented plaque on her right flank. It was started 3 years ago after a blunt trauma with no improvement and gradually enlarged (Fig. 1).

In past medical history, she had gastritis, hypothyroidism and polycystic ovary syndrome. Drug history included levothyroxine, lansoprazole and contraceptive pills.

In physical examination there was a pigmented deeply seated plaque with woody consistency on the right flank, measured 10 cm × 5 cm. Also there was periungual erythema without cuticular telangiectasia on her hands. There was no oral ulcer, cicatricial alopecia, lymphadenopathy, organomegaly, malar rash, muscle weakness, fever, weight loss and arthritis but she mentioned photosensitivity, morning stiffness, arthralgia and Raynaud's phenomenon.

Skin biopsy was made with patient's consent. Differential diagnoses were deep morphea, lupus panniculitis, sarcoidosis, subcutaneous T cell lymphoma (SCTCL), tuberculosis and cutaneous metastasis.

Histopathologic changes in hematoxylin and eosin (H&E) staining were as follows: Unremarkable epidermis, pigment incontinence, perivascular, periadnexal and perineural lymphocytic infiltration

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in dermis, lymphoid follicles with germinal centers associated with plasmacytic and neutrophilic infiltration in deep dermis and subcutaneous fat, lobular panniculitis with hyaline fat necrosis, septal thickening and membranocystic lipodystrophy. (Figs. 2a – 2e).

Periodic Acid Schiff (PAS) staining revealed mild and focal thickening of subepidermal basement membrane. Mucin deposition was detected in colloidal iron staining. There was no acid fast bacillus in Ziehl Neelsen staining. In immunofluorescence studies only trace and focal deposits of IgG along the dermo-epidermal junction were reported (Figs. 2f – 2h).

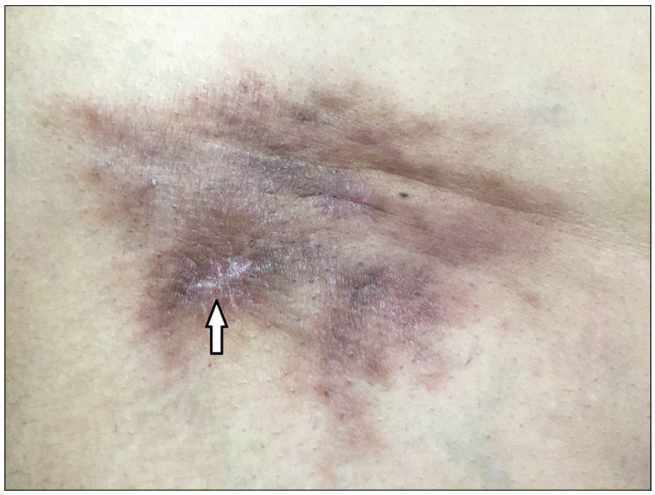

Figure 1: An indurated hyperpigmented plaque on the right flank. Arrowhead points skin biopsy site.

Immunohistochemistry (IHC) studies with CD3 (pan T cell marker), CD20 (pan B cell marker), Ki67, CD68 staining were made to differentiate between LEP and subcutaneous T-cell lymphoma. The IHC confirmed mixed lymphoid aggregations of CD20 positive B lymphocytes associated with CD3 positive T lymphocytes. Ki67 staining revealed germinal centers with expected elevated proliferation rate. CD68 was positive in scattered background histiocytes and follicular dendritic cells but there was no granuloma formation. According to these findings, SCTCL was ruled out (Figs. 3a – 3d).

Blood investigations including complete blood count, urea, creatinine, liver function test, calcium, phosphorus, creatine phosphokinase, lactate dehydrogenase and complement levels were within normal limits but following lab data were elevated: Erythrocyte sedimentation rate (54 mm/1 hr.), C - reactive protein (15 mg/l; norm up to 6), antinuclear antibody (ANA: 1/160 titer with homogenous pattern), anti-double stranded DNA antibody (45 U/ml, norm up to 25) and angiotensin converting enzyme (83 U/L, norm up to 67). Urine analysis revealed leukocyturia and trace proteinuria (15 mg/dl). Urine protein was

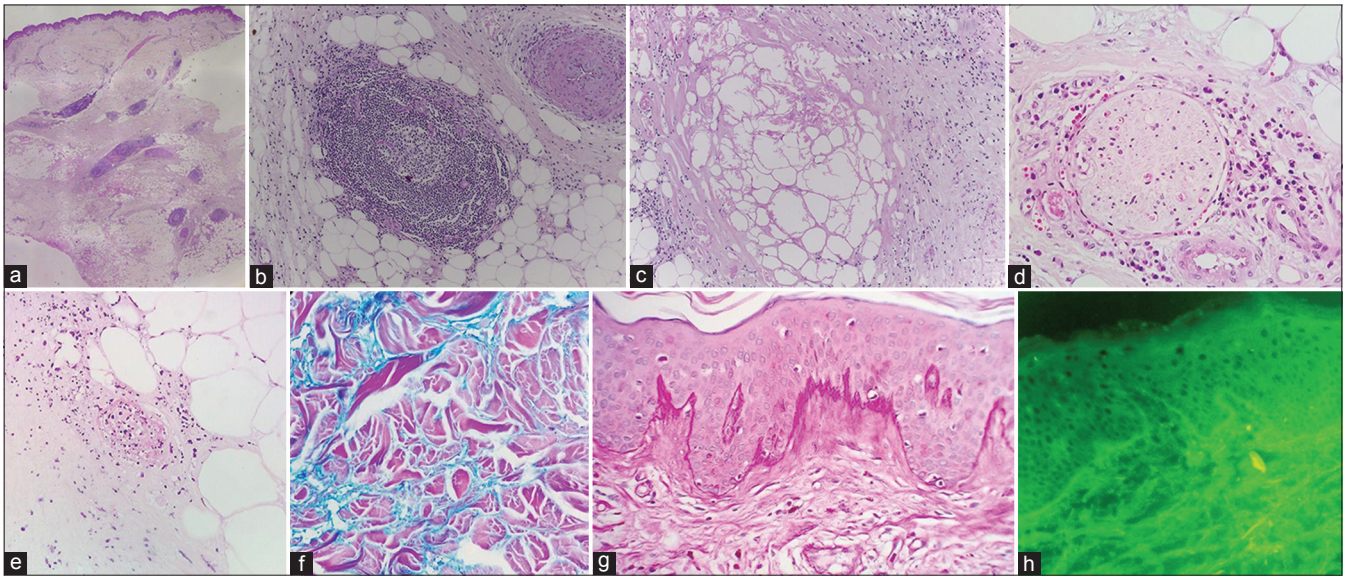

Figure 2: These photomicrographs show: a: Perivascular and periadnexal lymphocytic infiltration in dermis, dense lymphoid follicle aggregations in deep dermis and subcutaneous fat, lobular panniculitis and septal thickening in sub cutaneous fat. b: lymphoid follicle with germinal center associated with plasmacytic infiltration in subcutaneous fat. c: membranocystic lipodystrophy with arabesque structures and hyaline fat necrosis. d: Lymphocytic and plasmacytic perineural infiltration in deep dermis. e: Vascular impairment with neutrophilic infiltration and nuclear dust in sub cutaneous tissue. f: Mucin deposition in mid dermis. g: Mild and focal thickening of basement membrane. h: Trace and focal deposits of IgG along the dermo-epidermal junction. (a: H&E, original magnification × 40; b: H&E, original magnification × 100; c: H&E, original magnification × 100, d: H&E, original magnification × 400, e: H&E, original magnification × 400, f: colloidal iron staining, original magnification × 40, g: PAS staining, original magnification × 100, h: immunofluorescence study, original magnification × 100).

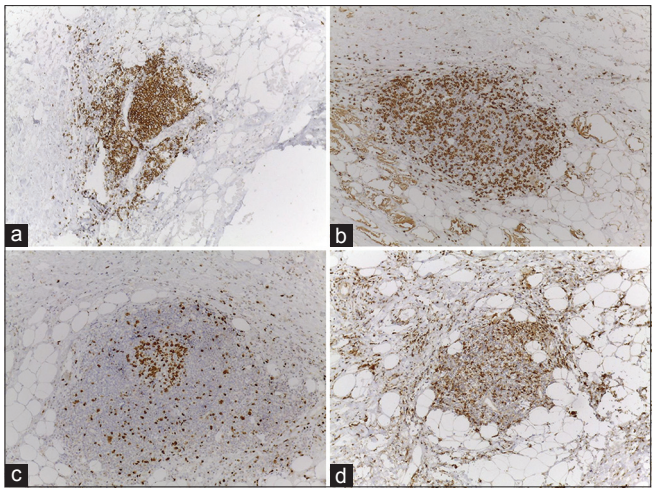

Figure 3: IHC staining results: a: CD 20 is densely positive in B cell component. b: CD3 is positive in concurrent T-cell component. c: In overall Ki67 is positive in 2%-4% of cells, but in about 70% of cells in germinal center cells. d: CD68 is positive in scattered histiocytes. (3a, b, c, d: original magnification × 400).

182 mg/24hrs (norm up to 150). Urine culture was negative. Imaging studies including chest radiography and abdominopelvic sonography were unremarkable but lesional ultrasonography revealed a hypoechoic region in subcutaneous fat.

According to clinicopathologic correlation and lab data, LEP was proposed. We treated her with oral hydroxychloroquine 400 mg daily for 12 weeks with a marked reduction in pain and induration. She was followed six monthly for any progression to systemic lupus erythematosus (SLE).

DISCUSSION

LEP is an unusual type of cutaneous lupus erythematosus which could be easily overlooked. Clinically it manifests as indurated subcutaneous painful plaques or nodules usually with normal overlying skin and mainly involves face, trunk, breast and proximal extremities [3,5], although epidermal changes including erythema, hyperpigmentation, poikiloderma, ulceration, discoid lupus erythematosus (DLE)-like features have also been reported [1,5]. It mainly affects adults aged between 20 to 60 years and women are almost twice as likely to be affected as men. Seventy percent of LEP cases have been associated with DLE but two to five percent of cases have been accompanied by SLE [6,7]. Most cases of LEP have mild and fluctuant courses but up to 15% of cases could be able to progress to SLE and 50% of them have evidences of SLE, so LEP could be a preceding feature of systemic involvement and all patients should be followed up meticulously especially in cases with positive ANA [1,3,6-8]. Arai, et al. reported positive ANA in 95.2% of LEP cases [8].

Pathophysiology of LEP is not clear but hereditary C4 deficiency and trauma have been incriminated and the role of ultraviolet is questionable because LEP usually involves proximal extremities [3]. In our case, previous trauma could be a triggering factor for antigen presentation. We considered pain in the lesion as a result of neural involvement which was seen in histopathologic evaluation.

Major histopathologic characteristics in LEP are as follows: Lobular lymphocytic panniculitis, lymphoid follicle formation, calcification, hyaline fat necrosis, lipomembranous changes due to vascular impairment and fibrin thrombosis. Other histopathologic characteristics include DLE- like changes in epidermis, mucin deposition (80% of cases), granuloma formation and plasmacytic infiltration. Positive lupus band and basement membrane thickening have been detected in up to 50% of cases [3,8,9]. An important differential diagnosis for LEP is SCTCL. Plasma cell infiltration, lymphoid follicle formation, mucin deposition, DLE-like epidermal changes, IHC findings and positive lupus band help to rule out SCTCL [1,10].

We treated her with hydroxychloroquine which is a disease modifier with different mechanisms and few complications [3]. For recalcitrant cases dapsone, thalidomide, cyclosporine and rituximab have been used [1].

CONCLUSION

An indurated subcutaneous painful plaque could be the presenting feature of LEP. Early diagnosis and appropriate therapy should be considered to prevent disfigurement and progression to systemic involvement.

Abbreviations

LEP: Lupus erythematosus panniculitis
SCTCL: subcutaneous T cell lymphoma
DLE: discoid lupus erythematosus
SLE: systemic lupus erythematosus
ANA: antinuclear antibody
H&E: Hematoxylin and eosin
PAS: Periodic Acid Schiff
IHC: Immunohistochemistry

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Our Dermatology Online

Case Report

Unusual presentation of cutaneous Leishmaniasis in pregnancy: A case report

Radia Chakiri[1], Salim Gallouj[1], Fatima Zohra Mernissi[1], Mouna Rimani[2]

[1]Department of Dermatology, Hassan II University Hospital, Fez, Morocco, [2]Center of Anatomopathology, Hassan, Rabat, Morocco

Corresponding author: Dr. Radia Chakiri, E-mail: r.chakiri.87@gmail.com

ABSTRACT

Cutaneous Leishmaniasis is a parasitic infection characterized by significant clinical variability. Unusual and atypical clinical aspects of infection have been reported in immunodeficient patients or associated with particular parasite species. We report a pregnant woman with unusual presentation of cutaneous Leishmaniasis.

Key words: Leishmaniasis; Skin, Pregnancy

INTRODUCTION

Worldwide, Leishmaniasis affects 112 million people in 88 countries, with a yearly incidence of 2 million cases [1]. The majority of these cases are cutaneous Leishmaniasis (CL), which is most common in adolescents and young adults from extremely poor rural areas [2,3].

Cutaneous Leishmaniasis (CL) is caused by a parasite from the genus Leishmania infection, and is transmitted to humans by the bite of female sand flies [4].

The clinical features of cutaneous Leishmaniasis (CL) may vary in terms of type and extension, ranging from single, chronic ulcerative lesions to disseminated nodular ones; however, several unusual and atypical clinical features of the disease have been reported in the literature [5-7].

Pregnancy is associated with an altered of human cell-mediated immuneresponse and an increased susceptibility to many infectious agents with atypical cutaneous presentation. Herein, we present a case of a particular clinical aspect of CT on the leg of a pregnant patient. The hypothesis of a possible role of pregnancy in this particular clinical presentation shall be discussed.

CASE REPORT

A 34-years-old woman,who was five months pregnant, lived in an area endemic for Cutaneous Leishmaniasis in northern Morocco; she was referred to our department because of a painful skin lesion that had been progressing for six months at the front of her right leg.

Dermatological examination showed that Tumoral and cauliflower-like lesion measured 10 cm long axis, adhered to deep planes and painful on palpation in the centerin the right leg (Fig. 1). It was thought to be Sarcoma, amelanotic melanoma, squamous cell carcinoma. The rest of the physical examination was unremarkable.

Histopathological examination of the biopsy obtained specimens demonstrated ulcerative changes and irregular acanthosis in the epidermis, namely, pseudoepitheliomatous hyperplasia. In dermis infiltration of lymphocyte, plasma cell and histiocyte with multinucleated Giant cell were shown. Leishman bodies were seen in (Fig. 2). With regards to the clinical and histopathological findings, the diagnosis of CL was made.

Complete biological tests were normal and HIV serology was negative for eliminating an immunosuppression.

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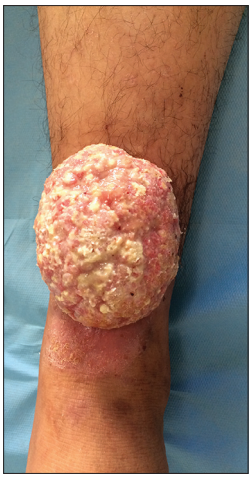

Figure 1: Cauliflower-like lesion of the right leg.

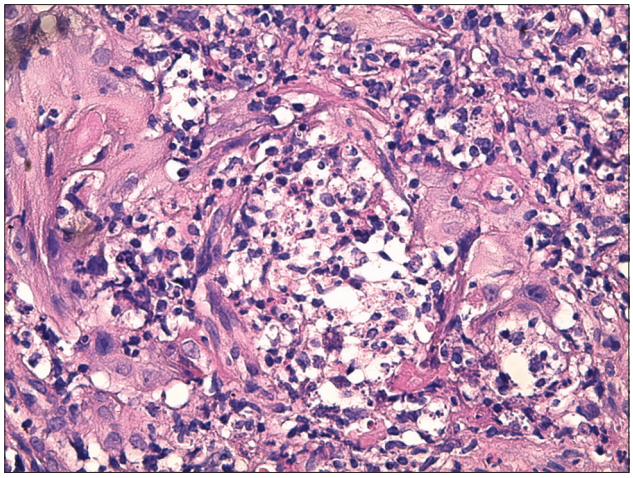

Figure 2: Leishman bodies.

The treatment consisted of surgical excision to relieve the patient because the pentavalent antimony is potentially abortogenic.

DISCUSSION

The term "Leishmaniasis" defines a group of vector-borne diseases caused by species of the genus Leishmania and characterized by a spectrum of clinical manifestations.

Parasite properties (infectivity, pathogenicity, and virulence), host factors, and host responses regulate heterogeneous disease expression [7].

The most common clinical form is the classical ulcer, with an indurate raised outer border and sharply incised central crater that usually self-heals over a period of months. The usual clinical presentations of Leishmaniasis are easily diagnosed by clinicians in endemic regions, but unusual forms may give rise to difficulties in the diagnosis and appropriate treatments. Cutaneous Leishmaniasis can produce a large variety of atypical and rare forms. There has been an increase in the number of papers reporting unusual clinical presentations, both for the Old and the New World [8-14].

In our Moroccan experience atypical and unusual clinical aspects of LC are observed especially with *Leishmaniatropica* [15].

This raises the question of the possible involvement of this species in our patient. For technical reasons, we did not perform the identification of the responsible strain.

Another factor that could be responsible for these particular clinical aspects would be pregnancy as in our case.

In contrast to the typical presentation of a well-demarcated ulcer with raised borders, CL during pregnancy is characterized by larger lesions with a highly atypical, exophytic appearance. As in our case, which raised concerns for other diseases, such as tuberculosis, chromomycosis or neoplasms? [3].

In a C57BL/6 mouse *L. major* model, larger CL lesions occurred during pregnancy, which correlated with decreased Th1 cytokine production [16]. The human cell-mediated immune response is altered during pregnancy [17], with an overcomepensation immediately after delivery.

The study of Conceição-Silva et al showed transient modulation of maternal immune responses during pregnancy as indicated by exacerbated cutaneous lesions, increased parasite burdens, and decreased levels of IFN-γ and NOS2 [18].

All hypotheses about the influence of pregnancy on the expression and evolution of CL converge to a possible decrease in the quality of the T-cell response against antigens of leishmaniasis during pregnancy. This immunodeficiency, possibly associated with other factors inherent in the host and parasite, could contribute to a change in the lesion appearance.

Treatment of pregnant CL patients is a debated issue [19-21], since there is no description of congenital infection, and many antileishmanial drugs, such as pentavalent antimony or miltefosine, are teratogenic [21,22]. Consequently, alternative therapies

should be evaluated in order to warrant safety and efficacy in this group of patients. Guimarães et al [23] showed that 40% of patients with atypical manifestation of CL were pregnant women and suggested that Amphotericin B should be considered as the drug of choice for all patients diagnosed with atypical CL. Intralesional treatment with meglumineantimoniate was successful in over 83% of patients treated who had contraindication to systemic therapy [24], but there is a lack of evidence demonstrating safety in pregnant women. As spontaneous healing has been reported to occur after delivery [25], several groups avoid the use of specific treatments and follow the patients by using local heating and/or antibiotic ointments to control lesion development and secondary infections. In our case surgery gave good results.

CONCLUSION

CL during pregnancy is characterized by larger lesions with a highly atypical exophytic appearance. No therapy is known to cure the disease during pregnancy, although postpartum cure has been found to be complete. CL during pregnancy has a notably different clinical presentation. It is important for physicians who are caring for patients in regions where the disease is endemic to recognize this presentation.

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Our Dermatology Online

Case Report

Metastatic melanoma masquerading as a furuncle

Imran Aslam[1], Jonathan Konopinski[2], Nasir Aziz[1]

[1]Department of Dermatology, Howard University, Washington D.C, USA, [2]Department of Pathology, George Washington University, Washington D.C, USA

Corresponding author: Dr. Imran Aslam, E-mail: iaslam@neomed.edu

ABSTRACT

Melanoma metastasizes to the skin in about 10-17% of patients. Although there are reports of metastatic melanoma masquerading as panniculitis and erysipelas, it is very uncommon for it to present as an inflammatory skin lesion. When malignant melanoma cells invade the superficial dermal lymphatic vessels it can result in erythema, edema and induration of the overlying skin. This presentation can be problematic for clinicians if they do not suspect melanoma and choose not to biopsy the lesion. We report a case of an elderly man with a history of invasive melanoma who presented with a furuncle-like lesion that was found to be in-transit metastatic melanoma.

Key words: Melanoma; In-transit metastasis; Furuncle

INTRODUCTION

Melanoma metastasizes to the skin in about 10-17% of patients. Although there are reports of metastatic melanoma masquerading as panniculitis and erysipelas, it is very uncommon for it to present as an inflammatory skin lesion. When melanoma cells invade the superficial dermal lymphatic vessels, they can cause erythema, edema and induration of the overlying skin. This presentation can be problematic for the clinician as a melanocytic neoplasm is rarely suspected. We report a case of an elderly man with a history of invasive melanoma who presented with a furuncle-like lesion that was found to be in-transit metastatic melanoma (ITM).

CASE REPORT

A 66 year-old Caucasian man presented with a 'boil' on his left leg. The spot had been present for about three months but was getting larger and painful 2-3 weeks prior to presentation. The patient denied any drainage, fevers, chills, or night sweats. His past medical history includes five primary melanomas, dysplastic nevi and multiple basal cell carcinomas. Of the five primary melanomas, three sites were invasive on the right chest, mid back and left calf, and the remaining sites were in situ on the left shoulder and left upper back. All of the melanomas had been excised prior to presentation. The invasive pT4b melanoma on the right chest was excised in June 2012 with wide local excision (unknown margins but histologically negative), and two sentinel lymph node biopsies (SLNB) taken from the right and left axillae were both negative for melanoma. The concerning spot on his left calf was close to a scar from an excised pT3b melanoma (stage IIB) that was ulcerated and had a depth of 3.8 mm and 12 mitotic figures. The leg melanoma was excised in August 2013 with a wide local excision (unknown margins but histologically negative), and two SLNB's were also taken from the left groin which were both negative for melanoma.

Examination of the left calf revealed a 2 cm round, fluctuant, tender, erythematous nodule without a central punctum located 4 cm from a large atrophic scar corresponding to the site of the prior excision (Fig. 1). There was no lymphadenopathy.

We used a 4 mm punch biopsy to make an incision and sent tissue for routine histology. The remaining purulent material was drained and cultured. Both gram stain and bacterial culture were negative. Histologic

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evaluation showed numerous atypical melanocytes that stained positive for S100 and HMB45, consistent with metastatic melanoma (Figs. 2 and 3).

Based on the diagnosis of in transit metastasis, the patient was upstaged to IIIC melanoma (T3bN2cM0). He was subsequently referred to medical oncology for further work up. Genetic testing of his melanoma revealed a BRAF wild-type, and a full body PET/CT scan detected bilateral pulmonary nodules, the largest of which was 1.1 cm located in the left upper lobe. The patient was subsequently started on the Bristol-Myers Squibb Early Patient Access protocol consisting of combination therapy with ipilimumab and novilumab. A restaging CT scan after cycle 4 demonstrated complete resolution of the pulmonary nodules. He was then continued on novilumab monotherapy for a total of 22 cycles. His treatment course was complicated by a variety of events including hypophysitis with adrenal insufficiency, transaminitis, sepsis and a defibrillator malfunction. Despite these setbacks, he was able to complete his immunotherapy regimen. Eighteen months after our discovery of the ITM, he is off treatment and his most recent restaging CT scans were negative.

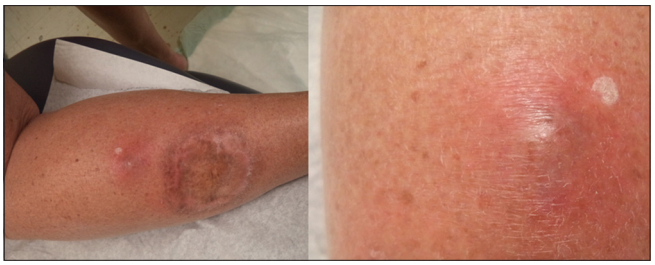

Figure 1: Left lower leg at initial presentation with close up view.

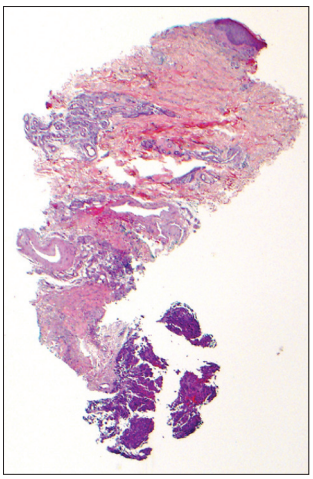

Figure 2: Skin, left lower leg, punch biopsy, low power: A basophilic nodule is seen in the reticular dermis at the base of the biopsy.

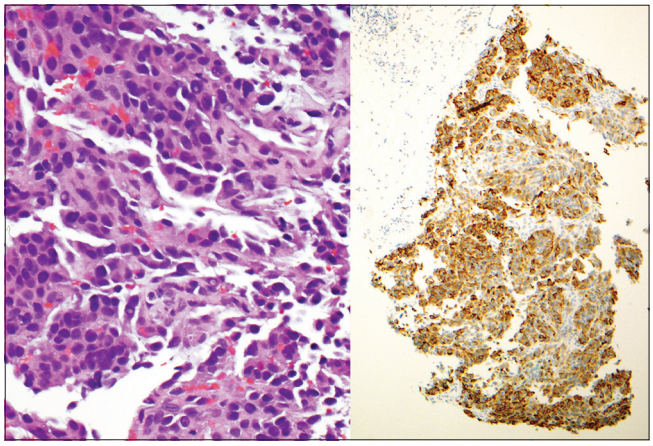

Figure 3: Skin, left lower leg, punch biopsy, immunohistochemistry/high power: High power: large pleomorphic epithelioid cells with hyperchromatic nuclei and conspicuous intranuclear inclusions. Immunohistochemistry: The atypical epithelioid cells are strongly positive for the melanocytic marker HMB 45.

DISCUSSION

Melanoma can be highly aggressive and metastasize to many organs including the gastrointestinal tract, liver, spleen, bone and brain. Prognosis is typically poor for patients with metastatic melanoma, but factors such as site of the first metastasis, number of metastatic sites and duration of remission variably affect prognosis [1]. Distant and visceral metastases have a worse prognosis than local soft tissue spread. Local soft tissue metastasis can be further categorized as satellite or in transit. Satellite metastases are located more than 0.05 mm but less than 20 mm from the primary lesion. In transit metastases or ITM's are located more than 20 mm from the primary lesion but not past the local lymph node basin [2]. Hence, our case illustrates an atypical presentation of ITM.

Although this specific presentation has yet to be described, several authors have documented unusual manifestations of ITM's. Shekhel et al described a case of ITM masquerading as lymphangietasis [3]. Similar to our case, the patient had a history of high risk melanoma in his lower extremity, and it was in this same leg where he developed his lymphangiectasis-like lesions. While ITM's can occur anywhere on the body, they have been noted to occur more frequently when the primary melanoma involves the lower extremity (19%) as opposed to other sites such as the head and neck (5%), trunk (9%), and upper extremity (8%) [4]. Also, ITMs on the extremities are associated with a better prognosis than ITMs on other sites [5].

Another unique presentation of ITM involved a 73-year-old female with a history of melanoma on her right achilles tendon who presented with a non-fluctuant erythematous plaque on her right anterior leg that clinically appeared to be panniculitis or cellulitis [6]. Once the lesion was biopsied and diagnosed as an ITM, she underwent a lymph node dissection of her groin that was also positive for melanoma. However, subsequent CT and PET scans of her chest, abdomen and pelvis were negative for any additional signs of metastatic disease, and the patient remained clinically stable without any additional symptoms.

Carcinoma erysipeloides or inflammatory carcinoma, is a condition in which an inflammatory response is triggered when malignant cells metastasize to superficial dermal lymphatic vessels resulting in erythematous plaques that resemble erysipelas. Although this phenomenon is most commonly seen in breast cancer, there are a handful of cases in which metastatic melanoma was the culprit [6-10]. One case involved an 87-year-old woman with a history of metastatic melanoma to the axillary lymph node who presented with inflammatory skin changes on her breasts. Her primary site of melanoma was unknown. The patient had tender, indurated, erythematous plaques involving both breasts without any underlying mass. Chest X-ray, mammogram and CT head were all unremarkable. A chest CT revealed enlarged axillary lymph nodes. A skin biopsy confirmed the diagnosis of inflammatory metastatic melanoma. In light of the patient's age and the extent of the area involved, no treatment was done per the family's request. At one month follow up, the patient remained asymptomatic and clinically stable [11].

Importantly, our patient had a negative SLNB at the time of the melanoma diagnosis on his calf. In patients with no clinical signs of nodal disease, the SLNB will detect nodal metastasis in 15-22% of cases [12]. The rate of ITM or local recurrence in patients with negative SLNB is reported around 4.8% [13]. While a negative SLNB is a good prognostic indicator, other factors such as primary tumor thickness and ulceration must be considered. Patients with negative SLNB and ulcerated primary tumor or increased Breslow thickness are at higher risk for in transit and distant recurrence as demonstrated in our patient [12,13].

Due to the paucity of case reports involving inflammatory metastatic melanoma, it would be premature to definitively comment on the prognostic implications of this rare presentation. However, it would be reasonable to assume this presentation is likely a poor prognostic indicator [11]. It is known for instance that inflammatory breast carcinoma portends a worse prognosis than other presentations of breast cancer, so inflammatory ITM may also follow similar suit. The few documented cases of inflammatory melanoma have occurred in the setting of fairly advanced disease. However, this could merely reflect the fact that authors are more likely to write case reports about metastatic melanoma rather than cases involving primary cutaneous disease. The prognosis of in-transit metastasis, regardless of inflammation, is considerably worse than local recurrence and is therefore classified as either stage IIIB or IIIC depending on lymph node involvement [14]. The 5 year survival rate for ITM has been reported to be 60.1% for skin metastasis only and 36.3% for skin and regional lymph node metastasis [15]. Despite the limitations, this case reinforces the importance of maintaining a strong degree of suspicion of inflammatory lesions located in the vicinity of high risk melanomas. We recommend practitioners to have a low threshold in biopsying such lesions.

