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Our Dermatology Online

Original Article

Scabious erythroderma - a rare clinical variant of scabies

Tatyana V. Sokolova[1], Uladzimir P. Adaskevich[2], Alexander P. Malyarchuk[1], Yulia V. Lopatina[3]

[1]Department of Skin and Venerial Diseases and Cosmetology, Medical Institute of Post-Graduate Education, Federal State Educational Institution of Higher Professional Education "Moscow State University of Food Production", Moscow, Russian Federation, [2]Department of Dermatovenereology, Vitebsk State Medical University, Vitebsk, Belarus, [3]Department of Entomology, Biological Faculty, M.V. Lomonosov Moscow State University, Moscow, Russian Federation

Corresponding author: Prof. Uladzimir P. Adaskevich, E-mail: vitebsk.derma@mail.ru

ABSTRACT

Background: Erythroderma (exfoliative dermatitis) is an emergency condition in dermatology in which not less than 90% of skin surface is affected. The presenting features are erythema, skin scaling and itching, fever and lymphadenopathy. The most common cause of erythroderma is a preexisting dermatosis (psoriasis, atopic dermatitis, eczema, seborheic dermatitis, lichen rubra pilaris, lichen planus, pemphigus foliaceous), drug reactions, lymphoma, leukemia and visceral neoplasias. Erythroderma is a diagnostically relevant presenting feature of Norwegian scabies. **The aim of investigation:** Is to describe clinical peculiarities of scabious erythroderma as a special rare form of scabies, to assess the number of scabies mites on the patient and in his/her environment and to work out the criteria of differential diagnosis with Norwegian scabies. **Material and methods:** We examined 5 patients with scabies and erythroderma as the main presenting feature. All patients were women aged from 42 to 89 years. The disease duration was from 8 months to 1 year. The causes of erythroderma were variable. Clinical and paraclinical methods of investigation alongside with dermatoscopy and microscopy were used. **Results** This is the description of a rare clinical form of scabies, scabious erythroderma. It is based on the analysis of the 5 cases of scabies, whose main clinical manifestation is diffuse erythroderma. The diagnostic criterias of scabious erythroderma and differential diagnosis of Norwegian scabies are given. The invasive potential of this form of the disease on the patient and beyond is evaluated for the first time.

Key words: Scabious erythroderma; Norwegian scabies; Dermatoscopy; The differential diagnosis

INTRODUCTION

Erythroderma is an inflammatory skin condition characterized by erythema and exfoliative dermatitis involving 90% and more of the entire skin surface. The initial lesions which are important keys for understanding the disease evolution are often occult [1]. The most common causes of erythroderma can include pre-existing dermatoses (psoriasis, atopic dermatitis, eczema, seborrhoeic dermatitis, lichen ruber pilaris, lichen ruber planus, pemphigus foliaceus, bullous pemphigoid), drug-induced eruption, lymphoma and leukemia, visceral neoplasias and other conditions [1-4].

Erythroderma is also a diagnostically relevant clinical manifestation of Norwegian scabies [1,5,6]. The latter was first described by Danielson and Boeck in Norway in 1848. *Crusted scabies* is another term used to name this condition. This name reflects the main clinical symptom of the disease – massive crusts which are formed in various areas of the skin surface. In addition to crusts and erythroderma, Norwegian scabiesis characterized by multiple burrow tracks, polymorphous eruption (papules, vesicles, pustules) and scales.

The etiology and peculiarities of the disease evolution have been quite competently systemized [5,7]. For the last two decades the cases of Norwegian scabies have

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been described in HIV-infected patients [8-11], in elderly and disabled people [12,13] and rarely observed in cases of brain astrozytoma [14], drug addiction [15], Down syndrome, diffuse fatty liver disease, anemia, parenchymatous dystrophy of visceral organs, cachexia [16], bullous pemphigoid treated with systemic c orticosteroids [17], congenital erythroderma [18], in patients taking novel immunosuppressive agents tozilisumab [19] and cyclosporine [20], in case of skin exposure to pesticides [21]. Rare cases of Norwegian scabies are also described without associated pathology: in a 24-year-old man [22], in a pregnant woman [23], in children [24,25].

Massive crusts are the main symptom of Norwegian scabies. Their thickness varies from several millimeters to 2-3 cm. In some cases crust layers may cover considerable areas of the skin surface forming a solid horny shield which limits body movements and makes thempainful. The crust colour varies greatly from dirty gray with a mixture of blood to yellowish-green, grayish-brown or alabaster-white. The crust surface is rough, fissured and covered with verrucous rupia-like proliferations. Crusts usually appear at the preferable sites of burrows (hands, feet, elbows, buttocks and other localizations). The upper crust layer is firm, the lower one is friable. Between these two layers a great amount of adult and immature mites can be found. On the inner crust surface one can see tortuous depressions which correspond to scabies mite burrows. The crusts firmly adhere to the skin surface and, if forcibly removed, leave large weeping erosions. The burrows with in the crusts are "many-storied". In the lower crustose layers, male and female mites, nymphs, larvae and eggs can be detected, and in the deep inner layers, dead mites and eggs, as well as empty egg shells are found. The number of mites on a sick patient is immense, so the Norwegian scabies is highly contagious with local epidemics breaking out around the patient.

Erythroderma is the second diagnostically relevant symptom of Norwegian scabies [6,13,16,26-31]. The cause of erythroderma in this case is considered to be *Staphylococcus aureus* colonizing mite burrows [32,33]. *Staphylococcus aureus* was found in mite burrows of an elderly patient with Norwegien scabies by scanning electron microscopy, bacterial analysis of burrow contents revealed *Staphylococcus aureus* and *Staphylococcus haemolyticus*. [34]. It is important to note the observation suggesting that erythroderma in Norwegian scabies arising on the background of both systemic and topical corticosteroid therapies appears earlier than in case when corticosteroid therapy is not administered [35,36].

Other diagnostically relevant criteria of Norwegian scabies are affected nails (nailplates easily crumble, they are grey with abumpy surface and not chededges, sometimes nail plates are completely lost and replaced by massive epidermal crustlike layers); enlargement of multiple lymph nodes (polyadenopathy); fever during the entire course of the disease; palmar-plantar hyperkeratosis; hair changes (dry, dull, ash-gray) up to alopecia; body malodour (reminiscent of sour dough) [6,26-31,37].

There are some case reports in medical literature describing highly contagious scabies with extensive erythroderma as the main clinical symptom [38,39]. This rare erythrodermic form of scabies is still insufficiently described in medical literature. That is why some authors, having found areas of hyperkeratosis (which are no crusts actually), diagnose such cases as Norwegian scabies [38-42]. In fact, the given form of the disease should be designated as scabious erythroderma. One can assume that there must be far more similar cases. Besides, it is recognized that Norwegian scabies may have a localized form with crusts developing only in certain areas of the skin surface [7,41,42].

The aim of our study was to describe peculiarities of the clinical course of scabious erythroderma as an independent rare variant of scabies, to estimate the number of mites on patients and in their surroundings and to work out criteria of differential diagnostics with Norwegian scabies.

MATERIALS AND METHODS

We observed 5 patients with scabies in whom erythroderma was the main clinical manifestation of the disease. All patients were women aged 42, 72, 76, 84 and 89. The duration of the disease was from 8 months to 1 year. The causes of the disorder were different in all the patients. The condition in the first patient (aged 42) developed on the background of systemic lupus erythematous. The complex therapy of this disease included prednisolone 60 mg/day during 3 months. In two patients (aged 72 and 76) allergic contact dermatitis and then drug-induced reaction were erroneously diagnosed. During 8-9 months the patients received systemic antihistamine, desensitizing drugs and topical glucocorticosteroids. Erythroderma

appeared two months after topical application of corticosteroids. The forth case was a 84-year-old patient of psychoneurologic department. Many years the patient took systemic psychotropic drugs for schizophrenia, fluocinolon acetonide was applied topically. The fifth patient (aged 89), in whom allergic dermatitis and then drug-induced reaction were diagnosed, received systemic antihistamine drugs, topical corticosteroids during one year and then three-month course of betamethasone. Erythroderma appeared after 2 months of betamethasone injections.

In all cases the diagnosis of scabies was confirmed by laboratory investigations. The laboratory methods included mite removal with the help of a needle, burrow and lesional skin scrapings with lactic acid application, dermatoscopy performed with the help of the dermatoscope DELTA 20 and microscopy with USB-microscopes of various modifications. The number of burrows was counted visually and by means of dermatoscopy and then the parasitary index was determined. In the fifth patient the number of mites on the apparently normal skin and in erythrodermic lesions was counted in the field of a standard dermatoscope with the area of 1 cm^2. The efficacy of scabies diagnostics by means of dermatoscopy and tape-test methods [43,44] was compared. In case of a tape test, a piece of transparent adhesive Scotch tape (2x5 cm) was applied on an affected site of the skin for several seconds and then quickly removed. The removed piece of tape was paced on the slide and viewed with the microscope. The quantities of mites in different stages of development were compared in two epidermal scrapings (from the abdomen and thigh) and in 4 Scotch-tests (from the foot, chest, back, thigh). The number of mites around the patient was determined on the sheet where the patient was lying. For this purpose the adhesive tape (2x5 cm) was applied to ten different sites on the sheet.

As an example we describe a case of a patient with scabious erythroderma diagnosed in June 2013 (Figs. 1-6). A 89-year-old patient admitted to hospital complained of the affection of the whole skin, moderate itch increasing in the evening and chills (in spite of high environmental temperature). The disease had lasted for one year. The patient did not connect any events with the onset of the disease and considered the skin changes to be a result of "allergy" (she had previously worked as a nurse). The first symptom of the disease was itch in the interscapular region. The itching sensation then gradually spread to other skin regions. The patient's daughter who cared for her mother also complained of slight itch. Both

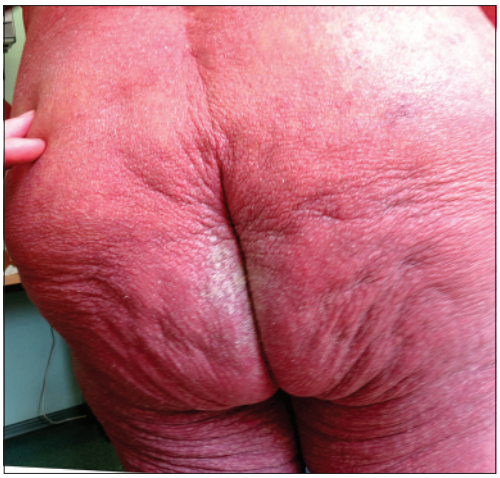

Figure 1: Focal hyperkeratosis on the buttocks in scabious erythroderma.

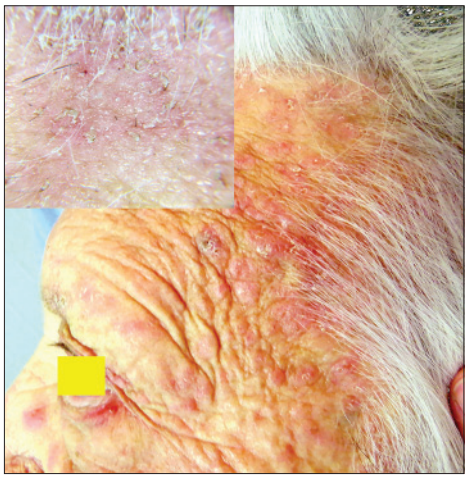

Figure 2: Mite burrows on the scalp at the frontal hair line in scabious erythroderma.

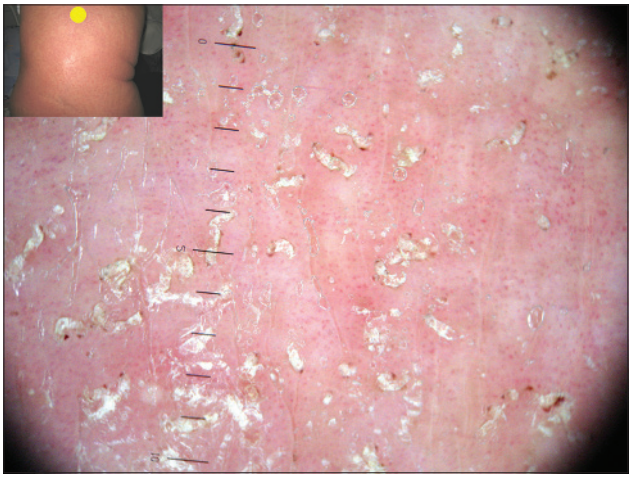

Figure 3: Mite burrows in the interscapular region in scabious erythroderma.

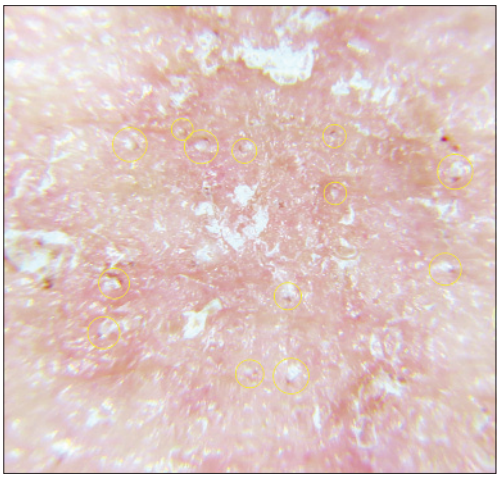

Figure 4: Mites outside the mite burrows in scabious erythroderma.

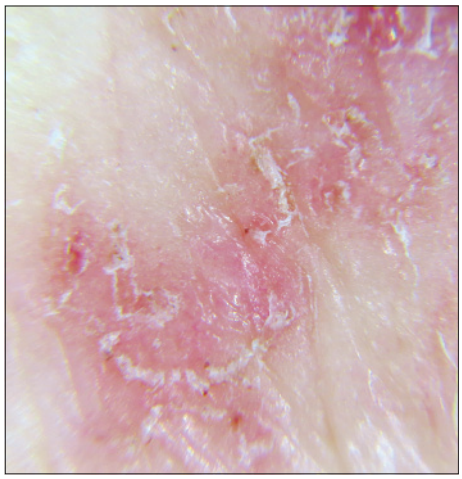

Figure 5: Mites in the apparently little-changed skin in the middle third of the shin in scabious erythroderma.

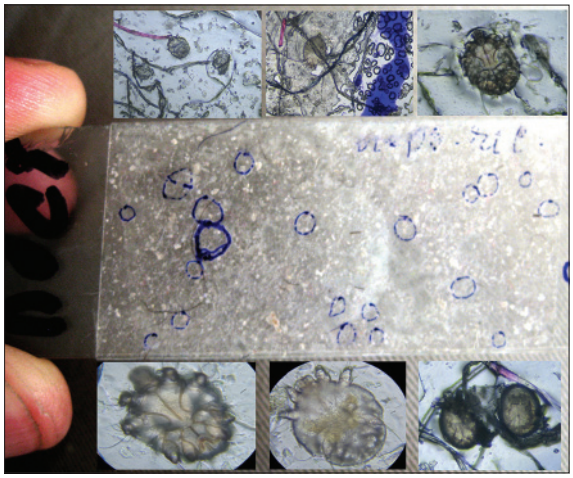

Figure 6: Scotch test (tape test) from the surface of bed linen: a – slide with the adhesive tape and visible parasitic elements,∂ – Parasitic elements stuck to the tape (eggs, larva).

women took antihistamine drugs and applied topical medicines against pruritus with no effects after this self-treatment. On admission to hospital the condition of the old patient was diagnosed as wide-spread allergic dermatitis. The patient was treated with antihistamine and desensitizing drugs and topical corticosteroid creams. Short-termin significant improvement was observed. The patient applied to 4 different doctors but the diagnosis remained the same and the treatment did not significantly differ from the previous one. The therapeutic measures brought no effect. Three months before admission to hospital the patient was administered 2 injections of betamethasone per month and topical corticosteroid creams (clobetasol, fluticasone). While the subjective perception of itch reduced, there appeared lesions of erythema which quickly spread and covered the whole skin surface creating the clinical picture of erythroderma. With the diagnosis "drug-induced eruption" the patient was admitted to hospital. The patient's condition on admission was satisfactory, the body temperature was normal. The state of the inner organs and the revealed pathology in general corresponded to the advanced age of the patient. The regional lymphnodes were painless and not enlarged.