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Our Dermatology Online

Case Report

Bowen's disease with multiple locations: Clinical presentation and therapeutic approach

Jean-Baptiste Andonaba[1], Nina Korsaga/Some[2], Boukary Diallo[1], Issouf Konate[1], Valentin Konsegre[3]

[1]Department of Dermatology and Venereology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Boni Nazi University of Bobo-Dioulasso, Higher Institute of Health Sciences (INSSA), Burkina Faso, [2]Department of Dermatology and Venereology Yalgado Ouédraogo University Teaching Hospital of Ouagadougou (CHUSS), Joseph Ki-Zerbo University of Ouagadougou, UFR/SDS Health Sciences (INSSA), Burkina Faso, [3]Department of Pathological Anatomy, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Boni Nazi of Bobo-Dioulasso (UPB), Higher Institute of Health Sciences (INSSA), Burkina Faso

Corresponding author: Prof. Jean-Baptiste Andonaba, E-mail: jb_andonaba@yahoo.fr

ABSTRACT

The Bowen's disease (MB), also known as squamous cell carcinoma in situ is a neoplastic skin disease that was clinically and histologically individualized by Darier in 1914. The isolated lesions in the majority of patients can be multiplied in 10 to 20% of cases. We report many locations which has posed problems of therapeutic choice. It is the case of a 35-year-old housewife, seen in consultation for red colored and squamous patches associated to pruritus and pain. On the skin, the examination found red colored and squamous patches, in projection, shaped rounded with a very slow evolution combining in a variable manner, rashes, scales, crusts and keratosis. Patches tended to grow progressively. The vulvar lesions were pigmented patches. In the mouth, we noted ulcers and a diffuse hypopigmentation with cheilitis, perlèche and odynophagia. The oncology checkup in search of another skin, mucosal and visceral cancer was done without any cancer found and the general condition was retained. The histopathology performed on two biopsies confirmed the diagnosis. Considering the spread of lesions and after a pretreatment evaluation, we put the patient under 5fluorouracil in cream on evening and under isotretinoin capsule with favorable evolution in the third week. The multiple sites of MB are rare but pose a management problem because of the evolutionary potential of each individual lesion in squamous cell carcinoma. The choice of treatment depends on the general condition of the patient, the expected efficacy of the treatment but also on its tolerance and cost.

Key words: Bowen's disease; Multiple locations; Symptoms; Treatment; Burkina faso

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Our Dermatology Online

Case Report

Maladie de Bowen à localisations multiples: présentation clinique et approche thérapeutique

Jean-Baptiste Andonaba[1], Nina Korsaga/Some[2], Boukary Diallo[1], Issouf Konate[1], Valentin Konsegre[3]

[1]Department of Dermatology and Venereology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Boni Nazi University of Bobo-Dioulasso, Higher Institute of Health Sciences (INSSA), Burkina Faso, [2]Department of Dermatology and Venereology Yalgado Ouédraogo University Teaching Hospital of Ouagadougou (CHUSS), Joseph Ki-Zerbo University of Ouagadougou, UFR/SDS Health Sciences (INSSA), Burkina Faso, [3]Department of Pathological Anatomy, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Boni Nazi of Bobo-Dioulasso (UPB), Higher Institute of Health Sciences (INSSA), Burkina Faso

Corresponding author: Prof. Jean-Baptiste Andonaba, E-mail: jb_andonaba@yahoo.fr

RESUMÉ

La maladie de Bowen (MB) est un carcinome in situ malpighien intra-épithélial relativement rare qui fut individualisée sur le plan clinico-histologique par Darier en 1914. Les lésions isolées chez la majorité des patients peuvent être multiples dans 10 à 20% des cas. Nous rapportons un cas à localisations multiples qui a posé des problèmes de choix thérapeutique. Il s'est agi d'une ménagère de 35 ans, vue en consultation pour lésions érythématosquameuses prurigineuses et douloureuses. Sur la peau, on retrouvait des plaques érythématosquameuses à peine saillante, discoïde avec une évolution très lente associant, de façon variable, un érythème, des squames croûtes et une kératose. Les lésions vulvaires pigmentées étaient en relief sous forme de plaques. Au niveau buccal on notait les lésions aphtoïdes et une leucoplasie diffuse avec chéilite, perlèche et odynophagie. Le bilan carcinologique à la recherche d'un cancer cutané, muqueux ou viscéral était sans particularité notable et l'état général était conservé. L'histopathologie réalisée sur deux biopsies a confirmé le diagnostic. Devant l'étendue des lésions et après un bilan préthérapeutique nous avons mis la patiente sous 5FU en crème le soir et sous isotrétinoïne gélule avec évolution favorable à la troisième semaine. Les localisations multiples de la MB sont rares mais posent un problème de prise en charge, compte tenu du potentiel évolutif de chaque lésion prise individuellement en carcinome épidermoïde. Le choix du traitement dépend de l'état général du patient, de l'efficacité attendue du traitement mais aussi de sa tolérance et son coût.

Key words: Bowen; Lésions multiples; Clinique; Traitement; Burkina faso

INTRODUCTION

La maladie de Bowen (MB) est un carcinome in situ malpighien intra-épithélial relativement rare. Décrite par John T. Bowen en 1912 qui avait déjà reconnu sa nature précancéreuse, elle fut ensuite individualisée sur le plan clinico-histologique par Darier en 1914. La MB atteint surtout l'adulte à tout âge. La courbe d'âge s'étale de 18 à 95 ans, avec une médiane à 65 ans. Les lésions peuvent être isolées ou multiples (10 à 20% des cas) [1]. Elle se présente sous forme de plaque persistante, progressive, plate, rouge, squameuse ou croûteuse induite par un carcinome intradermique et potentiellement maligne. Des cellules atypiques de l'épithélium malpighien prolifèrent dans la profondeur de l'épiderme. Les lésions peuvent se produire sur toute la surface de la peau ou sur les muqueuses. La MB peut progresser dans 3 à 5 p. 100 des cas en carcinome invasif, dans des délais très variables [2]. Elle s'associe volontiers à d'autres carcinomes cutanés (baso- ou spinocellulaires) [3]. Son caractère paranéoplasique comme marqueur de cancer viscéral associé est actuellement réfuté [4]. Les facteurs favorisants de maladie de Bowen sont: la lumière solaire, l'arsenic,

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l'immunosuppression, l'infection HPV [5]. Elle peut s'associer avec ou compliquer certaines dermatoses chroniques: lupus vulgaire, lupus érythémateux chronique. Nous rapportons un cas à localisations multiples posant le problème des indications des différents moyens thérapeutiques disponibles.

CASE REPORT

SN, 35 ans, ménagère a été vue en consultation pour lésions érythématosquameuses prurigineuses et douloureuses. L'évolution remonterait à trois mois marquée par la survenue de macules érythémateuses sur la région ombilicale qui se sont étendues secondairement sur le tronc, la région vulvaire et les quatre membres. Sur la peau, on retrouvait des plaques érythématosquameuses à peine saillante, discoïde avec une évolution très lente associant, de façon variable, un érythème, des squames croûtes et une kératose (Fig. 1a). À la palpation, les lésions étaient légèrement infiltrée, douloureuses avec signe de Nikolsky présent. Le prurit entraînait des exulcérations qui cicatrisaient pour laisser des cicatrices squameuses et pigmentées. Par endroits, les lésions de la peau prenaient un aspect annulaire et une évolution centrifuge. Les lésions vulvaires pigmentées étaient en relief sous forme de plaques (Fig. 2a). Au niveau buccal on notait les lésions aphtoïdes et une leucoplasie diffuse avec chéilite, perlèche et odynophagie. L'examen au spéculum n'a pas retrouvé une localisation de la maladie. L'histologie a montré un revêtement épidermique hyperkératosique parakératosique acanthosique, papillomateux et reposant sur une basale régulière. On observait au niveau du corps muqueux de Malpighi des cellules basophiles à noyaux élargis, hyperchromatiques et à nucléoles proéminents ainsi que des foyers de maturation kératosique (Fig. 3). Le bilan carcinologique à la recherche d'un cancer cutané, muqueux ou viscéral était sans particularité notable et l'état général était conservé. Devant l'étendue des lésions et après un bilan préthérapeutique nous avons mis la patiente sous 5FU en crème le soir et sous isotrétinoïne gélule (20 mg par jour). L'évolution a été favorable à la troisième semaine avec disparition de nombreuses lésions, blanchiments d'autres (Figs. 1b et 2b) et absence de nouvelles lésions et de signes fonctionnelles. Une surveillance mensuelle sous traitement a été instituée. Le pronostic chez notre patiente est bon au vu de la réponse thérapeutique sous cette bithérapie et l'absence d'un cancer associé.

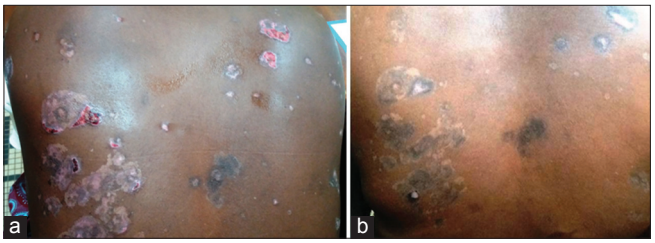

Figure 1: Lésions érythématosquameuses exulcérées par endroits, à contours polycycliques (1a). Evolution locale assez favorable après 3 semaines de traitement (1b).

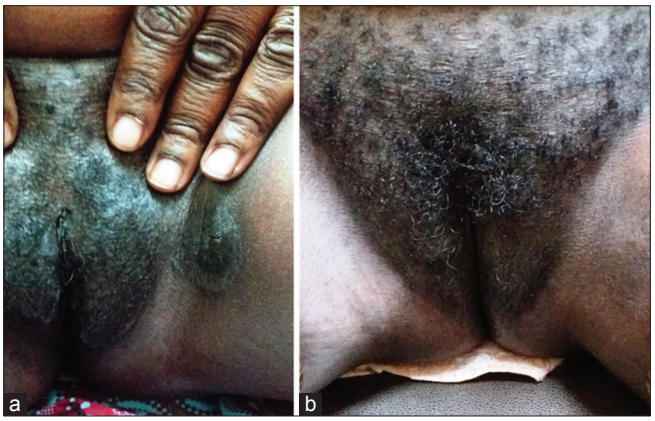

Figure 2: Lésions annulaires squameuses et hyperpigmentées sur l'aisne et la face externe des grandes lèvres (2a). Noter le nettoyage des lésions après 3 semaines de traitement (**2b**).

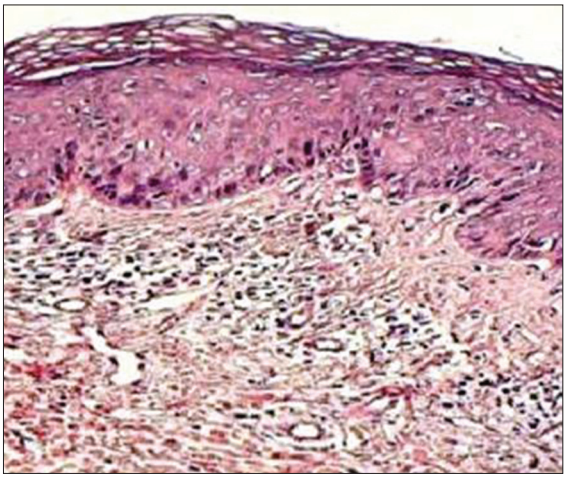

Figure 3: Images histopathologiques montrant une anarchie cellulaire et des atypies qui restent cantonnées à l'épiderme avec une basale épidermique respectée. On note un infiltrat inflammatoire du chorion.

DISCUSSION

Les formes multiples sont observées dans 10 à 20% des cas et les femmes sont les plus touchées [6]. La courbe d'âge s'étale de 18 à 95 ans, avec une médiane à 65 ans [1]. Notre cas remplissait tous les critères d'âge et de sexe. La MB atteint préférentiellement les zones photo exposées mais peut toucher n'importe

quelle zone de la peau, couverte ou non couverte et les muqueuses, surtout génitales. Les formes génitales touchent plus souvent l'adulte jeune avec une prédominance féminine [6]. Son diagnostic clinique peut être délicat surtout la forme génitale pigmentée observée dans notre cas et décrit par Bounouar et al. [7]. Cette difficulté diagnostique est accentuée par le fait que plusieurs maladies peuvent simuler une MB. Les diagnostics différentiels comprennent: le psoriasis, le lupus érythémateux, la verrue séborrhéique, la kératose actinique, le lichen verruqueux ou encore le carcinome basocellulaire superficiel. L'examen histopatologique est la clé du diagnostic de MB; elle montre des images habituellement caractéristiques. On note d'emblée une altération de la cellule malpighienne et une perte de l'architecture épithéliale normale cantonnée à l'épiderme. Cette anarchie cellulaire et les atypies restent cantonnées à l'épiderme et la basale épidermique est respectée comme dans notre résultat anatomopathologique. Il faut d'ailleurs s'assurer par des coupes sériées, surtout s'il existe une MB génitale, qu'il n'existe pas de rupture de la basale en aucun point du prélèvement. La maladie de Bowen peut progresser dans 3 à 5 p. 100 des cas en carcinome invasif, dans des délais très variables [2]. Elle s'associe volontiers à d'autres carcinomes cutanés (baso ou spinocellulaires) [3]. Ce qui justifie un bilan carcinologique qui peut revenir négatif comme dans notre cas (facteur de bon pronostic). Le traitement de choix reste l'exérèse chirurgicale précoce et complète, confirmée par l'examen histologique de la ou des lesions de MB compte tenu de son potentiel évolutif en carcinome spinocellulaire. La fréquence des récidives est environ de 5% pour les MB cutanées et de 10 % pour les localisations vulvaires si la marge d'exerce passe en peau saine. Au contraire, lorsque cette marge n'est pas atteinte, les récidives atteignent 50% dans les MB vulvaires. Cependant pour les localisations multiples comme dans notre observation, d'autres méthodes ont été proposées pour la destruction complète et précoce de la lésion de maladie de Bowen et le choix est fonction du type de lésion, du siège, de son évolution, de l'extension et du terrain. Il s'agit des agents antimitotiques locaux, de la radiothérapie, de la cryothérapie, du curetage-électrodessiccation, du laser, de la thérapie photodynamique et autres moyens thérapeutiques. L'étrétinate, l'isotrétinoïne et les interférons α et γ ont été essayés en cas de lésions multiples et surtout vulvaires associées à des lésions cervicales dysplasiques, sans que leur efficacité soit suffisante [8]. Dans la littérature, il n'existe actuellement pas d'essais cliniques contrôlés, randomisés entre notamment l'approche chirurgicale, les traitements topiques et la Mal-PDT (utilisation de l'aminolevulinate de méthyle ou MAL comme sensibilisateur associé à une thérapie photodynamique). Ceci est rappelé dans la méta-analyse publiée en 2013 et qui souligne que très peu de données méthodologiquement correctes sont publiées pour les approches chirurgicales et traitements topiques de la MB [9]. Concernant la Mal-PDT, en terme de clearance tumorale, elle parait significativement plus efficace que la cryothérapie, en revanche, il n'y a pas de différence statistiquement significative quand la PDT est comparée aux applications locales de 5-FU. De même cette méta analyse ne retrouve pas de différence statistiquement significative quand la cryothérapie est comparée aux applications locales de 5-FU. Nous avons choisi d'associer des applications locales de 5-FU + isotrétinoïne orale avec de bons résultats à la troisième semaine.

CONCLUSION

Les localisations multiples cutanéomuqueuses de la MB sont rares mais posent un problème de prise en charge, compte tenu du potentiel évolutif de chaque lésion prise individuellement en carcinome épidermoïde. Le choix du traitement dépend d'un certain nombre d'éléments comme: l'état général du patient, l'accès du patient et du praticien à tel ou tel type de traitement, l'observance du patient, l'efficacité attendue du traitement mais aussi sa tolérance et son coût. L'association 5-FU + isotrétinoïne s'est révélée à court terme efficace dans chez notre patiente avec des localisations multiples. Quelle que soit la méthode choisie, une surveillance régulière à vie du patient s'impose, afin de dépister précocement les récidives ou l'apparition d'une autre tumeur cutanée maligne non mélanocytaire notamment. Des travaux récents ont montré que la MB n'est pas un marqueur de cancer solide. Il n'est donc pas justifié de pratiquer des bilans répétés, traumatisants et coûteux, à la recherche d'un cancer viscéral chez les patients traités pour une MB.

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Our Dermatology Online

Case Report

Acquired elastotic hemangioma: A diagnosis to keep in mind

Sarra Ben Rejeb[1], Ines Chelly[1], Alia Zehani[1], Beya Chelly[1], Slim Haouet[1], Mourad Mokni[2], Nidhameddine Kchir[1]

[1]Pathology Department, Rabta Hospital, Bab saadoun, Tunisia, [2]Dermatology Department, Rabta Hospital, Bab saadoun, Tunisia

Corresponding author: Dr. Sarra Ben Rejeb, E-mail: *sarrabenrejeb88@yahoo.fr*

ABSTRACT

Acquired elastotic hemangioma is a relatively newly described cutaneous lesion that presents a characteristic clinicopathologic feature and which should be distinguished from other cutaneous vascular proliferations. Only 10 cases have been reported in literature. We herein describe another case of acquired elastotic hemangioma occurring in the cheek of a 64 year old woman.

Key words: Elastosis; Hemangioma; Basal cell carcinoma; Vascular

INTRODUCTION

Acquired elastotic hemangioma is a recently identified variant of hemangioma, firstly reported in 2002 by Requena et al [1]. Characteristically it is described as a slow growing, solitary erythematous, well defined and asymptomatic plaque which usually develops on sun damaged skin of upper extremities lesion. We herein report another case of acquired elastotic hemangioma occurring of the face.

CASE REPORT

A 64-year-old woman presented with an asymptomatic, erythematous slowly growing nodule of the cheek. Her family and medical history were unremarkable. Physical examination revealed erythematous, well-defined, non tender, slightly elevated, non blanching plaques of the right cheek. It measured 0.7cm in diameter. The suggested clinical diagnosis was basal cell carcinoma. Local surgical excision of the lesion was performed. Histopathologic examination revealed a band-like proliferation of capillary blood vessels involving mainly the superficial dermis and arranged parallel to the epidermis. No cytologic atypia or mitotic figures were seen. The neoformed capillaries were surrounded or intermingled with collagen bundle showing intense solar elastosis (Figs. 1 - 3). Inflammation was absent. On immunohistochemichemistry, the neoplastic endothelial cells of the neoformed capillaries were strongly positive for CD34 (Fig. 4). No staining with HHV8 was found. A peripheral ring of actin-positive (Alpha smooth muscle) pericytes were observed (Fig. 5).

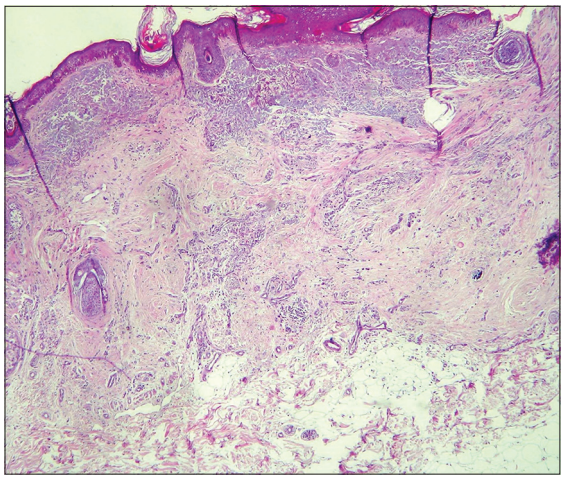

Figure 1: Band-like proliferation of capillary blood vessels intermingled with intense solar elastosis (HE x 100).

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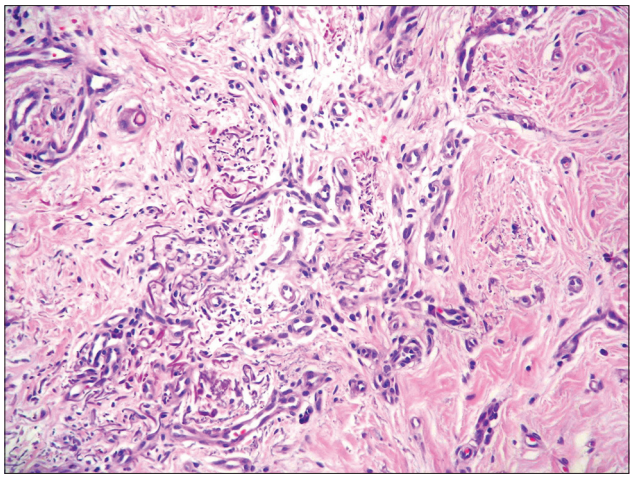

Figure 2: Proliferation of small blood vessels bordered with regular endothelial cells and surrounded by collagen bundle showing intense solar elastosis (HE x 200).

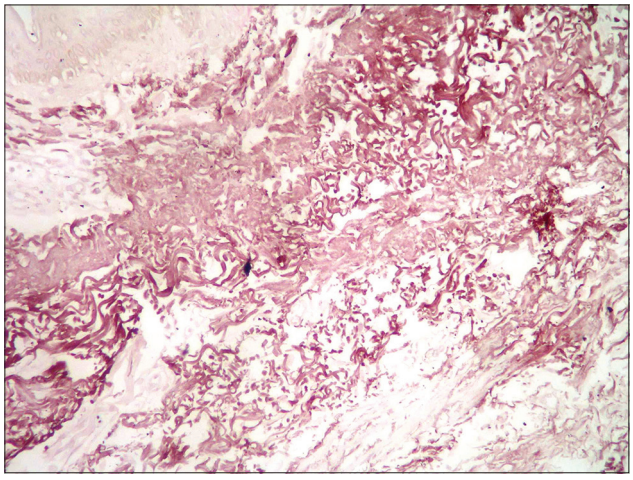

Figure 3: Elastosic collagen bundles (orcein coloration X 200).

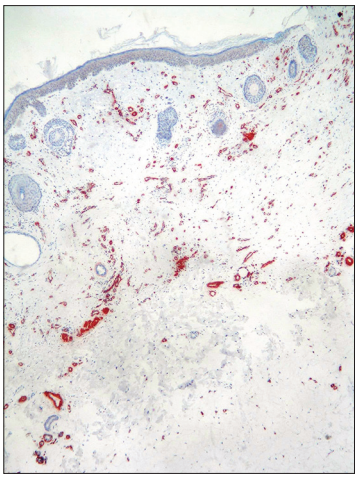

Figure 4: Positive staining of endothelial neoplastic cells for CD34 (IHC x200).

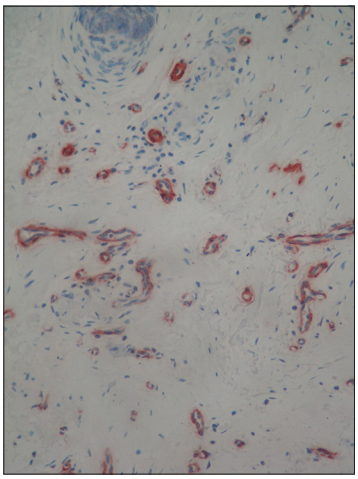

Figure 5: Positive staining of pericytes for alpha-smooth muscle (IHC x 400).

The diagnosis of acquired elastotic hemangioma was favored.

DISCUSSION

Acquired elastotic hemangioma (AEH) is a recently proposed entity described by Requena et al [1] and since there only 10 cases have been reported in litterature. A distinctive clinicopathological presentation allowed the authors to consider this condition as a separate entity [1-2]. This lesion classically occurs in middle aged or elderly women with the mean age of 64 years. Clinically, it presents as an irregularly shaped, slowly growing, well defined, non-blanching, erythematous to violaceous plaque, ranging from 2 to 5cm in diameter [1]. Generally the lesions are asymptomatic, but occasionally can be painful. They show a strong predilection for the extensor surfaces of the forearms, but may also be found on the lower lip, shoulder, nose, and neck [2]. Clinically, aquired elastotic hemangioma may be confused with a superficial basal cell or Bowen's disease [1]. Histologically, the classic finding is a band-like proliferation of capillary blood vessels arranged parallel to the epidermis and confined to the superficial dermis [3]. The vessels contain well formed round or elongated lumens lined by a single layer of monomorphous endothelial cells without any atypia or mitosis surrounded with a layer of pericytes. The capillary proliferation is separated from the epidermis by a zone of non involved papillary dermis. The epidermis is unremarkable or atrophic. The most attractive feature is the intense accompanying solar elastosis which is surrounding or intermingled with the capillaries [1-3]. Immunohistochemical studies demonstrated the endothelial nature of the neoplastic cells which are usually positive for CD31

and CD34 markers. The capillaries have a peripheral ring of actin-positive pericytes [1]. Acquired elastotic hemangioma was initially thought to be a true vascular tumor, however research has recently proposed a lymphatic origin after noting expression of D2-40 [2]. Proliferating markers Ki-67 and MPM2 stain only a few nuclei of the endothelial cells of the vessels [1,4]. Histopathologic differential diagnoses of AEH include cutaneous capillary proliferations that develop during adulthood, namely Mali's acroangiodermatitis, cherry angioma, acquired tufted hemangioma, hobnail hemangiomas and early Kaposi's sarcoma with a predominant angiomatous pattern. Kaposi's sarcoma histologically exhibits jagged, vascular spaces lined by thin endothelial cells with a lymphoplasmacytic infiltrate, red blood cell extravasation and positive staining for HHV8. An acquired tufted angioma shows a "cannon-ball" histopathological pattern with lobules of capillary tufts scattered in the dermis and subcutaneous fat. A targetoid hemosiderotic hemangioma displays dilated vascular spaces in the superficial dermis, lined by prominent hobnail endothelial cells and anastomosing collagen bundles with hemosiderin deposits [1]. The band-like capillaries arranged along the superficial dermis with solar elastosis is a unique feature characterizing acquired elastotic hemangioma. The etiology is still unknown, but the finding of solar elastosis supports the role of sun damage as an inciting cause. In most cases, there is no history of previous trauma. In all reported cases, acquired elastotic hemangioma behaves in a benign fashion [1-4].

CONCLUSION

Acquired elastotic hemangioma is a benign, asymptomatic lesion which commonly occurs on sun damaged skin. Treatment is unnecessary, but because of its misleading clinical presentation, a surgical excision is usually performed.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from the patient for publication of this article.

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Our Dermatology Online

Case Report

A rare cutaneous tumor: Dermatofibrosarcoma protuberans

Nuran Alli[1,2], Ahu Yorulmaz[2], Huseyin Ustun[3]

[1]Department of Dermatology, Kafkas University School of Medicine, Kars, Turkey, [2]Department of Dermatology, Ankara Numune Research and Education Hospital, Ankara, Turkey, [3]Department of Pathology, Kafkas University School of Medicine, Kars, Turkey

Corresponding author: Dr. Ahu Yorulmaz, E-mail: ahuyor@gmail.com

ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a rare indolent cutaneous tumor which has been considered as a low-grade dermal and subcutaneous fibrohistiocytic neoplasm. DFSP expands slowly but recurs frequently leading to the general assumption that DFSP is a locally aggressive neoplasm. This low-grade/borderline tumor which is generally found on trunk and proximal extremities of adults has limited potential for metastasis. Clinical presentation is usually typical with a red-brown or skin coloured indurated plaque with multiple nodules or protuberances. Histopathology of DFSP is also characteristical which demonstrates storiform pattern of uniform spindle cells infiltrating deep into the subcutaneous fat tissue constituting honeycomb appearence. Here, we report a case of DFSP in a 50-year-old woman who presents with a twenty year history of slowly growing mass on her left femoral area.

Key words: Dermatofibrosarcoma protuberans; Fibrohistiocytic; Spindle-shaped

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare low-grade soft tissue sarcoma, which usually tends to be localized though frequently exhibits signs of recurrence. Seldomly metastasizing, its locally aggressive behavior has been attributed to its tendency to multiple recurrences. Although it may arise anywhere on the body, typical site of involvement is the trunk and proximal extremities. DFSP is also an exceptional dermatological disease in that it is associated with a genetic translocation involving chromosomes 11 and 22 [t(17;22) (q22;q13)] [1-5].

CASE REPORT

A 50-year-old woman was admitted to our outpatient clinic with a twenty year history of slowly growing mass on her left femoral area. Her past and family history were unremarkable. Upon dermatological examination we observed a peripherally erythematous, centrally violaceous indurated plaque with multiple nodules or protuberances on her left femoral area (Fig. 1). Histopathological examination of lesional skin biopsy demonstrated storiform pattern of uniform spindle cells infiltrating deep into the

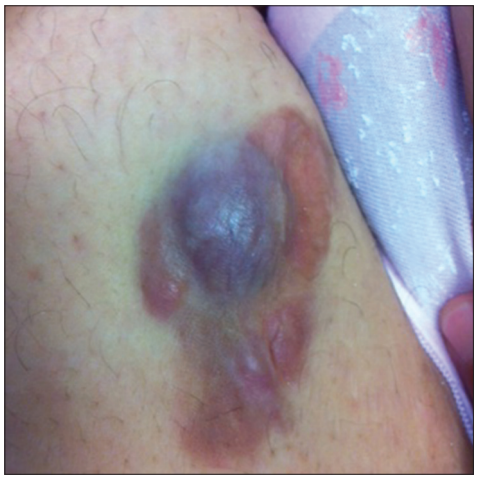

Figure 1: Peripherally erythematous, centrally violaceous indurated plaque with multiple nodules or protuberances on left femoral area.

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subcutaneous fat tissue constituting honeycomb appearance (Figs. 2 and 3). Immunohistochemically tumor cells stained positively for CD34, negatively for CD68 and 5% positively for Ki67 (Fig. 3). Based on history, clinical and histopathological findings, we made a diagnosis of DFSP and the patient was referred to general surgery and medical oncology departments for the complete excision of the tumor and follow-up of the patient.

DISCUSSION

Dermatofibrosarcoma protuberans (DFSP) is a rare monoclonal mesenchymal sarcoma. It differs from most of the soft tissue tumors because of the fact that it is indeed slowly progressive, locally aggresive tumor and has a high rate of recurrence rates after surgical treatment. DFSP is a rare tumor, its exact incidence is not known [1-5]. Recently it has been reported that the overall incidence of DFSP in United States is 4.1 per million person-years [6].

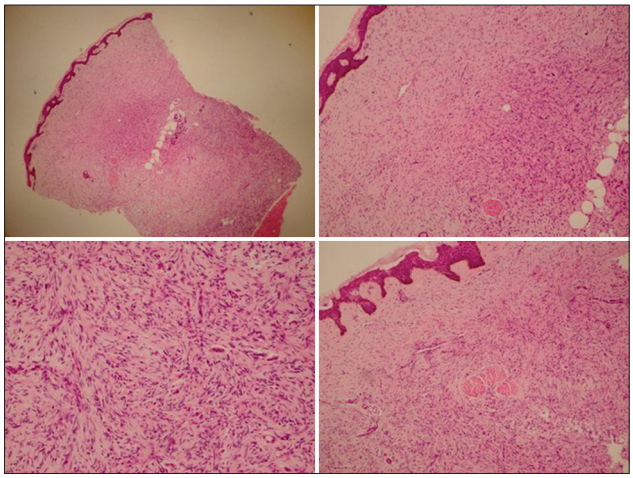

Figure 2: Histopathological features of the neoplasm demonstrating storiform pattern of uniform spindle-shaped cells with eosinophilic cytoplasm and hyperchromatic nuclei infiltrating deep into the subcutaneous fat tissue constituting honeycomb appearance (from left top to right bottom; H&E x10, x20, x40, x20).

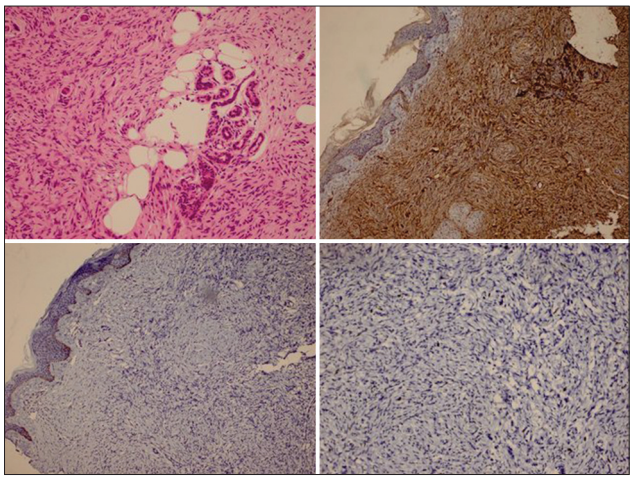

Figure 3: Histopathological features of the neoplasm demonstrating neoplastic cells infiltrating fat tissue (H&E x40, left top). Immunohistochemistry findings; tumor cells stained positively for CD34 (right top), negatively for CD68 (left bottom), 5% positively for Ki67 (right bottom).

We present this case because of the rare reported cases of DFSP in the literature. Our patient manifested typical features of DFSP, in that her history, clinical and histopathological findings were all consisted with the characteristics of DFSP. It is known that DFSP is generally located on trunk, however lower extremities are the second most common localization for DFSP [3]. Moreover, proximal regions of the limbs are more favored [4] as in our case. DFSP usually starts with one or more small, firm, flesh-coloured or pink-red dermal nodules. Over a period of time, these nodules coalesce and the tumor turn into a indurated, hard plaque with multiple nodules or protuberances. A rapid growth phase has been described, which is the time that the tumor enters an accelerated expansion period. As the tumor enlarges, a dusky-reddish blue discoloration surrounding the lesion appears. Most of the time initially painless lesion turn out to be a painful tumor. Moreover, ulceration along with discharge have been described for DFSP [1-4].

The lesion of our case also manifests typical histopathological features of DFSP. It is known that DFSP has a distinctive histologic appearance. In DFSP, the dermis and subcutaneous tissue are replaced by bundles of uniform, spindle-shaped cells. Tumor cells infiltrate and merge into the deeper dermis forming bands, in which this histopathological entity is called as storiform pattern. Immunhistochemical studies can be helpful in making the diagnosis of DFSP. In our cse, immunohistochemically tumor cells stained positively for CD34, negatively for CD68 and 5% positively for Ki67, which support the diagnosis of DFSP.

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Our Dermatology Online

Case Report

Primary cutaneous leiomyosarcoma revealed by soft tissue tumor recurrence

Jean-Baptiste Andonaba[1,4], Ollo Rolland Some[2,4], Bakary Gustave Sanon[3,4], Boukary Diallo[1,4]

[1]Department of Dermatology and Venereology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [2]Department of Surgical Oncology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [3]Department of General and Visceral Surgery, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [4]Polytechnic University of Bobo-Dioulasso (UPB), Higher Institute of Health Sciences (INSSA), Burkina Faso

Corresponding author: Prof. Jean-Baptiste Andonaba, E-mail: jb_andonaba@yahoo.fr

ABSTRACT

Background: Primary cutaneous leiomyosarcoma (LCP) is a malignant tumor that can originate from smooth muscles (hair arrestor or vessels of hypodermic tissue). Recidivism rates vary by type. We report two particular cases by the volume of their recidivism and to underline the difficulties of management. **Observations:** ZA, 41 years old, was received after surgery for a voluminous, painless, firm, mobile and ovoid mass of 7 cm on the knee. The tumor occupied mainly the superficial and reticular dermis. It did not have immunohistochemistry but a re-reading of the blade concluded at diagnosis. The assessment of the extension did not objectify anything and the patient lost sight of. KM, 36 years was received 3 months after surgery, under the same conditions for a voluminous ulcerous burgeoning tumor, oblong 9 cm long axis of the shoulder curve. The histopathological lesions were extended to the subcutaneous tissue. The extension report showed lymphadenopathy, hepatic and pulmonary metastases. The patient underwent clean surgery associated with adjuvant chemotherapy. **Conclusion:** These relapses have no reliable information on the prognostic factors of their initial management. Nevertheless, the major factor of recurrence remains the tumor clearance, probably not obtained during the first excision. Close multidisciplinary collaboration is essential for the appropriate management of LCP.

Key words: Cutaneous leiomyosarcoma; Surgery; Recurrence

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Our Dermatology Online

Case Report

Léiomyosarcomes cutanés primitifs révélés par une récidive tumorale des tissus mous

Jean-Baptiste Andonaba[1,4], Ollo Rolland Some[2,4], Bakary Gustave Sanon[3,4], Boukary Diallo[1,4]

[1]Department of Dermatology and Venereology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [2]Department of Surgical Oncology, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [3]Department of General and Visceral Surgery, Sourô Sanou University Teaching Hospital of Bobo-Dioulasso (CHUSS), Burkina Faso, [4]Polytechnic University of Bobo-Dioulasso (UPB), Higher Institute of Health Sciences (INSSA), Burkina Faso

Corresponding author: Prof. Jean-Baptiste Andonaba, E-mail: jb_andonaba@yahoo.fr

RESUMEN

Background: Le léiomyosarcome cutané primitif (LCP) est une tumeur maligne qui peut provenir des muscles lisses (arrecteur poil ou vaisseaux du tissu hypodermique). Les taux de récidive varie selon le type. Nous rapportons deux cas particuliers par le volume de leur récidive et pour souligner les difficultés de prise en charge. **Observations:** ZA, 41ans, a été reçue après chirurgie initiale pour une volumineuse masse indolore, ferme, mobile et ovoïde de 7cm sur le genou. La tumeur occupait principalement le derme superficiel et réticulaire. Il n'a pas eu d'immunohistochimie mais une relecture de la lame a conclu au diagnostic. Le bilan d'extension n'a rien objectivé et la patiente perdue de vue. KM, 36ans a été reçu 3mois après une chirurgie, dans les mêmes conditions pour une volumineuse tumeur ulcérobourgeonnante, oblongue de 9cm de grand axe du galbe de l'épaule. Les lésions histopathologiques s'étendaient jusqu'au tissu sous-cutané. Le bilan d'extension a montré des adénopathies et des métastases hépatiques et pulmonaires. Le patient a subi une chirurgie de propreté associée à une chimiothérapie adjuvante. **Conclusion:** Il s'agissait de récidives sans informations fiables sur les facteurs pronostiques de leur prise en charge initiale. Néanmoins le facteur majeur de récidive reste la clairance tumorale, probablement non obtenue lors des premières exérèses. Une étroite collaboration multidisciplinaire est indispensable pour la prise en charge adaptée des LCP.

Key words: Léiomyosarcome cutané; Chirurgie; Récidive

INTRODUCION

Le léiomyosarcome cutané primitif (LCP) est une tumeur maligne rare. Il représente 2 à 3% de l'ensemble des sarcomes des tissus mous [1]. Ils peuvent provenir du muscle lisse arrecteur du poil à l'origine du léiomyosarcome dermique encore appelée léiomyosarcome cutané ou des muscles lisses des vaisseaux du tissu adipeux donnant le léiomyosarcome sous cutané ou hypodermique. Les taux de récidive, métastase et mortalité sont moindres pour le premier type selon plusieurs études rétrospectives et les revues de cas [2]. Si les données sont peu fréquentes dans la littérature du fait de la rareté de ce cancer cutané, elles sont inexistantes en Afrique subsaharienne. Nous rapportons deux cas particuliers par le volume de leur récidive pour rapporter les difficultés diagnostiques et les facteurs de récidive monstrueuse.

CASE REPORT

ZA, ménagère de 41 ans, 2 mois après chirurgie exérèse a été reçue dans notre service pour une volumineuse

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masse indolore ferme ovoïde de 7 cm de grand diamètre sur le genou mobile par rapport au plan profond (Fig. 1). L'histopathologie a montré des lésions avec un modèle de croissance nodulaire. La tumeur était confinée à la peau et occupait principalement le derme superficiel et réticulaire. Il n'a pas eu d'immunohistochimie mais une relecture de la lame a conclu au diagnostic. Le bilan d'extension ne retrouvait pas de métastases. La patiente a été perdue de vue.

KM, ouvrier de 36 ans a été reçu 3 mois après une chirurgie pour tumeur ulcérée dans les mêmes conditions que le premier cas pour une volumineuse tumeur oblongue de 9 cm de grand axe du galbe de l'épaule présentant une zone de 3cm X 4cm, ulcérobourgeonnante (Fig. 2). La masse est aussi mobile par rapport au plan profond. Les lésions histopathologiques avaient un aspect comparable à celles du premier cas avec un siège dépassant le derme superficiel et réticulaire pour atteindre le tissu sous-cutané. Le bilan d'extension comportant une radiographie thoracique et une échographie abdomino-pelvienne a montré des adénopathies et des métastases hépatiques et pulmonaires. La patiente a subi une chirurgie de propreté associée à une chimiothérapie adjuvante à base de la doxorubicine et sels de platines et confié à un réseau de soins palliatifs.

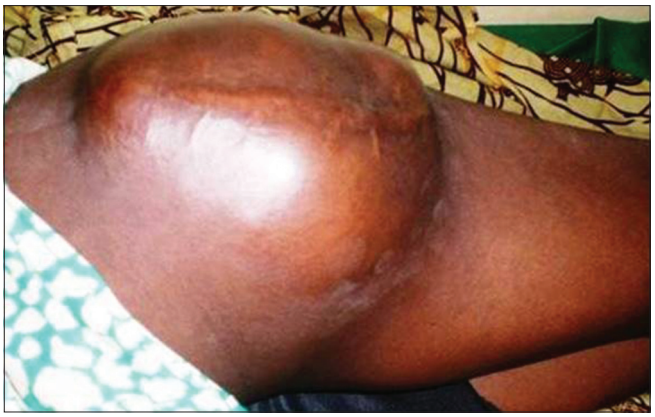

Figure 1: Récidive d'un léiomyosarcome du genou.

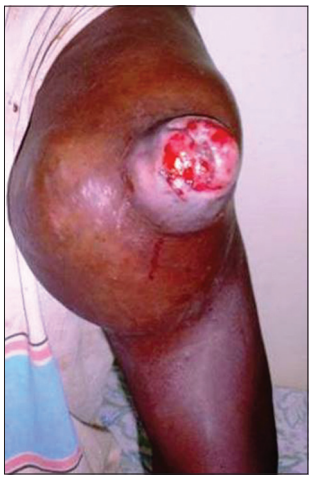

Figure 2: Récidive d'un léiomyosarcome de l'épaule: tumeur ulcérobourgeonnante.

DISCUSSION

Peu de cas de LCP sont rapportés notamment les cas de récidive dont les facteurs sont intimement liés à la clairance tumorale lors de la chirurgie initiale. LCP est le troisième cancer après l'histiocytofibrome fibreux malin et le liposarcome [3]. La tumeur survient généralement entre 50 et 70 ans avec une prédominance masculine [1,5]. Nos cas avaient un âge plus jeune (36 ans et 41ans), situation retrouvée dans les séries d'Auroy, Bernstein et al. [4,6]. L'aspect clinique n'est pas spécifique avec une large gamme de diagnostics différentiels: le carcinome à cellules squameuses, le mélanome achromique, et le carcinome baso-cellulaire [7]. Le LCP est généralement considérée comme un nodule solitaire; le nodule peut être lobulé, pédiculée ou ombiliquée avec une surface qui peut être lisse, indurée, ulcérée, écailleuse, verruqueux ou hémorragique [8]. Nous avons observé le caractère solitaire, nodulaire à surface lisse et ulcérée. C'est une masse à croissance rapide et le pronostic est sombre si la masse > 5 cm [8]. Pour nos deux cas les tailles sont volumineuses peu rencontrés dans la littérature même en cas de récidive. De plus une pseudocapsule inflammatoire fibreuse constitue une fausse limite qui trompe les opérateurs les moins avisés [9]. Ces cas illustrent la difficulté de définir avec précision les limites de la tumeur sur la base de l'imagerie seule et la clinique. Nos deux observations constituent des cas de récidive sans qu'on puisse avoir des données fiables sur les facteurs pronostiques de leur prise en charge initiale. Néanmoins le facteur majeur de récidive reste la clairance tumorale qui n'a pas pu être probablement obtenu lors de premières exérèses. Les conditions de leurs réalisations à savoir dans les structures sanitaires périphériques par des agents de santé moins qualifiés en chirurgie cancérologique expliquent leur exérèse par énucléation. Alors que l'on sait que le risque de réchute n'est pas nul même en cas de resection R0 des LMS dermiques qui récidivent peu [10]. C'est peut être ce qui explique que certains auteurs militent pour un une exérèse large avec 3-5 cm de clairance tumorale et une profondeur qui comprend le tissu sous-cutané et le fascia [11]. Cependant devant la localisation au

niveau des extrémités et dans le souci de préserver le maximum de tissu sain certaines études rétrospectives récentes [2,10] et une métaanalyse [12] prône une marge d'au moins 1cm pour réduire considérablement le risque de récidive locale et à distance. L'excision locale sans marges adéquates conduit à la récidive et augmente le risque de maladie métastatique et de mortalité. Nous notons un cas de métastase ganglionnaire et hépatique chez le cas de leiomyosarcome sous cutané. En effet ce risque semble plus élevé indépendamment de la marge de résection, sur les tumeurs sous cutanées [2]. La chirurgie avec un examen extemporané histologique des limites permet d'éviter des marges de résection proches de la tumeur [9]. Cependant l'extemporané n'est pas une recommandation car peu fiable dans les sarcomes. Un autre procédé de traitement est une opération micrographique de Mohs pour assurer l'élimination complète de la tumeur [13] qui serait plus indiqué sur des tumeurs initiales de petites tailles et/ou de localisation préjudiciable pour des exérèses larges. Il nécessite une pratique courante pour la lecture microscopique. Pour nos cas de récidive la taille et l'existence de métastases dans un cas et l'inexpérience de la pratique constituent individuellement des contre –indications. La Cryochirurgie a également été utilisée chez des patients âgés. Les thérapies adjuvantes comprennent la radiothérapie, la chimiothérapie et la thérapie de cobalt supervoltage [8]. Cependant le LCP a été rapporté comme radiorésistante; également la chimiothérapie avec la doxorubicine a échoué dans certains cas [1]. Si les léiomyosarcomes cutanées sont reconnus avec un taux de récidive locale de 30-50% et rarement métastaser, les léiomyosarcomes sous-cutanées se reproduisent dans un maximum de 70% et le taux métastatique a été rapportée chez 30-40% des cas selon certains auteurs [14].

CONCLUSION

Les récidives locales et les métastases à distance peuvent survenir des mois ou années après l'excision initiale. La corrélation anatomoclinique et immunohistochimie sont obligatoires pour le diagnostic définitif. L'importance des besoins en suivi à long terme doit être soulignée pour les LCP. Une étroite collaboration entre dermatologues, chirurgiens, cancérologues et pathologistes est indispensable pour la prise en charge adaptée de cette affection au CHU Sourô Sanou de Bobo-Dioulasso.

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Our Dermatology Online

Case Report

Rapidly enlarging giant facial mass: Initial presentation of blastic plasmacytoid dendritic cell neoplasm

Gulsen Akoglu[1], Sibel Orhun Yavuz[2], Aydan Kilicarslan[2], Tekin Guney[3]

[1]Department of Dermatovenereology, Ankara Ataturk Training and Research Hospital, Ankara, Turkey, [2]Department of Pathology, Ankara Ataturk Training and Research Hospital, Ankara, Turkey, [3]Hematology Clinics, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

Corresponding author: Dr. Gulsen Akoglu, E-mail: gusemd@yahoo.com

ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological malignancy characterized by proliferation of plasmacytoid dendritic cell precursors. Herein, we describe a 65-year-old male presented with a 6 month history of a progressively enlarging purple mass over his forehead. The histopathological examination revealed non-epidermotropic, dermal, and subepidermal homogeneous infiltration with moderate-sized cells resembling lymphoblasts or myeloblasts. The neoplastic clone diffusely stained positive with CD4 and CD56. They were negative for CD3, CD20, pax-5, CD30, myeloperoxidase, and TdT. Rearrangement studies for T and B cell receptor were negative. Ki-67 proliferation index was 80%. Involvement of multiple lymph nodes was detected. Bone marrow biopsy was normal. The patient was put on six cycles of R-CHOP chemotherapy which was successfully cleared all lesions. A rapid recurrence was observed after 1.5 months. While being prepared for autologous stem cell transplantation, the patient died due to rapidly onset myelosuppression and systemic infections. In conclusion, BPDCN should be in the clinical and histopathological differential diagnosis of rapidly developing tumoral cutaneous lesions. Early diagnosis is important to initiate aggressive treatments in BPDCN, in which skin involvement is very frequent.

Key words: Blastic plasmacytoid dendritic cell neoplasm; Differential diagnosis; Skin; Therapy

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological malignancy. The disease was named as CD4+/CD56+ hematodermic neoplasm or NK cell lymphoma until immunophenotypic and gene expression features of the neoplastic cells showed the resemblance of plasmacytoid dendritic cells (pDC) [1].

BPDCN usually occurs in elderly, especially in men, with a mean age of 60-70 years. The prognosis is poor. Skin involvement is usually present at the diagnosis [2]. Herein, we report an elderly patient having a diagnosis of BPDCN and details of clinicopathological features and the follow up observations.

CASE REPORT

A 65-year-old male presented with a 6 month history of an enlarging purple mass over his forehead. He had undergone a skin biopsy in another health centre before and diagnosed as having atypical T cell infiltration. He was referred us for advanced investigations. The patient was on antihypertensive treatment and he had a 45-pack year history of smoking. In the initial dermatological examination, a 5x4 cm sized and 1 cm elevated firm, purplish mass with overlying telangiectasias and a small crust were observed on the forehead. The otherwise body skin was normal. Organomegaly was not detected. Multiple firm and immobile lymphadenopathies largest measuring 3x3 cm in size were palpated over right cervical area. An incisional skin biopsy was performed

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from the cutaneous lesion. After obtaining skin biopsy, multiple erythematous nodules and plaques with a diameter ranging from 0.5 to 1.5 cm developed and facial lesion progressively enlarged up to 14 x 12 cm within 2 weeks (Figs. 1 and 2).

The histopathological examination of the forehead and trunk lesions revealed non-epidermotropic, dermal, and subepidermal homogeneous infiltration with moderate-sized cells resembling lymphoblasts or myeloblasts. The neoplastic clone diffusely stained positive with CD4 and CD56. They were negative for CD3, CD20, pax-5, CD30, myeloperoxidase (MPO), and terminal deoxynucleotidyl transferase (TdT). Receptor rearrangement studies for T and B cell were negative. Ki-67 proliferation index was 80% (Fig. 3). Depending on these features, the patient was diagnosed as having BPDCN.

The patient was consulted to hematology clinic. Total blood count with differential, erythrocyte sedimentation rate, liver and kidney function tests, beta 2 microglobulin and lactate dehydrogenase levels were within normal limits. Bone marrow biopsy was normal. Cranial tomography did not show bone or parenchymal involvement. Thoracoabdominal tomography was normal. Whole body 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography-computed tomography (PET-CT) imaging revealed increased uptake in soft tissue lesion on forehead, bilateral submandibular, bilateral cervical and right supraclavicular, and bilateral axillary lymph nodes, and increased metabolic activity in parotid glands. The patient was put on six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine) chemotherapy which was successfully cleared all lesions. However, a rapid recurrence was observed at 1.5 months after the end of therapy. Although the patient was then treated with palliative radiotherapy and SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) chemotherapy, relapses occurred. While the patient was being prepared for autologous stem cell transplantation, he died due to rapidly onset myelosuppression and systemic infections.

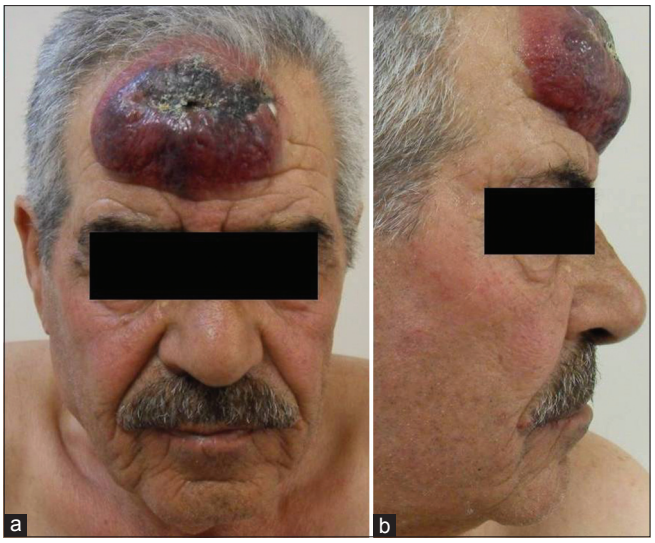

Figure 1: (a and b) Rapidly enlarging purple mass over forehead.

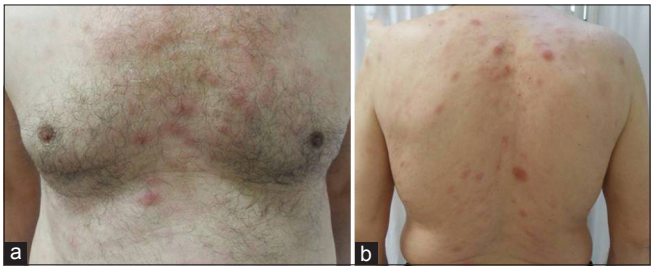

Figure 2: (a and b) Multiple lesions over trunk.

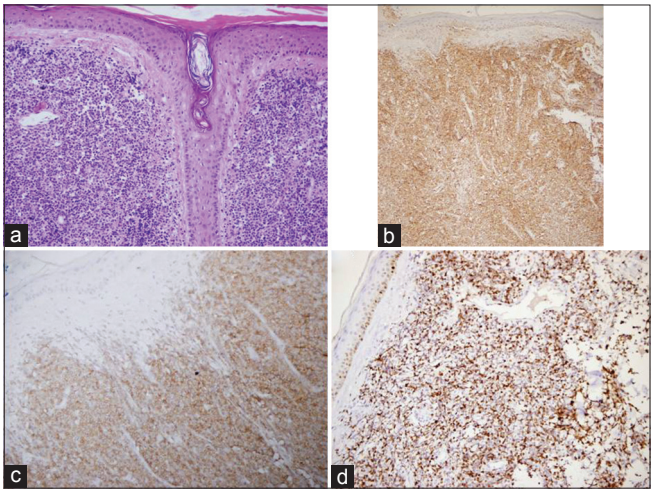

Figure 3: (a) Non-epidermotropic, dermal, and subepidermal homogeneous infiltration with moderate-sized cells resembling lymphoblasts or myeloblasts (haematoxylin and eosin, original magnification x 200); (b) cells diffusely stained positive with CD4 (x 100); (c) cells diffusely stained positive with CD56 (x 100); (d) Ki-67 proliferation index was 80% (x 200).

DISCUSSION

BPDCN usually presents with cutaneous lesions as nodules, bruise-like patches, and disseminated skin lesions. There is no correlation between clinical presentation and prognosis depending on clinical experiences of a large number of study population [2]. The first presentation is usually one or two isolated cutaneous nodules. In the present case, the initial

presentation of BPDCN was a rapidly evolving tumoral mass. Disseminated lesions developed rapidly in the disease course.

BPDCN is a dermal neoplasm spearing epidermis with a grenz zone, frequently infiltrating into subcutaneous fat tissue [3]. BPDCN is consisted of small to medium sized cells with irregular nuclear contours. The typical feature of these cells is having positive cell surface markers for CD4, CD56, CD123 and T cell leukemia/lymphoma 1 (TCL1). Only a few CD4- CD56 + cases of BPDCN are reported [4]. Expression of specific antigens for T and B cell lineages, granulocytes, and monocytes is lacking. Depending on these features, neoplastic cells are accepted to originate from pDC. The main differential diagnoses of BPDCN includes myeloid sarcoma/acute myeloid leukemia (myeloid leukemia cutis), T cell lymphoblastic leukemia/lymphoma (T-ALL/LBL), NK cell lymphoma/leukemia, and mature T cell lymphoma/leukaemia [3,5]. In our case, initial and early cutaneous involvement should have been differentiated from myeloid leukemia cutis. Both neoplasms are morphologically indistinguishable and skin is commonly involved [6]. Myeloperoxidase is more specific for myeloid lineage than CD68 positivity. Negative staining for MPO generally helps to rule out myeloid sarcoma as in our case. However, rarely seen MPO negative leukemia cutis is a challenging problem. Cronin et al. suggested that MPO negative cases with negative for CD4, CD56, CD123, or Tcl-1, or positive for only CD56 are myeloid leukemia cutis [7]. In our case, MPO negativity together with CD4 and CD56 positivity drew away the diagnosis of myeloid leukemia cutis. T-ALL/LBL is a neoplasm that includes CD3+, CD2+, and TdT+ cells and clonal T cell receptor rearrangement, which are T cell specific features. Lack of these T cell markers helped us to rule out T-ALL/LBL. NK/T cell lymphoma nasal type expresses CD56; however, angiocentric and angiodestructive growth pattern are not features of BPDCN. Although cutaneous T cell lymphomas resemble BPDCN, negative T cell receptor gene rearrangement supported BPDCN in our case.

In the present case, detailed immunophenotypic analysis provided us to rule out the differential diagnoses and supported the diagnosis of BPDCN in our case. In a recent study, the typical cells of BPDCN were demonstrated to be resting pDC [8]. Since myelodysplasia and acute myeloid leukemia develop in the course of BPDCN, pDC are strongly suggested to belong to the myelomonocytic lineage. Therefore, BPDCN was classified in the category of acute myeloid leukemia and related precursor neoplasms in 2008 World Health Organization Classification of Haematopoietic and Lymphoid Tissue [1,3].

Prognosis in BPDCN is aggressive and poor. Mean survival time is about 12 months. Advanced age and advanced stage are poor prognostic factors [2]. As soon diagnosed by cutaneous findings, involvement of lymph nodes and leukemic dissemination are observed [7]. Initial response to multiagent chemotherapy is very rapid and favorable; however, recurrences develop rapidly, resulting in poor prognosis [9]. In the present case, almost all cutaneous lesions regressed rapidly in the first course of chemotherapy. Unfortunately, new lesions were observed within 2 months after ceasing therapy. These were resistant to chemotherapy and survival time from the diagnosis was 15 months. In the current management of BPDCN, aggressive therapies including allogenic hematopoietic stem cell transplantation are recommended as soon as the diagnosis was made [10].

In conclusion, BPDCN should be in the clinical and histopathological differential diagnosis of rapidly developing tumoral cutaneous lesions. Early diagnosis is important to initiate aggressive treatments in BPDCN, in which skin involvement is very frequent.

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Our Dermatology Online

Case Report

Neurofibromatosis type 1 with localized unilateral hyperhidrosis: A rare association

Snehal Balvant Lunge, Anvitha Chidanand

Department of Dermatology, Venereology and Leprosy, Jawaharlal Nehru Medical College, KLE University, Belagavi, India

Corresponding author: Dr. Snehal Balvant Lunge, E-mail: drsnehallunge@gmail.com

ABSTRACT

Unilateral hyperhidrosis is a rare entity with primary and secondary causes. So far in literature, the associations documented with this entity rarely include neurofibromatosis. This association, however has been reported previously and perhaps is a more frequent incidence than is being recognized. Here we report a case to emphasize this association.

Key words: Localized unilateral hyperhidrosis; Neurofibromatosis type 1; Partial unilateral lentiginosis

INTRODUCTION

Localized unilateral hyperhidrosis (LUH) is a term coined to describe excessive sweating over a well circumscribed part of the body [1]. It is a rare entity and can be primary or secondary to other disorders (Table 1) [2]. We hereby report a case of an association between unilateral localized hyperhidrosis and Neurofibromatosis type 1 (NF 1), which seems to be a rare one as is evident from the lack of it's documentation in literature.

CASE REPORT

A 34-year-old female patient complained of profuse sweating over the fingers of her left hand, since childhood that had no obvious precipitating factors. The same area was affected always. There were no associated symptoms like by flushing, excessive salivation, lacrimation, orthostatic hypotension, causalgia or headache. The patient's past history was unremarkable with no history of trauma or any drug intake. Similar complaints were absent in the family.

On examination, the fingers of her left hand were moist. Starch-iodine test revealed localized areas of excessive sweating over the fingers of left hand (Fig. 1). On further examination, she had multiple brownish patches measuring more than 1 cm, suggestive of cafe-au-lait macules scattered on both sides of the trunk and shoulders (Fig. 2). She had unilateral tiny hyperpigmented macules distributed over left side of face and neck including her left upper extremity, suggestive of Partial unilateral lentiginosis (PUL). Bilateral axillary freckling (Fig. 3) was observed. Ophthalmological examination revealed Lisch nodules on the iris of right eye (Fig. 4) and alterations in iris pigmentation. Magnetic Resonance Imaging of cervico thoracic region showed a plexiform neurofibroma (Fig. 5). The results of laboratory tests including endocrinological examination were normal. No abnormality was detected on magnetic resonance imaging of the brain and brainstem. The presence of cafe-au-lait macules (>6, >1.5cm), axillary freckling, plexiform neurofibroma and lisch nodules confirmed the diagnosis of NF1 according to the diagnostic criteria of NF 1 [3]. The patient had no cardiovascular or gastrointestinal complaints, and his chest X-ray was normal. The results of the complete blood count, hepatic and renal function tests were within the normal ranges. The histopathological examination of a skin biopsy of the hyperhidrotic area and symmetrically opposite side of normal skin showed no increase or abnormality of eccrine glands. The patient was diagnosed as having LUH and NF1.

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Table 1: Localized hyperhidrosis causes

Spinal cord injury
Hyperhidrosis associated with autonomic dysreflexia
Hyperhidrosis due to orthostatic hypotension
Gustatory hyperhidrosis
Frey's syndrome
Granulosis rubra nasi
Functional and true sweat gland naevi
Intrathoracic neoplasia
Sweating associated with local skin disorders
Glomangioma
Pachydermoperiostosis
Blue rubber bleb naevi
Pretibial myxoedema
Burning feet syndrome
POEMS syndrome
Idiopathic unilateral circumscribed hyperhidrosis
Compensatory
After sympathectomy, or with partial anhidrosis

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes

DISCUSSION

Hyperhidrosis can be classified as emotional, generalized and localized [4]. Localized unilateral hyperhidrosis can be further categorized as gustatory, cutaneous-disease-associated and idiopathic variants [5]. The area of the body that demonstrates excessive sweating may give a clue to the cause; e.g. pathogenic gustatory sweating occurs mainly on the face, idiopathic hyperhidrosis is located mainly on the forearm and forehead of otherwise healthy people and is restricted to an area of less than 10 x10 cm [6]. Idiopathic LUH has none of the typical triggering factors found with essential hyperhidrosis. The attacks occur with no apparent cause even in sleep [7]. Cutaneous-disease-associated variant of LUH will have associated cutaneous features; e.g. palmoplantar keratodermas, glomus tumor, blue rubber bleb nevus, POEMS syndrome [8-11].