Local status. The process was of a universal character with erythroderma covering the whole skin surface of the body. The skin was dusky red, dry and in some areas scaling with signs of infiltration, pigmentation and lichenification. The skin felt warm, firm and rough. White dermographism was observed, but crusts were absent. In the areas of the intergluteal cleft (Fig. 1) and elbows there were foci of grey hyperkeratosis with firmly adherent scales. Scratch marks were hardly present. On the background of moderate facial hyperemia there were red infiltrated lesions on the forehead, chin, eyelids, ears, cheeks, and the vermillion border of the lips. The skin of the scalp was pale without any signs of inflammation. On the skin of the shoulders and lower legs there were small isles of normal skin. The inflammatory changes of the palmar and plantar surfaces were insignificant. Multiple fresh and destroyed burrows of various lengths were observed predominantly in the skin folds. The number of burrows detected without using a dermatoscope made up 186 on the palms, 81 on the soles and 34 on the areolas. Burrows in other skin regions were poorly visualized without a dermatoscope.

Laboratory data. Moderately elevated WBC count ($13{,}6\times10^9$/L), ESR 3 mm/h, hypoproteinemia 52 g/L. Other blood biochemistry values and urine analysis were within the normal range.

Dermatoscopy. In all areas of the skin surface multiple mite burrows were found, including the face, frontal hairline on the head (Fig. 2), interscapular (Fig. 3) and pubic (Fig. 4) regions. Mites (from 5 to 30 on 1 cm^2) were detected beyond the burrows (Fig. 4) even in only slightly changed areas (Fig. 5). The number of mites was the biggest in those areas of the skin surface where the inflammatory changes were the most dramatic ones. In order to compare the effectiveness of visual and dermatoscopic methods for detecting mites, the parasites were counted on the palm skin surface with the area of 4 cm^2. Only female mites located in the burrows were visually detected (total 19). Twice as many mites (total 41) were found by means of dermatoscopy, including parasites beyond the burrows. Microscopy of skin scrapings yielded the following results (Table 1).

The number of parasitic elements clearly depended on the size of the skin area to be scraped. In scrapings from the thigh (6x8 cm) 17 parasitic elements were revealed and in scrapings from the abdomen the number of such elements was 25. Adult mites (male and female) prevailed (40,5%), eggs made up 33,3% of all parasitic elements, empty egg shells and larvae accounted for 19,1% and 7,1% of elements, respectively. The obtained data show a high level of mite colonization in those areas of the skin surface which are only insignificantly affected in case of common scabies. The prevalence of female mites and empty egg shells in skin scrapings speaks for the presence of such burrows which, in case of common scabies, are usually found on the hands, wrists and feet.

For the diagnosis of scabies tape-tests were used. Their results are given in Table 2.

By means of tape-tests taken from 4 sites of the skin surface 15 mites in various stages of development were found. The adult mites (imago) dominated including 6 female and 3 male mites. Larvae (6) and nymphs (1) were also detected, but there were no eggs or egg shells. Mites were found not only in sites of typical burrow localization (feet) but also in those areas of the skin surface where, in case of common scabies, elements of metamorphic stage of the life cycle are localized (abdomen, thigh, chest).

While comparing the effectiveness of dermatoscopy and tape-test methods a considerable advantage of dermatoscopy was evident. The number of mites revealed in 4 tape-tests on the area of 10 cm^2 varied from 2 to 6 parasites. Dermatoscopy of the site with the same area revealed 35 mites on the foot, 12 on the abdomen, 22 and 15 on the thigh and chest, respectively.

Three tape-tests were made with the sheet on which the patient was lying (Fig. 6 a, b) which revealed 9 female mites, 6 male mites, 11 larvae, 1 nymph and 4 eggs. These results speak for a high invasive potential of this scabies form. All family members who cared for the patient also had scabies.

With regard to clinical, dermatoscopic and microscopic data the diagnosis of scabies in the form of scabious erythroderma was made. The patient was treated with benzyl benzoate ointment 20%. The next day the efficacy of the treatment was assessed in terms of mobility of parasites. Mobility was observed in 67% of mites extracted from the burrows and in 92% of mites removed from the apparently normal skin. In tape-tests taken from the patient's sheet 23 mites of 27 (85,2%) retained their mobility. Benzyl benzoate ointment was applied on the whole skin surface once a day in the evening for 7 days. Simultaneously, loratadine was administered. On day 8 a significant reduction of infiltration and hyperemia was observed and the number of mites on dermatoscopy decreased

Table 1: Parasitic elements in epidermal scrapings

Site of scrapings	Female mites	Male mites	Larvae	Nymphs	Eggs	Egg shells	Total
Scraping from the thigh (6X8 cm)	6	6	0	0	3	2	17
Scraping from the abdomen (20X10 cm)	4	1	3	0	11	6	25
Total	10	7	3	0	14	8	42

Table 2: Parasitic elements in tape-tests taken in various areas of the skin surface

Site of scrapings	Femalemites	Male mites	Larvae	Nymphs	Eggs	Egg shells	Total
Foot	1	3	2	0	0	0	6
Abdomen	0	0	2	0	0	0	2
Thigh	4	0	0	0	0	0	4
Chest	1	0	1	1	0	0	5
Total	6	3	5	1	0	0	15

to 1-3 per cm^2, no mobile mites were found. Tape tests taken from the skin surface and the sheets were negative. The following therapy included desensitizing (sodium thiosulfate) and antihistamine (chlorpheniramine) drugs, as well as topical application of emollients (cold cream).

DISCUSSION

The analysis of the 5 clinical cases allows scabious erythroderma to be singled out as a separate rare form of scabies. The clinical diagnostic criteria of this form are as follows:

- Development of the disease on the background of taking medicines which reduce itch, such as systemic and topical corticosteroids, psychotropic, antihistamine and desensitizing drugs. The suppression of itch reduces scratching thus preserving mites in the skin. So the population of mites is uncontrolledly increasing.
- Considerable duration of the disease (> 8 months) with early erythroderma appearing 2-3 months after administering systemic and topical corticosteroids, often in combination with antihistamine and/or psychotropic drugs.
- Peculiar character of itch: less severe, diffuse, increasing in the evening, without scratch marks. Patients usually do not scratch but rather rub the skin with their hands.
- Generalized erythema with infiltration (erythroderma) and xerosis with minimal scaling.
- Areas of hyperkeratosis on the sites of constant pressure (buttocks, elbows).
- Crusts are absent.
- Presence of only small pustules with slight infiltration at the base (osteofolliculitis).
- A great number of burrows at the sites of preferable localization (hands, wrists, feet): 50-310 in an anatomic region.
- Presence of burrows on the face, neck and in the interscapular region where they are usually absent in case of common scabies.
- Prevalence of the so-called metamorphic burrows (2-3 mm long) which are mostly made by immature parasites (larvae, nymphs) [5].
- Persistent white dermographism.
- Mites are visualized by dermatoscopy not only in burrows but also on erythrodermic as well as on apparently normal skin.
- All persons in contact with the patient are infested.

Scabious erythroderma is a rare clinical form of scabies. In fact, this form precedes Norwegian scabies which is mainly characterized by erythroderma and multiple crusts. Since scabious erythroderma has not been previously singled out as a separate form of scabies, many authors regard it as Norwegian scabies taking hyperkeratotic layers for crusts to which the former do not belong. Since the data of medical literature obtained by means of electron microscopy and cultural analyses confirm the colonization of burrows in Norwegian scabies by *Staphylococcus aureus*, it can be assumed that, in the first stage, this agent acts as a superallergen causing an allergic reaction which reminds reactions in drug eruption, atopic dermatitis (Hill's erythroderma), psoriasis, and other skin diseases. This reaction is then followed by a severe exudation and massive multilayer crusts are formed, often on the sites where burrows are located. In this case we deal with Norwegian or crusted scabies.

Norwegian or crusted scabies and scabious erythroderma have many features in common:

- Both forms appear on the background of conditions considerably reducing itch, which contributes to a rapid growth of mite colonization of the patient.
- Intense erythroderma is one of the diagnostically relevant criteria in both cases.
- Sites affected are the face, neck and scalp.
- Multiple burrows are present in sites of their typical localization (hands, wrists, feet, elbows, male genitalia).
- On the background of erythroderma follicular papules are present in the areas of apparently normal skin; lenticular papules are found on male genitalia and, in both sexes, in axillar pits, on the abdomen and buttocks; besides, a small number of vesicles are seen on hands and feet.
- Microepidemics arise around such patients: infested are family members, medical personnel and other patients sharing the same ward.

However, there are some significant differences between these two forms of scabies which are listed in Table 3. They are helpful for making differential diagnosis between Norwegian scabies and scabious erythroderma.

The first place in the diagnostic efficacy belongs to dermatoscopy, the second - to microscopy of epidermal scrapings and the third one - to tape-tests. Our experience shows that in patients with common scabies mites are extremely rarely detected by means of tape-tests.

Table 3: Differential diagnostics of Norwegian scabies and scabious erythroderma

Features	Norwegian scabies	Scabious erythroderma
Most frequent causes	Immunosuppression connected with long-term use of hormones and cytostatics in case of organ transplants and severe diseases (leukemias, Bloom syndrome, systemic lupus erythematosus and the like), as well as disorders of peripheral sensitivity (leprosy, amyelotrophy, syringomyelia, cerebral palsy and the like) and constitutional anomalies of keratinization (vitamin A deficiency); in HIV-infected persons, in cases of dementia, Down syndrome, infantilism, idiocy, on the background of generalized candidiasis, psoriatic erythroderma, atopic dermatitis and other skin diseases.	Long-term use of systemic and topical corticosteroids, antihistamine and psychotropic drugs in case of incorrect diagnosis.
Itch	Often completely absent or weak in the sites where crusts are localized	Weak, diffuse. Patients usually do not scratch but rather rub the skin with their hands
Main clinical symptom	Multiple massive crusts on the background of erythroderma	Only erythroderma
Onset of erythroderma	Late (in 8-12 months after infestation)	Early (in 2-3 months after onset of corticosteroid therapy)
Localization of hyperkeratotic areas	Palms, soles	Sites of pressure (elbows, buttocks)
Number of mites	Immense; cannot be counted	Up to 30 per 1 cm^2
Tape-test on the skin surface	Always a great number of mites in all tests	Single mites
Tape-test on the sheet	A great number of mites	Moderate quantities of mites
Detection of burrows	Mostly in the sites of typical localization (hands, wrists, male genitalia)	In any site of the skin surface, including the face, neck, scalp and interscapular region
Character of burrows	Typical mite burrows, 5-7 mm long, prevail	Short burrows, 2-3 mm long, prevail which are made by immature parasites
Affection of nails	Often	Absent
Lymphadenopathy	Practically always present	Absent
Increased body temperature	Often	Absent
Changes of hair colour, alopecia	Often	Uncommon
Malodour of the body	Frequent symptom	Absent

The examination of bed linen used by patients with scabious erythroderma demonstrates high contagiousness of this scabies form. Hence, on admission of such patients to hospital, or while treating them at home, their underwear and bed linen must be daily disinfected.

CONCLUSION

This is the description of a rare clinical form of scabies, scabious erythroderma. It is based on the analysis of the 5 cases of scabies, whose main clinical manifestation is diffuse erythroderma. The diagnostic criteria of scabious erythroderma and differential diagnosis of Norwegian scabies are given. The invasive potential of this form of the disease on the patient and beyond is evaluated for the first time.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Original Article

Investigation of adropin and IMA levels in psoriasis and their relation to duration and severity of disease

Suzan Demir Pektas[1], Gokhan Pektas[2], Aynure Oztekin[3], Tuba Gokdogan Edgunlu[4], Sevim Karakas-Celik[5], Salim Neselioglu[6], Ozcan Erel[6]

[1] Department of Dermatology, Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey, [2]Department of Internal Medicine, Mugla Sitki Kocman University Faculty of Medicine, Trainig and Research Hospital, Mugla, Turkey, [3]Department of Dermatology, Hitit University Faculty of Medicine, Corum Trainig and Research Hospital, Corum, Turkey, [4]Department of Medical Biology, Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey, [5]Department of Molecular Biology and Genetic, Bulent Ecevit University Faculty of Science Zonguldak, Turkey, [6]Department of Biochemistry, Yildirim Beyazit University, Faculty of Medicine Ankara, Turkey

Corresponding author: Dr. Suzan Demir Pektas, E-mail: suzandpektas@gmail.com

ABSTRACT

Background: Psoriasis is an immunologically mediated and inflammatory skin disease, which is closely associated with some comorbid conditions such as cardiovascular disease and insuline resistance. It has identified that adropin is important for regulation of glucose, lipid metabolisms, energy and homeostasis. Ischemia Modified Albumin (IMA) generated by reactive oxidant radical is found to be sensitive marker of ischemic heart disease related to oxidative stress. We aimed adropin and IMA levels in psoriasis patients in comparison with healthy controls and their possible relation with duration and severity of disease. **Materials and Methods:** A total of 44 patients and 43 controls were included in this cross-sectional study, and disease severity was evaluated according to psoriasis area severity index (PASI) scoring. Demographic data, clinical features, anthropometric measures and laboratory findings were recorded in all study subjects. Serum adropin and IMA levels were measeured using enzyme-linked immunosorbent assay (ELISA) kit. **Results:** Psoriasis patients had higher values for IMA and C-reactive protein (CRP) compared to the control group. Adropin levels was decreased in the serum of psoriasis patients. The PV patients with PASI>10 had significantly lower adropin than psoriasis patients with PASI≤10, but had no significant different IMA levels between psoriasis patients with PASI≤10 and PASI>10. Duration and severity of disease and CRP levels positively correlated with IMA and negatively correlated with adropin in psoriasis patients.**Conclusion:** These findings indicate the relationship between psoriasis and significantly decreased adropin and increased IMA, along with chronic inflammation and oxidative stress, as associated mainly with long disease duration and severe disease.

Key words: Psoriasis; Adropin; Ischemia Modified Albumin

INTRODUCTION

Psoriasis is immune-mediated chronic and recurrent, sistemic inflammatory skin disease, which is closely associated with oxidative stress (OS). Most characteristic skin lesions are red, scaly sharply demarcated, indurated plaques [1,2]. The etiological and genetic factors for psoriasis is yet not exactly known. But some of reasons like skin infection, drugs, trauma, emotional stress, smoking and alcohol are influences the clinical development of psoriasis [1-3]. In the previous studies, psoriasis is reported to be related to systemic diseases such as hyperlipidemia, hypertension, insulin resistance (IR), metabolic and cardiovascular diseases (CVD) [4-10]. Psoriatic inflammation leads to development of these diseases [5,10]. In fact, psoriasis has been shown to be an independent risk factor for these systemic diseases [4,10]. The increased incidence of cardio-metabolic diseases in psoriasis is caused by underlying systemic inflammation together with

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increased frequency of traditional cardio-metabolic diseases risk factors, which have been in patients with psoriasis [4-7,10].

Adropin is identified protein encoded by the energy homeostasis-associated gene (En-ho) in the brain and liver [11]. It has a role in the maintenance of the insülin resistance and energy homeostasis, related to atherogenesis [11,12]. Adropin affects adiposity and is involved in preventing insülin resistance, dyslipidemia, and impaired glucose tolerance [12-14]. It has reported that increased level of adropin has been shown in various tissues of diabetic rats [14]. In another study, it has determined that lower adropin level leads to endothelial impairment and dysfunction [12]. Furthermore, low serum adropin introduced as a merker of clinically relevant coronary atherosclerosis [12-14].

Ischaemia-modified albumin (IMA), is measured by the albumin cobalt binding test, is reported as a promising marker for cardiac ischaemia [15,16]. Recent studies reported that IMA is also increased in cardio-metabolic diseases associated with OS such as hypercholesterolaemia, renal disease, polycystic ovary syndrome, obesity and type 2 diabetes mellitus [17-19]. It was reported that IMA levels are higher in patients with psoriasis than in healthy controls in patients with psoriasis in studies of Ozdemir M et al. [20], Isik S et al. [21] and Chandrashekar L et al. [22] Three studies reported that increased IMA levels of psoriasis patients is associated with increased systemic inflammation and OS in psoriasis [20-22].

We tried to to find outwhether serum adropin and IMA in patients with psoriasis, and to determine the relationship of serum adropin and IMA with demographic, clinical and laboratory characteristic.

MATERIALS AND METHODS

This cross-sectional study was performed in accordance with the guidelines of Helsinki Declaration and it was approved by the local ethical committee.

Subjects

This study reviews 44 patients with psoriasis who were admitted to the department of dermatology and 41 healthy volunteers. The patients with psoriasis plaques, the patients who received topical treatment for the last four weeks, the patients who received systemic treatment in the last three months, the patients with concurrent systemic disorders (coronary artery disease, liver failure, renal failure, malignancy etc), the patients who had a habit of smoking and/or alcohol consumption, the patients with pregnancy and the breastfeeding patients were excluded. Special care was exercised to match the study and control groups for age and sex. Demographic features, anthropometric measures and blood pressure values were recorded. Psoriasis duration was obtained by self report of the patients. Age, weight, height, and body mass index [BMI; weight (kilograms)/height (meters)^2] were evaluated at baseline. fasting plasma glucose (FPG), CRP and lipid profile [total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)] at diagnosis as metabolic analysis were performed. Low density lipoprotein cholesterol (LDL-C) (LDL=total cholesterol- [HDL + (Triglyceride/5)]) were calculated as previously described. Disease severity was assessed by PASI and grouped as A PASI score below or equal 10 was defined as "mild disease" and above 10 was defined as "moderate-severe disease".

Collection of Blood Samples

Venous blood samples were collected in the early morning following a 8-hour-long fasting period. Sodium citrate and ethylenediamine tetraacetic acid (EDTA) were used as anticoagulants in the collection of these samples. It was made sure that none of the samples was icteric or hemolyzed. Then the samples were centrifuged at 3600 rpm for 10 minutes and kept at -80°C until analysis.

Laboratory Analysis

Serum CRP levels were measured by turbidimetry (660 nm/700 nm) with a Cobas 6000 Analyzer (Roche Diagnostics, USA). Results were compared with those obtained using typical immunoturbidometry. FPG was measured with Cobas 6000 Analyzer (Roche Diagnostics, USA) by using the UV hexokinase method. Triglyceride and total cholesterol was determined with the enzymatic colorimetric assay, HDL-C was determined with the homogenous enzymatic colorimetric assay [23]. Serum IMA levels were measured by using colorimetric assay method previously described by Bar-Or et al. (24). This colorimetric method is based on biochemical properties of albumin to bind exogenous cobalt. In brief, 200 lL of a subject serum was added to 50 lL of 0.1% cobalt II chloride (CoCl2, 6H2O) (Sigma-Aldrich Chemie

GmbH Riedstrasse 2, Steinheim, Germany) followed by mixing and 10 minutes of incubation in the dark at 37 C to allow for cobalt albumin cobalt binding. Then, a total of 50 lL dithiothreitol (DTT) were added as a coloring agent. After 2 minutes of incubation, 1 mL of 0.9 sodium chloride was added in order to reduce the binding capacity. The blank was prepared similarly with distilled water instead of DTT. The absorbance of samples was measured at 470 nm using a spectrophotometer (Jenway 6315 UV/visible Scanning Spectrophotometers, United Kingdom). IMA results were expressed in absorbance units (ABSUs). Each sample was measured in duplicate and the mean value was reported. Serum adropin levels were determined by ELISA method using an appropriate commercial kit (Cusabio Biotech Co., Wuhan, China). The minimum detectable dose of adropin was 0.0156 ng/ml.

Statistical Analysis

To complete statistical assessments, the Statistical Package for Social Sciences (SPSS) software for Windows 18 (IBM SPSS Inc., Chicago, USA) was used. Continuous variables were expressed as mean±standard deviation. The normality of distribution of continuous variables was evaluated by the Kolmogorov–Smirnov, and therefore compared with independent sample Student t-test or Mann–Whitney U-test. Categorical variables were compared with chi-square statistic or Fisher's exact test when appropriate. The Pearson/Spearman correlation analysis was also used to analyze the relationship between numeric parameters. A *p*-value less than 0.05 was considered to be statistically significant.

RESULTS

The patient group included 44 psoriasis patients (20 males and 24 females). The control group included 41 age- and sex- matched healthy individuals (23 females and 18 males). The characteristics of the study groups are summarized in Table 1. Psoriasis patients had significantly higher values for BMI (27.7±5.2 kg/m^2 vs. 23.3±1.4 kg/m^2,p<0.001) compared to the controls. Psoriasis patients had significantly higher mean FPG (89±14.5 mg/dL vs. 83.8±8.2 mg/dL, p<0.001, Table 1), CRP (19.9±3.4 mg/dL vs. 3.4±0.8 mg/dL, p<0.001, Table 1) and triglyceride levels (126.6±60.2 mg/dL vs. 104.2±55.5, p<0.05, Table 1) compared to the control group. When compared to controls, adropin levels (137.4±49.2 ng/ml vs. 169.0±43.9 ng/ml, p<0.001, Table 1) were found to be lower in psoriasis patients

Table 1: Comparison in the characteristics of the control and psoriasis groups

Parameters	Control group N: 41	Psoriasis group N: 44	*P*
F/M	23/18	24/20	NS
Age (year)	32.2±8.1	33.5±8.7	NS
BMI (kg/m^2)	23.3±1.4	27.7±5.2	<0.001
Duration of disease (years)	-	10.0±1.9	
PASI	-	9.9±3.2	
CRP (mg/dL)	3.4±0.8	9.9±3.4	<0.001
FPG (mg/dL)	83.8±8.2	89±14.5	<0.001
LDL (mg/dL)	94.2±34.7	98.7±33	NS
Triglyceride (mg/dL)	104.2±55.5	126.6±60.2	<0.05
TC (mg/dL)	173.8±41.7	175.5±38.1	NS
HDL (mg/dL)	57.2±15	51.9±15.3	NS
Ischaemia-modified albümin (ABSU)	0.4±0.1	0.6±0.1	<0.001
Adropin (ng/ml)	169.0±43.9	137.4±49.2	<0.001

Data werepresented as mean ± SD

N=number of volunteer; NS=nonsignificant; BMI=body mass index; F/M females/males; PASI=Psoriasis area severity index; FPG=Fasting plasma glucose; CRP=C-reactive protein; LDL=low-density lipoprotein; TC=Total cholesterol; HDL=high density lipoprotein.

while IMA levels (0.6±0.1 ABSU vs. 0.4±0.1 ABSU, p<0.001, Table 1), were found to be higher in psoriasis patients.

According to disease severity, psoriasis patients were divided into two groups: 29 psoriasis patients with PASI≤10 (20 females and 7 males), 15 psoriasis patients with PASI>10 (6 females and 9 males). Table 2 summarizes the characteristics of the healthy controls, psoriasis patients with PASI≤10 and PASI>10. When compared to healthy controls, psoriasis patients with PASI≤10 and PASI>10 had significantly higher BMI and FPG, (p<0.05 for all, Table 2). The psoriasis patients with PASI≤10 and psoriasis patients with PASI >10 had significantly lower adropin values than healthy controls (p<0.05 for all, Table 2). The psoriasis patients with PASI>10 had significantly higher disease duration and PASI values than psoriasis patients with PASI≤10 (p<0.001 for both, Table 2). The psoriasis patients with PASI>10 had significantly higher CRP values than psoriasis patients with PASI≤10 (p<0.05 for both, Table 2). The psoriasis patients with PASI>10 had significantly lower adropin levels than psoriasis patients with PASI≤10 (p<0.05, Table 2). There were no statistically significant differences in IMA levels between the groups (p> 0.05 for all, Table 2).

Table 3 shows the correlations among BMI, disease duration, PASI and CRP with adropin and IMA parameters in psoriasis patients. We founded that psoriasis patients had adropin was negatively correlated

with duration of disease, PASI and CRP (r:-0.763, r: -0,741 and r:-0,682, p<0.001 for all, Table 3). On the other hand, a positive correlation between IMA levels and duration of disease, PASI and CRP was observed (r:0.448, r:0.438 and r:0.439, p<0.05 for all, Table 3).

DISCUSSION

Psoriasis is a chronic and immune mediated skin disease accepted as a significant risk factor for CVD [5-7]. Adropin and IMA are accepted to partipicate a play role in the development and progression of some disease related to inflammation [11-13,15-19]. This study aimed to investigate how adropin and IMA levels are altered in psoriasis patients and whether adropin and IMA levels correlate with the severity and duration of psoriasis. In this study, patients with psoriasis were shown to have significantly lower levels of adropin and higher levels of IMA than healthy controls. We found a significant difference between the adropin levels of the patients with moderate to severe psoriasis and the patients with mild psoriasis, but there was no significant difference between the IMA levels of the two groups. It was founded that psoriasis patients had adropin levels was negatively correlated with disease duration and PASI, while IMA levels was positively correlation between disease duration and PASI.

Neutrophils seem to play an effective role to the development of inflammation and oxidative stres in this disease [25,26]. That is, inflammatory cytokines and OS markers are increased within tissues and peripheral circulation of the patients with psoriasis [26,27]. Inflammatory cytokines such as E-selectin, intracellular adhesion molecule-1, haptoglobin, interleukins (IL) and tumor necrosis factor-alpha (TNF-□) participate in the proliferation of keratinocytes within psoriatic lesions [25-27].

Adropin play a role in the maintenance of energy homeostasis and insulin response, closely related to atherogenesis [28]. Lower serum adropin level has recently been shown in studies investigating CVD risk leads to endothelial impairment and dysfunction, a marker for early event in atherogenesis and onset of CVD as well as a marker for clinically relevant coronary atherosclerosis [13]. It is well known that psoriatic inflammation leads to development of CVD and psoriasis has been an independent effector for CVD [5-9]. In this study, patients with psoriasis

Table 2: Comparation of the characteristics of the healthy controls, psoriasis patients with PASI≤10 and PASI>10

Parameters	Control (n=41)	Psoriasis patients with PASI≤10 (n=29)	Psoriasis patients with PASI>10 (n=15)	p-value
F/M	23/18	20/7	6/9	NS
Age (year)	32.29±8.1	33.6±9.3	33.1±7.8	NS
BMI (kg/m²)	23.3±1.4	28.1±5.2	26.8±5.3	<0.05†‡
Duration of disease (years)		9.4±1.8	11.4±1.6	0.001§
PASI		8.1±1.2	13.4±3.1	<0.001§
CRP (mg/dL)	3.4±0.8	8.3±2.3	13.1±3.0	<0.05†‡§
FPG (mg/dL)	83.8±8.2	85.9±22.6	90.6±7.7	<0.05†‡
LDL (mg/dL)	93.7±34.8	99.2±29.7	100.1±34.1	NS
Triglyceride (mg/dL)	104.2±55.5	122.6±63	128.7±59.7	NS
TC (mg/dL)	173.8±41.7	174.8±35.0	177.8±44.7	NS
HDL (mg/dL)	57.2±15	55.4±17.1	50.1±14.3	NS
Ischaemia-modified albumin (ABSU)	0.4±0.1	0.6±0.0	0.6±0.2	NS
Adropin (ng/ml)	169±43.9	150.4±553.5	112.2±26.4	<0.05†‡§

Data werepresented as mean ± SD

N=number of volunteer; NS=nonsignificant; F/M=females/males; PASI=psoriasis area severity index; BMI=body mass index; FPG=Fasting plasma glucose; CRP=C-reactive protein; LDL=low density lipoprotein; TC=Total cholesterol; HDL=high density lipoprotein

Table 3: Correlation of adropin and ischaemia-modified albumin with characteristics in psoriasis patients

	BMI		Duration of disease		PASI		CRP	
	r	p	r	p	r	p	r	p
IMA	0.167	NS	0.448**	<0.001	0.438**	<0.001	0.439**	°<0.001
Adropin	–0.177	NS	–0.763**	<0.001	–0.741	<0.001	–0.682	<0.001

The *P* values < 0.05 were assessed as statistically significant; they were presented in bold.

IMA = ischaemia-modified albumin

BMI = body massindex; PASI = psoriasisareaseverityindex; CRP = c-reactive protein.

who did not have any major CVD risk factors were shown to have higher levels of CRP and lower levels adropin than the controls lacking any majör CVD risk factors. Morever, we found that adropin levels of the patients with moderate to severe psoriasis lower than patients with mild psoriasis. The adropin correlated negatively with disease severity, disease duration and CRP in all psoriasis patients. The decresed adropin possibly reflects the association between psoriasis inflammation and CVD risk in psoriasis patients without any concomitant CVD risk factor presence.

The increase in the generation of reactive oxygen species (ROS) by neutrophils, keratinocytes and dermal fibroblasts plays a key factor in the pathogenesis of psoriasis. It has been postulated that the increase in the production of inflammatory cytokines by neutrophils, keratinocytes and dermal fibroblasts triggers oxidative stres [26,29-31].

IMA is an oxidatively modified form of albumin. IMA has been studied and regarded as a sensitive biomarker for the diagnosis of oxidatie stress (OS) related clinical conditions [16-19]. It was reported that IMA levels increase in the progression of metabolic syndrome [18], hyperlipidaemia [19], type 2 DM [32] myocardial infarction [33], coronary artery disease [34], which are also associated with psoriasis. Isik S et al. [21] reported that IMA increased in patients with psoriasis and it was correlated with disease duration but was not correlated with PASI. Ozdemi M et al. [20] reported that IMA levels are higher in patients with psoriasis than in healthy controls and IMA did not correlate with any disease characteristics. Chandrashekar L et al. [21] reported that serum IMA levels were significantly elevated and IMA showed a significant positive correlation with PASI score in psoriasis. In three study, reserchers reported that increased IMA levels support the role of OS role in the systemic inflammation seen in pathogenesis of co-morbidities associated with psoriasis, and especially with long disease duration and severe disease. Complying with studies of Isik S et al. [21], Ozdemir M et al. [20], Chandrashekar L et al. [21], we founded that psoriasis patients had significantly higher IMA levels than the controls. There were no statistically significant differences in IMA levels between the patients with moderate to severe and mild psoriasis. The IMA correlated positively with CRP as well as disease duration and PASI in all psoriasis patients. This findings suggested that increased IMA may reflect OS with associated chronic inflammation in patients with psoriasis and increased OS may contribute to development of CVD, as associated mainly with long term disease duration and severe disease. Such a contradictory finding of correlation according to other studies may be attributed to the differences in demographic and clinical characteristics of the reviewed patients, variations in biochemical measurement methods and heterogeneity in study populations.