No discernible cause of hyperhidrosis could be found in our patient and the absence of triggering factors was compatible with idiopathic LUH. Skin biopsy of the hyperhidrotic site excluded associated cutaneous disorders. On physical examination, she had cafe-au-lait macules (>6, >1.5cm), axillary freckling and lisch nodules. She also had PUL over the left upper body. The lesions of partial unilateral lentiginosis can appear anywhere on the body but the upper extremities are more affected than the lower ones [12]. The coexistence of neurofibromatosis with partial unilateral lentigines raises the possibility that partial unilateral lentigines could be a variant or forme fruste of segmental neurofibromatosis [13]. Magnetic Resonance

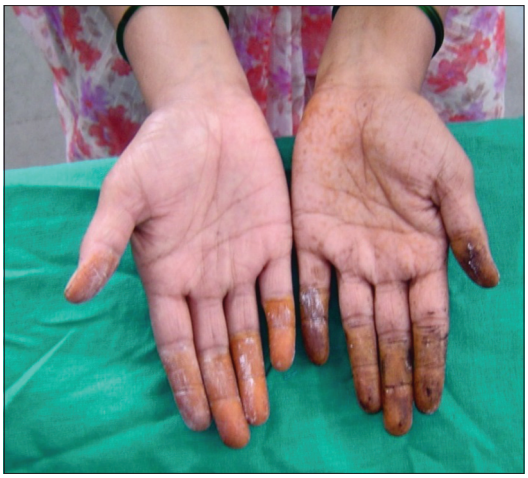

Figure 1: Starch iodine test demonstrating unilateral localized hyperhidrosis over fingers of the left hand.

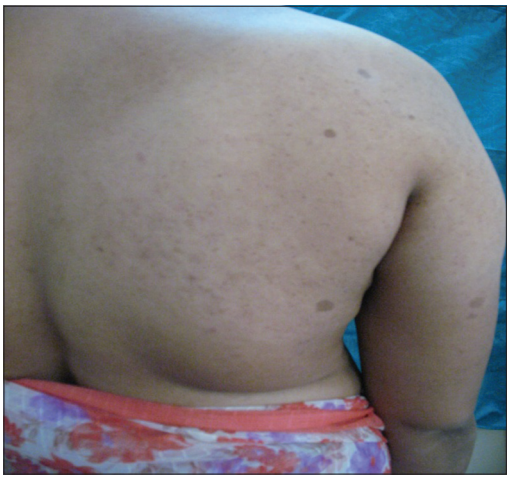

Figure 2: Cafe-au-lait macules, measuring >1.5 cm scattered on the back.

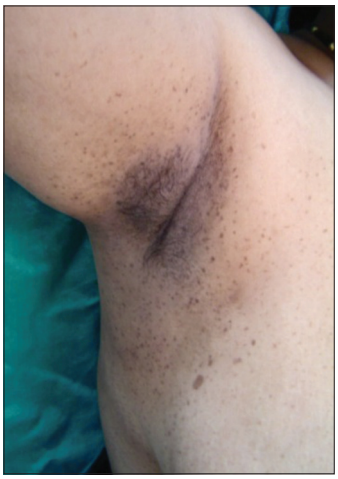

Figure 3: Axillary freckling (Crowe's sign).

Imaging of cervico thoracic region showed a plexiform neurofibroma. The case was categorized as NF1. NF1 is

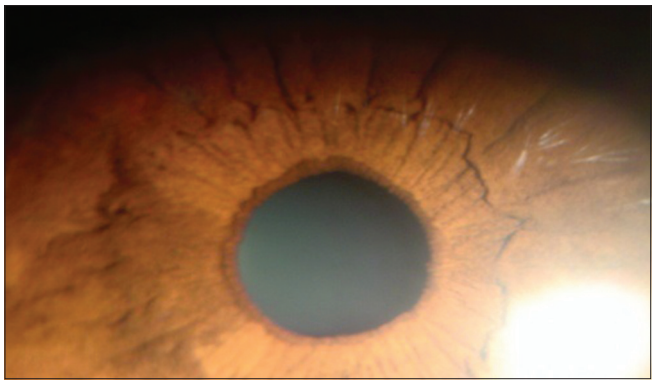

Figure 4: Lisch nodules with alterations in pigmentation.

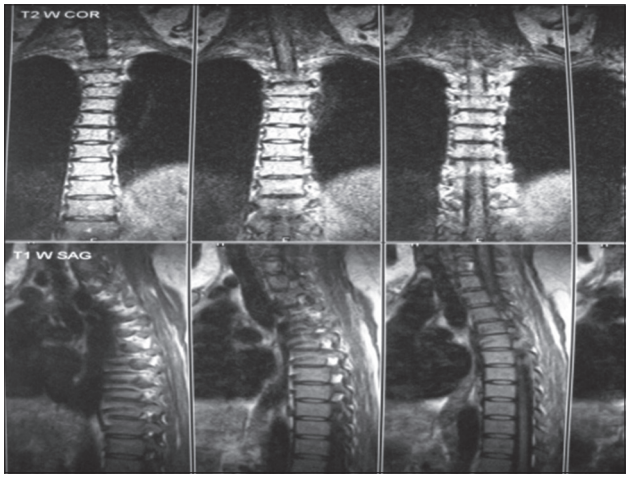

Figure 5: MRI of cervico thoracic region showing plexiform neurofibroma.

known to have many associations, but LUH has not been documented in the literature so far [6]. A case report of this association, however has been presented by Emel Bulbul Baskan et al in 2005 [14]. The pattern of LUH was different in that case and there was no conclusive evidence to support the association.

CONCLUSION

The lack of understanding of the etiopathogenesis of LUH is a major lacuna in detecting the underlying cause of this disorder, making the associated features difficult to elucidate. New associations will, perhaps be the gateway to better understanding of the underlying pathogenesis.

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Our Dermatology Online

Case Report

Unusual acne conglobata case mimicking cervicofacial actinomycosis: A case report with literature review

Magdalena Piotrkowicz[1], Tomasz Wasyłyszyn[2], Katarzyna Borowska[3]

[1]Depatrment of Internal Medicine with Cardiology Unit, District Hospital in Pułtusk, Pułtusk, Poland, [2]Department of Dermatology, Military Institute of Medicine in Warsaw, Warsaw, Poland, [3]Department of Histology and Embryology with Experimental Cytology Unit, Medical University of Lublin, Lublin, Poland

Corresponding author: Prof. Katarzyna Borowska, E-mail: k_borowska@wp.pl

ABSTRACT

Acne vulgaris is one of the most common skin diseases and one of the most frequent diagnoses for patients who visit a dermatologist. The present article describes one of the most severe kinds of acne - acne conglobata, which in a presence of deep inflammation and concomitant general symptoms, is often described as acne fulminans. The authors discuss about case requiring differentiation of acne conglobata and cervicofacial actinomycosis.

Key words: Acne vulgaris; Acne conglobata; Actinomycosis

INTRODUCTION

Actinomycosis is a bacterial infection caused by Gram positive, anaerobic or microaerophilic bacilli, Actinomyces spp. These are higher prokaryotic bacteria belonging to the family Actinomyceataceae. The most frequent pathogen species encountered is *Actinomyces israelii* [1] but many different species have been described and are associated with pathogenic conditions specific to anatomical sites [2,3]. Based on the site affected, actinomycosis is clinically classified into cervicofacial, pulmonothoracic and abdominocervical forms, of which the most common form is cervicofacial. Cervicofacial actinomycotic lesions usually present as single or multiple cysts and abscesses or indurated lumps with fistulation and a discharge of sulfur granules [4]. While acne vulgaris is a very common disease, the cases of actinomycosis are relatively rare.

CASE REPORT

A 16-year-old patient reported to the clinic with skin lesions involving the face, mainly at the mandibular area. These were in form of pustules healing as scabs and eventually leaving scars in the upper part of the cheeks. In the lower parts of the face there were several cyst tumors the size of hazelnuts; inflamed and painful, palpably soft covered with shining red skin. One of the cysts broke during the examination revealing inside the presence of discharge containing yellow grains of a soft substance (Fig. 1). These were very similar to so called "sulfur grains" found in actinomycosis. The disease lasted for at least four years, but during final year, the cysts appeared to introduce a serious discomfort to the patient as besides the increasing pain, he reported an occasional fever. The patient was treated with numerous oral antibiotics, including tetracycline, limecycline, azitromycine and clindamycine. Besides topical treatment with antibiotic solutions, and benzoyl peroxide was performed. No improvement was noticed. While the clinical picture obviously suggested acne, authors hypothesised that there might also be an actinomycosis as a complication or as a separate phenomenon. For this reason, a microscopic examination of the "sulfur grain" obtained during examination, stained with methylene blue was performed at the first visit (Fig. 2). It revealed numerous segmented neutrophils

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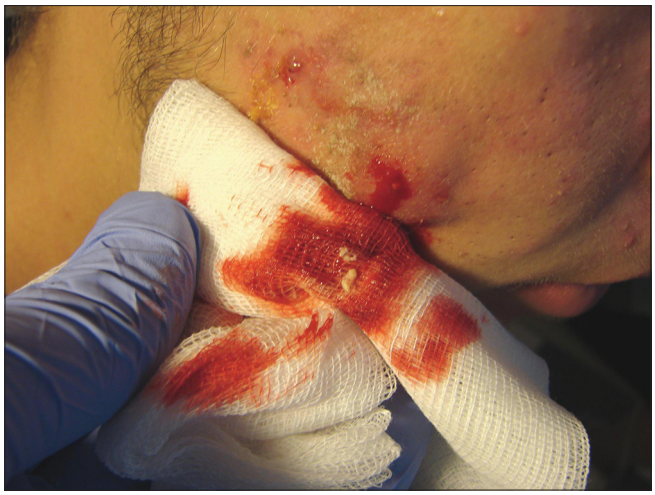

Figure 1: Discharge containing grains of the yellow substance. This phenomenon is very similar to so called "sulfur grains" found in actinomycosis.

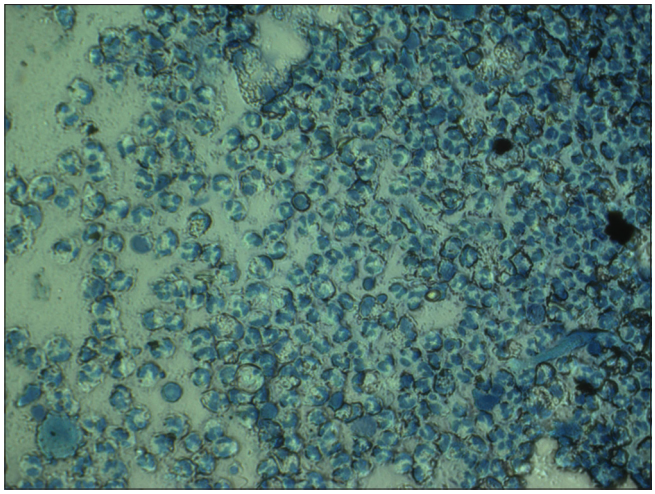

Figure 2: Microphotograph of the grain obtained during examination stained with methylene blue. No signs of actinomyces filiae.

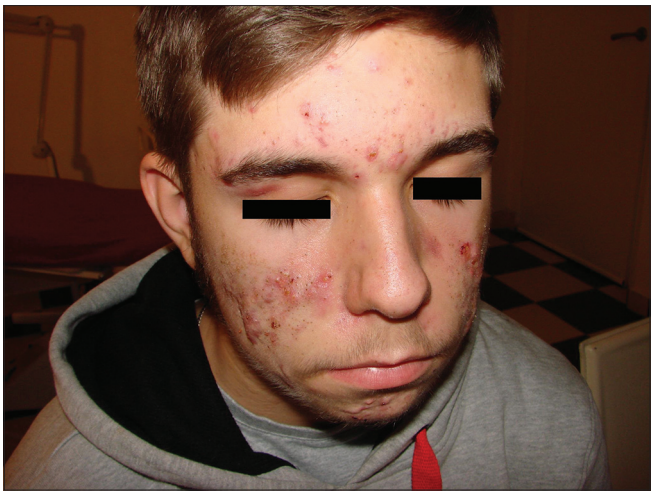

Figure 3: Clinical status before treatment. Please note large cyst on the right cheek.

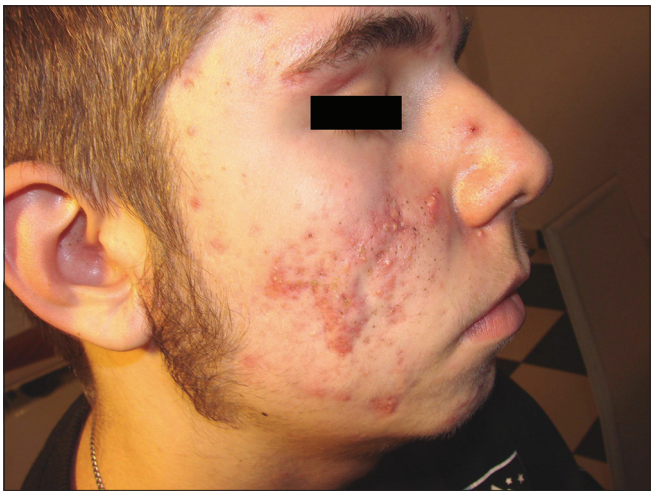

Figure 4: Clinical status during the treatment course showing partial improvement.

but no signs of filaments typical for actinomycosis. A second sample was sent to the laboratory to perform aerobic and anaerobic cultivations – after two weeks, both turned out to be negative. In spite of the serious clinical condition of deep inflammatory cysts with concomitant discomfort, the authors decided to introduce a low dose of oral prednisone (30 mg/day) along with oral Amoxiciline/clavulanate compound (2x1 g/day). The latter was discontinued after two weeks when negative bacteriological tests arrived. Topically, authors prescribed a preparation liquid containing chloramphenicol and resorcine, 3.5% of each in a 60% ethanol base twice a day. On a visit after two weeks, the inflammatory cysts appeared to be much smaller (less than half of initial status) but still persisted (Fig. 3). But most importantly, the patient did not report discomfort related with the disease anymore. The authors decided to slowly withdraw the prednisone during the next four weeks. After the prednisone was withdrawn, the patient was administered oral nabumetone (non – steroid anti inflammatory agent) in a dose of 1 g per day; topical treatment remained unchanged. Nabumetone was administered for another eight weeks. During this time, the large cysts have been disappearing, but slowly. At this point, the authors added to the existing topical treatment a prepared ointment containing cinnabar and sulfur (Rp. Mercury Sulfide 0.3, Precipitated Sulfur 4,0, Vaseline 10.0, Zinc Paste ad 30,0). During another four weeks of treatment, almost all the inflamed tumors disappeared, leaving numerous scars and crusts (Fig. 4). Patient remains under observation.

DISSCUSION

Acne vulgaris is one of the most common skin diseases [5] and one of the most frequent diagnoses for patients who visit a dermatologist [6]. It is a chronic inflammatory disorder of the pilosebaceous unit and is characterised by non-inflammatory (comedones) and inflammatory lesions (papules, pustules, and nodules). The pathogenesis of acne vulgaris is complex and includes features of follicular hyperkeratosis, seborrhoea, bacterial colonisation and inflammation [7]. The present study reveals one of the most severe kinds of acne - acne conglobate, which in a presence of deep inflammation and concomitant general symptoms (pain, fever), is often described as acne fulminans. It is difficult to say whether the case described was complicated by actinomycosis; indeed, some clinical dates suggested it, but in spite of numerous systemic antibiotics used prior to the microbiological examination, its negative result is not surprising. While the clinical picture obviously suggested acne, authors hypothesised that there might also be an actinomycosis as a complication or as a separate phenomenon, as it was previously reported [8]. For this reason, a microscopic examination of the "sulfur grain" obtained during examination, stained with methylene blue was performed at the first visit (Fig. 2). Nevertheless, the inflammatory nodules and cysts in acne vulgaris should be differentiated with cysts present in a cervicofacial actinomycotic infection. The authors are aware of the fact that oral prednisone is often being improperly or unnecessarily prescribed these days, but this acne case is one of those where the introduction of a small dose of systemic corticosteroids might be necessary.

It is Propionibacterium acne that seems to play an important role in the pathogenesis of acne vulgaris because eventually it can lead to the presence of inflammatory cysts. These can create an important therapeutic problem even after the eradication of bacteria. Propionibacterium acne is an anaerobic, gram-positive pathogen that colonises in sebaceous follicles. Its cultures supernatants contain lipases and have been shown to activate inflammatory receptors, such as toll-like receptor 2 [9]. Propionibacterium acnes induced chemotactic factors may play an important role in attracting neutrophils to the pilosebaceous unit – hence the presence of neutrophiles in cysts in our study. Consequent release of lysosomal enzymes by the neutrophils leads to the rupture of the follicular epithelium and inflammation [10]. Propionibacterium acnes induces the monocytes in acne lesions to produce high levels of IL-1 and tumor necrosis factor-α (TNF-α) [11]. This process will give rise to inflammatory lesions: pustules, papules, nodules and cysts like in the above mentioned case.

While the eradication of bacteria is relatively simple these days, the damage that it leaves behind is not. Therefore, the authors suggest in conclusion that Acne conglobata should be understood as a case of acne where, due to the presence of lysosomal enzymes in affected follicles, destruction leaves large cysts characterized by a very chronic course. The management of acne at this stage seems no longer to be anti – microbic. Systemic anti-inflammatory agents are often necessary here; either non-steroid or low dose corticosteroids.

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Our Dermatology Online

Case Report

Pyoderma gangrenosum among children in Senegal: 6 cases

Boubacar Ahy Diatta, Fatou Fall Toumbou, Assane Diop, Saer Diadie, Maodo Ndiaye, Moussa Diallo, Suzanne Oumou Niang, Assane Kane, Mame Thierno Dieng

Department of Dermatology, Cheikh Anta Diop University of Dakar, Dakar, Senegal

Corresponding author: Dr. Boubacar Ahy Diatta, E-mail: ahydiatta@yahoo.com

ABSTRACT

The pyoderma gangrenosum (PG) is a chronic ulcerative neutrophilic dermatosis rare in children. It is often associated with chronic inflammatory bowel disease, some systemic diseases and leukemias. We report six cases in children. We collected six cases, the average age was 10 years (4-15 years), the sex ratio was 0.16 (5 boys and 1 girl). The ulcerated clinical form of PG was noted in all children. The topography was in the lower limbs in five cases and in the cephalic extremity in three cases. The mean duration of evolution was 2 years (15 days-7 years). PG was associated with ulcerative colitis in one case. Oral corticosteroids were administered in all cases at a dose of 0.5 to 1 mg/kg. The complete healing of the cutaneous lesions was obtained. Two children were lost to sight. Our study reports a male predominance of PG in children with ulcerative clinical form of the limb and association with ulcerative colitis. Corticosteroids appear to be efficient, but may be limited by their complications.

Key words: Pyoderma Gangrenosum; Children; Senegal

INTRODUCTION

Pyoderma gangrenosum (PG) is a chronic, recurrent ulcerative inflammatory disease that is part of the nosological framework of neutrophilic dermatoses. They are characterized by non-infectious infiltration of the skin by morphologically normal neutrophils [1,2]. It is often associated with chronic inflammatory bowel disease (IBD), some systemic diseases and to leukemias [1-4]. In tropical Africa the PG in children has been rarely reported and may be confusing with primitive bacterial dermatoses at this age. We report 6 cases.

CASE REPORTS

Case 1

A 12-year-old boy was received for ulcerations on the scalp after a period of evolution of 5 years. He was in poor health. The weight was 30 kg, the size at 1.35 m and the temperature at 37.3°C. Physical examination showed ulcerations with an irregular and atrophic border on the limbs and face.The complete blood cell count (CBC) showed neutrophil leukocytosis at 25.000/mm^3, C reactive protein at 48mg/l, anemia at 6 g/dl and accelerated erythrocyte sedimentation rate (ESR). All infectious samples were sterile. The child received prednisone at 1 mg/kg/day and a blood transfusion. Complete scarring of skin lesions was noted at 6 months of follow-up. He had an obesity after 2 years of treatment.

Case 2

A 9-year-old boy was received for ulcers on the lower limbs after a period of evolution of 15 days. He was in poor health with temperature at 38,2°C. The physical examination noted an ulcero-necrotic closet with infiltrated border, shredded of the lower limbs. Histology showed a non-specific polymorphic inflammatory infiltrate in dermis. Colonoscopy revealed a congestive and hemorrhagic rectocolitis.

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The CBC showed anemia at 3.9 g/dl, neutrophilic leukocytosis at 44000/mm^3, C –reactive protein at 92 mg/l and accelerated erythrocyte sedimentation rate. All infectious samples were sterile. He had received betametasone at 1 mg/kg/day and a blood transfusion. Complete scarring of the skin lesions was noted after a 7-month follow-up.

Case 3

A 15-year-old boy was received for ulcerations on the scalp and the leg after a period of evolution of 8months. He was in poor health with and temperature at 36.2°C. The physical examination noted an ulcerated helmet of the scalp overflowing on the frontal lobe and parietal lobes with an atrophic border. Histology was not contributory. The CBC showed neutrophilic leukocytosis at 12700/mm^3, C-reactive protein at 192 mg/l, anemia at 10.3 g/dl and accelerated erythrocyte sedimentation rate. All infectious samples were sterile. He had received prednisone at 1 mg/kg/day. Healing of the skin lesions was noted at 3 months of follow-up and he was lost sight.

Case 4

A 10-year-old boy was received for ulcerations on the leg and the face after a period of evolution of 7 years. The physical examination showed an ulcerated cupboard on the leg and the face. The CBC noted anemia at 10 g/dl, neutrophilic leukocytosis at 11000/mm^3, C-reactive protein at 48 mg/l and accelerated erythrocyte sedimentation rate. All infectious samples were sterile. He had received prednisone at 1.5 mg/kg/day. Full healing of the skin lesions was obtained after 12 months of follow-up. He presented obesity after 2 years of treatment.

Case 5

A 15-year-old girl was received for ulcerations of the leg after a period of evolution of one month. Physical examination noted ulcerous lesions with a purulent background at both legs (Figs. 1a and 1b). Histology noted a dermal infiltrate of non-altered neutrophilic polynuclear in interstitial clusters between collagen fibers (Fig. 2). The CBC showed neutrophilic leukocytosis at 12000/mm^3, C-reactive protein at 92 mg/l and accelerated erythrocyte sedimentation rate. All infectious samples were sterile. She received prednisone at 1 mg/kg/day. Healing of skin lesions

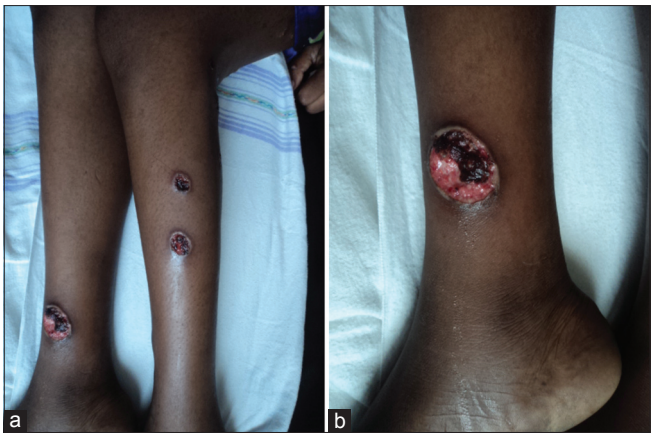

Figure 1: Multiple ulcers with infiltrated border of the leg.

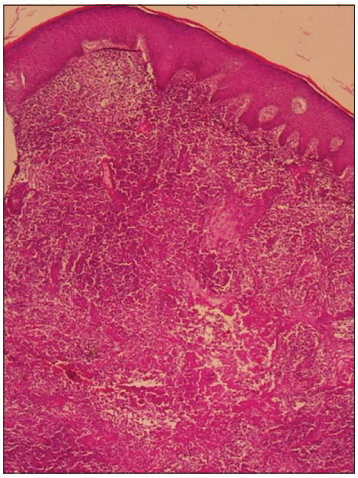

Figure 2: Dermal infiltrate of non-altered neutrophilic polynuclear in interstitial clusters between collagen fibers. HE X 100.

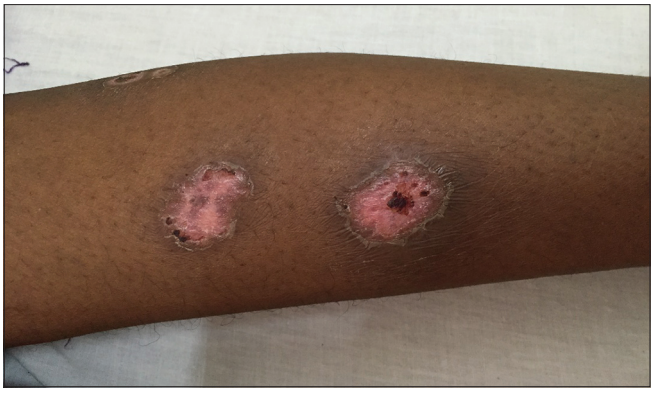

Figure 3: Ulcer healing at one week of corticosteroid therapy

(Fig. 3) was obtained after 12 months of follow-up and she was lost sight.

Case 6

A 4-year-old boy was received for diffuse cutaneous ulcerations of the leg and trunk after a period of

Table I: Summary of cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	M	M	M	M	F	M
Age (years)	12	9	15	10	15	4
DE	5 years	15 days	8 months	7 years	1 month	1 month
Clinical form	Ulcer	Ulcer	Ulcer	Ulcer	Ulcer	Ulcer
Topography	Members Head	Members	Members Head	Members Head	Members	Members
Associated disease	None	UC	None	None	None	None
Corticoïdes	Yes	Yes	Yes	Yes	Yes	Yes
Healing	Yes	Yes	Yes	Yes	Yes	Yes
Complications	Obesity	None	None	Obesity	None	None

DE: Duration of symptoms; UC: Ulcerative colitis; M: Male; F: Female

evolution of one month. He was in poor health with a fever at 39°C. Physical examination showed rounded ulcerations on the trunk and lower limbs. The histology noted an infiltrate of polynuclear neutrophils of the dermis. The CBC showed neutrophilic leukocytosis at 20000/mm^3, anemia at 7 g/dl, C-reactive protein at 92mg/l and accelerated erythrocyte sedimentation rate. All infectious samples were sterile. He received prednisone at 1 mg/kg/day. Skin lesions were healed after 3 months of follow-up.

DISCUSSION

We reported six cases of pediatric PG with diagnosis based on semiological characteristics, histology in some cases, and leukocytosis without bacterial infections (Table 1). Our observations are remarkable for the delay in consultation, the difficulty of the diagnosis due to the diversity of the causes of cutaneous ulcerations in tropical pathology, the multiplicity of lesions, the cephalic localization and the constancy and severity of the anemia. These pediatric forms represent 30% of the PG in Dakar [3]. A delay in consultation was noted with an average duration of symptoms evolution of 2 years. This seems to be related to the inaccessibility of the population to specialized care and diagnostic wandering. The diagnosis of PG is essentially clinical. Other studies have proposed diagnostic criteria for PG, but he is stay still a diagnosis of exclusion [1,5-7]. The difficulty of the diagnosis is related to the clinical polymorphism and to the multiple causes of infantile cutaneous ulcerations in tropical pathology. The ulcerated clinical form was noted in all cases with a predominant topography in the lower limbs in 83%. This may be related in part to minor trauma to the limbs at this age responsible for a pathergic phenomenon. The cephalic localization, also referred to as " malignant pyoderma ", was noted in three cases, and according to some authors it constitutes a particular aggressive form of ulcerative PG [4,6,8-10]. Histology had noted in our study a dermal neutrophilic infiltrate in 50% of cases. It allows an orientation towards a neutrophilic dermatoses and an anatomo-clinical confrontation. The etiology of pyoderma gangrenosum remains unknown [10]. Some etiological factors have been mentioned, notably genetic factors and an extrinsic or intrinsic anomaly of the neutrophilic polynuclear [1]. The association with ulcerative colitis is common in pediatric forms of PG [2,3]. General corticosteroids appear to be efficient as evidenced by the complete healing of ulcers in our cases. The prognosis depends on recurrences and corticosteroids complications associated with long-term treatment.

CONCLUSION

Our study confirms some known feature of PG among children in Senegal with a possible association with Inflammatory Bowel Diseases. The PG in children poses diagnostic problems because of the diversity of causes of cutaneous ulceration in tropical countries.

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Our Dermatology Online

Case Report

Cutaneous infection by *Mycobacterium fortuitum*

Verónica Rotela, Maria Elena Ibáñez, Beatriz Di Martino Ortiz, Oilda Knopfelmacher Domínguez, Mirtha Rodríguez Masi, Lourdes Bolla Argüello de Lezcano

Department of Dermatology, Faculty of Medical Sciences, Clinicas Hospital, National University of Asuncion, Paraguay

Corresponding author: Prof. Dra. Beatriz Di Martino Ortiz, E-mail: beatrizdimartino@gmail.com

ABSTRACT

Mycobacteria are aerobic, non-spore forming, gram positive, acid-fast bacilli, which affect skin, subcutaneous tissue, and other organs and systems. *Mycobacterium fortuitum* produces cellulitis, abscesses, papules-pustules, nodules and ulcers with serosanguinolent, purulent material, and subcutaneous necrosis. A 61-year-old woman, presents a case of two months of evolution that begins with reddish grain from an insect sting. After immersion in the Mexican Sea, it worsens, increases in quantity, is blistered and has brownish secretion; Physical examination shows erythematous plaque, with punctate orifices with hematic and meliceric crusts; Pustules and satellite papules, on the anterior aspect of the right leg. Histopathology: Suppurative dermal granulomas, centered by acute leukocyte infiltrate, with liquefactive tissue necrosis, surrounded by chronic inflammation with macrophages, plasma cells, lymphocytes, multinucleated giant cells. The first skin culture returns negative; in the second skin culture, fast-growing, non-pigmented atypical mycobacteria. Molecular detection is performed by Polymerase Chain Reaction: *Mycobacterium fortuitum*. Treatment with Ciprofloxacin 500 mg every 12 hours, with resolution of the table to the eighth month. A case of cutaneous infection by *Mycobacterium fortuitum*, related to the immersion in the sea and corals, whose diagnostic process has been difficult and was achieved by techniques of advanced molecular biology.

Key words: Atypical mycobacteria; *Mycobacterium fortuitum*; Infections

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Case Report

Infeccion cutanea por *Mycobacterium fortuitum*

Verónica Rotela, Maria Elena Ibáñez, Beatriz Di Martino Ortiz, Oilda Knopfelmacher Domínguez, Mirtha Rodríguez Masi, Lourdes Bolla Argüello de Lezcano

Department of Dermatology, Clinicas Hospital, Faculty of Medical Sciences, National University of Asuncion, Paraguay

Corresponding author: Prof. Dra. Beatriz Di Martino Ortiz, E-mail: beatrizdimartino@gmail.com

RESUMEN

Las micobacterias son bacilos aerobios, no formadores de esporas, gram+, Bacilo Acido-Alcohol Resistentes que afectan piel, tejido celular subcutáneo, y otros órganos y sistemas. *Mycobacterium fortuitum* produce celulitis, abscesos, pápulo-pustulas, nódulos o úlceras con material sero-sanguinolento, purulento, y necrosis subcutánea. Mujer de 61 años, presenta 2 meses de evolución que inicia con grano rojo por picadura de insecto, luego de la inmersión en el mar en México empeora, aumenta en cantidad, se ampollan y presentan secresión amarronada; al examen físico presenta eritematosa, con orificios puntiformes con costras hemáticas y melicéricas; pústulas y pápulas satélites; en cara anterior de pierna derecha. Histopatología: Granulomas dérmicos supurativos, centrados por infiltrado leucocitario agudo, con necrosis licuefactiva tisular, rodeados de inflamación crónica con macrófagos, plasmocitos, linfocitos, células gigantes multinucleadas. El primer cultivo de piel retorna negativo, en el segundo cultivo de piel se aísla Micobacteria atípica no pigmentada de crecimiento rápido; se realiza detección molecular por Reacción en cadena de Polimerasas: *Mycobacterium fortuitum*. Se realiza tratamiento con Ciprofloxacina 500 mg cada 12 hs, con resolución del cuadro al octavo mes. Se presenta un caso de infección cutánea por *Mycobacterium fortuitum*, relacionado a la inmersión en el mar y corales, cuyo proceso diagnóstico ha sido dificultoso y se logró mediante técnicas de avanzada biología molecular.

Palabras claves: Micobacterias atípicas, *Mycobacterium fortuitum*, Infecciones

INTRODUCCION

Las infecciones por micobacterias atípicas se encuentran en constante aumento, y afectan piel, tejido celular subcutáneo, y otros órganos y sistemas [1]. Son de distribución mundial, se encuentran en la naturaleza colonizando agua, suelo, material vegetal, aire, animales, plantas o material quirúrgico. Son saprófitos, oportunistas en el hombre y no se transmiten de persona a persona [2,3].

La transmisión puede realizarse a través de las vías respiratoria y digestiva, o mediante inoculación directa en el caso de la piel, o por diseminación hematógena a partir de un foco visceral [1].

Este género incluye a *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. leprae* y un grupo de micobacterias denominadas atípicas, no patógenas en individuos sanos, pero si en condiciones de inmunosupresión, sobre todo por el incremento de pacientes inmunocomprometidos, el virus de la inmunodeficiencia humana y los tratamientos inmunosupresores. Las lesiones cutáneas pueden constituir el primer o único signo de infección [2].

Son bacilos delgados de forma recta o ligeramente curvada, aerobios, inmóviles, no formadores de esporas, difíciles de teñir con la tinción de Gram, aunque se consideran gram positivos. Resisten la decoloración en las tinciones con ácido-alcohol

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(BAAR: bacilo ácido alcohol resistente) y mantienen el primer colorante como carbolfucsina (tinción de Ziehl-Neelsen y Kinyoun) o fluorocromos (auramina-rodamina).

Entre los factores de riesgo de infección se citan: tabaco (66%), EPOC (42%), infección por VIH (26%) y alcoholismo (20%), así como también procedimientos invasivos [1].

Para la confirmación diagnóstica se requiere de: Biopsia cutánea, cultivo del material de biopsia o de la secreción obtenida por aspiración, identificación de la micobacteria para establecer su sensibilidad, por lo cual los estudios bioquímicos y la PCR son los procedimientos más útiles.2 Los avances en las técnicas de cultivo y moleculares han permitido que en la actualidad se hayan descrito cerca de 200 especies de micobacterias [4].

La clasificación de Runyon de 1954, modificada en 1974, está basada en las características de crecimiento de las micobacterias atípicas, según el tiempo de crecimiento y su capacidad de pigmentación.

Micobacterias de crecimiento lento: más de 7 días.

Micobacterias de crecimiento rápido: menos de 7 días.

Fotocromógenas: si producen colonias no pigmentadas en la oscuridad, pero pigmentadas si se exponen a la luz.

Escotocromógenas: si producen colonias amarillas o naranjas con y sin luz, incluso algunas incrementan los pigmentos tras la exposición, y no cromógenas, si son siempre no pigmentadas [1].

Son micobacterias atípicas de interés dermatológico (Tabla 1): *Mycobacterium fortuitum*, micobacteria atípica no pigmentada de crecimiento rápido, correspondiente al grupo IV según la clasificación de Runyon; produce en piel celulitis, abscesos, lesiones pápulo-pustulosas, nódulos o úlceras que drenan material sero-sanguinolento o purulento con zonas de necrosis subcutánea [1].

Tabla 1: Micobacterias atípicas de interés dermatológico

Especie	Grupo de runyon
M. kansaii, M. marinum	I
M. scrofulaceum, M. szulgai, M. gordonae.	II
M. avium-intracellulare, M. haemophilum M. ulcerans	III
M. fortuitum, M. chelonae, M. abcessus	IV

CASO CLINICO

Mujer de 61 años, procedente de medio urbano, docente, portadora de púrpura pigmentosa crónica y sobrepeso, que consulta por lesión sobre elevada roja en pierna derecha de 2 meses de evolución, relacionada a picadura de insecto. 48 hs después viaja a México y luego de la inmersión en el mar, aumenta el número de lesiones, las mismas se ampollan, ulceran, y presentan secreción amarronada en una oportunidad, y purulenta persistentemente. Consulta en varias ocasiones con facultativos, recibiendo tratamientos con cefalexina, ciprofloxacina, y metronidazol, de manera irregular e incompleta, sin mejoría del cuadro.

Examen Físico

Placa eritemato-descamativa, ovalada, de 8 x 5 cm, límites netos, bordes irregulares, sobre la que asientan múltiples úlceras redondeadas cubiertas por costras hemáticas y melicéricas, rodeada de pápulas eritematosas satélite, asentada en cara anterior de tercio superior de pierna derecha (Figs. 1 y 2).

Auxiliares del Diagnóstico

- Frotis y cultivo de secreción purulenta, primer cultivo de piel, cultivo para hongos, PCR para

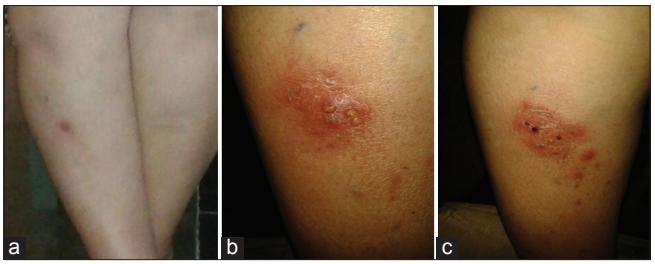

Figure 1: Clínica. (a) Lesión inicial: pápula eritematosa. B. A las 48 horas: placa eritematosa con pústulas (b), A los 2 meses: placa eritemato-descamativa con úlceras con costras hemáticas y melicéricas (c), en pierna derecha.

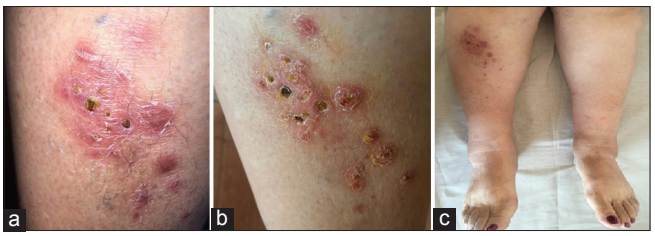

Figure 2: Clínica (a y b). Placa eritemato-descamatica, ovalada, de 5 x 8 cm de dm, múltiples úlceras redondeadas cubiertas por costras hemáticas y melicéricas y pápulas eritematosas satélite, algunas con descamación blanquecina en collarete, localizadas en pierna derecha. (c) Visión panorámica de la lesión.

Leishmania, reacción de Montenegro: Negativos.
- Zielh-Neelsen para BAAR: Negativo.

Frotis y cultivo de secreción purulenta	Leucocitos 20-30/campo Hematíes: 10-20/campo Gram: No se observan bacterias No se obtiene desarrollo bacteriano a los 7 días
Hisopado nasal para *Staphiloccocus aureus*	Negativo
Ecografía de piel y partes blandas pierna derecha	Engrosamiento difuso de piel y tejido celular subcutáneo. No se observa afectación ósea
Radiografía de Tórax	Parámetros normales

Se procede a toma de material para histopatología y nuevos cultivos.

Histopatología

Grandes granulomas supurativos formados del centro a la periferia: 1. necrosis licuefactiva central, 2. empalizada de células inflamatorias (linfocitos, plasmocitos, macrófagos, algunos de apariencia epitelioide y células gigantes multinucleadas), y 3. zona externa fibrosa (Figs. 3 y 4).

Técnicas especiales (PAS, GIEMSA, Ziehl Neelsen, PCR para Leishmaniasis, Reacción de Montenegro): negativas.

Segundo Cultivo de Piel

Se aísla micobacteria atípica no pigmentada de crecimiento rápido, se realiza detección molecular (Fig. 5).

Segundo Cultivo de Piel Se aísla micobacteria atípica no pigmentada de crecimiento rápido	Detección molecular de Micobacteria Atípica: se obtienen bandas de 234/118/88 bp con Bstell (Eco 911) y de 147/124/63 pb con HAE III: *Mycobacterium fortuitum*; concordante con las características fenotípicas como velocidad de crecimiento y pigmentación de las colonias Método: Reacción en Cadena de Polimerasas asociada a Análisis de Patrón Enzimático (PRA)

Metodología Microbiológica

Fueron realizados estudios microbiológicos para micobacterias y hongos. Previa maceración de la muestra, para la búsqueda de micobacterias fue realizada una coloración de Ziehl Neelsen y el cultivo en medios de agar sangre y Lowestein Jensen e incubados a 35°C y, para el estudio micológico fue realizado un examen directo con KOH al 10 % y cultivado en agar Sabouraud + Cloranfenicol, incubados tanto a 28 y 37°C. El examen directo para hongos y la coloración de Ziehl Neelsen, resultaron negativas.

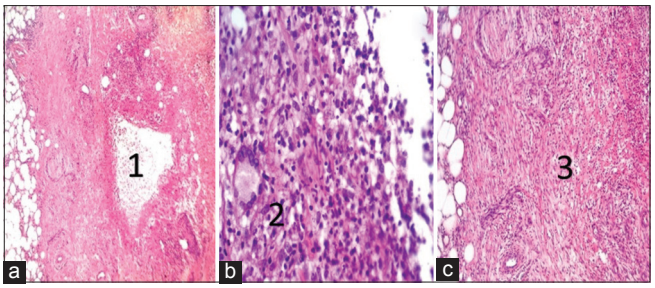

Figure 3: Histopatología. Grandes granulomas supurativos constituidos del centro a la periferia: (a) Necrosis licuefactiva central. (b) Empalizada de células inflamatorias (linfocitos, plasmocitos, macrófagos, algunos de apariencia epitelioide y células gigantes multinucleadas). (c) Fibrosis.

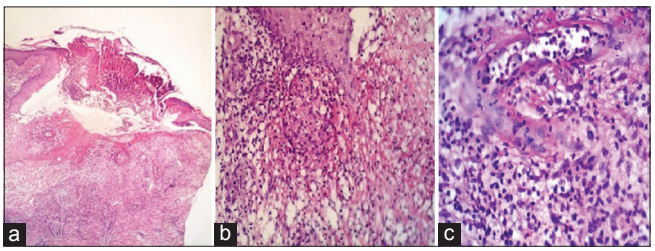

Figure 4: Histopatología. (a) Granulomas supurativos con extrusión del contenido purulento. (b) Granulomas en el borde de la zona abscedada. (c) Vasos dilatados y congestivos, con abundantes neutrófilos intraluminales y fenómeno de marginación típico de procesos inflamatorios agudos.

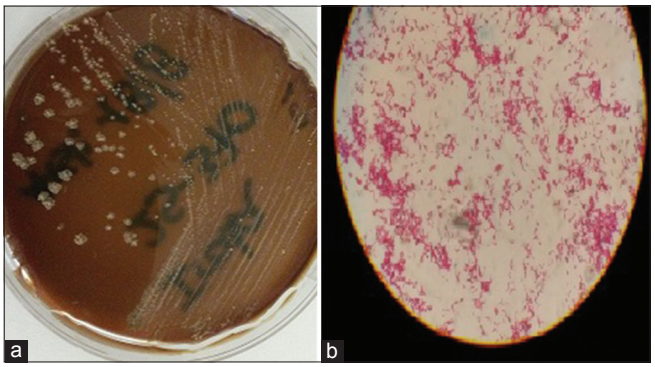

Figure 5: Microbiología. (a) Escasas colonias secas, de color crema compatibles con micobacterias de crecimiento rápido. (b) Coloración de Ziehl Neelsen: bacilos ácido alcohol resistentes (BAAR), finos y curvos.

En medio de Lowestein Jensen, a los 5 días se obtuvo desarrollo de escasas colonias secas, de color crema compatibles con micobacterias de crecimiento rápido, la que fue confirmada mediante la coloración de Ziehl Neelsen que a la observación microscópica mostró bacilos ácido alcohol resistentes (BAAR), finos y curvos.

La identificación a nivel de especie fue realizada mediante el método de reacción en cadena de la polimerasa asociada a restricción enzimática (PRA), utilizando la cepa de referencia *M. tuberculosis 14323*

como control de amplificación e identificación. Se realizó extracción de ADN, según el protocolo descrito por van Soolingen et al [5], se prepararon diluciones de 50-100 ng/ul del ADN y se amplificó el gen que codifica la proteína heat shock (proteína de choque térmico) de 65-kDa utilizando los cebadores Tb11 y Tb12 descriptos por Telenti et al [6], seguido de la digestión del producto con enzimas de restricción HaeIII (Wako, Japón) y BstEII (BioLabs, UK) y la corrida electroforética en gel de poliacrilamida con marcador de peso molecular de 50 pb (Wako, Japón). Los tamaños de las bandas fueron determinados mediante el software KODAK (Kodak Digital Science-1D Image Análisis Software). Las identidades de las cepas se obtuvieron introduciendo los tamaños de las bandas en la página web PRA-SITE [7], teniendo en cuenta además las características de velocidad de crecimiento y pigmentación. La micobacteria fue identificada como *Mycobacterium fortuitum* (Fig. 6).

Diagnóstico: Infección de Piel por Micobacteria atípica, Mycobacterium fortuitum.

Tratamiento y Evolución

Antibiograma: Buenos halos de inhibición frente a ciprofloxacina, amikacina, tetraciclina.

Se inicia tratamiento con ciprofloxacina 500 mg/12 hs por 6-8 meses. Se realizan controles mensuales, notándose mejoría progresiva, disminución de lesiones y de signos inflamatorios, con resolución completa al octavo mes de tratamiento, con cicatrización e hiperpigmentación residual (Fig. 7).

DISCUSION

Las micobacterias no tuberculosas pueden causar infecciones de la piel y tejido celular subcutáneo generalmente después de un antecedente traumático en piel como inyecciones, laceraciones, depilación, contacto con acuarios e intervenciones quirúrgicas, como la mesoterapia, donde se citan con más frecuencia micobacterias de crecimiento rápido como *M. chelonae, M. abscessus y M. fortuitum* en el contexto de brotes epidémicos [8].

Las manifestaciones clínicas cutáneas son polimórficas, entre las que se encuentran: nódulos, fístulas, úlceras, abscesos, pápulas eritematosas, placas eritemato descamativas, lesiones eritemato violáceas, eritema nodoso, entre otras.

Las biopsias de las micobacteriosis cutáneas producen un gran espectro histológico sin correlación con la especie de micobacteria. Santa Cruz et al. describieron siete patrones: granulomas tuberculoides, abscesos, infiltrado difuso de histiocitos, paniculitis, inflamación crónica inespecífica, granulomas sarcoideos y nódulos pseudo reumatoides, predominando los dos primeros. Se han descrito multitud de formas intermedias y la aparición de varios patrones en la misma lesión [9,10]. En inmunodeprimidos el infiltrado inflamatorio tiende a ser más profundo y más difuso, con formación constante de abscesos, mientras que la formación de granulomas es más frecuente en inmunocompetentes. También destacan que la duración de la enfermedad guarda relación con el patrón histológico observado [10].

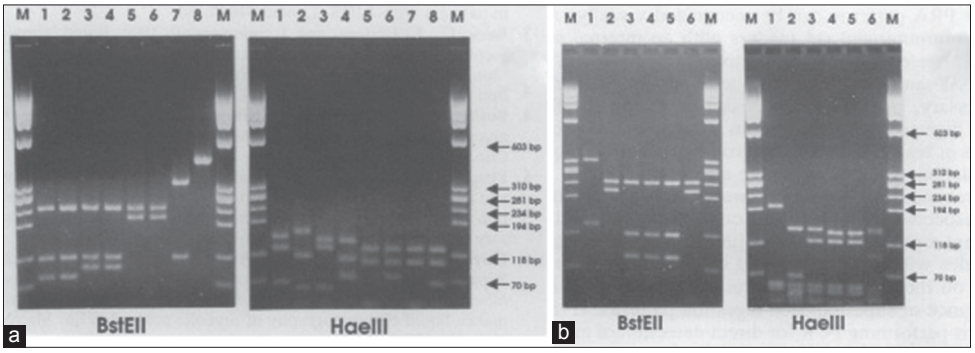

Figure 6: Biología Molecular: (a) PRA de las siguientes micobacterias de crecimiento lento seleccionadas: complejo *M. tuberculosis* (línea 1), *M. gordonae* (línea 2), *M. intracellulare* (línea 3), *M. malmoense* (línea 4), *M. avium* (línea 5), *M. kansasii* (línea 6), y *M. szulgai* (línea 8; no digerido con BstEII). Línea M, marcadores de masa molecular. Las micobacterias de crecimiento fastidioso tales como la recientemente descrita "*M. genavense*" (línea 7) también pueden ser identificadas por PRA. (b) La PRA permite la diferenciación de las siguientes cepas del complejo *M. fortuitum* al nivel de la subespecie: *M. chelonae subsp. Chelonae* (línea 1), *M. chelonae subsp. Abscessus* (línea 2), *M. fortuitum subsp. Fortutum* (línea 3), *M. fortuitum subsp.* Tercera variante ATCC 49403 y ATCC 49404 (líneas 4 y 5, respectivamente, patrones idénticos), y *M. fortuitum subsp. Peregrinum* (línea 6). Línea M, marcadores de masa molecular.[6]

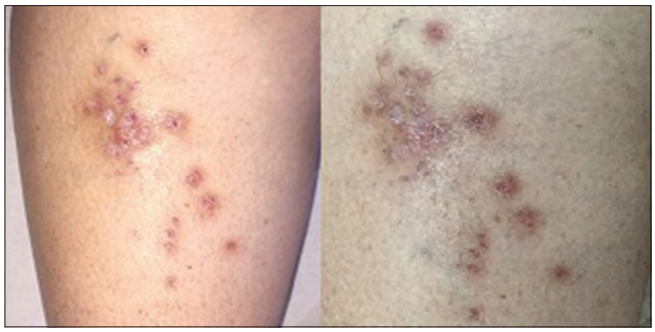

Figure 7: Evolución. Mejoría con disminución progresiva de las lesiones y signos inflamatorios, hasta resolución completa con cicatrización e hiperpigmentación residual.

Mycobacterium fortuitum fue descrito por primera vez como patógeno en las ranas, por lo que al ser reconocido como especie en 1923 se le dio el nombre de *Mycobacterium ranae*. La denominación de *M. fortuitum* le fue dada por Da Costa Cruz en 1938, cuando lo aisló de abscesos subcutáneos producidos por inyecciones de vitaminas. En 1955 fue perfectamente caracterizado por Gordon y Smith, pero no fue hasta 1972 cuando se aceptó definitivamente el nuevo nombre. Durante muchos años la cepa aislada por Da Costa Cruz se ha utilizado como cepa tipo de *M. fortuitum biovar fortuitum*. Las especies que integran el complejo *M. fortuitum*, *a* diferencia de las que integran el complejo *M. chelonae*, reducen los nitratos a nitritos y asimilan el hierro del citrato de hierro amoniacal dando lugar a colonias de color marrón oscuro en medio de Löwenstein-Jensen al que se ha incorporado este compuesto.

Son responsables de infecciones cutáneas polimórficas, queratitis, endoftalmitis, artritis supurativas, osteomielitis, endocarditis, meningitis, peritonitis, infección urinaria crónica, otitis media secundaria a la implantación de tubos de timpanostomía y bacteriemias asociadas a catéteres [11].

El tratamiento predeciblemente más eficaz frente a estos microorganismos es la escisión quirúrgica de todos los tejidos afectados. Desafortunadamente, esto no suele ser posible en la mayoría de casos y debe utilizarse tratamiento con antibióticos. *M. fortuitum* es generalmente sensible a la amikacina, cefoxitina, imipenem, ciprofloxacino, ofloxacino, sulfonamidas, claritromicina, y un 40% de las cepas son sensibles también a la doxiciclina. Se utilizan generalmente combinados en esquemas extensos, de varios meses de duración [12].

Siempre se debe sospechar infecciones por micobacterias no tuberculosas, en lesiones inflamatorias de curso crónico y con falta de respuesta a los tratamientos antibióticos habituales [4].

El diagnóstico correcto y el tratamiento precoz constituyen son los retos más importantes a los que nos enfrentamos con este tipo de microorganismos. El proceso diagnóstico en este caso ha sido largo y engorroso, y se ha tenido que recurrir a múltiples biopsias, y técnicas de avanzada Biología molecular para determinar la etiología de las lesiones cutáneas; el diagnóstico se realizó mediante Reacción en Cadena de Polimerasas asociada a Análisis de Patrón Enzimático (PRA).

El caso presentado está relacionado a un viaje y contacto con el mar y corales, sin historia previa de procedimientos quirúrgicos o invasivos, en paciente inmunocompetente, con buena evolución luego de tratamiento dirigido.

CONCLUSIÓN

Las micobacterias atípicas pueden causar infecciones de piel, tejido celular subcutáneo y otros aparatos y sistemas; generalmente son no patógenas en seres humanos, pero las infecciones están en aumento debido a condiciones de inmunosupresión. Se presenta el caso de una mujer de 61 años de edad, aparentemente inmunocompetente, que presenta lesión cutánea que empeora luego de la inmersión en el mar en México, recibe tratamiento infructuoso por dos meses, y tras múltiples biopsias para histopatología y cultivos, se detecta por biología molecular con Reacción en Cadena de Polimerasas asociada a Análisis de Patrón Enzimático, infección por *Micobacterium fortuitum*, se realiza tratamiento antibiótico dirigido con óptima resolución.

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Our Dermatology Online

Case Report

Terra firma forme dermatosis and plica neuropathica - case report

Rakesh Bharti

Department of Dermatology, Bharti Dermacare and Research Centre, Amritsar, Punjab, India

Corresponding author: Dr. Rakesh Bharti, E-mail: rakeshbharti1@gmail.com

ABSTRACT

Although Dirty Duncan Dermatosis and Plica Neuropathica are two different entities. Yet they have a common denominator of disturbed state of mind. Presenting here a case, who suffered from both,but forty years apart and with disturbed state of mind both times.

Key words: Terra firma-forme; Duncan dermatosis; Dermatitis neglecta

INTRODUCTION

Duncan first described this condition,less than thirty years ago [1]. The addition of words "Dirty Dermatosis" gives a feeling that this may be related with not so good hygiene of a person. TFFD however is distinguished from Dermatosis Neglecta arbitrarily by presence of adequate hygiene [2,3].

Plica neuropathica, also called plica polonica, felting or bird's nest hair, was first described by Le Page in 1884It too presents as a compact mass of scalp hair with irregular twists and irreversibly entangled plaits that form a firm to hard impenetrable mass of keratin cemented together with dirt and exudates. it has been attributed to longitudinal splitting or weathering of hair shaft due to vigorous friction and frequent use of harsh shampoos and harsh cleansers; and/or due to keeping of long hair with poor hair care or its neglect. This entity has been also found to be more frequent among psychologically disturbed women due to the repeated manipulation of the hair [4-8].

Do the two conditions have anything in common.

This is a case report just as to create awareness about the TFFDso as to facilitate prompt diagnosis,avoid unnecessary invasive investigations (biopsy) and endocrine evaluation and also to give readers a food for thought-thought of linkage of two disorders in mind.

CASE REPORT

53 year old man presented with four weeks or so history of an asymptomatic brown rash on thighs, and legs. The patient assured daily shower with good quality soap and was not having any bad body odor at all. He gave the history of some disturbed state of mind due to his son's failure to get a VISA. On further interrogation, he revealed history of some hair dreadlocks in childhood, just like Indian sadhus, after his failure in a class (suggestive of mental stress) He remembered that he has to get his head shaved due to those stranded hair in childhood.

Physical examination revealed palpable, papillomatous blackish plaques on both thighs and legs. The examination also revealed that he is a hairy guy. Suspecting TFFD, the black pigmentation was tried to be rubbed off with spirit, but to limited success. The patient was then asked to go home, take a shower and use a hard scrub. Patient returned after about an hour,with no change in the clinical picture. At this juncture then, isopropyl

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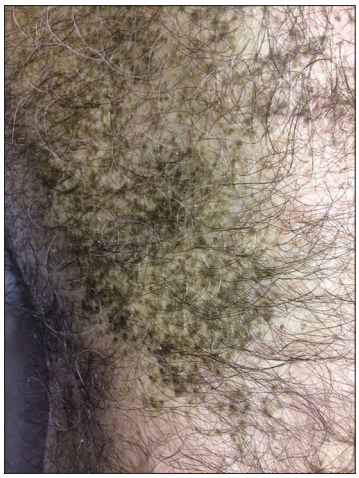

Figure 1: Before cleaning with Isopropyl alcohol.

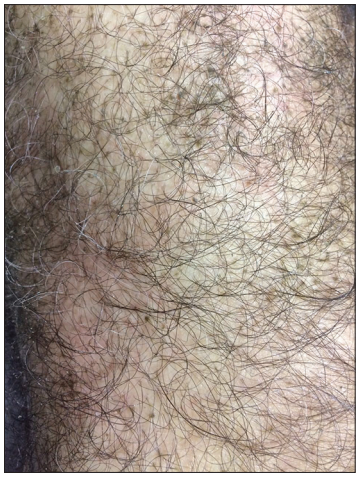

Figure 2: After cleaning with Isopropyl alcohol.

alcohol was procured from a nearby laboratory and a sample area could then be completely rubbed off blackish pigmentation (Figs. 1 and 2). Patient was sent off with the instructions about the method of cleaning with Isopropyl alcohol, a session of counseling to cope up with his mental tension and prescription of clonazepam 0.25 mg at bed time for two weeks.

DISCUSSION

Terra firma-forme dermatosis derives its name from the: Latin phrase terra-firma meaning dry land (dirt). The condition was first described by Duncan and thus also known as Duncan's dirty dermatosis, so as to honor the physician first describing it. Terra firma-forme dermatosis is characterized by brown, dirt-like discoloration that cannot be removed by bathing with water or rubbed off with routine detergent soap. It has most often been seen in children, but it has also been described in adults. The condition most often involves the neck and trunk but has also been reported on the scalp] and the pubic region.In my case it involved both thighs and legs.

The cause of the condition remains unknown. The condition, however may look like Acanthosis nigricans, lichen amyloidosis, confluent and reticulated papillomatosis or dermatitis neglecta even. If suspected rubbing with isopropyl alcohol with some persistant pressure, dirt my come off, as it occurred in my case. This simple trick then, can save the patient from undergoing invasive investigations like biopsy and detailed endocrinological blood tests [2,3].

Plica neuropathica first described by Le Page in 1884 was attributed to the strange occurrence to nerve force by him but was considered a "visitation from God' by the parents of his case, a 17 year old girl [4,5]. This condition is also common among Indian Sadhus (ascetics), who do not take care of their hair and don't trim them. People have entangled plaits that form firm to hard impenetrable mass of keratin cemented together with exudates and dirt. The exact aetiopathogenesis of this condition is not known. It has,however, been attributed to longitudinal splitting or weathering of hair shaft due to friction, frequent use of shampoo and or keeping long hair with poor hair care or its neglect [6,7]. This entity has also been found commonly in psychologically disturbed persons due to repeated manipulation of hair [5,8]. In the present case of TFFD, patient gives the history of Plica neuropathica in childhood and also history of some mental disturbances at present. This makes me think of a common linkage of physical and mental status of TFFD. More insight, however is needed.

CONCLUSION

Although Terra Firma –forme Dermatosis and Plica neuropathica appear to be two distinct entities altogether, yet the occurrence of two in the same person (separated by forty years) with disturbed state of mind, failure in exam in childhood and failure of his child in later life, gives us a food for thinking. Also, considering the condition by an alert dermatologist can save the patient from invasive and elaborate investigations.

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Our Dermatology Online

Review Article

Modern approach to facial skin defects reconstruction

Mateusz Kister[1], Katarzyna Borowska[2], Michał Gontarz[1], Bartłomiej Zoń[3], Grażyna Wyszyńska-Pawelec[1], Jan Zapała[1], Barbara Jodłowska-Jędrych[2]

[1]Department of Cranio-Maxillofacial Surgery, Jagiellonian University Medical College, Rydygier Hospital, Cracow, Poland. [2]Department of Histology and Embryology with Experimental Cytology Unit, Medical University of Lublin, Poland, [3]Clinical Department of Plastic, Reconstructive Surgery and Burns Treatment, Military Medical Institute, Warsaw, Poland

Corresponding author: Mateusz Kister, mateuszkister@gmail.com

ABSTRACT

Reconstruction of a facial defect is usually a challenging endeavor. The article aims to describe different types of flaps that might be used to restore such deformities- including their characteristics, indications and guidelines that should be followed in the reconstructive procedures.

Key words: Facial deformities; Flaps; Head and neck skin reconstruction

INTRODUCTION

Facial deformities are tremendously challenging conditions that in majority of cases require a reconstruction. They might be congenital or acquired and depending on their severity the following defects are distinguished: craniofacial, maxillofacial and dento-facial. In some instances, facial defects might be caused by the surgical intervention especially when the objective of a surgery is tumor resection.

Head and neck skin cancers constitute up to 12.2% of malignant tumors in Poland. Among all of them Basal Cell Carcinoma (BCC) is the most common. Due to its nature and prognosis, the most up to date protocol states that it should to be resected with at least 4 mm margin of healthy tissue [1]. The more malicious the tumor is, the wider margin of a healthy tissue needs to be resected. For example, for Squamous Cell Carcinoma (SCC) 1 cm of healthy tissue margin needs to be surgically removed and when it comes to malignant melanoma (MM) the value of pT indicating the size of the tumor is the determinant. Adequate margins of 4 mm for low-risk SCC and 6 mm for high-risk SCC have been demonstrated by direct tumor extension from the clinical margin, BCC's more than 2 cm require margins as wide as 10 mm, as do tumors with aggressive histological growth patterns, such as superficial BCC of the trunk and morpheaform lesions. A 2 mm margins yields a cure rate of 94% in small (less than 1 cm) nodular BCC. Margins of 3-5 mm around a tumor and extending into subcutaneous fat are recommended for primary BCC less than 2 cm in diameter. Every type of tumor requires unique approach which is outlined by World Health Organization (WHO). Based on clinical experience those requirements are being constantly updated to get the best possible results.