In conclusion, we evaluated adropin and IMA levels and their relationship with duration and severity of disease in psoriasis patients in this study. We founded that IMA increased and adropin decreased in psoriasis patients. Cardiovascular risk factors such as higher BMI, dyslipidemia, FPG and CRP values were found to be more common in psoriasis patients. Additionally, psoriasis patients were demonstrated to have a significant positive correlation among IMA, disease duration, PASI and CRP paramaters, while a positive correlation among adropin, disease duration, PASI and CRP parameters. Chronic inflammation may play a role in the pathogenesis of increased OS in psoriasis. However, these findings should be interpreted carefully as the power of this study is limited by its relatively small cohort and lack of prospective data. In order to determine role of OS and sistemic inflammation on this disease or to understand the association between OS, psoriasis and metabolic disorders, further studies including large number of patients are needed.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Original Article

Metastatic melanoma in Florida, 1996-2010: Racial, demographic, occupational and tumor characteristics, and burden of metástasis

Frederick N. Bebe[1], Shasa Hu[2], Tony L. Brown[3], Orien L. Tulp[4]

[1]Kentucky State University, College of Agriculture, Food Science and Sustainable Systems Frankfort, KY; USA, [2]University of Miami, Miller College of Medicine Miami, Florida, USA, [3]University of Science, Arts and Technology, Monserrat, West Indies - College of Medicine and Graduate School, Denver, CO 80033, USA, [4]University of Science, Arts and Technology, Monserrat, West Indies - College of Medicine and Graduate School, Denver, CO 80033, USA

Corresponding author: Dr. Frederick N. Bebe, E-mail: frederick.bebe@kysu.edu

ABSTRACT

Background: Recent decades have witnessed an increase in melanoma more than any other cancer, resulting in a 2010-2014 age-adjusted incidence rate (IR) and mortality rates of 22.3 and 2.7 per 100,000, respectively. Florida's IR is the 2nd highest in the nation and mortality rate has doubled since 1975. Although metastatic melanoma (MM) is less frequent among minorities, it has been increasing steadily over the years. The purpose of this study is to describe the demographic, occupational, tumor characteristics and the burden of metastasis of patients diagnosed with metastatic melanoma in Florida between 1996 and 2010. **Materials and Methods:** A dataset of 80,349 Non-Hispanic Whites (NHW), African Americans (AA) and Hispanics Whites (HW) stage III and IV metastatic melanoma patients at presentation was obtained from Florida Cancer Data System (FCDS). Demographic information, occupational status and measures related to age at diagnosis, primary site and laterality, histology, grade and staging are reported. Data were analyzed using SAS. Means ± SD, frequencies, percentages and chi-square tests were employed at $P < 0.05$. **Results:** Fifteen counties out of 67 accounted for 72% of all cases; 61% of the patients were married at time of diagnosis. Forty-eight percent reported having state-sponsored coverage, while 60% never smoked. Sixty-nine percent were diagnosed with tumors of the trunk, shoulder and hip; laterality was evenly-distributed between left 39% and right 37%. More AA and HW had tumors that were either moderately or poorly-differentiated. **Conclusions:** This study confirms well-established race/ethnicity, gender and age disparities in metastatic melanoma diagnosis – majority white and male, and majority of the cases between ages 56 and 71. However, unlike previous studies, laterality was evenly-distributed and majority of AA and HW were diagnosed with moderately or poorly-differentiated tumors.

Key words: Occupation; Demography; Tumor characteristics; Metastatic melanoma; Ethnicity

INTRODUCTION

Recent decades have witnessed an increase in the incidence of melanoma of the skin more than any other cancer, predominantly in adults and resulting in an incidence rate of 3-7% per year [1-2]. The 2010-2014 age-adjusted incidence and mortality rates were 22.3 and 2.7 per 100,000, respectively [3]. Melanoma of the skin represents 5.2% of all new cases of cancer in the US. It is estimated that 87,110 new cases of invasive melanoma will be diagnosed in the US in 2017 and about 9,730 will die of the disease. The median age at diagnosis for melanoma of the skin was 64, while that at death was 70 [3]. Overall, melanoma is the sixth most common cancer in men and seventh most common in women; rates are higher for men than for women, and for whites than for all other races combined [3,4].

Florida's incidence rate of melanoma is the 2nd highest in the nation. An estimated 4,928 people were

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diagnosed with melanoma in 2011 in Florida [5]. Melanoma is responsible for about 75% of all skin cancer deaths in Florida; about 741 people die of it each year. Since 1975, the death rate of those over 50 in Florida has doubled [5]. Although, melanoma is less frequent among minorities – Hispanics (HIS) and African Americans (AA) - it has been increasing steadily over the years [6]. It is estimated that for people born in 2006, 1 in 53 will be diagnosed with melanoma - nearly 30 times the rate for people born in 1930 [5]. The age adjusted incidence rate from 2006-2010 per 100,000 population for metastatic melanoma was 26% among whites, 4.5% for Hispanics and 1% for AA [7].

It has been suggested that the lower incidence rate of melanoma in HIS and AA compared to NHW could be attributed to the protective effect of darker skin pigmentation, and therefore, perhaps less important role of sun exposure in melanoma development in HIS and AA [8-10]. Melanin in dark skin persons may function as an optical filter that increases the efficiency of DNA repair mechanisms, thus reducing the likelihood of melanoma [11,12]. However, the increase of metastatic melanoma over the past few decades among minorities indicates that melanin may only confer partial photo-protection. Therefore other unknown factors may be influential. Elder [10] suggested that acral lentiginous melanoma ALM), the most common subtype in minority populations may be an etiological agent for melanoma other than sun exposure, as it mostly occurs in parts of the body usually protected from the sun and with similar frequencies at different latitudes. The increase in incidence has also been variously attributed to upward class mobility amidst intermittent sun exposure in occupational and recreational settings, and continued ozone depletion [8,10,13]. In addition, there have been several reports of a positive correlation between melanoma incidence and socioeconomic status, level of education, inadequate health insurance and socio-cultural values [8,14-17]. The purpose of this study was to provide an in-depth description of the general demographic, occupational, tumor characteristics and the burden of metastasis of patients diagnosed with metastatic melanoma in Florida between 1996 and 2010.

METHODS

Study Population and Measurements

The Florida Cancer Data System (FCDS) database was accessed to identify NHW, AA and HIS patients with metastatic melanoma, specifically those with localized, regional and distant metastasis (stage III and IV) at presentation. A password protected full CD was obtained of cases reported to the FCDS from 1996-2010, including an Acquisition Manual and Data Dictionary for code identification and reference. The study protocol was reviewed and approved by the Florida Department of Health Institutional Review Board and Florida Bureau of Epidemiology. The dataset contained 80,349 patients diagnosed with metastatic melanoma in Florida between 1996 and 2010.

Demographic information included sex, race, marital status, country of birth, state of birth, county of birth, insurance status, history of tobacco use, and occupational status. Measures related to age at diagnosis, primary site and laterality of the tumors, major histology types, and the distribution of grade and stage of the cancers were reported. For descriptive purposes, race/ethnicity was defined as White for all non-Hispanic whites, African American for all who identified as black and Hispanic for all hispanic whites.

Statistical Analysis

Data were analyzed using the Statistical Analysis Software SAS version 9.4.; SAS Institute, Cary, North Carolina. Descriptive statistics were employed for the whole study data, except where data on specific variables were not otherwise reported. Means and standard deviations were calculated to describe continuous variables, while frequencies and percentages were used to describe categorical variables. Meanwhile chi-square tests were used to test the association between categorical variables, with p-value set at 0.05 for significance.

RESULTS

Demographic Measures

Eighty-four percent of the cases were born between 1916 and 1961. Patients were representative of about 50 countries. Of the patients whose country of birth was known, 34% were born in the United States; 36% or more of the patients were born or came from nine countries – Argentina, Canada, Columbia, Cuba, Germany Italy, Poland, Puerto Rico and USA (Data not shown). Table 1 reports the frequency distributions of county of birth and occupational distribution data of metastatic melanoma patients. Fifteen counties out of 67 accounted for 72% of all metastatic melanoma cases

Table 1. County of birth and occupational distribution of patients diagnosed with metastatic melanoma in Florida 1996-2010

County	Frequency	Percent	Occupation	Frequency	Valid %§
Palm Beach	5055	10.87	Transportation & material moving	2942	9.2
Broward	4503	9.68	Sales and office	1370	4.4
Miami-Dade	2922	6.28	Healthcare practitioners & tech.	1203	3.9
Pinellas	2868	6.17	Management	1195	3.8
Hillsborough	2549	5.48	Office and administrative support	1131	3.7
Lee	1963	4.22	Education training & library	1093	3.5
Polk	1937	4.17	Construction and extraction	785	2.5
Orange	1815	3.90	Business & financial operations	679	2.2
Brevard	1709	3.67	Architecture & engineering	481	1.5
Sarasota	1495	3.21	Frontline production	460	1.5
Duvall	1484	3.19	Protective services	401	1.5
Pasco	1440	3.10	Legal services	399	1.3
Volusia	1360	2.92	Miscellaneous (un-coded)	17275	21.5*
Collier	1220	2.62	Missing (NOS)	49204	61.2*
Lake	1059	2.28			
Total		71.76			

15 Counties out of 67 account for 72% of all metastatic melanoma cases diagnosed in FL between 1996 and 2010
**Actual % of the total patient population of 80,349. §Percent excluding missing values*

diagnosed in FL between 1996 and 2010 (Fig. 1). Out of over 400 occupations, 12 occupations were associated with 39% (valid %, i.e. excluding missing values) of the patients. The demographic characteristics of patients diagnosed with metastatic melanoma in Florida from 1996-2010 are shown in Figure 2. Non-Hispanic Whites accounted for 95% of all metastatic melanoma cases diagnosed, while males formed the majority of the cases at 61 percent, as compared to 39 percent for females. A frequency distribution of the marital status of subjects indicated that 61% of those with recorded status were married and 27% either single or divorced.

Primary payer information at diagnosis (Fig. 2) indicated that up to 20% of the patients were either self-pay, not insured or payer information was not available. However, private insurance and government sponsored programs (Medicare/Medicaid/Tricare etc.) accounted for 32 and 48%, respectively. Meanwhile, 60% of patients (excluding missing values) diagnosed with metastatic melanoma had never used cigarettes, while 13% and 28% were current and previous users, respectively (Fig. 2).

The time-trend in melanoma diagnosis indicates a steady increase in the incidence rate from 1996-2010, an average increase of approximately 6.7% or approximately 9.8%, 5.7% and 4.8% every 5 years consecutively (1996-2000; 2001-2005; 2006-2010) (Fig. 2a). An age distribution of the metastatic melanoma cases shows that 55% were diagnosed between the ages of 56 and 79, 80 percent between 31 and 79, while only 3% were below the age of 30 (Fig. 2b).

Tumor Characteristics

The reporting sources for most of the metastatic melanoma tumors were predominantly hospital (outpatient/inpatient or surgery units) and physician or private practitioner offices (data not shown). The frequency distribution of the primary site of reported tumors shows that the trunk, shoulder, hip, face and neck were the most predominant sites of metastatic melanoma invasion, constituting 90% of the total (Table 2). Analysis of the dataset indicates that most of the tumors occurred on the right or left of the paired organ of origin or primary (76%), or from an unpaired primary site (13%) - Table 2. Meanwhile, the tumor's resemblance to normal tissue or degree of differentiation of patient tumors (as reported) is described by its grade. Table 2 shows that only about 17% bore any resemblance to normal tissue, while the rest were either moderately, poorly or totally undifferentiated. At diagnosis, metastatic melanoma is usually classified as either Localized invasive, Regional Spread, or Distant spread. Table 2 indicates that the majority of the patients diagnosed at presentation had tumors (62%) that were localized or that had not spread beyond the primary location identified. Only about 11% had achieved regional or distant spread.

An important criteria in classifying metastatic melanoma is by histologic type. A frequency distribution analysis of the dataset revealed that the major histologic types - nodular melanoma (NM), lentiginous maligna melanoma (LMM), superficial spreading melanoma (SSM) and acral lentiginous melanoma (ALM) - accounted for at least 20% of the total cases

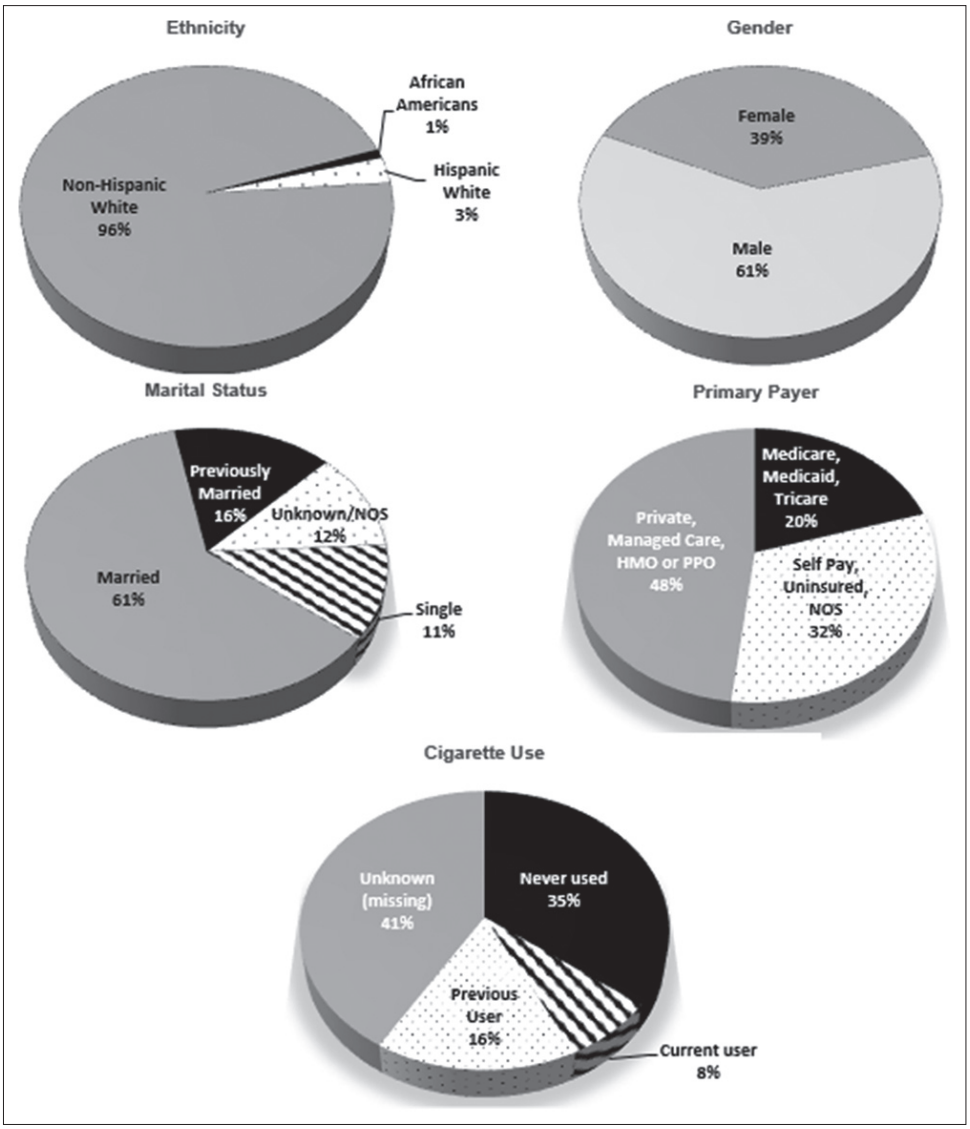

Figure 1: Demographic characteristics of patients diagnosed with Metastatic Melanoma in Florida 1996-2010.

specifically designated, with another 37% receiving the general designation of malignant melanoma (Table 3). Meanwhile, when distributed by gender, males dominated in each major histologic type.