The reconstruction of a facial defect is not an easy endeavor, as it involves a comprehensive understanding of human anatomy, facial defect itself- its location, prognosis; patient age and general condition. Moreover, the surgery itself requires a skillful operator capable of handling both hard and soft tissues to obtain good aesthetic and functional results [2].

The timing of the reconstruction depends, among other factors, upon the type of a facial defect. Many of the congenital facial deformities require reconstruction shortly after birth and might involve more surgical interventions in the future in order to accomplish the desire effect. The same goes for the surgical approach, as it can vary in invasiveness, aesthetic outcome, length of the procedure, safety of the patient and the long-term prognosis.

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The correction of skin defects includes direct closure, local flaps, tissue grafts and free tissue transfers [3] (Fig. 1). Local skin flaps, when designed and performed in proper manner, allow prompt reconstruction with sufficient blood supply, fast healing time and acceptable visual outcome.

The term *flap* originates from the Dutch word '*flappe*', meaning something suspended extensive and loose, attached only by one side [4]. The term 'flap' refers to a unit of soft tissue that is being transferred from one site to the other while keeping its own sufficient blood supply by the pedicle. When the unit of tissue is being transferred without its own blood supply then it is referred to as a tissue graft. Appropriate preparation of a skin graft takes more time than reconstruction involving skin flap, but the latter should potentially bring better aesthetic result [5].

The site from which the tissue is being harvested is often referred to as a donor site while the recipient site applies to the region to which the graft is transferred to. The history of flap surgery dates back to 600 BC when nasal reconstruction by soft tissue flap harvested from patient's cheek has been mentioned for the first time [4].

Every surgeon aims for the best possible aesthetic outcome, thus the subunit principles should act as the foundation for a proper restoration. Attention should be paid to the unique colour, shade and texture of a skin, hair growth or subunit junctions as no single flap is ideal for each and every deformity. Every patient and each defect should be treated as an individual case for which a detailed analysis should be made and a long-term prognosis assessed. Skin flaps vary in shape and form and they range from a non-compound units of skin to being a composite of few different types of tissues including muscles, bone, fascia or fat.

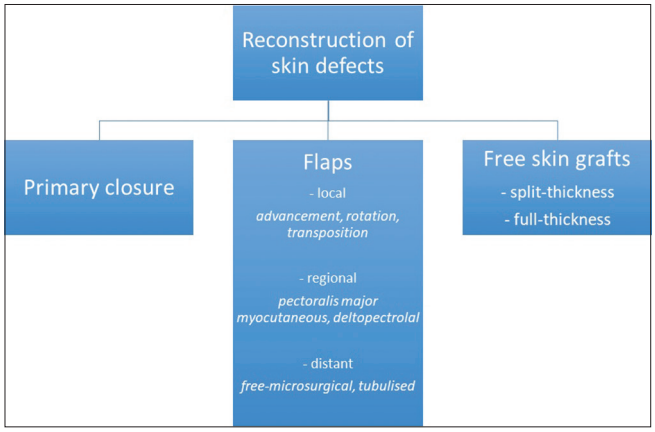

Figure 1: Types of skin reconstruction.

It is not our objective to discuss in details different types of flaps as we aim to outline the general characteristics associated with different flaps based on our clinical experience and up to date literature.

Guidelines for correct flap design

Every reconstructive procedure requires detailed planning and comprehensive preparation as each case is unique. First thing that should be considered is a selection of the exact donor site that would provide sufficient tissue for the reconstruction [6]. Also, the way of closing the donor site should be considered at this point. The most common approaches include skin flap or skin graft transferred from distant or nearby location [7].

Other things, like requirements of shade, texture, size, presence of hair or its lack, size and thickness of skin should also be addressed in order to achieve the best possible functional and aesthetic outcome. Additionally, any possible risks for patient, probable side-effects and complications of surgery should be assessed. Next, preparation of the recipient site should follow.

Skin flaps are transferred from donor site to the recipient site sustaining their own blood supply. It is crucial that they retain their vascularity. That is why the most fundamental rule that needs to be obeyed when planning flaps in the head and neck region is the ratio between pedicle width and length of the flap which should be 1:2-1:6.

There are several ways by which a skin flap can be expanded. In some cases, an artificial expander can be placed underneath the designed flap. The other option is to line the flap with skin graft in a two-stage procedure, when second step will follow the first surgical intervention in approximately 14 to 21 days. The partial rising of a flap that is left in its original location will aid to its expansion and improvement of vascularity. This phenomenon is being explained by the occurrence of vasodilation that is said to last between 18 and 36 hours after the skin flap is raised. It should be noted, however, that vasodilation does not occur during the second surgery. Nonetheless, the technique of delaying the flap improves its blood supply and decreases the chances of ischemia and flap necrosis. That is why it is commonly used in more advanced and challenging reconstructions [8].

Different types of reconstruction

Simple excision that is followed by wound closure with released wound edges is considered to be one of the simplest procedures of removing skin tumors. This method usually brings satisfactory aesthetic outcomes [9,10] (Fig. 2). Even better results can be obtained when the course of the RSTL (relaxed skin tension lines) is obeyed. That type of lines was introduced by Borges and appears across whole body, mostly overlapping with natural folds with the exceptions of nose, lower lip and chin [11].

In most cases the simplest methods of reconstruction, including skin grafts, should be considered before more complex techniques are implemented. The most common donor sites for skin grafts harvested in the head and neck region are retro-auricular area and clavicular region, due to suitable shade and texture comparable to facial skin (Fig. 3).

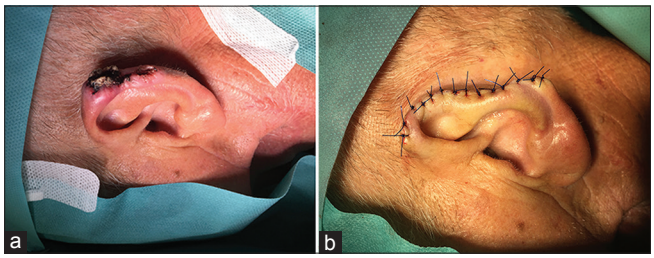

Figure 2: Simple excision technique presented on patient's left ear helix. Performed under local anesthesia.

Depending on the site to which the flaps are transferred, the regional and distant flaps are distinguished. The latter, which are used to cover nonadjacent deformities, might be raised as free microvascular flaps [10]. Free flaps are transferred from a donor site with own vascular pedicle and anastomosed to recipient vessels by microsurgical methods. The tubulised flap (Filatov flap), on the other hand, is moved from donor site to the other with its lateral borders sewn together which results in lower risk of infection and contraction of the flap. Its new blood supply will come directly from the distant pedicle of the flap. The regional flap is moved from donor to recipient site and pedicle is cut after two to three weeks [9,10,12] (Fig. 4).

Local flaps are categorized according to the following criteria: composition, type of blood supply, method of movement. Composition refers to the tissues from which the flap is formed. As far as the blood supply is concerned, it can be random based on the rich subdermal vascular plexus or axial- getting its blood supply form a certain blood vessel. Yet, a lot of the head and neck flaps have random blood supply. The third feature - method of movement, is the most important. Based on the type of movement, advancement, interpolation, transposition and pivot/rotation various flaps are distinguished [9].

An advancement flap is relocated in only one direction- in a straight path into the defect. It is commonly

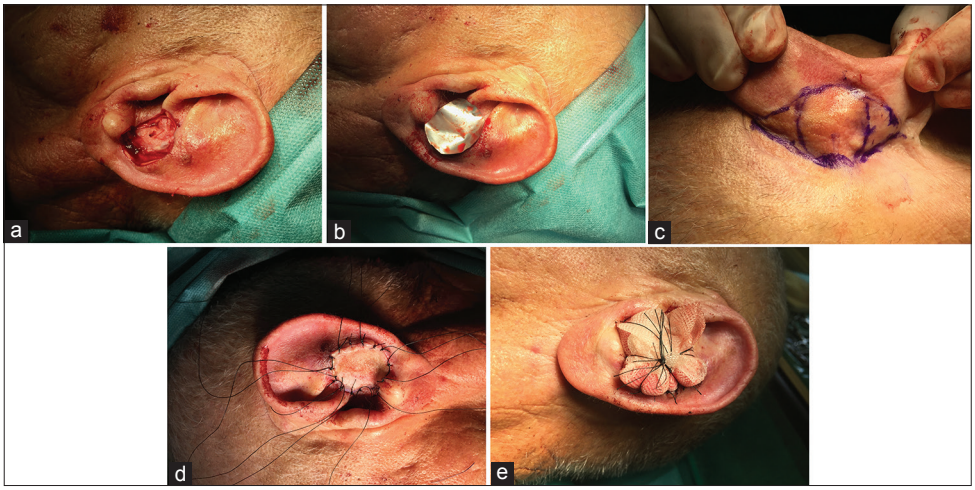

Figure 3: Full-thickness skin graft from retro-auricular site for defect reconstruction. Performed under local anesthesia. (a). The BCC excision with adequate margin. (b). The operative wound is measured using prepared matrix (usually sterile suture packing). (c). Using our matrix, the diameter of full-thickness skin graft is planned. Surgical blade is used to harvest a full-thickness skin graft. The wound outline is initially marked over the donor region. Usually its size is increased by 3-5% to compensate for primary contracture. Firstly, skin is incised and lifted with a skin hook. Any residual adipose tissue must be removed from the underneath of the graft since fat is poorly vascularized and can obstruct direct contact between the graft and the transplant area. Both full thickness and split grafts can be so called 'pie-crusted' that would let wound fluid to leak through the graft rather than cause its accumulation and thus preventing adherence. (d). The graft restoring wound is sutured using once short once long silk suture. (e). Sterile sponge covered in Xeroform net is tied using prepared sutures pressing the graft into the wound base. This would be removed after 5 days leaving all the sutures short for the next 5 up to 10 days.

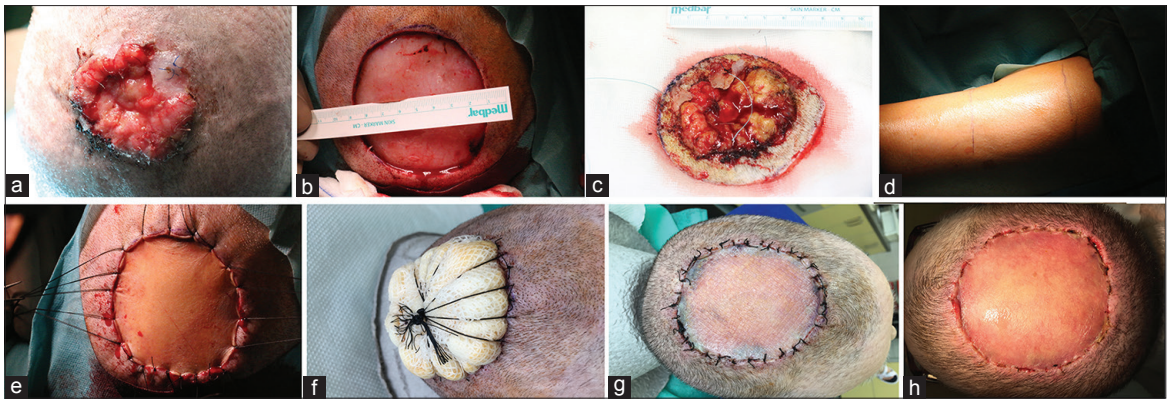

Figure 4: Split-thickness skin graft used for reconstruction of an extensive scalp defect. Performed under general anesthesia. (a). 90-year old patient with advance BCC of the scalp. (b). Post – excision of BCC. (c). Excision of basal cell carcinoma with the margin of macroscopically healthy tissue. (d). Left tight. The outline of the graft has been marked. Device called 'dermatome' is used for harvesting split-thickness skin graft where the depth and size of needed graft can be selected. Skin has been lubricated with paraffin prior to the usage of a device. (e). Placement of the skin graft. (f). "Tie-over" bolster dressings constructed from foam rubber Xeroform folded over moistened cotton balls or sponge is required for correct healing process. (g). Early removal of surgical dressing 5 days postop. (h). Removal of all remaining sttiches. Wound heals properly.

used in cheek, eyebrow, as well as forehead. It should be noted that Burrow's triangles excision at the base of the flap are crucial in order to prevent skin from 'dog-ear' formation [3]. A V-shaped flap is a unique type of an advancement flap used to restore a facial defect, especially on a cheek. After the donor site is closed, Y shaped suture line remains. The V-Y flap, on the other hand, is pushed rather than overextended into the defect and it causes a suture line of Y configuration [12].

Transposition flap is another type of flap. It should be longer than the defect, as transposition reduces its length. The flap moves laterally into the defect and the donor site might be closed either directly or indirectly. Examples of this kind of tissue restoration include Z-plasty, S-plasty, bilobed flap, the rhomboid flap, kite flap (Fig. 5).

The S- plasty in many instances can yield more aesthetically desired outcome for excision of a contour of a skin lesion without the necessity for a flap surgery. The procedure itself is quite simple: outline skin lesion to be removed by marking the S-shape around the lesion, make the S-shaped incision, secure hemostasis and place sutures. The advantages of this technique include, easier control of the wound tension, good aesthetic outcome and amplified length to width ration due to S-shaped incision [13].

The kite flap is a triangular flap attached to the subcutaneous tissue. It is one of the most efficient ways of reconstructing minor to medium sized cheek defects. This method is believed to have a practical and

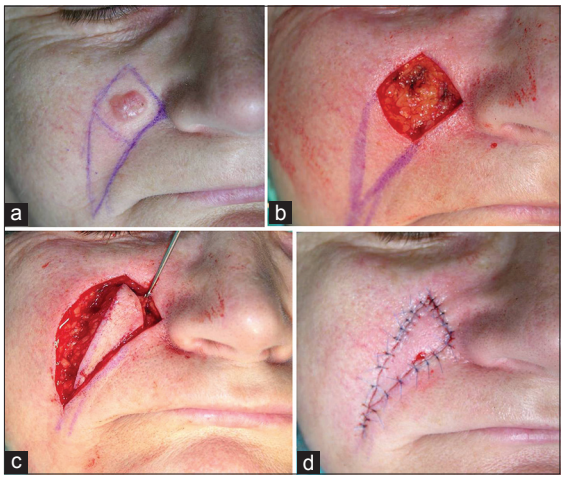

Figure 5: Island flap. Performed under local anesthesia. (Kite flap with a deep pedicle on the cheek used to reconstruct the operative defect with reshaping nasolabial fold. This kind of flaps supplies blood on vertical perforating vessels emanating from a deep source).

aesthetic advantage especially when compared to skin grafts or other local flaps in the cheek [14].

Reconstruction of lip and nasal defects

Lip and nasal defects are considered to be tremendously challenging to restore as they form the central part of the face.

In case of pathological lesions of the lower lip, W-Y excision often combined with vermilionectomy is used. The larger lesions, may require more invasive approach like Karapandzic, Bernard, Abbe, Estlander flaps. A recent 25-year retrospective study involving 2,152 patients with lip cancer revealed that 81 percent lesions occurred on the lower lip and higher prevalence was noted in males [12].

The purpose of the lip reconstruction is to restore the continuousness of the orbicularis oris muscle, mucous membrane and skin tissue. In order to achieve the best aesthetic outcome, the attention should be paid to the facial symmetry both at rest and during facial movements (Fig. 6).

Nasal deformities are among of the most perplexing facial defects to correct due to their complex structure, involvement of many components – mucosal lining, skin, bone, cartilage and vast variation of the skin tone and texture.

It is believed that the nasal tip and the lower third of a nose are the most challenging to restore. Probable restorative options include, skin graft, bi-lobe flap, single lobe flap, nasolabial flap, forehead flap or dorsal nasal flap [15]. The latter one, which consists of dorsal nasal skin from upper two thirds and glabella, is the most commonly used.

The dorsal nasal flap has many advantages: an excellent aesthetic result due to skin tone and texture match, acceptable scar and single stage method. Yet, the dorsal nasal flap cannot be used in defects of the nasal tip that are wider than 2 cm in diameter (Fig. 7).

The forehead flap and nasolabial fold flap are considered to be the gold standard for nasal reconstruction, as both have reliable pedicle and provide amount of tissue sufficient for reconstruction of practically all nasal defects, including complex defects of nose and cheek (Fig. 8).

Figure 6: The W-Y plasty. Performed under general anesthesia. (a). One-stage SCC on lower lip excision combined with vermilionectomy procedure and selective bilateral neck dissection. (b). Patient is using nasogastric tube which provides quicker healing process. (c). Symmetry and maintained function 2 years after surgery

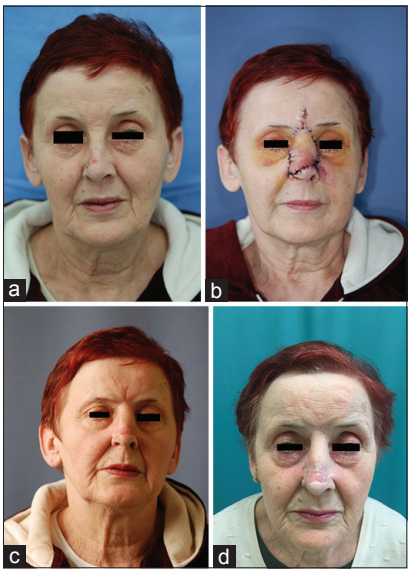

Figure 7: The Daniel Marchac's (lateral nasal) flap. Performed under general anesthesia. (a). 70-year old patient who underwent several procedures of simple non-radical excisions of BCCs from nasal skin in other medical units. (b). At our Department patient was qualified for the wide excision of postoperative scars and immediate flap reconstruction. In this type of reconstruction, the combination of V-Y and Z-plasty closure was used in glabellar region. (c). Short term result after sutures removal. (d). Result after 1 month.

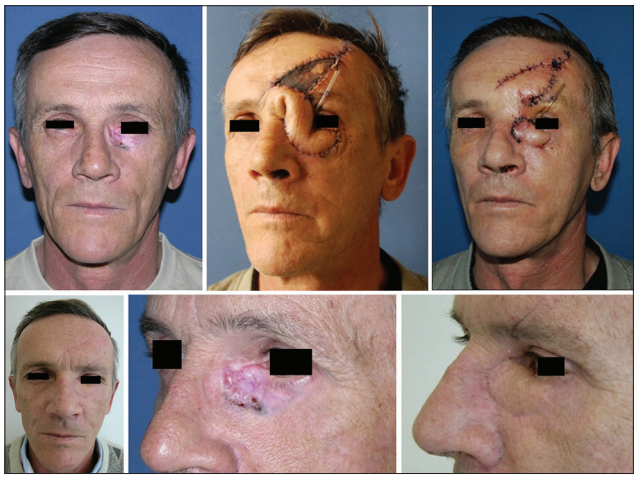

Figure 8: Supratrochlear artery (off-midline) forehead skin flap. Also, known as the Millard's flap, the surgeon who contributed significantly in its design. Performed under general anesthesia. (Two stage procedure containing surgical intervention followed by the carrier segment section after 14 days. In this case because of close infiltration to lower eye lid the lacrimal canaliculus was found and protected by plastic tube with open inside before making any cuts. The defect left by the carrier segment is closed in two layers and that left by the paddle is covered by split-thickness skin graft taken from thigh).
Photographies have been originally published in Zapała J, Wyszyńska-Pawelec G. "Wybrane Zagadnienia z Onkologii Głowy i Szyi".

Examining the skin flap

Once a flap has been successfully planned and implemented, the attention should be paid to monitoring its viability. This principle applies to every kind of facial flap. A prompt identification of ischemia and blood congestion, is crucial in averting subsequent flap necrosis and flap failure. Clinical observation is considered to be the best method to evaluate a skin flap. Based on the color of a flap the initial assessment might be made, as a very pale flap may indicate arterial deficiency, whereas a blue one - a failure of venous outflow. Additionally, an evaluation of a bleeding time after puncturing the flap with a small needle is still assumed to be one of the most trustworthy methods of clinical evaluation [10,16,17].

Objective tests, like pH monitoring, Doppler ultrasound [17], surface temperature monitoring, thermography [16,18] or transcutaneous oxygen tension (pO2) [18,19,20] can be helpful in early detection of flap ischemia [17-19].

CONCLUSION

The aim of reconstruction of facial skin defects is to obtain the best possible aesthetic and functional result. Every case should be approached in an individual manner as no two patients, nor two facial defects are the same. Although we have described many various flaps, based on our clinical experience and it can be concluded that local flaps provide the most satisfactory results and should be considered as the first choice for the reconstruction of facial defects.

The success of the restorative surgery not only depends on the selected technique, or the type of flap used, but also on the skills of a surgeon performing the reconstructive procedure.

Through the last few decades rapid progress in microsurgical techniques is observed and free tissue transplants can now be used more frequently in reconstruction of skin defects. Although, free flaps enable to reconstruct large defects, their colour and texture differ from facial skin.

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Our Dermatology Online

Clinical Image

Outcome of psoriasis vulgaris on a child with localized scleroderma

Mariem Mohamed, Ines Lahouel, Jameleddine Zili

Dermatology Department, Fattouma Bourguiba University Hospital, Monastir, Tunisia

Corresponding author: Dr. Mariem Mohamed, E-mail: mariemmohamed79@yahoo.fr

A 13-year-old girl was followed by our department for linear morphea type of the right thigh. The diagnosis of linear scleroderma was held on the clinical appearance and skin biopsy data. She was treated by a daily application of a topical combination of a corticosteroid and an analog of vitamin D (Daivobet® ointment) leading to stabilization and softening of the lesion (Fig. 1). Eight months later, the patient developed non-pruritic erythematous and squamous plaques localized on the morphea monomelic plaque and healthy skin (Figs. 2a and 2b). The diagnosis of psoriasis vulgaris was retained from the clinical and histological features.

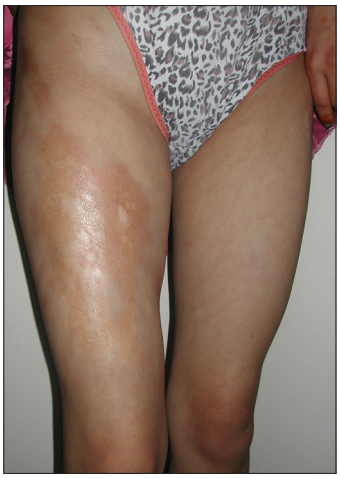

Figure 1: Linear monomelic morphea in the right thigh.

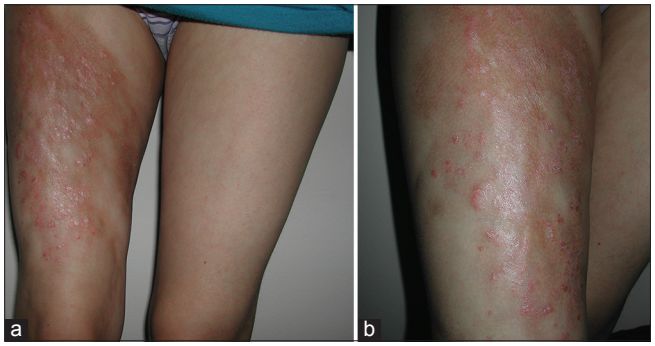

Figure 2: (a and b) Non-pruritic erythematous and squamous plaques localised on the morphea monomelic plaque. There are no lesions in the other healthy thigh.

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Our Dermatology Online

Clinical Image

Sarna noruega en un paciente inmunodeprimido [Norwegian scabies in an immunocompromised patient]

Patricia Chang[1], Zonia María Quijada Ucelo[2]

[1]*Department of Dermatology, Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala,*
[2]*Residente III de Medicina Interna Hospital Universitario Esperanza, Guatemala*

Corresponding author: Dra. Patricia Chang, E-mail: pchang2622@gmail.com

Paciente masculino de 50 años de edad, diabético hospitalizado en el Servicio de Cirugía por síndrome pulmón atrapado con ventana torácica por tuberculosis pulmonar en tratamiento con antifímico con etambutol 1200 mg, isoniazida 300 mg y rifampicina 600 mg cada día desde hace 1 mes, que por presentar lesiones escamosas de piernas y pies se realiza interconsulta a dermatología.

A la evaluación dermatológica presenta dermatosis diseminada a tórax anterior, espacios interdigitales de manos, miembros inferiores con predominio en su tercio distal, dorso de pies (Figs. 1 et 2), alrededor de los ortejos (Figs. 3a et 3b) y planta de los pies constituida por placas escamosas, algunas de éstas de color amarillento con aspecto psoriasiforme, costras hemáticas (Fig. 4). Resto del examen físico paciente caquéctico en malas condiciones generales y nutricionales.

ANTECEDENTES FAMILIARES NEGATIVOS

Inicia su padecimiento hace 7 meses con aparición de ligera picazón en diferentes partes del cuerpo la cual se fue aumentando y en el último mes la piel se volvió muy seca y sumamente pruriginosa, solo había estado recibiendo para su resequedad aceite mineral 2 veces al día.

Con los datos clínicos se diagnosticó sarna noruega, por lo que se realiza examen directo y microscopia de las escamas de la región subungueal del primer ortejo derecho y de las placas escamosas del dorso de los pies.

El examen directo del primer ortejo mostró la presencia de un acaro (Fig. 5) y la microscopia de huevos de *Sarcoptes scabiei* (Fig. 6)

Se le administró tratamiento vía oral con ivermectina a 200 mcg/kg de peso con buena respuesta al tratamiento con 3 dosis de ivermectina.

COMENTARIO

La escabiosis o sarna es la infección parasitaria causada por el ácaro *Sarcoptes scabiei* variable *hominis*, que resulta en una erupción con intenso prurito y con un patrón característico pápulas con distribución corporal en axilas, codos, glúteos, área genital y peri umbilical. En su forma más severa esta condición clínica es llamada sarna costrosa o noruega, se da en pacientes con algún tipo de inmunosupresión y con otras características clínicas, que se mencionaran adelante [1,2].

Con una prevalecía mundial alrededor de 300 millones de casos al año, lo que ha significado un serio problema de salud pública en países desarrollados y tercermundistas. La sarna ocurre en ambos sexos, en todas las edades, grupos étnicos y niveles socioeconómicos; predomina en invierno y es favorecida por malos hábitos de higiene [2,3]. La cantidad de parásitos en una persona se correlaciona con el índice de contagiosidad, ya sea

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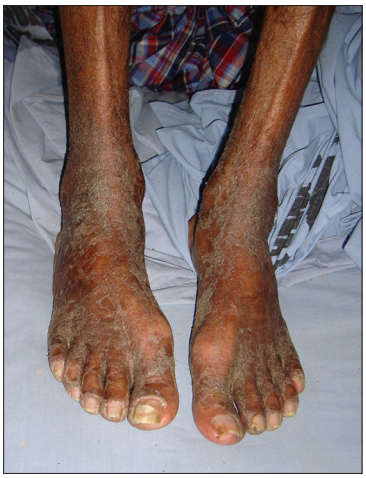

Figure 1: Placas escamosas en el tercio distal de piernas.

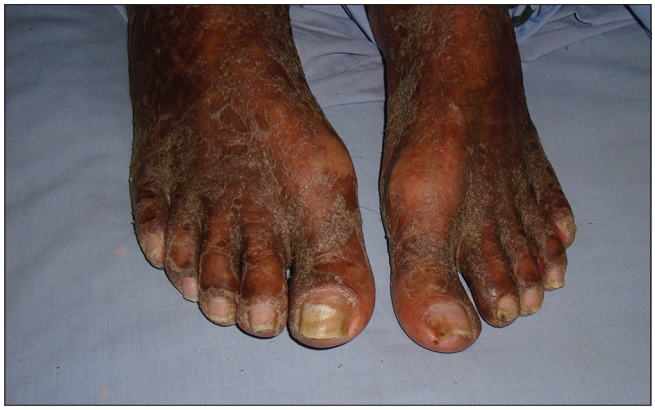

Figure 2: Acercamiento de las placas escamosas en dorso de ortejos.

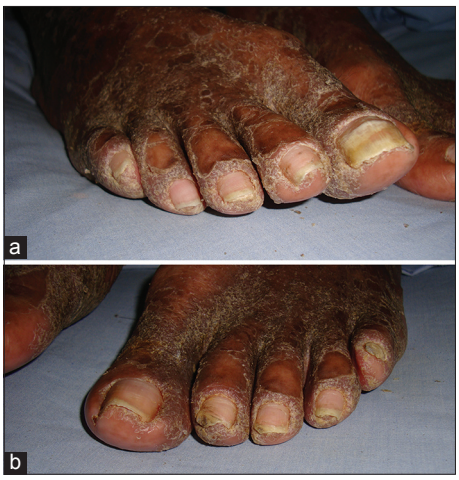

Figure 3: (a, b) Placas escamosas alrededor de los ortejos.

directa (piel a piel) o indirecta (a través de la ropa de cama infestada, ropa u otros fómites). Es común la trasmisión entre miembros de la familia, personal institucionalizado y pareja, predominantemente en homosexuales [1,4].

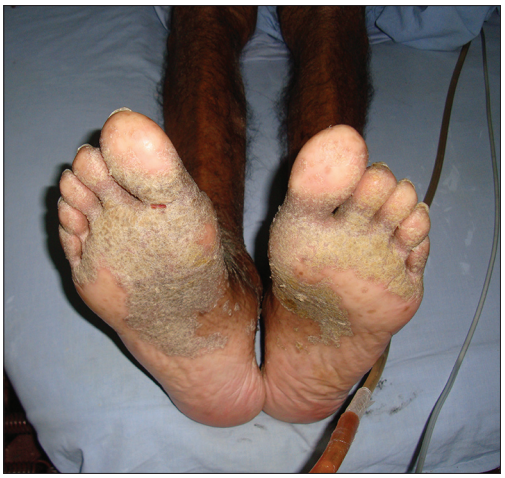

Figure 4: Al examen directo presencia de un acaro.

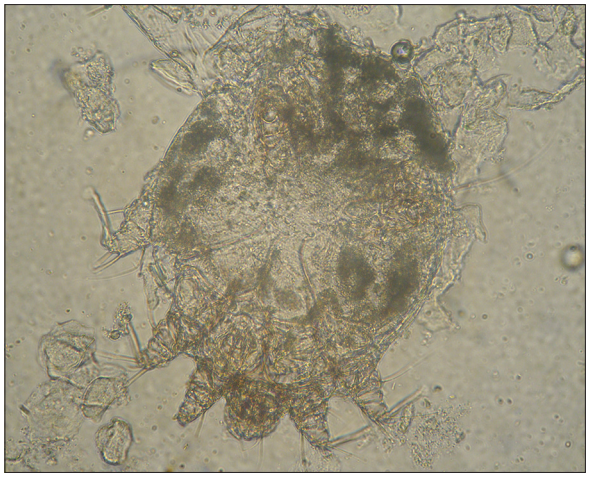

Figure 5: Examen directo presencia de huevos de *Sarcoptes scabiei.*

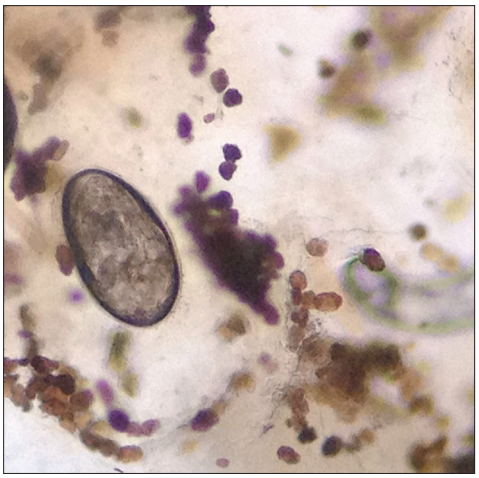

Figure 6: Eggs of sarcoptes scabiei.