Table 4 is a cross table of gender, grade and age across race categories. In both male and female categories, NHW dominated the representation reporting more than 95% in each category. Results of the chi square test indicated that the null hypothesis of no significant association between race and gender was rejected at.05 level of significance (χ^2 = 66.273, p = <.001). Thus, the proportion of males and females was not same across different ethnic categories. In the cross between race and grade, NHS dominated the representation as well, reporting more than 95% in each category. Results of the Chi square test indicated that the association between race and grade was slightly significant (χ^2 = 10.485, p =.045).

Summary of results of analysis of variance (ANOVA) F-test for homogeneity of age distribution across races indicated that mean age across races was not comparable as mean age for HIS was less than mean age reported for NHW (M = 63.17) and AA (M = 62.281). Thus, the null hypothesis of no significant difference in mean age across races must be rejected at.05 level of significance. The mean age distribution was not the same across different racial categories (p = <.001).

DISCUSSION

It is well documented that Florida has many advantages for studying melanoma (especially among minorities

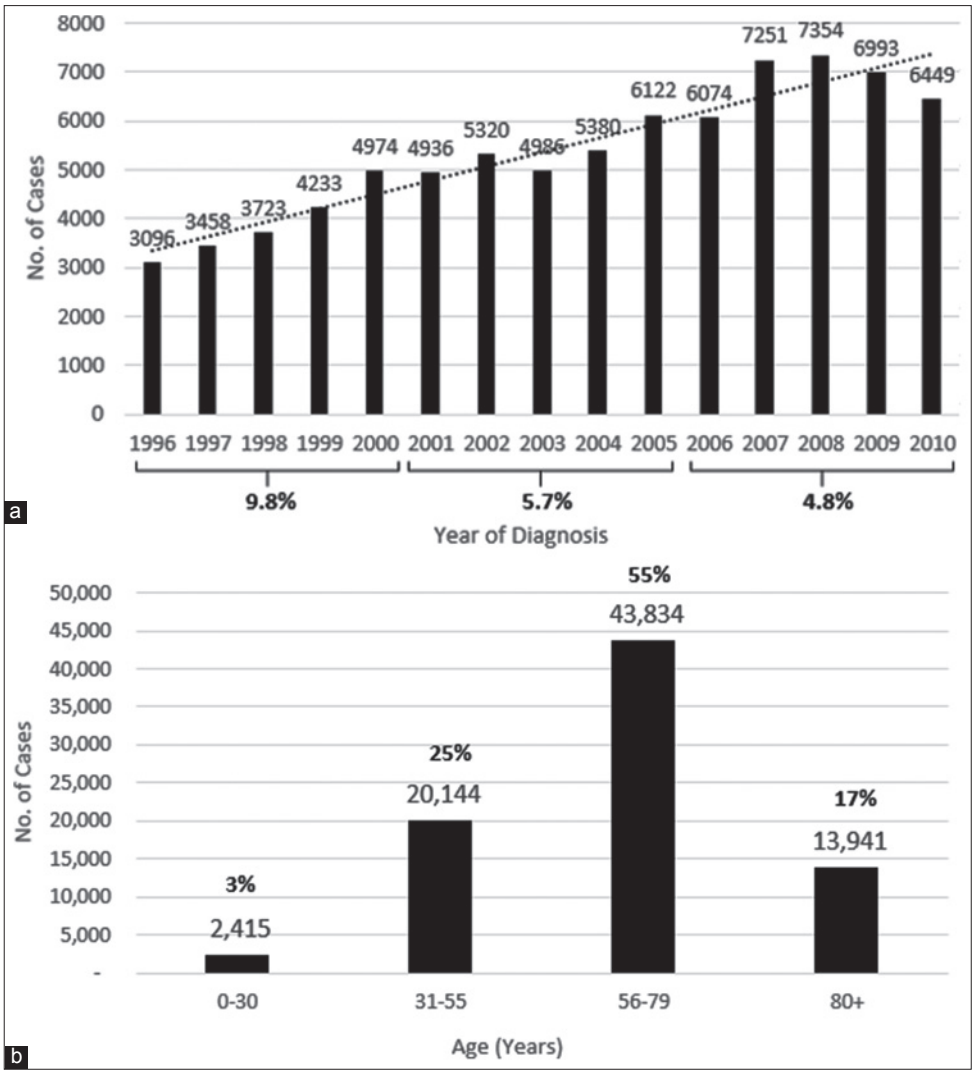

Figure 2: (a) Time Trend in Metastatic Melanoma Diagnosis in Florida 1996-2010. (b) Metastatic Melanoma in Florida - Age at Diagnosis, 1996-2010 .

AA and HIS) in that it is ethnically and racially diverse, with the second highest incidence rate in the US [4,7,18]. Diversity in the metastatic melanoma patient population in this study is indicated by the fact that the patients represented 50 countries (including the US), and distributed among all the counties in Florida. However, fifteen Florida counties accounted for 72% of all metastatic melanoma cases diagnosed - the first 5 being Palm Beach, Broward, Miami-Dade, Pinellas and Hillsborough, almost all of which are located on the southern west and east coasts (Fig. 1).

The incidence rate for melanoma as a whole has been reported to be 2.8% and 3-7% per year for Florida and the US, respectively [3,4,17]. The latest SEER Stat Fact Sheets for Melanoma 2016, report an increase of 1.4% each year for the last 10 years [3]; the age adjusted incidence rate for malignant melanoma has been shown to be consistently higher for males than for females, irrespective of race [3,5,9]; and for whites than for all minority populations combined. In addition, from 2009 to 2013, melanoma has been frequently diagnosed among people between the ages of 55 and 64, with a median age of 63 [3]. However, summary data in this study revealed that stage 3 and 4 metastatic melanoma diagnosis in Florida had been increasing yearly by an average of 6.7% between 1996 and 2010. A very large majority were NHW (95%); HIS and AA were 3% and 1% respectively, and 55% of all cases diagnosed were between the ages of 56 and 79, while 80% were between the ages of 31 and 79. This study confirms SEER report of consistently higher incidence for males than for females – 60.5% and 39.3%, respectively [3]. Similarly, when patients with metastatic melanoma in situ and node negative plus or minus ulceration (stage 1 and 2) were excluded in a comparison of gender and race, or

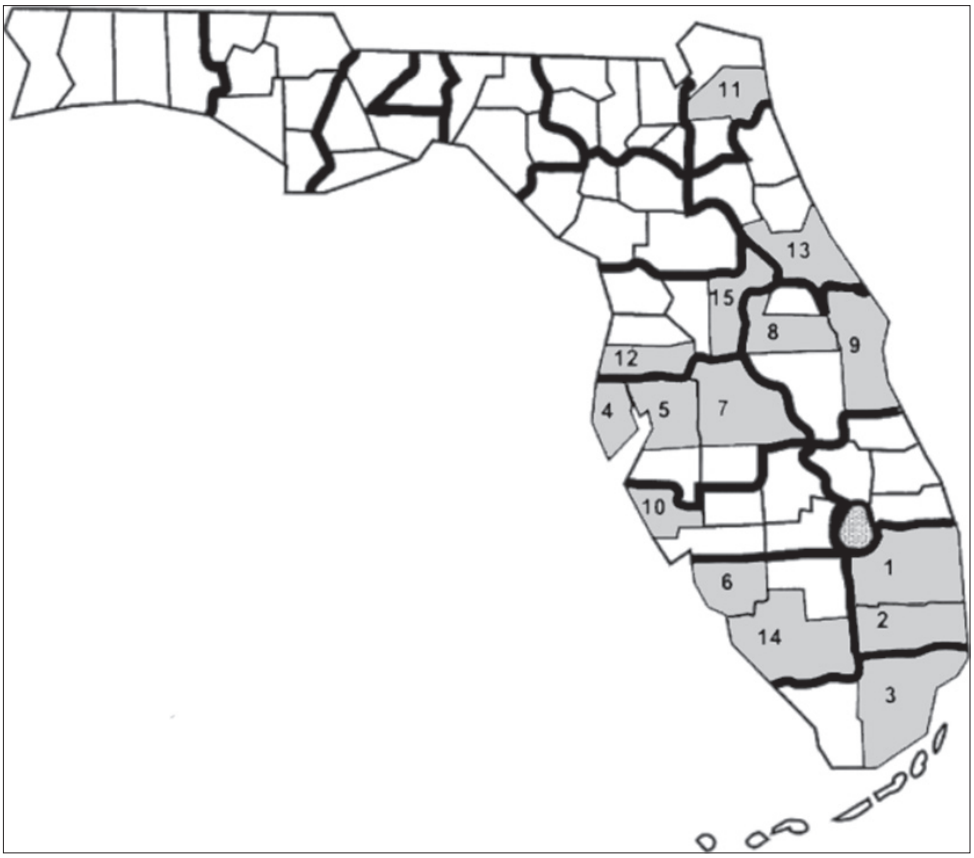

Figure 3: Counties with Highest IR of Metastatic Melanoma (See Table 1).

age and race, the proportion of males and females and the mean age distribution were not the same across race categories (χ^2 = 66.3, p=<.001 and F = 42.8, p = <.001, respectively).

Several studies have suggested that patients without medical insurance or those with Medicare/Medicaid are more likely to present with late-stage cancer (including melanoma) than those with private or managed care insurance [19-21], and that irrespective of health insurance racial minorities have an increased risk of diagnosis at late stage [20,21]. Halpern et al., reported late stage melanoma odds ratio of 2.3 (2.1-2.5) and 3.3 (3.0-3.6) for uninsured patients and Medicaid-insured patients respectively, compared to the privately insured [21]. Although this paper does not report on the effect of insurance status on ethnicity, a frequency distribution of primary payer shows that the majority of patients (48%) had government sponsored coverage (Medicare, Medicaid, Tricare), compared to private coverage (32%) and self-pay/uninsured (20%).

The association of marital status with metastatic disease and survival has been reported in a few melanoma studies, with unmarried patients at significantly higher risk than married patients. While controlling for a number of variables, Reyes et al. reported that older widowed patients were likely to be diagnosed at late stage and at greater risk of death than older married patients [22]. Similarly, McLaughlin and colleagues after adjusting for a series of factors indicated that unmarried patients had a higher risk of late stage diagnosis of cutaneous melanoma, with men having a 50% increased risk than women [23]. This study shows that for those metastatic melanoma patients diagnosed in Florida between 1996 and 2010 and whose marital status was reported, 61% of them were married at time of diagnosis, while only 11% were unmarried.

The occupational distribution of patients diagnosed with metastatic melanoma was varied. It was based on the 2010 Census of Occupation Codes and defined as the type of job patients were engaged in for most of their working life. There was an almost even distribution between outdoor (transportation and material moving, construction and extraction, architecture and engineering, frontline production protective services) and indoor reporting occupations (sales and office, healthcare practitioners and technicians, management, office and administrative

Table 2: Primary site, laterality, grade and stage distribution of tumors of patients diagnosed with metastatic melanoma in Florida, 1996-2010

Site Code	Description	Frequency	Percent
C443	Skin of face	11200	13.9
C444	Skin of scalp and neck	6179	7.7
C445	Skin of trunk	23609	29.4
C446	Skin of upper limb and shoulder	19639	24.4
C447	Skin of upper limb and hip	12090	15.0
	Other plus NOS§	7632	9.5
Laterality Code	**Description**	**Frequency**	**Percent**
0	Not a paired site	10712	13.3
1	Right: Origin of primary	29654	36.9
2	Left: Origin of primary	31265	38.9
	Other	8718	10.8
Grade	**Description**	**Frequency***	**Percent***
1	Well differentiated	134	16.83
2	Moderately differentiated	168	21.11
3	Poorly differentiated	346	43.47
4	Undifferentiated	148	18.59
Stage of Tumor		**Frequency**	**Percent**
Localized		49728	61.9
Regional		4097	5.1
Distant		1950	2.4
Unknown (missing)		24576	30.6

§NOS=Not otherwise stated; *Excludes undetermined or missing values

Table 3: Tumor histology of patients diagnosed with metastatic melanoma in Florida, 1996-2010

Type	Description	Frequency	%	Male	%	Female	%
8720	Malignant Melanoma*	29299	36.5	17679	60.3	11620	39.7
8721	Nodular Melanoma	3707	4.6	2392	64.5	1315	35.5
8742	Lentigo Maligna Melanoma	1968	2.5	1295	65.8	673	34.2
8743	Superficial Spreading M.	8497	10.8	4919	57.9	3578	42.1
8744	Acral Lentiginous M.	533	0.7	280	52.5	253	47.5
8745	Desmoplastic Melanoma	804	1.0	585	72.8	219	27.2
	Other/NOS	35541	44.2				

*General description

support, education training and library business and financial operations, legal professions) in this study. However, with the exception of transportation and material moving, and construction and extraction, indoor occupations reported patients made up the greatest percentage of those diagnosed with metastatic melanoma. Indeed, Rigel reported greater association of melanoma incidence with indoor workers and those with higher education occupations [24], while Lee and Strickland found that clerks and salesmen had greater rates than skilled manual workers [25]. Similarly, in a study of British and Swedish cancer registries Vagaro et al. reported many high level education occupations with highest associated melanoma risk such as airline pilots, accountants, dentists, finance and insurance brokers. Outdoor workers may have an altered melanoma risk because of ultra violet exposure resulting in an inverse association of high occupational sun exposure with melanoma [26].

An important adverse effect variable or risk factor for a variety of malignancies is tobacco use. But results of studies evaluating the association of tobacco smoking and melanoma have been mixed and far from being causal. Danish and Swedish studies on the association of melanoma and smoking, alcohol and other factors have indicated that the risk of metastatic melanoma was not influenced by smoking [27,28]. On the other hand, Freedman et al. and Odenbro et al. reported current smokers, smoking for long durations or previous smokers had a reduced risk for metastatic melanoma as compared to those who never smoked, and that the mechanism for such an inverse associated is yet to be investigated [29,30]. On the contrary, smokers have been reported to having greater odds of presenting with late-stage disease [31], with smoking shown to facilitate the spread of metastasis as smokers or more ex-smokers than life-long non-smokers initially presented for melanoma treatment with established metastasis [32]. Although the association between cigarette use and

Table 4: Gender, grade and age across race categories for patients diagnosed with metastatic melanoma in Florida, 1996-2010

Race	Sex		Total	(χ^2)	P-value		
	Male	Female					
NHW	27300	17393	44693	66.273	<.001		
	(96.64)	(95.26)					
AA	120	154	274				
	(0.42)	(0.84)					
HIS	828	711	1539				
	(2.93)	(3.89)					
Total	28248	18258	46506				
Race	**Grade**						
	1	**2**	**3**	**4**	**Total**	**(χ^2)**	**P-value**
NHW	131	158	329	142	760	10.49	0.045
	(97.76)	(94.05)	(95.09)	(95.95)			
AA	0	0	8	1	9		
	(0.0)	(0.0)	(2.31)	(0.68)			
HIS	3	10	9	5	27		
	(2.24)	(5.95)	(2.60)	(3.38)			
Total	134	168	346	148	796		
Race	**N**	**Mean Age**	**SD**	**F**	**P-value**		
NHW	44693	63.1724	16.52542	42.78	<.001		
AA	274	62.2810	17.08751				
HIS	1539	59.2144	17.43852				

Values in parenthesis are percentage to the column total

melanoma was not evaluated in the present study, it is clear that the majority of patients diagnosed with metastatic melanoma had never smoked (60%) as compared to current or previous smokers (40%), at time of diagnosis.