Sarna costrosa es una forma altamente infecciosa, por un fracaso de la respuesta inmune del huésped para controlar la proliferación del ácaro en la piel, causando

Table 1: Factores predisponentes para padecer sarna costrosa

Factores de riesgo para desarrollar sarna costrosa.
Trastornos mentales: demencia en adultos mayores, síndrome de Down.
Diabetes mellitus.
Infección por VIH
Malnutrición: déficit de vitamina A, beriberi.
Enfermedades infecciosas: tuberculosis, lepra.
Radioterapia.
Fármacos inmunodepresores: corticoides y citostáticos.
Lesiones medulares: siringomielia, tabes dorsal.
Trastornos linforreticulares: leucemia, linfoma.
Higiene deficiente.
Enfermedades reumatológicas: artritis reumatoide, LES

así hiperinfestación. Este fracaso compromete la inmunidad celular adaptativa y por lo tanto la pobre la respuesta proliferativa linfocítica a estímulos y a algunos patógenos [1,4,5]. La inmunidad celular adaptativa se ve afectada con algunos medicamentos y condiciones como tuberculosis, diabetes mellitus, etc [5].

Factores predisponentes para padecer sarna costrosa son trastornos mentales como síndrome de Down, diabetes mellitus, infección por VIH, malnutrición, enfermedades infecciosas como tuberculosis, radioterapia, fármacos inmunodepresores, linfoma (Tabla 1) [1,2,4,6].

A diferencia de la sarna vulgar, la sarna costrosa puede afectar cualquier parte del cuerpo, pero predominan áreas de presión, particularmente las palmas y plantas, además de cuero cabelludo. Se caracteriza por pápulas rojas, placas psoriasiformes, fisuras, costras hemáticas y placas hiperqueratósicas de color amarillo [6-8]. Otros hallazgos son engrosamiento de las uñas, alopecia, hiperpigmentación, eosinofilia y piodermia con adenopatías. El prurito puede estar ausente y no es tan intenso como en la de la sarna vulgar [4].

El diagnóstico se basa en la historia clínica y distribución de las lesiones. Algunos estudios como dermoscopía, "tape test" y rapado de piel confirman la sospecha, aunque resultados negativos no excluyen el diagnóstico [1,3]. El rapado de piel se realiza en las regiones laterales de las manos, dedos, e hiponiquio que es donde más se concentran ácaros. Se debe tener presente algunos diagnósticos diferenciales como psoriasis, eczema atópico, enfermedad de Darier, dermatitis de contacto, ictiosis e incluso farmacodermia [4,6,8].

Considerando la toxicidad y efectividad de varias terapias, la ivermectina por vía oral y crema de permetrina al 5% son la terapia de primera línea [9]. Se ha reportado que monoterapia con ivermectina vía oral a dosis de 200 mcs/kg ha sido efectiva, algunos autores recomiendan repetir dosis a los 10 ó 15 días. Se ha encontrado curación con una sola dosis en 27.5%, con una segunda dosis en 57.5% y con una tercera dosis en 7.5%. Es decir, 92.5% de pacientes se cura con una, dos o tres dosis. Ha sido de controversia combinar el tratamiento oral con permetrina 5%, ya que en enfermedades tan extensas hay escasa penetración cutánea del fármaco [3,4,8]. El prurito puede ser controlado con antihistamínicos por dos semanas hasta que el tratamiento sea efectivo. Cualquier complicación de infección de tejidos blandos y piel se recomienda de ser tratado con antibióticos sistémicos [1,6].

Del caso presentado, nos encontramos ante un paciente inmunodeprimido con tres situaciones que lo predisponían a padecer sarna costrosa: Diabetes mellitus, tuberculosis pulmonar y desnutrición crónica del adulto, éstas afectaron la respuesta de la inmunidad celular adaptativa del individuo, lo que permitió la proliferación de las lesiones cutáneas; a pesar de esto el paciente tuvo una excelente respuesta con dos dosis de ivermectina

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Our Dermatology Online

Letter to the Editor

Cellular phone dermatitis at an unusual site

Osung Kwon, Yongwoo Choi, Hyun Chung, Joonsoo Park

Department of Dermatology, School of Medicine, Catholic University of Daegu, Namgu, Daegu, South Korea

Corresponding author: Joonsoo Park, M.D., Ph.D., E-mail: ashkwon@naver.com

Sir,

Since Pazzaglia et al [1] reported cell phone dermatitis in 2000, a lot of cases and original articles were reported worldwide. Cellular phone dermatitis is a type of allergic contact dermatitis due to the direct contact with the metal from cellular phone, usually due to nickel. The typical locations of the lesions are ear, cheek, and periocular area [2]. Herein, we report a case of cellular phone dermatitis in unusual location, the buttock.

A 47-year-old woman presented with 1x2cm sized erythematous to brownish patch on her right buttock area (Fig. 1). The lesion started as small patch four months ago. She complained of severe itching and tingling sensation. She did not have any past history of skin disease and denied any allergic condition. The punch biopsy was performed on the lesion. On histopathologic examination, the lesion showed spongiosis of basal layer and lymphohistiocytic infiltration in papillary dermis (Fig. 2). On the next visit under the impression of contact dermatitis, the history was retaken carefully. She reported that she was working in a manufacturing plant and when she was working, she sweated a lot because of the high temperature. She also reported that she often contained her cellular phone in her right back pocket of pants. Patch test was performed using contact dermatitis kit (True test, Smartpractice demark aps, Hillerod, Denmark) and the result showed a 2-day + and 4-day ++ reaction on nickel sulphate (Fig. 3). She was diagnosed as allergic contact dermatitis due to nickel from cellular phone and the lesion got improved after antihistamine and topical steroid treatment.

As the worldwide use of cellular phone is increasing, cases of cellular phone dermatitis is also increasing [3]. Unlike the other cases, the location of lesion was buttock in this case and it was difficult to suspect the cellular phone dermatitis at first sight. In authors knowledge this is the first case of cellular phone dermatitis occurring on buttock. People often carry their cellular phone in the back pocket of their pants, so buttock also should be regarded as occurring lesion

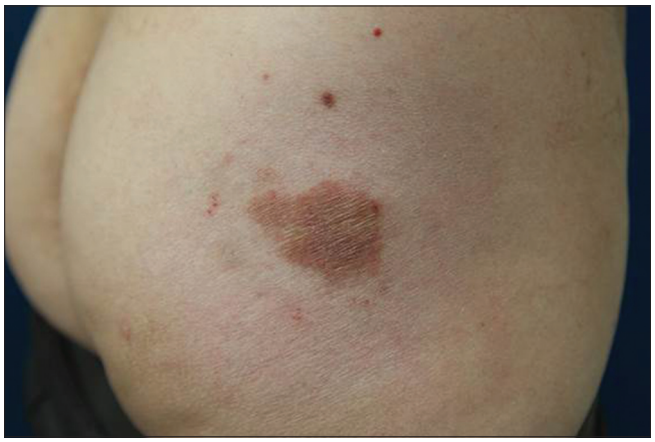

Figure 1: Erythematous to brownish patch on her right buttock area.

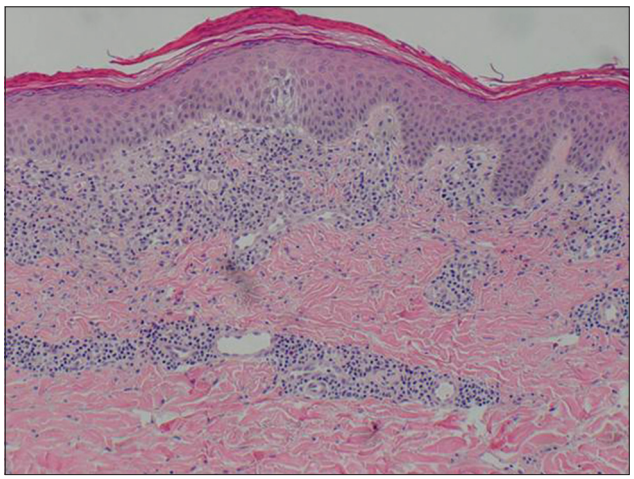

Figure 2: Histopathologic examination revealed sponiosis of basal layer and lymphohistiocytic infiltration in papillary dermis. (H&E, X 100)

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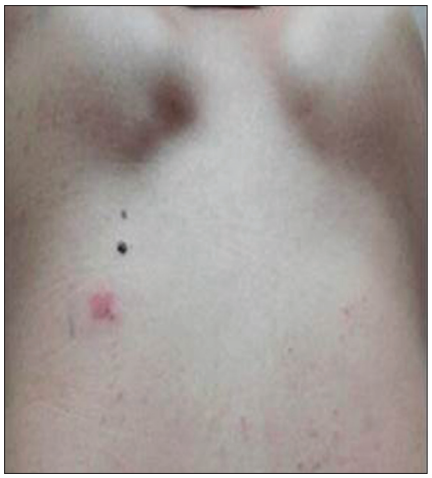

Figure 3: Three months after discontinuing of the drug shows improved skin lesion with noticeably regressed grouped skin colored papules leaving subtle hyperpigmentation.

of cellular phone dermatitis. Also when a patient is in condition of lots of sweating, it could precipitate the penetration of nickel to skin and increase the occurrence of contact dermatitis [4].

In conclusion, cellular phone dermatitis should be considered in the differential diagnosis of contact dermatitis of face, thigh, and buttock as well. If the cellular phone dermatitis is suspected patch test and dimethylglyoxime test may be helpful in establishing the diagnosis.

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Letter to the Editor

Psoriasiform drug eruption provoked by oriental herbal decoction 'Hyeonggaeyeongyotang'

Osung Kwon, Hyun Chung, Joonsoo Park

Department of Dermatology, School of Medicine, Catholic University of Daegu, Namgu, Daegu, South Korea

Corresponding author: Joonsoo Park, M.D., Ph.D., E-mail: ashkwon@naver.com

Sir,

Specialization of treatment in traditional Korean medicine has increased the number of patients seeking traditional medicine, as well as in the frequency of related adverse events. There are currently several medical issues in Korea, including rational issues, due to the use of traditional medicine without the approval of the Korean Food Drug Administration. Herein, we present a case of psoriasiform drug eruption that developed after ingesting a medicinal decoction prepared at a clinic without precise standards for ingredients, method of use, or dosage.

A 5-year-old female patient presented with papules on both knees that accompanied with pruritus, and had insidiously spread for one month. Numerous skin-colored hyperkeratotic slightly annular-shaped papules were elucidated on both knees (Fig. 1). Some of the papules were observed to form clusters. Koebner phenomenon and Auspitz's sign was not present. Two months in prior, the patient visited an oriental clinic to treat rhinitis and was prescribed to take hyeonggaeyeongyotang, an herbal decoction, every day for one month. The patient was generally in good health with no specific family history of skin diseases. Laboratory tests were nonspecific except for elevated liver enzyme. Skin biopsy was performed on the left knee and revealed parakeratosis ith variably elongated epidermis and superficial perivascular infiltration of lymphocytes (Fig. 2a). Higher magnification revealed few eosinophils and flattened granular layer (Fig. 2b). The patient was diagnosed with psoriasiform drug eruption, and was instructed to halt previous decoction. After one week, the lesions began to improve and significantly recovery was noticed after three weeks (Fig. 3).

Psoriasiform drug eruption is a general term for diseases that occur after medication and presents clinical and histological traits similar to psoriasis. Diagnosis is based on histology and a causal relation of medication use is crucial. The disease occurs after medication and improves after stopping medication. The distribution of lesions and scaling are known to be milder than psoriasis. Koebner phenomenon and Auspitz's sign are known to be less common in psoriasiform drug eruption [1].

The relationship between drug and cutaneous eruption was assessed accordingly to the criteria set by and the present case scored a total of 6 points, indicative

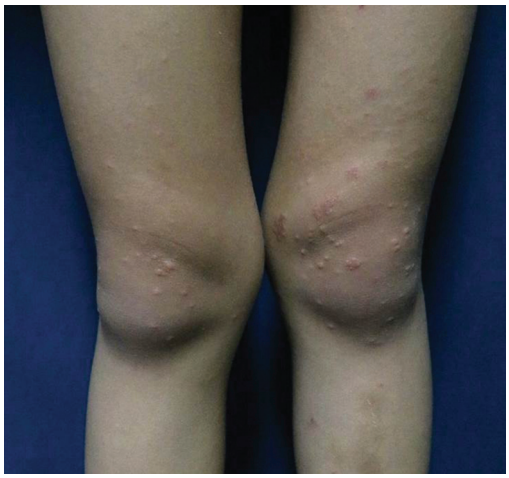

Figure 1: Clinical image on initial visit displaying numerous skin colored hyperkeratotic papules Three months after discontinuing of the drug shows improved skin lesion.

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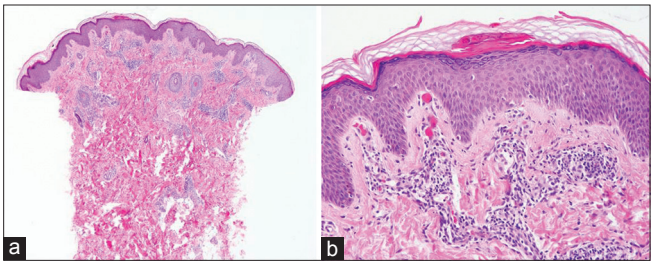

Figure 2: a) Histology revealed irregular acanthosis, focal parakeratosis with variably elongated epidermis and superficial perivascular infiltration of lymphocytes (H&E x20). b) Higher magnification revealed extravasation of clumped erythrocytes with few eosinophils (H&E x200).

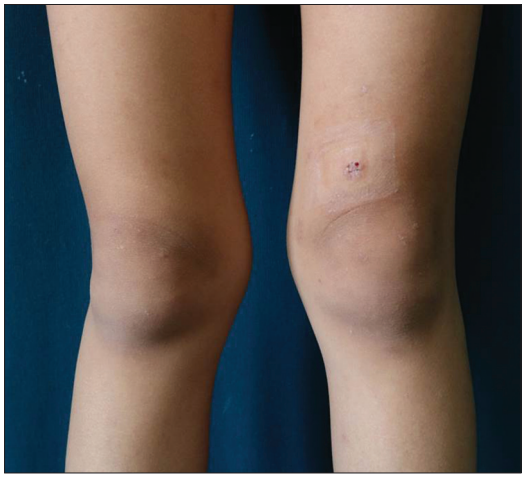

Figure 3: Three months after discontinuing of the drug shows improved skin lesion with noticeably regressed grouped skin colored papules leaving subtle hyperpigmentation.

of a high correlation [2]. The rapid response upon discontinuing the drug along with no other causative factors further supplements a high association between the herbal medication and cutaneous eruption [1,2].

Copious number of adverse effects is being reported after administration of traditional Korean medicine. Kim et al reported that among these event, skin rash was the second most common side effect followed by gastrointestinal symptoms from herbal medications [3]. The patient in our case was prescribed with Hangyeyeongyotang and the ingredients in the prescription contained herbs such as *hyeonggae* (*Schizonepeta tenuifolia*), *yeongyo* (*Forsythia viridissima*), *jisil* (*Poncirus trifoliata*), *gilgyeong* (*Platycodon grandiflorum*), *gamcho* (*Glycyrrhiza glabra*), *danggwi* (*Angelica gigas*), *jagyak* (*Paeonia lactiflora*), and *cheongung* (*Cnidium officiale*). Combining research of these individual ingredients report hepatotoxicity and non-specific skin eruption which was seen in our patient, further suggests likelihood of psoriasiform drug eruption [4,5].

No single case reporting an association between herbal medicine and psoriasiform drug eruption has been reported. Lack of accurate research due to the current system, wherein herbal medicines are prescribed without criteria for ingredients, method of use, dosing may hinder further elaboration. This case underlines the importance of drug ingredient analysis to avoid recurrence and difficulties in treatment and finding the cause of the eruption.

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Letter to the Editor

'Mace sign'- A definitive sign of trichotillomania?

Subrata Malakar[1], Samipa Samir Mukherjee[2]

[1]Department of Dermatology, Rita Skin Foundation, Kolkata, India, [2]Department of Dermatology, Cutis Academy of Cutaneous Sciences, Bangalore, India

Corresponding author: Dr. Samipa Samir Mukherjee, E-mail: drsamipamukherjee@gmail.com

Sir,

Patchy hair loss is a commonly encountered clinical scenario in day to day practice. Alopecia areata and trichotillomania are the commonest differential diagnosis to be considered. Trichotillomania is characterized as an obsessive compulsive hair pulling leading to the clinical manifestations of patchy hair loss affecting the vertex or parietal areas. This condition resembles alopecia areata (AA), since both disorders are initially non-scarring and may be patchy. Dermoscopy serves to be an important non invasive tool for differentiating between the two. Although multiple signs and features of both the entities have been described in literature till date a specific feature to distinguish between the two still remains elusive. We herein try to describe the 'Mace' sign which to the best of our knowledge is the most specific diagnostic feature of trichotillomania.

We had three different patients visiting our out patient department with history of patchy hair loss. The details of the patient profile has been given below (Table 1). All the three patients were diagnosed clinically as trichotillomania and dermoscopy was further done to substantiate the diagnosis.

Dermatoscopy is an useful non invasive tool that helps in diagnosis and also has the advantage of increasing patient compliance by actually demonstrating the nature of the problem to the care- givers, bystanders and the patient. Although multiple dermatoscopic features have been described for trichotillomania there is a significant overlap in the findings with other disorders like alopecia areata and tinea capitis to name a few. Fractured shafts are suggestive of trichotillomania, while the presence of exclamation mark hairs is indicative of AA [1]. Another study in 2014 documented the presence of irregularly broken, v-sign, flame hairs,hair powder and coiled hairs.Flame hairs, v-sign, tulip hairs, and hair powder were newly identified in this study [2].

Table 2 presenting Dermoscopic feature.

As it may be seen from the above table that mace sign is a consistent finding in all the three cases of trichotillomania. Although multiple dermatoscopic signs have been described in both the disorder the quest for the most specific sign continues which would clinch the diagnosis. We herein describe the 'mace' sign for broken terminal hairs which are uniform in diameter and pigmentation with a bulging distal end. The bulging distal end resembles the head of a mace and the longitudinal proximal end resembles the handle of the mace (Figs. 1a and 1b). The roughness of the shaft in Mace Sign also points towards manipulation of the hair by pulling and playing with it (Fig. 2).

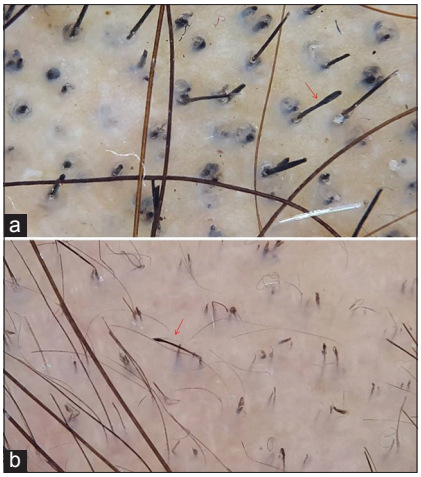

Figure 1[a] and b: Bulging distal end resembles the head of a mace and the longitudinal portion resembles the handle of a mace.

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Table 1: The patient profile and details

	Patient 1	Patient 2	Patient 3
Age	29 years	7 years	16 years
Sex	Female	Female	Male
Clinical presentation	Patchy hair loss since 8 months	Patchy hair loss since 2 months	Patchy hair loss since 3 weeks
Treatment history	Treated with native home remedies	No treatment taken	No treatment taken
Leading question of stress was asked	Positive history	No answer	Negative history
Any other associated findings	History of nail biting	Nil	Nil
Significant history past/family/personal	Nil	Nil	Nil
Examination of the patch	Irregular oval shaped patch on the scalp with broken hair of varying lengths	Irregular patch on the scalp with broken hair of varying lengths	Irregular patch on the scalp with broken hair of varying lengths with similar patchy loss noted over the eyebrow
Provisional diagnosis	Trichotillomania	Trichotillomania	Trichotillomania

Table 2: Dermoscopic features of the scalp involved

Feature	Patient 1	Patient 2	Patient 3
Black dots	+	+	+
Yellow dots	+	-	-
Broken hair	+	+	+
Flame hairs	+	+	+
V sign	+	-	-
Tulip hairs	+	-	-
Hook hair	+	-	-
Hair powder	+	+	-
Vellus hair	-	+	-
Mace sign	+	+	+

Table 3: Dermatoscopic features of mace sign hair, exclamation mark hair and tulip hair comparison

Structural difference	Mace hair	Exclamation mark hair	Tulip hair
Hair shaft characteristics	Bulging at the distal end Uniform hair shaft diameter Hair shaft is rough	Frayed distal end which is thicker Thicker distal end with a narrow proximal end Hair shaft is smooth	Black mark at tip of the hair thus resembling a tulip flower Uniform hair shaft diameter
Colour	Uniform and darker than surrounding hairs	Proximal end is hypopigmented and distal end is hyperpigmented	Light colored hair shafts with dark distal end
Conditions in which it may be seen	Exclusively in Trichotillomania	Alopecia areata, Trichotillomania	Trichotillomania, Alopecia areata.

These mace hairs structurally differ from the tulip hair and exclamation mark hair in the following (see table 3).

We propose that the mace hair sign may be a result of pulling, playing and manipulating the hair by the patient which leads to the structural deformities of the hair. The bulging distal end could occur due to splaying of the end leading to flattening giving the appearance of a bulge in 2 dimensional view.

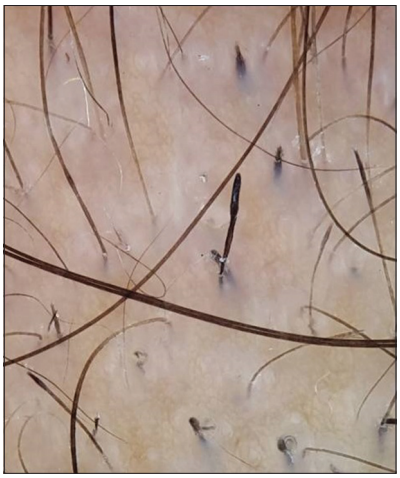

Figure 2: Roughness of the hair shaft noted in a mace sign hair

We believe that this is the first time that this sign is being reported and further continuous observations need to be made regarding this type of hair to deem it as the most specific sign of trichotillomania.

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Our Dermatology Online

Letter to the Editor

Trichoscopy in anagen effluvium: Extensive peripilar sign

Malakar Subrata, Mehta Purva, Malakar Surit

Rita Skin Foundation, Kolkata, India

Corresponding author: Dr. Mehta Purva, E-mail: purvamehta86@gmail.com

Sir,

Peripilar sign also called as perifollicular hyperpigmentation or brown perifollicular discolouration on trichoscopy, denotes a brown halo surrounding a hair follicle. It corresponds to perifollicular lymphocytic infiltrate [1,2]. It is known to occur in conditions like androgenetic alopecia and telogen effluvium. In these conditions, when the peripilar sign is extensively seen on trichoscopy, it is regarded as a poor prognostic factor for hair loss [3,4]. Peripilar sign in also seen on healthy scalp where the perifollicular discolouration is limited to a few hair follicles (<5%) [3].

We present two cases of anagen effluvium where the peripilar sign was extensively seen on trichoscopy (Figs. 1-4).

As mentioned before, peripilar sign has been documented in androgenetic alopecia and telogen effluvium. There are various hypotheses that could explain the occurrence of peripilar sign in anagen effluvium. Although perifollicular inflammation is known to be the cause of peripilar sign; its etiopathogenesis is still unknown in its entirety. It has been postulated that perifollicular inflammation could result due to the effect of ultraviolet rays, chemical exposure, melanocytes etc [5,6].

Patients suffering from anagen effluvium have significant hair loss thus exposing a large surface area of their scalp to ultraviolet rays. This additional exposure and effect of ultraviolet rays could be a contributing factor to perifollicular inflammation in anagen effluvium.

Inui et al have already speculated that the occurrence of peripilar sign in Asians is a result of postinflammatory hyperpigmentation [7]. In our case, both patients being Asian, peripilar sign could be attributed to the presence of melanocytes. This finding is akin to honeycomb pigmented network, which is a trichoscopic finding on

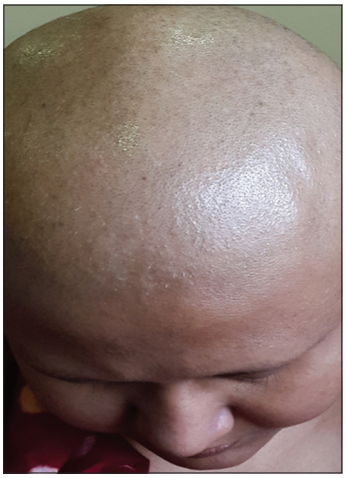

Figure 1: Anagen effluvium in a patient post chemotherapy.

Figure 2: Extensive perifollicular brown pigmentation/peripilar sign evident on trichoscopy in the same patient.

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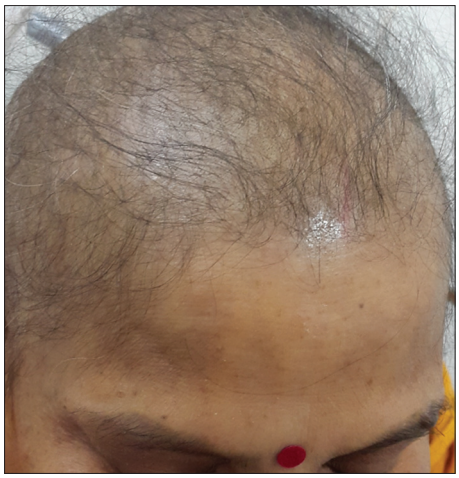

Figure 3: Anagen effluvium following chemotherapy.

Figure 4: Extensive peripilar sign in the same patient of anagen effluvium.

normal scalp. It is essentially a mosaic of contiguous brown rings but is commonly seen in people with darker skin or in bald Caucasians who have had chronic sun exposure [8].

Our patients were subjected to intensive chemotherapy which resulted in anagen effluvium. Thus, prolonged chemical exposure could be a causative factor for peripilar sign in anagen effluvium as mentioned before [5,6].

To the best of our knowledge this is the first report of peripilar sign in anagen effluvium. However further evaluation of subjects with anagen effluvium is necessary to document not only the presence of peripilar sign but also its origin and prognostic significance.

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Our Dermatology Online

Letter to the Editor

Dermoscopy unveils the mystery of a deceptive nodule!

Subrata Malakar[1], Samipa Samir Mukherjee[2]

[1]Department of Dermatology, Rita Skin Foundation, Kolkata, India, [2]Department of Dermatology, Cutis Academy of Cutaneous Sciences, Bangalore, India

Corresponding author: Dr. Samipa Samir Mukherjee, E-mail: drsamipamukherjee@gmail.com

Sir,

Dermoscope is an office based non invasive diagnostic tool based on the principle of compilation of a magnifying component with a light source. Polarized dermoscopy enables examination of the reflection of light shone over the epidermal surface without actual physical contact. Besides the routine use of this tool in the diagnosis of dermatological disorders, they also provide a wider range of applications for the practitioner. Reports state that up to 38% of soft tissue foreign bodies (STFBs) are neglected in initial clinical examinations in emergency departments, and 25% of all STFBs are presented weeks, months, and even years after a penetrating injury [1,2]. The limited size of broken particles, thorns, wood splinters or glass splinters make it extremely difficult to detect in the skin. Only magnification can reassure that a disturbing skin lesion is free of a foreign substance which can lead to a delay in the healing process. We herein describe a case of persistent nodule for last four years diagnosed as retained suture material granuloma through dermoscopy.

A 45 year old farmer, with the history of walking barefoot presented to the outpatient department with a minimally tender inflamed nodule over the dorsum of the right foot of 4 years duration. History revealed on and off swelling of the lesion with one episode of pus discharge about 4 years back for which surgical intervention was done at a local hospital. Although the discharge resolved post the intervention the wound did not seem to reduce and went on to slowly increase in size and become a hyperpigmented firm nodule with minimal tenderness and inflammation at present (Fig. 1). A biopsy of the lesion was planned keeping in mind the possibility of a granulomatous origin.

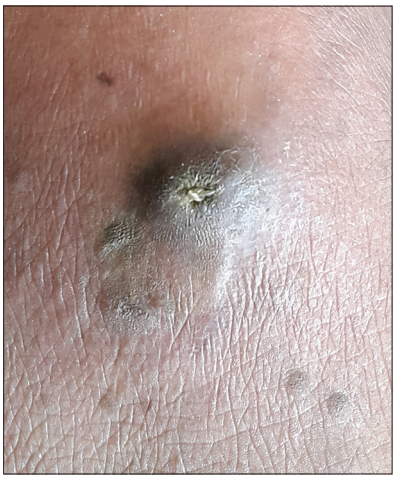

Figure 1: Solitary hyperpigmented nodule over dorsum of foot.

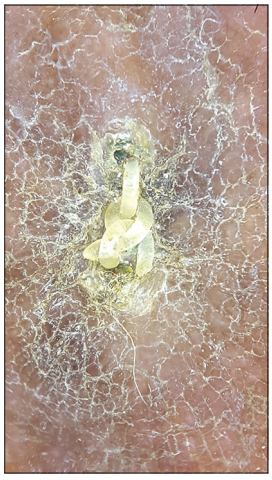

Figure 2: Dermatoscopy showing suture knot in the centre of the lesion.

However as a routine diagnostic procedure dermoscopy of the lesion was done which revealed a knot leading to the confirmation of diagnosis of a retained suture material granuloma (Fig. 2). The patient was further managed with removal of the retained suture and topical corticosteroids to reduce local inflammation.

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The likelihood of STFB oversight depends upon the presence of clinical signs like tenderness, swelling, and hematoma following injury as well as on the nature, size, location, and number of foreign bodies. Retained foreign bodies may be the result of post traumatic incident, negligence by patient or iatrogenic. The limited size of broken particles, thorns, tiny gravel pieces, wood splinters or glass splinters make it extremely difficult to detect in the skin. Only magnification can reassure that a persistent skin lesion is free of a foreign substance which can lead to a delay in the healing process. Although there has been a report on dermoscopic prevention of retained sutures [3], to the best of our knowledge this is the first case report from India where the retained foreign body was detected on dermoscopy thus avoiding the need for biopsy. We reinforce the use of dermoscope in routine clinical practice especially in resource poor areas where the need for biopsy may thus be obviated.