It has often been reported that the anatomical distribution of melanoma is different between Whites and minority populations, with Whites developing more of their lesions on sun-exposed surfaces and African Americans and Hispanics predominantly on sun-protected acral sites [33-39]. Acral lentiginous melanoma incidence in African Americans has been estimated to be 60% to 70% [37,40,41], compared to approximately 5% in Whites in whom superficial spreading melanoma predominates [42]. Although some studies have shown that the most common histologic types of metastatic melanoma among all racial groups is SSM or LMM, this study reported (in descending order) that NM, LMM, SSM and ALM were the most important histologic types. However, a direct comparison may not be possible because of the overall low incidence rate of melanoma among minorities; as ALM has been found to be similar or with equal frequency between whites and minority populations in some studies [43,44]. The distribution of metastatic melanoma primary site in this study clearly shows that 69% of metastatic melanoma patients were diagnosed with tumors of the trunk, shoulder and hip, all sun-protected sites consistent with a potential diagnosis of ALM. However, of the 20% of patients whose histologic types were positively identified, less than 1% were classified as ALM.

Laterality describes the side of a paired organ, or side of the body on which the reportable tumor originated and is applicable to the primary site only (44). There has been a dearth of studies on the laterality of metastatic melanoma and probably none comparing ethnic groups. This study of metastatic melanoma patients suggests an almost even distribution of laterality diagnosis between left 39% and right 37% - a difference of only 2%. However, two multicenter or country studies of cutaneous melanoma laterality reported consistently higher left to right ratios greater than 1 with no significant differences by sex or age group [45] or left to right ratios greater than 1 for clinical characteristics and a higher left side frequency of about 15% [46]. It is thought that asymmetric melanocytic distribution, differences in sun exposure and embryonic developmental characteristics to a lesser extent, instead of chance are likely explanations for the observed left-sided excess of invasive cutaneous melanoma [45,46].

Advanced stage melanoma at presentation (stage III and IV) in association with poor survival rates among African Americans and Hispanics compared to Whites has been the subject of a number of studies [3-6,8,9,18,36,47-50]. Even when adjusted for site of primary, histologic type and other variables,

African Americans and Hispanics were still more likely than White to be diagnosed with late stage disease: 32% vs 13% [34] or 14% vs 4% [52]. The present study shows a weak association between race and grade ($X^2 = 10.5$, p=.048). In addition, more AA and HIS had tumors that were either moderately or poorly differentiated, thus placing them at regional or distant metastatic stage at diagnosis. The weak level of significance may be due to the low incidence rate in minority populations and the number of patients with reported tumor grade at diagnosis.

This study draws its strength not only from the availability of a large dataset for studying metastatic melanoma, but also from the many advantages Florida has in that it is ethnically and racially diverse, with the second highest incidence rate in the US [9,15,18]. This diversity in the metastatic melanoma patient population in this study is indicated by the fact that the patients represented 50 countries and distributed among all the counties in Florida.

However, a number of limitations are worth noting. The incidence rate for AA and HIS patients (5% and 1% respectively), was too low to perform an in-depth analysis and may have significantly reduced the statistical power. Complete records were not available for many patients. Patients with not otherwise stated (NOS) or missing values were excluded from some analysis. Excluding patients with missing values may introduce bias and further reduced the power of the study. Classification of metastatic melanoma as NOS histologically seems to be a common problem with registry data. The weak level of significance between race and grade may be due to the low incidence rate in AA and HIS, and the number of patients with reported tumor grade - an important limitation in this study.

CONCLUSION

The focus of this study on metastatic melanoma has not only confirmed existing data but revealed a number of points that need to be emphasized: 15 Florida counties out of 67 accounted for 72% of all metastatic melanoma patients, the majority of whom reported having government sponsored insurance coverage and mostly sustained by outdoor occupations, while over a third had been current or previous smokers. Sixty-nine percent of patients were diagnosed with tumors of the trunk, shoulder and hip, all sun-protected sites consistent with a potential diagnosis of ALM. There was a slightly significant association between race and grade with more AA and HIS having tumors that were either moderately or poorly differentiated, thus placing them at regional or distant metastatic stage at diagnosis. This study revealed that metastatic melanoma diagnosis in Florida had been increasing yearly by an average of 6.7% between 1996 and 2010 and that unmarried patients had a higher risk of late-stage diagnosis than married patients. Given that Florida has the second highest population aged 65 and over in the US, the implications for metastatic melanoma prognosis and survival are yet to be studied. More so, this study suggests an almost even distribution of laterality diagnosis between left 39% and right 37% and confirms the well-established race, gender and age disparity in metastatic melanoma diagnosis – majority white and male, and majority of the cases between 56 and 71 years of age.

More studies are needed on tumor histology and in the identification of laterality, with comparison among ethnic groups. There has been a dearth of studies on the laterality of metastatic melanoma and probably none comparing ethnic groups. This study shows clearly that Florida should place more emphasis and resources on prevention and management of metastatic melanoma, especially in those areas and populations most affected.

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Our Dermatology Online

Original Article

Tinea caused by Microsporum gypseum

Edoardo Torres – Guerrero[1], Claudia Jessica Espinoza – Hernández[2], Stephanie Arroyo – Camarena[2], Carlos Enrique Atoche – Diéguez[1]

[1]Sección de Micología, Centro Dermatológico "Dr. Fernando Latapí". Mérida, Yucatán, México, [2]División de Dermatología, Hospital "Dr. Manuel Gea González". Ciudad de México, México

Corresponding author: Dr. Edoardo Torres - Guerrero, E-mail: lalotorresg@yahoo.com.mx

ABSTRACT

Background: Tinea is a superficial mycoses caused by pathogenic, keratin digesting fungi, called dermatophytes. In Mexico, the most frequent agent is *Trichophyton rubrum*, and on the other hand, *Microsporum gypseum* is the most important geophilic one, however this is infrequent. **Objective:** To determinate the frequency and prevalence of *M. gypseum* infections in a Dermatological Center of Mexico. **Methods:** Descriptive, retrospective, observational and transversal study of a 14 years (2002 – 2016) period. All the patient charts with *tinea* due to *M. gypseum* confirmed by culture were included. The following data were analyzed: gender, age, occupation, provenance, time of onset and clinical features. Descriptive statistics were used. **Results:** A total of 3,921 mycological studies were done with 64 isolations of *M. gypseum* (1.7% of the total). 21.88% were students and 20.32% were mature adults. The body regions involved were head/neck (34.3%), trunk (21.8%), forearms (15.6%) and thighs (10.9%). **Study Limitations:** Some limitations of our work were the study period and the number of negative cultures from the total performed at our micology laboratory. **Conclusions:** *Microsporum gypseum* has a wide world distribution however clinical cases due to this agent are scarce. This is one of the largest compilations of clinical cases due to this pathogen. Students and housewives were the main affected. It could be due to play on the ground, contact with pets, or domestic duties.

Key words: *Tinea*, ringworm, *Microsporum gypseum*, Epidemiology

INTRODUCTION

Tinea (ringworm or dermatophytosis) are superficial mycoses caused by pathogenic, keratin digesting fungi, called dermatophytes; these belong to four genera: *Trichophyton*, *Microsporum*, *Epidermophyton* and *Chrysosporium*. They infect skin, nails and hair; which may occasionally invade deeper tissues [1,2].

Dermatophytosis can be classified as superficial (*tinea capitis*, *tinea corporis*, *tinea cruris*, *tinea manuum*, *tinea pedis*, *onychomycosis* and *tinea imbricata*), and deep infections (*tinea barbae*, kerion celsi, favus, trichophytic granuloma, dermatophytic mycetoma and dermatophytic disease [Hadida]). The severity and course of the infection depends on the causative agent and the host immune response [2].

This is a worldwide disease, but it predominates in tropical countries and it can be seen in different socioeconomic levels. Based on the transmission mechanism, the different causative agents can be acquired from the environment (geophilic dermatophytes), from infected animals like cats, dogs, rodents and cattle, among others (zoophilic dermatophytes) or from infected people (anthropophilic fungi) [2,3].

In Mexico, the most frequent agent is *Trichophyton rubrum*, an anthropophilic dermatophyte, and on the other hand, *Microsporum gypseum* is the most important geophilic one, however this last is an infrequently isolated agent [1].

To determinate the frequency and prevalence of *M. gypseum* infections in a Dermatological Center of

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Mexico (Centro Dermatológico de Yucatán [CDY]. Dr. "Fernando Latapí").

MATERIAL AND METHODS

Descriptive, retrospective, observational and transversal study of 14 years (2002 – 2016) performed at the Dermatological Center in Yucatan, Mexico. All the patient charts with *tinea* due to *M. gypseum* confirmed by culture were included. The following data were analyzed: gender, age, occupation, provenance, time of onset and clinical features. Descriptive statistics were used.

RESULTS

In the period mentioned above, a total of 3,921 mycological studies were done with 64 isolations of *M. gypseum* (76.5% corresponding to female patients), which represents 1.7% of the total of cases, with a higher prevalence in 2011 (Table 1).

The average age of the affected patients was 16 years old (range 8 – 46 years) and the mainly affected group was school-age children (6 to 11 years old) followed by mature adults (35 to 59 years old). The majority of the patients were students followed by housewives. The results are shown at tables 2 and 3.

Thirteen cases (20.3%) were acute (< 15 days), 22 (33,3%) subacute (16 to 30 days) and 29 (45.3%) chronic (> 30 days) with an average evolution time of 21 days.

The main body regions involved were head and neck (Fig. 1) (34.3%), trunk (21.8%), forearms (Fig. 2) (15.6%) and thighs (10.9%). The results are presented in table 4.

Thirty-seven patients (57.82%) were from Merida; two patients from each other populations (Tekax, Kanasín and Muna) were reported (3.15% in each case); several individual cases were from other municipalities of the State, and finally two patients were from neighboring entities (Fig. 3).

DISCUSSION

Tineas are mainly caused by antrophophilic or zoophilic dermatophytes worldwide, such as *T. rubrum* and *M. canis*, however, geophilic fungi have a more extended geographic distribution such as *Microsporum gypseum* [4] which is the most important soil acquired pathogen but clinical cases due to this agent are scarce. This causative agent can affect cats, dogs, rodents and horses, and in humans, in some cases, it can cause *tinea corporis*, *tinea capitis* and *tinea faciei* [5].

This has been demonstrated by some epidemiological and environmental studies such as the conducted by Kachuei et. al in Iran, who reported a frequency of *M. gypseum* of 12.4% from soil samples in a collecting from 16 townships of Isfahan province [6]; and it was isolated in 1.1% of 15,684 samples of dogs and cats in Italy by Nardoni et. al. [7].

Table 1: *Microsporum gypseum* isolations per year and number and gender of affected patients

Year	Mycological studies	*M. gypseum* positive isolations	Prevalence
2002	220	3	1.3
2003	250	2	0.8
2005	267	2	0.7
2006	228	3	1.3
2007	245	3	1.2
2008	302	3	0.9
2009	251	5	1.9
2010	244	9	3.6
2011	265	10	3.7
2012	252	4	1.5
2013	288	2	0.6
2014	279	8	2.8
2015	287	2	0.6
2016	271	8	2.9
Total	3921	64	1.7
Number and gender of affected patients			
Male		Female	
15 (23.4%)		49 (76.5%)	
100%			

Table 2: Frequency of *M. gypseum* per age group

Age	*M. gypseum* (%)
Infants (0-1 years)	1 (1.57)
Preschoolers (2-5 years)	11 (17.17)
Scholar age (6-11 years)	14 (21.88)
Adolescents (11-19 years)	10 (15.63)
Adults	
Young adults (20-35 years)	9 (14.07)
Mature adults (35-59 years)	13 (20.32)
Elderly (>60 years)	6 (9.38)

Table 3: Distribution of *M. gypseum* per occupation

Occupation	Frequency of *M. gypseum* n(%)
Infant and preschooler	11 (17.1)
Student	25*(39.1)
Employee	7 (10.9)
Professional	5 (7.8)
Housewife	15 (23.4)

*14 students were female and 11 were male.

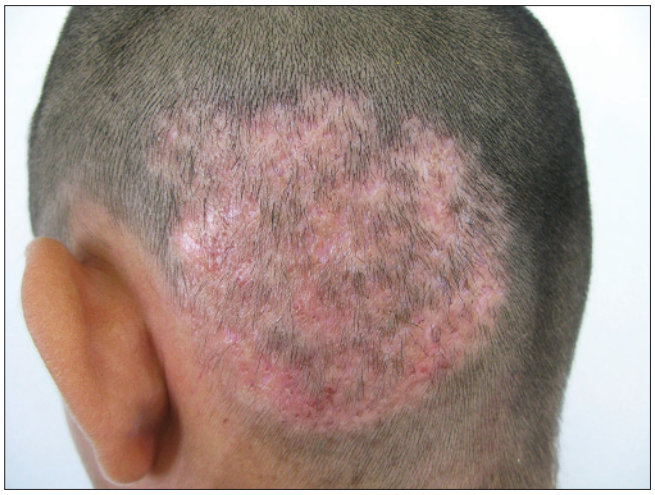

Figure 1: *Tinea capitis* (Kerion Celsi).

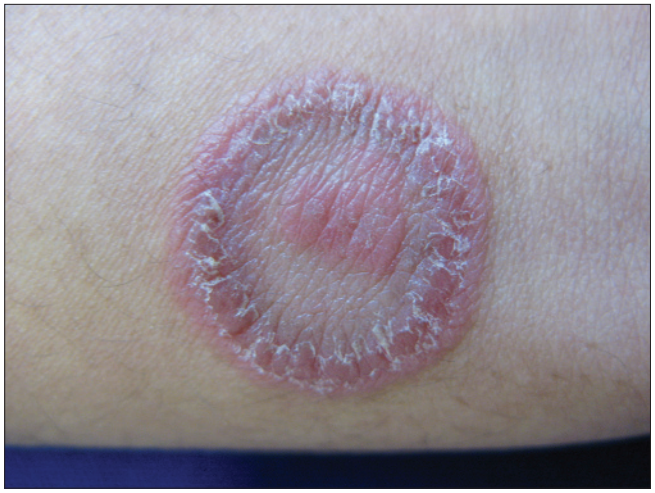

Figure 2: *Tinea corporis* due to *M. gypseum.*

Figure 3: Yucatan State map and number of cases in each municipality.

Worldwide, this pathogen has been reported in several series and case reports, but it has been infrequent. In our study, we collected 64 cases in a period of 14 years, corresponding to 1.7% from a total of 3921 mycological studies.