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Letter to the Editor

Vascular pattern of milia on dermatoscopy

Subrata Malakar[1], Samipa Samir Mukherjee[2]

[1]Department of Dermatology, Rita Skin Foundation, Kolkata, India, [2]Department of Dermatology, Cutis Academy of Cutaneous Sciences, Bangalore, India

Corresponding author: Dr. Samipa Samir Mukherjee, E-mail: drsamipamukherjee@gmail.com

Sir,

Vascular structures in dermoscopy have an important role to play in the categorization of lesions as benign or malignant. Some of the more characteristic findings like crown vessel, comma vessels can help in narrowing down the diagnosis further. Although there has been significant work in dermoscopy for pigmentary disorders, evidence and literature is yet to build with regards to vascular patterns in common dermatological conditions for ease of recognition and diagnosis. We herein describe the vascular pattern that is noted in 2 cases of milia. Similar vascular pattern may occur in basal cell carcinoma that could be misleading and thereby defining the pattern in benign conditions like milia should be considered a necessity.

A 55 year old lady presented with a skin colored asymptomatic lesion over the outer corner of the left eye of almost nine months duration for which no treatment was taken. Clinically she was diagnosed as colloid milium since the papule was firm with a whitish hue and absence of central umbilication. We went on to see the pattern under dermoscopy to confirm the diagnosis by ruling out the differentials. Dermoscopy revealed arborising vessels from the periphery traversing the length of the lesion. White structure less areas were noted interspersed with yellow structureless areas (Fig. 1).

The second case was that of a 30 year old lady who presented with an asymptomatic skin colored lesion over the left nasal ala of one year duration. On clinical evaluation a firm, painless, sessile papulonodule was noted over the left nasal ala and the differentials considered were that of sebaceous hyperplasia and milium. Dermoscopy of the lesion revealed arborising vessel arising from the periphery and crossing a significant length of the lesion along with yellowish white globules (Fig. 2).

Milia most often than not is a clinical diagnosis however can pose a diagnostic challenge in the very young, sun aged face and in the elder individuals. The vascularity of milia and other architectural elements helps in differentiating it from other differentials. In both our cases we found linear arborising blood vessels which were 'in focus' and bright red in colour confirming their epidermal position traversing the length/breadth of the lesion after arising from the periphery. As opposed to blood vessels which are dermal in nature would be pink in colour, less prominent and 'out of focus' due to dispersion of light through the dermal connective tissue [1]. Of note is the fact that the number of these vessels in the lesion may not be very many and thus may be referred to as lonely arborising vessels that may traverse the length of the lesion.

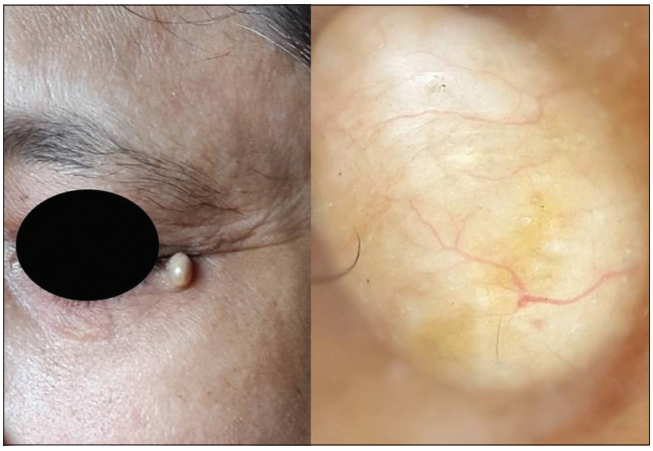

Figure 1: Yellowish to skin colored papulonodule at the outer corner of the eye, dermatoscopy showing yellowish whie structureless areas and arborising vessels arising from periphery traversing the length of lesion.

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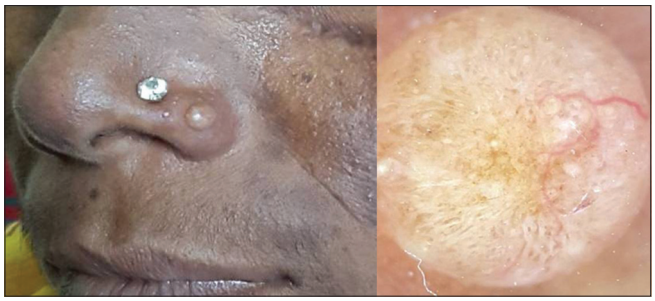

Figure 2: Skin colored papulonodule over the left nasal ala, dermatoscopy showing arborising vessels crossing the length of the lesion and yellowish white milia like cysts structures.

The finding of yellowish white structureless areas to globules on dermoscopy is similar to the milia like cysts that have been described as variously sized white or yellowish structures in seborrhoeic keratoses and congenital melanocytic nevi [2-4].

Superficial vessels are not seen in dermatoscopy of a normal skin, however when present one must think of inflammatory conditions, basal cell carcinoma or topical steroid induced skin atrophy. The vessels in the papillary dermis are visible as dots due to their orientation in a vertical direction and proliferation may be seen in conditions like psoriasis. The sub papillary plexus vessels are oriented horizontally and become visible in inflammatory conditions or when the skin is stretched.in milia there is stretching of the overlying skin leading to apparent upliftment of the subcapillary plexus thereby making these vessels visible of which the pattern has been described.

A milia can be differentiated from a molluscum contagiosum on the absence of crown vessels, mixed flower pattern of vessels and absence of the central orifice [5]. The dermoscopy of sebaceous hyperplasia has been described as a combination of yellowish nodules with crown vessels that are not arborizing [6]. Thus a milium can be differentiated from molluscum contagiosum and sebaceous hyperplasia predominantly on the vascular pattern and partly due to the other associated structural findings. To the best of our knowledge the vascular pattern in a milia has not been reported.

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Letter to the Editor

Skin wrinkles on the wrists: A new occupational skin disorder in dentists?

Funda Tamer[1], Evren Sarifakioglu[2]

[1]Department of Dermatology, Medical Park Hospital, Ankara, Turkey, [2]Evren Sarifakioglu Dermatology Clinic, Department of Dermatology, Ankara, Turkey

Corresponding author: Dr. Funda Tamer, E-mail: fundatmr@yahoo.com

Sir,

A 48-year old Caucasian female presented with skin wrinkles on the wrists bilaterally. The patient stated that these lesions have been present for the last ten years and they became deeper gradually. She didn't use any antiaging products or suncreen for her hands and upper extremities regularly. Dermatologic examination revealed bilaterally symmetrical distributed linear skin wrinkles on the dorsal site of both wrists (Fig. 1). The patient was a dentist and she admitted that she usually extend her wrists while working. Therefore, the patient was advised to avoid the palmar extension and change position as often as possible.

A variety of occupational health problems have been reported in dental health care providers. Some of these disorders may be life threatening or they may lead to reduced productivity. Dentists are at risk of some infectious diseases including tuberculosis, Human Immunodeficiency Virus, hepatitis B virus and hepatitis C virus infections. In addition, low back pain, hand and wrist complaints are the most common musculoskeletal problems in dentists [1,2]. They may develop contact dermatitits due to latex allergy and frequent use of dental instruments or some chemicals like disinfectants, detergents and solvents [1,3]. Exposure to mercury from amalgam fillings may result in neurological symptoms [1]. Furthermore, ionizing radiation used in dentistry, chromium and beryllium in dental prosthesis and mercury have carcinogenic effects. It has been suggested that dentists are at risk of some malignancies like bladder, brain, intestine and lung cancer, leukemia and malignant lymphomas [4].

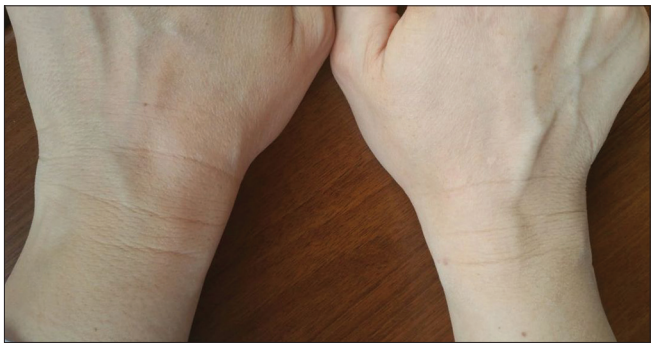

Figure 1: Bilateral, lineer, deep wrinkles on the dorsal aspect of the hands and wrists.

Occupational skin disorders are very common and most of the cases are contact dermatitits due to irritants or allergens. Kurpiweska et al. reported work related skin diseases in certain occupations. They found that 64% of the dentists had skin disorders on hands and forearms and wearing protective gloves were the main cause in 35% of the cases [3].

Ultraviolet radiation plays important role in the formation of wrinkles. Moreover, Fijumira et al. reported relationship between facial movements and wrinkling of the skin. They took photographs of 66 healthy women during rest and facial movements like raising eyebrows or closing eyes tightly. They showed similar distribution patterns of the wrinkles both in static and the dynamic states. Furthermore, the degree of wrinkles in the same facial region were correlated in static and dynamic states [5].

The patient we presented above had lineer wrinkles on the dorsal site of her hands and wrists due to repetetive muscle movement of the upper extremities while working. There

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wasn't any other underlying condition in the development of skin wrinkles and she didn't have any sign of premature skin aging. Therefore, we suggest that prolonged extension of the hands and wrists may lead to deep wrinkles on the dorsal site of the hands and wrists in dentists.

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Letter to the Editor

Triple histology of an extracted polytef (gore-tex) implant

Ana Maria Abreu Velez[1], William E. Silver[2], Michael S. Howard[1]

[1]Georgia Dermatopathology Associates, Atlanta, Georgia, USA, [2]Silver Plastic Surgery Center, Atlanta, Georgia USA

Corresponding author: Ana Maria Abreu Velez, M.D., Ph.D., E-mail: abreuvelez@yahoo.com

Sir,

Fillers, including Gore-Tex, have been long utilized for reconstructive procedures as well as for esthetic purposes. We report a 46 year female, who presented to the plastic surgeon to remove a previous nasolabial implant. The tissue was removed and examined using hematoxylin and eosin staining. Three histologic patterns were seen: 1) encapsulation around a large part of the material without giant cells, nor inflammation; 2) peripheral colonization by fibrous tissue, blending with normal soft tissue, and 3) thickening of adjacent skin. We thus document a mixed histologic pattern, featuring a partial peri-implant fibrous capsule, fibrous tissue merging with surrounding normal soft tissue and focal skin thickening.

Case: A 46 female patient visited the plastic surgeon to obtain an esthetic repair, secondary to a 23 year old surgical lip and nasolabial groove correction. The patient told the doctor that she had a previous Gore-Tex implant, which she wanted to remove and replace with Restylane. Informed consent was obtained. The plastic surgeon removed the Gore-Tex material [1-3], and sent it for histologic examination. Our H&E staining was performed as previously described [4].

Review of the H&E sections demonstrated histologic alterations around the foreign material. Fibrous encapsulation was seen around a large part of the material; however, neither foreign body giant cells nor inflammation were noted (Fig. 1). In other areas, the porous Gore-Tex mesh displayed peripheral fibrous tissue, merging with normal tissue; other parts of the specimen demonstrated thickening in adjacent skin.

Gore-Tex is known to be a safe implant material [1-3]. However, its use may lead to clinical problems. The

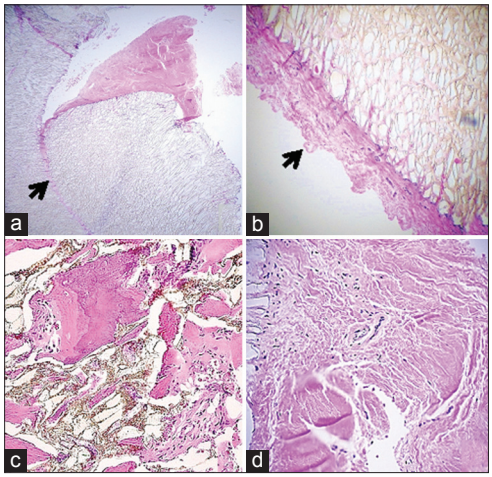

Figure 1: (a-d) Histologic changes associated with the Gore-Tex graft, utilizing H&E staining. In (a and b) we highlight encapsulation of the porous Gore-Tex material at 100x and 400x, respectively (black arrows). In (c) we highlight Gore-Tex graft material, surrounded by fibrous tissue ingrowth. In (d) we document a thickened skin dermis, present around one side of the extracted Gore-Tex graft.

nasolabial folds represent facial sites frequently complained about by esthetic patients in all age groups, especially when aging. Gore-Tex was commonly used in the 1990s for a few esthetic surgeries, including lip augmentation. Gore-Tex has also been used in other procedures including rhinophasty; laryngoplasty; artificial tracheal implants; tendon, vascular and heart valve reconstructions; cardiac bypass grafts; aortic-pulmonary shunts; mandibular augmentation and periodontal procedures [1-3].

More recently, modern fillers including Restylane, Radiesse, Juvederm®, Voluma, Belotero, Perlane and Sculptra have become available. Many patients currently visit plastic surgeons and dermatologists, requesting removal of previous Gore-Tex grafts with such a modern replacement.

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Our findings are consistent with selected previously documented histologic features, including fibrous tissue interfacing with normal soft tissue, and the changes in skin thickness. However, in contradistinction to one previous report [5], we observed no calcifications, inflammation or foreign body giant cells. In addition, we did observe a partial peri-implant fibrous capsule. We conclude that in our case, the surrounding tissue around the Gore-Tex implant demonstrated no notable inflammation, and that a peri-implant fibrous capsule was also present. Thus, we recommend that all removed implants be presented for histologic review.

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Our Dermatology Online

Letter to the Editor

Atypical neuralgia associated with cervical and thoracic herpes zoster infection

Anna Lis-Święty, Anna Michalska-Bańkowska, Agata Zielonka-Kucharzewska

Department of Dermatology, Medical University of Silesia, Katowice, Poland

Corresponding author: Dr. Anna Lis-Święty, MD., PhD., E-mail: annadlis@neostrada.pl

Sir,

Herpes zoster (HZ) afflicts usually older adults and causes significant suffering from acute and chronic pain, or postherpetic neuralgia (PHN).

We report a case of 79-year-old woman who presented to the Dermatology Department with a 5 days of worsening papulovesicular/vesical rash in the C7-T2 dermatomes on the left side but no other symptoms like pain, itching, hyperaesthesia, paraesthesia (Fig. 1a-c). Other abnormal findings included: Aype II of diabetes, arterial hypertension, coronary heart disease and atrial fibrillation on long-term therapy with amlodipine, verapamil, ramipril, amiodarone and metformin. HZ infection was considered and the patient was administrated aciclovir at a dose of 800 mg 5 times a day for 7 days in the treatment. From the second day of this therapy the new vesicles were not observed, and the skin condition improved. However, after a week from the end of the antiviral treatment severe neuralgia in the left upper limb occurred. The patient received systemic analgesics (paracetamol, tramadol) for 10 days to control the pain. The recurrence of the rash and pain was not observed during the 12 months follow-up.

Painless HZ is not common, but not all that rare, and has been previously reported [1]. Nevertheless, the mechanism of painless HZ is unknown. The varicella- zoster virus (VZV) reactivation leads to inflammatory changes in the dorsal root ganglia, where the focal extravasation, oedema and lympocytic infiltration are formed [2]. The virus penetrates along the sensory nerves to the skin. The acute pain is presumably due to the VZV-induced demyelination of sensory nerve fibres. The severity and extent of HZ skin lesions correlate with the intensity of pain [2].

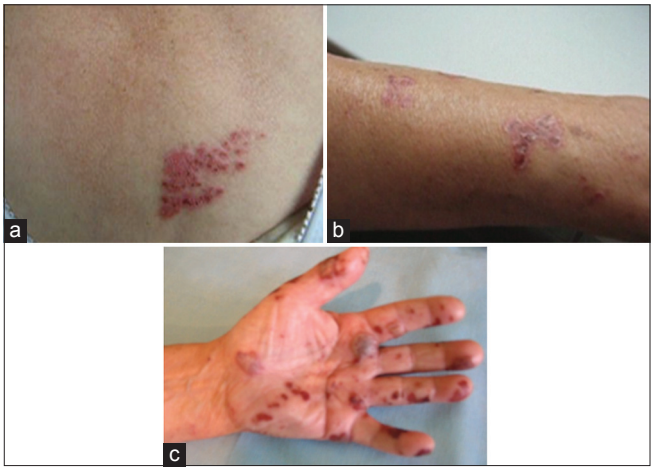

Figure 1: Unilateral papulovesicular/vesical rash on the left side of the chest and left upper limb (a and b). Haemorrhagic vesicles and blisters localized on the hand (c).

We described a patient with multiganglionic HZ invloving adjacent ganglia. Despite severe and extensive skin lesions our patient did not complain of pain in the initial phase of HZ infection. As the reason of painless HZ we considered the coexistence of neuropathy linked to diabetes and chronic amiodarone treatment. However, the severe pain occurred a week after the patient was successfully treated with acyclovir. The observed pain resolved in 10 days using systemic analgesics. One could speculate that the lack of pain in acute HZ was due to a severe VZV viremia, which destroyed ganglia and peripherial nerves and caused abnormal nociception. Therefore, it can be assumed that the pain occurred after the beginning of regenerative processes in the injured ganglia and peripherial nerves. In spite of the predisposing

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factors as senility, female gender, severe extension of skin lesions, the chronic PHN did not occur [3]. The randomized examinations and meta-analysis proved that the antiviral treatment in HZ significantly reduces the risk of long-lasting pain [4]. Oral administration of aciclovir significantly reduced frequency of PHN [5].

The painless onset of HZ may cause diagnostic problems. Nonetheless, unilateral vesicular rash on an erythematous base with a dermatomal distribution is sufficiently distinctive that a clinical diagnosis of HZ is usually accurate. The early diagnosis of HZ and antiviral treatment in our patient probably prevented the chronic PHN.

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Letter to the Editor

Post-vomiting purpura

Badrilal Meghwal[1], Manisha Balai[2]

[1]Department of Pediatrics, RNT Medical College, Udaipur, Rajasthan, India, [2]Department of Dermatology, RNT Medical College, Udaipur, Rajasthan, India

Corresponding author: Dr. Badrilal Meghwal, E-mail: drblmeghwal@gmail.com

Sir,

We report a case of 7-year-old female child who presented with multiple, asymptomatic, purpuric lesions over face after a single episode of forceful vomiting. On examination the lesions were purpuric but not palpable. They were localized to bilateral periorbital regions (Fig. 1), slightly extending to the cheeks. (Fig. 2). The child was otherwise healthy and there was no previous history of any similar lesions in the past in the patient or his family. There were no skin lesions elsewhere, including mucosa. There was no history of any trauma, fever and sun exposure. There was no history of drug intake.

Laboratory investigations including complete blood count, bleeding time, clotting time, and prothrombin time were normal. The lesions subsided without treatment within a period of seven days.

We present this case to highlight the rare but definite entity called post-vomiting purpura. Purpura/petechie around the eyelids are classically seen while performing the Valsalva manoeuvre, but in practice they are more likely after severe coughing or vomiting, and also described after endoscopy [1,2]. The aetiology is a sudden rise in the venous and capillary pressure in the head and neck caused by a rise in intrathoracic pressure during vomiting. The lesions are self-resolving and no specific intervention other than patient counseling is required [3,4].

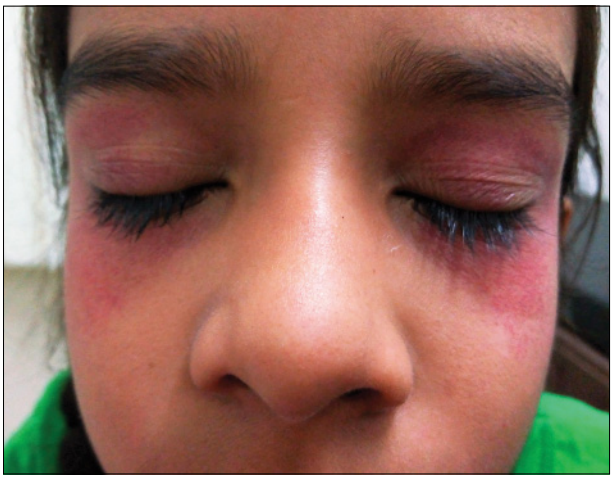

Figure 1: Purpuric lesions bilateral periorbital area after vomiting.

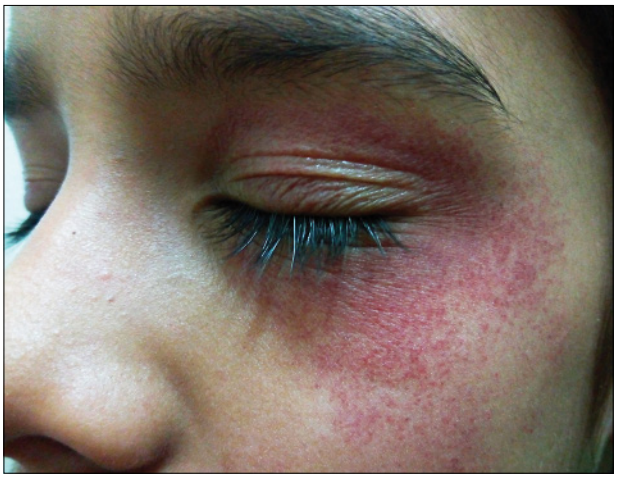

Figure 2: Left lateral view showing purpuric lesions extending to cheek.

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Our Dermatology Online

Letter to the Editor

Granulomatous reaction following mantoux test: A rare complication

Chirag Ashwin Desai

Department of Dermatology, Kasturmahal Polyclinic, Sion (east), Mumbai, India

Corresponding author: Dr. Chirag Ashwin Desai, E-mail: 83.chirag@gmail.com

Sir,

Tuberculosis (TB) is one of the major public health problems in our country. More so with growing resistance of mycobacterium tuberculosis to various drugs, treatment of this disease is becoming more complex. Various factors like high cost, limited resources and poor performance of diagnostic tests make diagnosis of this disease more difficult. Tuberculin skin testing (TST) is one of the diagnostic modalities to detect TB in an individual.

A 13-year-old boy came with the chief complaint of a recently developed asymptomatic lesion on left forearm which was gradually increasing in size. On inquiry the patient had a chronic cough for which he had visited a physician 15 days back. He has advised a battery of investigations including hemogram, chest x-ray, Mantoux test and sputum for acid fast bacilli. One week following the Mantoux test, the patient reported an increase in redness and hardness at the site of test which progressed to a current state of his lesion. On examination, there was a 5 cm x 7 cm ulcerated area with rolled up edges and surrounding induration. No pain or tenderness was associated with this lesion. A biopsy was done to determine the nature of this lesion as it did not appear to be usual ulceration that occurs with severe Mantoux positivity (Fig. 1).

Biopsy from the edge of the lesion revealed a hyperplasia of epidermis with well formed tuberculoid granulomas in the dermis comprising of epithelioid cells, lymphocytes and Langhans giant cells with some caseous necrosis in the centre of the granuloma (Figs. 2 and 3). A final diagnosis of tuberculoid granulomatous reaction following Mantoux test was kept. The patient did follow up once after the biopsy for the report following that he was lost to follow-up.

TST was originally developed by Robert Koch in 1890; however, the intradermal mode of administration was described by Charles Mantoux in 1912 [1,2]. There are various factors both in the host and in the test that lowers the sensitivity and specificity of this

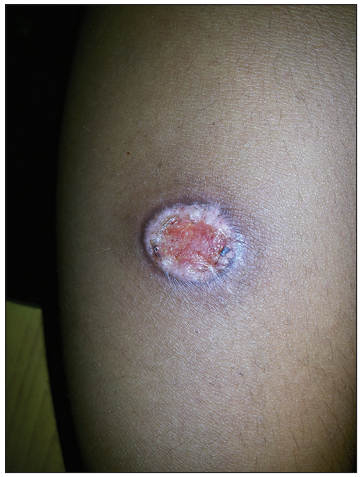

Figure 1: Single indurated and ulcerated plaque over left forearm.

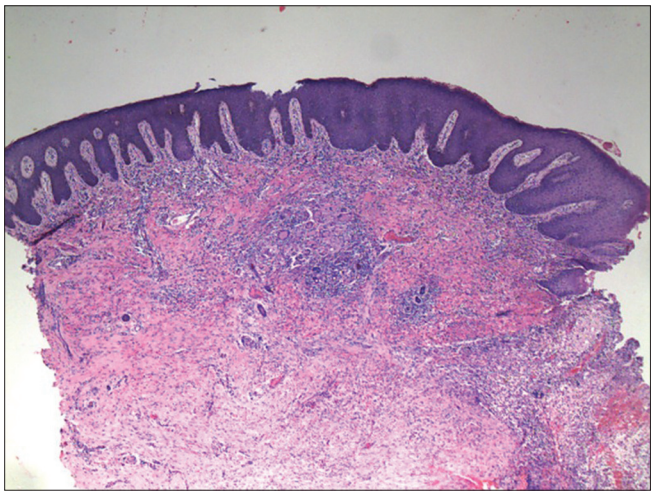

Figure 2: Epidermal hyperplasia with tuberculoid granuloma in the dermis (H&E x 4).

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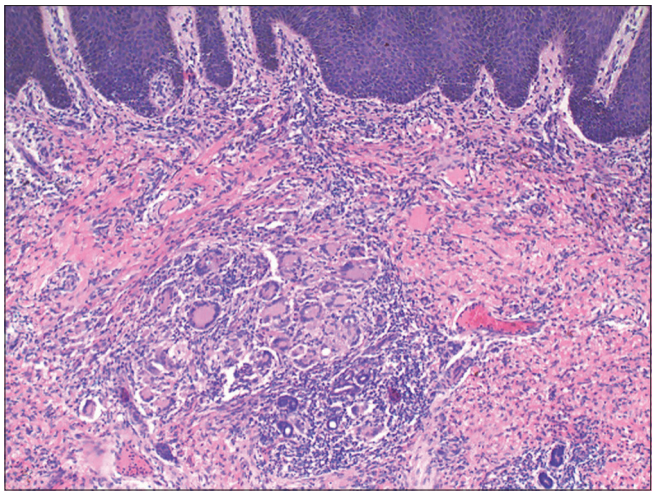

Figure 3: Granuloma showing langhans giant cells, epitheloid cells and lymphocytes (H&Ex10).

test, consequently, the test may be positive in an un-infected child and negative in a patient with full blown TB [1].

The tuberculin that is used presently for the test is called purified protein derivative (PPD), derived from cultures of mycobacterium tuberculosis. A standard dose of five tuberculin units (0.1 ml) is injected intradermally on left forearm of the patient and the reaction is read after 48 to 72 hours. Features of reaction include erythema and induration at the injection site. The amount of induration is measured transversely to the long axis of the forearm and is recorded in millimeters [1].

This is a form of delayed-type hypersensitivity reaction. Occasionally there may be vesiculation and necrosis at the site. Adverse effects associated with this test include allergic reactions in form of excessive redness and swelling of the arm, urticaria at the site, vesiculation and ulceration at the site, foreign body reaction to the injected material. Regional lymphangitis and adenitis have also been reported. Lesser known adverse effects include anaphylactic reaction and granulomatous reaction at the injected site [2].

This case shows a granulomatous reaction at the site of injection which is an entity with fewer reports in the literature.

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Our Dermatology Online

Letter to the Editor

Multiple piloleiomyomas

Salwa Mejri[1], Salsabil Attafi Sahli[2], Sana Bouchouicha[1]

[1]Department of Dermatology, Regional Hospital of Menzel Bourguiba, Menzel Bourguiba, Tunisia, [2]Department of Pathology, Regional Hospital of Menzel Bourguiba, Menzel Bourguiba, Tunisia

Corresponding author: Dr. Salsabil Attafi Sahli, E-mail: sehlisalsabil@hotmail.com

Sir,

Cutaneous leiomyomas (CL), also referred to as leiomyomas cutis, are an uncommon benign tumor of smooth muscle origin [1,2]. They may be sporadic or inherited occuring as a part of Reed's syndrom or the hereditary leiomyomatosis and renal cell cancer syndrom [2,3]. The skin is the second commonest location for leiomyomas representing aproximatly 75% of extra-uterine leiomyomas [4,5]. According to the smooth muscle of origin and the clinicopathological characteristics, CL are classified as pilar or piloleiomyoma (PL), angioleiomyomas and genital leiomyomas [1-6]. PL derive from the arrector pili muscle. Theys represent the most common type of CL [5,7].

We report the case of multiple PL in a 61 year-old woman with no medical history. She presented with firm, pink-red and painful papulo-nodular lesions with a zosteriform disposition. The lesions were evolving for 10 years, measuring between 1mm and 5mm and sitting in the back and extremities (Fig. 1). The patient had a surgical excision of one nodule. The histological examination showed a non-encapsulated tumor arranged in interlacing bundles of smooth muscle fibers admixed with collagen in the upper dermis. There were neither vascular component nor myxoid or cystic changes. The tumor cells stained positively against smooth muscle actin. The S100 protein was negative. The diagnosis of multiple piloleiomyomas was retained. The patient was treated medically with nifedipine associated to cold prevention. The clinical course showed amelioration of the symptoms and especially a pain relief.

CL are rare representing almost 5% of all leiomyomas [4]. Literature concerning the pilar subtype of CL is scant and generally limited to case reports or non-standardized studies of limited number [1,5].

PL may be solitar or multiple. Theys appear preferentially in adulthood but they may occur in any age [4]. The sex distribution is not clear [2,4,5] but according to some studies [2], multiple PL occur preferentially in young male patients aged between 10 and 30 years. Contrary, solitary PL appear usually later than their multiple counterparts, especially in women [2]. Unlike, our patient is an elderly women. The lesions had appeared at the sixth decade and the diagnosis of multiple cutaneous piloleiomyomas was retained ten years later.

The distribution of multiple lesions is variable. They are often situated around Blaschko's lines, linear, segmental, and zosteriform variants have been also described [5].

PL are typically firm, red-brown to flesh-colored papulonodules, measuring between 3 mm and 20 mm, located on the trunk or extremities [5].

The most important clinical symptom of CL is pain, present in almost 90% of cases. It can be provoked by cold, contact, pressure or emotion [5].

The presence of multiple CL can be associated whith hereditary leiomyomatosis and renal cell cancer (HLRCC) [3,5].

The differential diagnosis includes other painful skin tumors such as neurilemmoma, angiolipoma, glomus tumor, neuroma and granular cell tumor. Histologically, it may be confused with other CL (angioleiomyoma and genital leiomyoma), cutaneous neurofibromas

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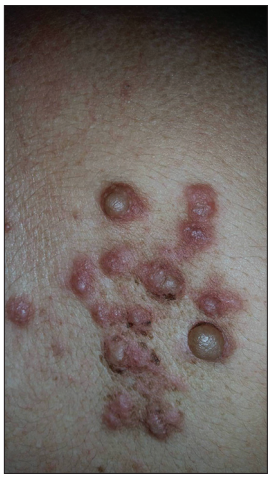

Figure 1: Multiple papulo-nodular lesions with a zosteriform disposition.

which are not painful and stains positively with S100 protein [2,4,5].

Surgical excision is the treatment of choice for isolated PL or those in limited number [4-6]. For multiple lesions, several treatment modalities have been employed such as ablative, topical, or systemic treatments with no evidence on their efficacy [5-7].

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