Table 4: Involved corporal regions

Topography	n (%)
Head and neck	22 (34.3)
Scalp	7 (10.9)
Face	8 (12.5)
Forehead	2 (3.1)
Preauricular region	2 (3.1)
Nose	2 (3.1)
Cheek	1 (1.5)
Trunk	14 (21.8)
Upper limbs	15 (23.5)
Forearm	10 (15.6)
Hand	5 (9.2)
Low limbs	11 (17.1)
Thigh	7 (10.9)
Leg	4 (6.2)
Mixed topographies	2 (3.1)

In Greece, Maraki et. al isolated this fungus in 1.5% of the cases of 2674 samples from 2004 to 2010 [8]. In Brazil, Heidrich and colleagues [9] obtained 14,214 positive cultures from 36,446 cases of dermatophytosis in 16 years, isolating *M. gypseum* in 122 cases (1.35%). This data is proportionally similar to our findings, but higher than 0.47% of frequency reported by Zida et. al. in Burkina Faso [10], similar to 0.1% and 0.33% reported by Rezaej-Matehkolaej and Bassiri-Jahromi, respectively, in Iran [11,12] from a total of 4120 clinical samples, and similar to data reported by Sei in Japan where only three cases from a total of 36,052 samples of outpatiens were caused by *M. gypseum* [13]. Moreover, in an epidemiological study conducted by Pérez-González in Spain over a two-year period, this causative agent was isolated only in one case of *tinea pedis* [14].

This result is similar to the obtained in a previous epidemiological study conducted by García et. al in Guadalajara, Mexico, with 2227 samples from children with lesions suspicious for *tinea*, where *M. gypseum* was found in 1% of the cases [15].

On the other hand, some reports document a higher prevalence of this fungus such as Paudel and colleagues who published 8.33% of a total of 110 samples of suspected cases of dermatophytosis in Nepal [16] or the study conducted by Romano et. al in Sienna, Italy, with a frequency of 6.8% in a period from 2005 to 2006 [17].

The predominance of females in our study was very marked respect to males (76.5% vs 23.4% respectively). This data is similar to Heidrich in Brazil with a male-female ratio of 1:4.64 in his study [9].

Conversely, other studies conducted in Nepal, Iran and Japan reported a calculated male: female ratio of 1.39:1 [11,13,16], however, these numbers are from global results of these studies without a real proportion between genders of infected patients with *M. gypseum*.

The most affected age groups were 11 to 19 years and 35 to 59 years. Those results are similar to those obtained by Heidrich et. al. who reported a predominance among young males and mature females in two age peaks with an average age of 7 years for male patients and an average age of 32.5 years for women; our patients were equally affected in the main infected group (scholar age) with seven boys and seven girls for a total of 14 patients with a 1:1 ratio; and an evident female predominance among the second most important group (12 females and one male patient) [9].

In other studies, with general statistics of dermatophytosis, the results were different to ours. For example, Paudel in Nepal reported a predominance of general dermatophytosis among patients from 21 to 30 years; and Rezaej published a predominance in patients from 21 to 30 years and lower frequency in patients from 11 to 20 years old (opposite to our results, where the principal groups were 6 to 11 years old [14 patients], 35 to 59 years old [13 patients] and 12 to 19 years old [10 patients]) [11,16].

Respect to the frequency by occupation, students (39.1%) and housewives (23.4%) were the main activities (Table 3). It is partially concordant with the predominance of women among our patients, but it contrasts with the results obtained by Heidrich who reported a predominance of young males and mature women in his study. [9].

The head was the most frequent topography, affecting 22 patients (34.3%) with an involvement of the face in eight individuals and scalp in seven patients (all those last patients with inflammatory *tinea capitis*); followed by upper limbs (23.5%) and the trunk (21.8%) (Table 4). The frequency of *tinea corporis* was 77.8% of the total. These results are very similar to the data obtained by Heidrich et. al. in Brazil where a predominance of the face was reported, with a frequency of 19.3% of the total, followed by the scalp with 11.7% and arms with 10% [9] and a frequency of *tinea corporis* of 46.2% of the total; a low propensity for the feet and toenails in both studies was found (opposite to the predilections for *Trichophyton*). Previous studies conducted in Mexico reported the isolation of *M. gypseum* in 2% from samples of patients with *tinea capitis* and *tinea corporis* but this percentage of *tinea capitis* and *corporis* was much lower than in our study (13 and 22% respectively), but with a similar predilection for patients between 3rd and 5th decades of the life for the last clinic form [15]. In a previous epidemiological study conducted by Martínez et. al in Guatemala, *M. gypseum* was the most frequent etiological agent of *tinea faciei* [18]. In other study conducted in Northeast Brazil, Silva-Rocha isolated *M. gypseum* from two samples of patients with *tinea* of glabrous skin and in one sample from toenail of a total of 113 positive cultures collected between 2013 and 2014 [19]. On the other hand, Zida et. al, in a study conducted in Burkina Faso identified *M. gypseum* only in samples of two patients with *tinea* on upper and lower limbs [10]; and in Barcelona, Pérez-Gónzalez isolated *M. gypseum* only in one case of a scholar age patient with *tinea pedis* [14].

Microsporum gypseum is a geophilic dermatophyte with a wide world distribution, however it is an infrequently isolated agent. It has been identified in epidemiological studies conducted by Bhagra in Brazil, in 71 cases over 30 years and in some microepidemics reported in Ivory Coast, England, Colombia and Brazil. Lavalle identified this fungus in Mexico in 41 cases from a total of 11,148 dermatophyte isolates over a period of 45 years [20-22].

In spite of its relative low frequency, *M. gypseum* is the most important geophilic dermatophyte, because it is a soil resident. This condition can predispose children who play on the ground or those who have contact with pets like cats and dogs or other domestic animals in which this dermatophyte has been isolated, usually as asymptomatic carriers without infection [9]. This could explain the predilection of this causative agent to infect children and people who perform domestic duties (due to the high exposure of glabrous skin to the environment, associated with daily habits, life style and the high probability of trauma with contaminated items, with two age peaks such as those found in our study) [19], especially in suburban and rural environments where dirt floors are common.

Moreover, it has been observed that inflammatory *tinea capitis* (Kerion Celsi) is more commonly caused by *M. gypseum* and *M. canis* (and less frequently by *T. tonsurans*). This can be explained because the enzymatic profile of *M. gypseum* is very similar to *M. canis* as evaluated in Barcelona by Bruguera et. al. using qualitative and semi-qualitative methods as API

ZYM®, concluding that both fungi have almost the same enzymes (alkaline phosphatase, esterase, esterase lipase, lipase, leucine arylamidase, valine arylamidase, acid phosphatase, phosphoamidase, β – glucosidase, N – acetyl β glucosaminidase and α – mannosidase [23].

These series compiles the epidemiological data of an infrequent but important pathogen fungus that is a relevant cause of inflammatory dermatophytoses such as Kerion Celsi, moreover this causative agent has been uncommon in previous studies conducted by other authors, but the climatic conditions of temperature and humidity of the Yucatan peninsula (the weather in 84.5% of its territory is hot and humid with a minimum temperature of 16° C, maximum of 36° C and average of 26° C) [24] seems to be appropriate to the development of these species; in addition, almost half of the patients were from rural areas of the Yucatan State (Fig. 1), which is one of the environmental characteristics of *M. gypseum*'s habitat, as we mentioned above.

CONCLUSION

This work is one of the largest compilations of clinical cases of dermatophytoses due to this causative agent, which presents difficulties on its treatment when affect the scalp due to its capability to trigger a severe inflammatory immune response. So, mycological diagnosis is very important not only to determinate a therapeutic regimen for the patients, but also it can help to definite an approximate social – economic situation and life conditions of the people who suffer this disease, because it is important to emphasize that in Merida City, most of people lives in houses with gardens and ground backyards where frequently does gardening activities and it is probably that there are the biological niches of the causative agents.

Study Limitations

Some limitations of our work were the study period and the number of negative cultures from the total performed at our micology laboratory.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Brief Report

The prediction of the percentage of tattoo ink that is able to penetrate the stratum corneum in different races

Piotr Brzezinski[1], Lorenzo Martini[2]

[1]Institute of Biology and Environmental Protection, Pomeranian Academy, Slupsk, Poland, [2]University of Siena, Department of Pharmaceutical Biotechnologies, Via A. Moro 2, 53100 Siena, Italy

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

ABSTRACT

Background: Tattoos have always had an important role in ritual and tradition. **Material and Methods:** We have decided to scrutinize how much inks generally used by tattooists are able to penetrate the stratum corneum of the epidermis, keeping on account that it is always better pigments and carriers that constitute the ink do not penetrate deeper into the dermis, as ink can carry inside the human body bacteria and heavy metals or organic compounds too often very perilous to health. To examine this peculiar concern we have determined the percentage of seven common inks,employed by tattooists, that is able to link to the dead keratin of the stratum corneum of white,black and Asian individuals. We have collected samples of calluses of thee subjects, (black,white and Asiatic persons) praying an operator of an atelier of pedicure to give us fresh and just cut off calluses from different women and men. **Results:** Generally it can be asserted that the major penetration into the stratum corneum of the ink is observed in Asiatic persons, followed by White individuals and finally by Black subjects. **Conclusion:** The uptake increases according to the colours of the rainbow. Violet uptake by keratin of Stratum Corneum is minimum and Red uptake is maximum.

Key words: Tattooing; China ink; Heavy metals; Substantivity; Carbon black

INTRODUCTION

Tattooing has existed since 12,000 years BC. The purpose of tattooing varies from culture to culture and its place on the time line.

Tattoos have always had an important role. In Borneo, women tattooed their symbols on their forearm indicating their particular skill. If a woman wore a symbol indicating she was a skilled weaver, her status as prime marriageable "item" was increased. Tattoos around the wrist and fingers were believed to ward away illness. Throughout history tattoos have signified membership in a clan or society.

In recorded history, the earliest tattoos can be found in Egypt during the time of the construction of the great pyramids. Around 2000 BC tattooing spread to China. The Greeks used tattooing for communication among spies. Romans marked criminals and slaves. The Ainu people of western Asia used tattooing to show social status.

In the west, early Britons used tattoos in ceremonies. In Japan, at first, tattoos were used to mark criminals.

In the late 1700s, Captain Cook made several trips to the South Pacific. The people of London welcomed his stories and were anxious to see the art and artifacts he brought back. Returning form one of this trips, he brought a heavily tattooed Polynesian named Omai. He was a sensation in London. Soon, the upper- class were getting small tattoos in discreet places. For a short time tattooing became a fad.

What kept tattooing from becoming more widespread was its slow and painstaking procedure. Each puncture

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of the skin was done by hand the ink was applied. In 1891, Samuel O'Rtiely patented the first electric tattooing machine. It was based on Edison's electric pen which punctured paper with a needle point. The basic design with moving coils, a tube and a needle bar, are the components of today's tattoo gun. The electric tattoo machine allowed anyone to obtain a reasonably priced, and readily available tattoo. As the average person could easily get a tattoo, the upper classes turned away from it.

By the turn of the century, tattooing had lost a great deal of credibility. Tattooists worked the sleazier sections of town. Heavily tattooed people traveled with circuses and "freak Shows." In the 1930s tattooing shops embodied a star attraction for years in traveling circuses and faires.

With world war I, the flash art images changed to those of bravery and wartime icons.

In the 1920s, with prohibition and then the depression, Tattoing lost its appeal.

After world war II, tattoos became further denigrated by their associations with Marlon Brando type bikers and Juvenile delinquents. Tattooing had little respect in American culture. Then, in 1961 there was an outbreak of hepatitis and tattooing knew another epoch of momentaneous decadence.

In the late 1960s, the attitude towards tattooing changed.

Today, tattooing is making a strong comeback. It is more popular and accepted than it has ever been. Current artists combine the tradition of tattooing with their personal style creating unique and phenomenal body art. With the addition of new inks, tattooing has certainly reached a new plateau.

Humans have marked their bodies with tattoos for thousands of years. These permanent designs—sometimes plain, sometimes elaborate, always personal—have served as amulets, status symbols, declarations of love, signs of religious beliefs, adornments and even forms of punishment.

Nowaday it can be asserted that 1 in 5 adults have tattoos, up from 14% in last century.

Tattoo ink is composed of two components: the carrier and the pigment. The role of a carrier is to work as a suspension to keep the pigment evenly mixed and free from pathogens. Material safety data sheets (MSDSs) obtained from INTENZE inks, a popular tattoo ink retail company, show that their most common carriers consist of glycerin, water, isopropyl alcohol, and witch hazel. Either single use of one of these carriers or a mixture of similar carriers seems to be the common practice across most ink companies and artists [1].

It is notorious, regrettably, that manufacturers are not required to reveal their ingredients or conduct trials, and recipes may be proprietary. Professional inks may be made from iron oxides (rust), metal salts, plastics. Homemade or traditional tattoo inks may be made from china ink, soot, dirt, blood, or other ingredients.

Heavy metals used for colors include mercury (red); lead (yellow, green, white); cadmium (red, orange,yellow); nickel(black); zinc (yellow,white); chromium (green); cobalt (blue); aluminium (green, violet); titanium (white); copper (blue, green); iron (brown, red, black); and barium (white). Metal oxides used include ferrocyanide and ferricyanide (yellow, red, green, blue). Organic chemicals used include azo-chemicals (orange, brown, yellow, green, violet) and naptha-derived chemicals (red). Carbon (soot or ash) is also used for black. Other elements used as pigments include antimony, arsenic, beryllium, calcium, lithium, selenium, and sulphur [2] (Table I).

Violet Manganese Violet (manganese ammonium pyrophosphate),Various aluminum salts

Table 1: The main tattoo inks used throughout the world

True Black	Acrylic Resin, Pigment Black (Carbon Black), Glycerin, Water, Isopropyl Alcohol, Witch Hazel
High White	Acrylic Resin, Titanium Dioxide, Water
Red Cherry	Acrylic Resin, Pigment Red 210, Pigment Blue 15, Glycerin, Water, Isopropyl Alcohol, Witch Hazel
Hard Orange	Acrylic Resin, Pigment Orange 13, Pigment Red 210, Glycerin, Water, Isopropyl Alcohol, Witch Hazel
Bowery Yellow	Acrylic Resin, Pigment Yellow 65, Titanium Oxide
Dark Green	Acrylic Resin, Pigment Green, Glycerin, Water, Isopropyl Alcohol, Witch Hazel
Baby Blue	Acrylic Resin, Titanium Dioxide, Pigment Blue 15, Glycerin, Water, Isopropyl Alcohol, Witch Hazel
Deep Indigo	Acrylic Resin, Pigment Violet 1, Titanium Oxide, Glycerin, Water, Isopropyl Alcohol, Witch Hazel
Violet	Manganese Violet (manganese ammonium pyrophosphate),Various aluminum salts Quinacridone, Dioxazine/carbazole

Quinacridone, Dioxazine/carbazole

A variety of medical issues can result from tattooing. Because it requires breaking the skin barrier, tattooing may carry health risks, including infection and allergic reactions [2-4]. Modern tattooists reduce such risks by following universal precautions, working with single-use items, and sterilising their equipment after each use.

Dermatologists have observed rare but severe medical complications from tattoo pigments in the body, and have noted that people acquiring tattoos rarely assess health risks *prior* to receiving their tattoos. Some medical practitioners have recommended greater regulation of pigments used in tattoo ink. The wide range of pigments currently used in tattoo inks may create unforeseen health problems.

Since tattoo instruments come in contact with blood and bodily fluids, diseases may be transmitted if the instruments are used on more than one person without being sterilised. However, infection from tattooing in clean and modern tattoo studios employing single-use needles is rare. With amateur tattoos, such as those applied in prisons, however, there is an elevated risk of infection.

MATERIALS AND METHODS

As we have referred before, we have prayed an operator of a boutique of pedicure to give us fresh and just cut off calluses of white,black and Asiatic people.

We have wighed the single samples (21 samples:7 of white person, 7 of black person,7 of Asiatic persons) and we adjust the real quantity to 200 mg, so that each sample weighs about 200 mg.

We prepared 21 flasks (50 ml) and fill them up with 0.03% ink solutions (the seven colours of the rainbow or of the painter's palette, that generally include black and white,even if we exluded these latter since white do not absorbe at UV spectrometry and black absorbes 99% at all the scales of wavelenght).

So we prepared sevens solutions containing seven tattoo inks and we had to insert the calluses in the seven solutions and shared in 21 flasks, in order to have a UV spectrum of each of everyone after 1 hour and after 12 hours.

It is well known that the following are the wavelenght the seven colours absorbe in the UV spectrometer.

Violet: 400 - 420 nm; Indigo: 420 - 440 nm; Blue: 440 - 490 nm; Green: 490 - 570 nm; Yellow: 570 - 585 nm; Orange: 585 - 620 nm; Red: 620 - 780 nm.

Solutions 0.03% of the different inks are tested to evaluate the UV absorbance and we have confirmed that the peaks of the relative maximum absorbances were the following:

Violet: 0.8; Indigo: 0.9; Blue: 0.8; Green: 0.7; Yellow: 0.8; Orange: 0.9; Red: 0.9.

And this mean that at the corrisponding wavelength each colour reveals almost the maximum of absorbance (scale 0-1).

Since it is possible, owing to the Lambert Beer's law to calculate the concentration (m/ml) of a known solution, we have extrapolated the 21 peaks of absorbances after one hour and after 12 hours.

In Table 2 it is observable the lowering of concentration of the single tattoo inks solutions after one and 12 hours, keeping on account that the original peaks of absorbances are those reffered before and that concentrations have been calculated thanks the Lambert Beer's law according to every measured peak of UV absorbances.

Table 2: Value of concentration of the single tattoo inks solutions after one and 12 hours.

Ink in the diverse skin	Concentrations after 1 hour	Concentrations after 12 hours
Violet on A	0.019	0.016
Violet on W	0.024	0.022
Violet on B	0.028	0.021
Indigo on A	0.019	0.017
Indigo on W	0.022	0.018
Indigo on B	0.024	0.021
Blue on A	0.022	0.020
Blue on W	0.023	0.021
Blue on B	0.025	0.022
Green on A	0.015	0.013
Green on W	0.017	0.014
Green on B	0.019	0.016
Yellow on A	0.013	0.010
Yellow on W	0.013	0.011
Yellow on B	0.018	0.016
Orange on A	0.012	0.009
Orange on W	0.014	0.010
Orange on B	0.016	0.012
Red on A	0.010	0.008
Red on W	0.012	0.009
Red on B	0.014	0.011

Legends: Symbols A, W and B indicate the Asian, the White people and the Black ones

RESULTS

It is clear that the concentrations of the solutions do increase from Asian skin, to White and then to Black skin.

This corresponds to a major penetration in Stratum corneum as the concentration calculated after 12 hours indicates the difference of the original concentration of tattoo ink and the final concentration that remains in solution and therefore it means that the minor is the concentration of the remnant solution, the major is the penetration in the Stratum Corneum.

It is noticeable, and suggestive, that the colour uptake from keratin of the Stratum Corneum, increases from Violet to Red inks.

In Table 3 it is possible to state the percentages of colour intake by keratin of S.C. of the single inks in Asian,White and Black skins.

CONCLUSIONS

We can assert what already has been referred by manifold AA [5,6] that is that even in case of inks, the penetrabilty of the stratum corneum and epidermis is major in Asiatic people, followed by White and Black persons.

Notwithstanding these confirmations, we have indivituated which is the maximum penetration (and thus the colour uptake by the keratin of Stratum Corneum) of each colour and results are surprising, since the uptake increases according to the colours of the rainbow.

Violet uptake by keratin of Stratum Corneum is minimum, Red uptake is maximum.

Table 3: The percentages of colour intake by keratin

Tattoo colour on diverse skin	Percentages of colour uptake by keratin of S.C.
Violet on A	18
Violet on W	13
Violet on B	13
Indigo on A	17
Indigo on W	16
Indigo on B	14
Blue on A	15
Blue on W	13
Blue on B	13
Green on A	23
Green on W	21
Green on B	18
Yellow on A	30
Yellow on W	27
Yellow on B	18
Orange on A	33
Orange on W	30
Orange on B	25
Red on A	37
Red on W	33
Red on B	27

Legends: Symbols A, W and B indicate Asian, White and Black skins.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Brief Report

Dermatological manifestations in the intensive care unit – A prospective study

Heena Gupta[1], Mrinal Gupta[2]

[1]Governement Medical College, Jammu, India, [2]Consultant Dermatologist, Treatwell Skin Centre, Jammu, India

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

ABSTRACT

Background: Intensive care unit is a specialized controlled unit where the critically ill patient is dependent on the caregivers. **Aims:** This study was carried out to study the dermatological manifestations in patients admitted in intensive care unit. **Materials and Methods:** It was a prospective study carried out over a period of six months where the patients admitted in the intensive care unit having some dermatological manifestations were examined and the findings were noted. **Results:** A total of 273 patients were examined (M: F 154:119) were examined out of which 50 patients (18.31%) (M: F 31:19) were having some dermatological manifestations. The age range of patients ranged from 3 years to 84 years with a mean age of 46.356.43 years. The stay in ICU varied from 3-43 days with a mean of 17.15 days. Infectious diseases constituted 52% (n=26) of the dermatological conditions with the most common being fungal infections (26%, n=13) and bacterial infections (16%, n=8). Among the non-infectious dermatoses, the most common were drug reactions (24%, n=12), followed by friction blisters (12%, n=6) and dermatitis (4%, n=2). **Conclusions:** Dermatological diseases are common in patients in intensive care unit which can have an impact on the duration of stay, alteration in therapy and mortality among the patients.

Key words: Dermatological disorders, Comorbidity, Drug reactions, Intensive care unit

INTRODUCTION

Intensive care unit (ICU) is a specialized unit to manage critically ill patients. As the patient is already on life support, on multiple medications and immobile, it creates an environment for growth of organisms which can lead to a variety of nosocomial infections including cutaneous infections [1,2]. Moreover, as the mobility of the patient is impaired, the chances of complications like decubitus ulcers are increased manifold. Various dermatological problems may develop in ICU patients as a result of primary pathologies, their complications, and complex treatment regimens used for therapy. Dermatological conditions can increase the risk of complications, increase in the stay duration, can lead to alteration in the treatment regimens and can also increase the morbidity and mortality [3,4].

We undertook this study to study the dermatological manifestations in the patients admitted in the intensive care unit.

MATERIALS AND METHODS

It was a prospective study carried out over a period of six months in which all the patients admitted in the intensive care unit were examined for the presence of any dermatological condition and the findings were recorded in a predesigned proforma by a dermatologist. Age, sex, comorbid conditions, dermatological disorders, tissue culture results, time to consultation, duration of ICU stay were recorded among patients admitted to ICU.

RESULTS

A total of 273 patients were examined (M: F 154:119) were examined out of which 50 patients (18.31%) (M:F 31:19) were having some dermatological manifestations. The age range of patients ranged from 3 years to 84 years with a mean age of 46.356. 43 years. The stay in ICU varied from 3-43 days with a mean of 17.15 days.

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Among the dermatological conditions, infectious diseases constituted 52% (n=26) of the total disease load. Fungal infections were the most common infectious diseases, constituting 26% (n=13) of the total disease with dermatophytoses (n=7) being the commonest in the form of tinea cruris (n=3), tinea pedis and manuum (n=2) and onychomycosis (n=2) followed by Candidiasis (n= 6) in the form of oral thrush (n=4) and balanoposthitis and vulvovaginitis (n=1 each). Bacterial infections constituted 16% (n=8) of the infectious conditions which included wound infections (n=4), furunculosis and carbuncles in 4% (n=2) erysipelas and cellulitis in 25 each (n=1). Among the non-infectious dermatoses, the most common were drug reactions (24%, n=12) in the form of maculopapular drug rash in 14% (n=7), acneiform eruption in 45 (n=2), Stevens Johnson's syndrome and Toxic epidermal necrolysis in 4% (n=2) and fixed drug eruption in 2% (n=1). It was followed by friction blisters (12%, n=6) and dermatitis (4%, n=2). Urticaria, psoriasis and vasculitis were seen in one patient each.

DISCUSSION

In an intensive care unit, prolonged immobilization, malnutrition, impaired tissue perfusion, immune system dysfunction, fluctuations in body temperature, inadequate hygiene, hyperpyrexia, medications, and skin injuries may cause the disruption of the skin barrier function, which predispose the patients to a large number of dermatological disorders ranging from infections to non infectious dermatoses like drug reactions and frictional blisters [1-4]. The incidence of dermatological disorders in patients in ICU has been reported to vary from 2.2% to 21.5% [3,5]. In agreement with the literature, our study demonstrated an incidence of 18.31%.

Skin infections constitute the major dermatological manifestations in the ICU. Fischer et al reported an incidence of 29% of different skin infections whereas Emre *et al* reported an incidence of 38.9% [2,5]. Among the infections, fungal infections are the most common infections with Candida being the most commonly implicated pathogen, which is attributed to increased humidity, administration of broad spectrum antibiotics, parenteral nutrition, immunosuppressive agents, and comorbidities [2,6]. In our study, the incidence of infective skin disorders was 52%, among which fungal infections were the most common with dermatophytoses constituting 14% of the total infection load, followed by Candidiasis in 12%. The low incidence of bacterial infections could be attributed to the co administration of antibiotics to the patients.

Drug reactions constitute another major dermatological manifestation in the ICU with various studies reporting an incidence varying from 9.3% to 21.6% [2-5,7]. Emre *et al* reported that drug reactions occurred in 14.5% of patients staying at intensive care units with maculopapular rash being the most common subtype [2]. Antibiotics and chemotherapeutic agents are the most common drugs implicated in causing drug reactions. Anticonvulsive agents, allopurinol, diuretics, and non-steroidal antiinflammatory drugs may also cause drug reactions [7]. In our study, drug reactions constituted 24% of all dermatological manifestations and maculopapular drug reactions were the most common type.

Apart from the drug reactions, other non infectious dermatoses like friction blisters, vasculitis, seborrheic dermatitis are also very common in patients in ICU. Emre *et al* reported that dermatoses are observed at intensive care units at a rate of 46.6%, and the most common pathologies were frictional bullae and allergic contact dermatitis, whereas, Fischer *et al*, reported an incidence of 49.4% [2,5]. Another study reported that the most common skin disorders were stasis dermatitis (25%) and diaper dermatitis (25%) in medically treated critically ill patients [8]. In our study, apart from drug reactions, the most common dermatoses were friction blisters (12%, n=6) and dermatitis (4%, n=2). Urticaria, psoriasis and vasculitis were seen in one patient each. Immobilization, numerous medications, higher age increase the fragility of skin, therefore when frequent friction is applied, it leads to friction blisters. Moreover, continuous use of topical irritant agents like electrodes, chlorhexidine also predispose to the development of eczemas in the already fragile skin [9,10].

Skin diseases can markedly prolong the stay in ICU. Many factors including age, multiple comorbid conditions, duration of ICU stay, time to consultation, and mortality contribute to the development of dermatological disorders. Increased cooperation is needed among ICU physicians and dermatology department to reduce the dermatological complications, increase the quality of patient care, shorten hospital stay, and reduce mortality rate.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Brief Report

A simplest method to avoid inflammation and infection after the insertion of a piercing (even using the safest metal), by using quaternium-15

Lorenzo Martini[1], Piotr Brzezinski[2]

[1]University of Siena, Department of Pharmaceutical Biotechnologies, Via A. Moro 2, 53100 Siena, Italy, [2]Institute of Biology and Environmental Protection, Pomeranian Academy, Slupsk, Poland

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

ABSTRACT

Background: The novel fashion of youngest boyd and girls to insert piercings even in the most hiddenparts of the body (heritage of troglodytes and cavernicolous persons) cause always infections and our attention is focused on a novel practice to defeat this typology of infection, avoiding to use generical over the counter creams that are perilous and do not solve the problem. **Material and Methods:** A 19 years old girl after a piercing in her nostril with brownish discharge from her nose and felt nausea. **Results:** Was used 0.2% solution of quaternium-15 in white rubbing ethanol, instead low dosages of triclosan. The duration of the tratment lasted 10 days and the quantity of brown mucus decreases day after day from the infected nostril of the volunteer. **Conclusions:** Till 2016 even in the US triclosan was considered the best remedy to combact infections caused by metal insertions in skin:now even in Europe its use has been restricted to 0.3%, although this percentage is completely unuseful to treat all microbiota that can invade skin injured by the insertion of a metal. The usage of an ethanolic solution of quaternium-15 is very efficient.

Key words: Piercings; Staphylococcus epidermidis; Corynebacterium; Propionibacterium; triclosan; Quaternium-15

INTRODUCTION

When a piercing is new, it's normal to see some swelling, redness, or discoloration around the site. Some clear discharge that dries and forms a crystal-like crust around the piercing. These symptoms should get better over time, not worse.

Two of the most common complications are allergic reactionsand bacterial infections. Allergic reactions happen if you're allergic to the type of metal being used. For example, piercing jewelry made of nickel is known to cause allergic reactions in susceptible people [1].

Metals that are safe for body piercings include:
- surgical steel
- solid 14-karat or 18-karat gold
- niobium
- titanium
- platinum

Bacterial infections arise when bacteria from dirt or foreign objects get into the open piercing while it's still healing. Remember, piercings are open wounds that need to be kept clean.

Signs of an allergic reaction include:
- development of an itchy, inflamed rash around the piercing that spreads to a larger area
- a pierced hole that looks larger than before
- tenderness that may come and go

Signs of infection include:
- severe swelling with pain and redness

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- yellow, green, gray, or brown discharge that has an odor
- red lines that radiate from the piercing site
- fever, chills, dizziness, upset stomach, or vomiting

If there is a suspect of an infection, don't remove the jewelry on your own, unless your doctor tells you to do so. Most piercings don't need to be removed to treat infections. Keeping the piercing hole open allows pus to drain. Allowing the hole to close may trap the infection inside of your body, causing an abscess to form [1,2].

Microorganisms colonizing the skin have long been of interest to dermatologists and microbiologists [3]; our knowledge of these microorganisms has, until recently, been gleaned through culture-based studies. Historically, *Staphylococcus epidermidis* and other coagulase-negative staphylococci have been regarded as the primary bacterial colonizers of the skin. Other microorganisms that are generally regarded as skin colonizers include coryneforms of the phylum Actinobacteria (the genera *Corynebacterium*, *Propionibacterium* and *Brevibacterium*) and the genus *Micrococcus*. Gram-negative bacteria, with the exception of some *Acinetobacter* spp., are generally not isolated from the skin, but are thought to arise in cultures owing to contamination from the gastrointestinal tract [4,5].

Non-bacterial microorganisms have also been isolated from the skin. The most commonly isolated fungal species are *Malassezia* spp., which are especially prevalent in sebaceous areas. The *Demodex* mites (such as *Demodex folliculorum* and *Demodex brevis*), which are microscopic arthropods, are also regarded as part of the normal skin flora. *Demodex*mites feed on sebum and are more prevalent following puberty, preferring to colonize sebaceous areas of the face[3]. *Demodex* mites may also feed on epithelial cells lining the pilosebaceous unit, or even on other organisms (such as *Propionibacterium acnes*) that inhabit the same space. The role of commensal viruses has not been studied, and investigations are limited by the available molecular and microbiological means to identify and characterize viruses.

Cleaning the piercing is important, both to prevent and treat an infection. Experts recommend cleaning a piercing no more than twice each day. Some physicians suggest to use a saltwater mixture (1/2 teaspoon sea salt per 1 cup of water) to help remove any dried healing secretions followed by a gentle, mild antibacterial soap and water cleansing. No alcohol nor hydrogen peroxide should be employed, as these can dry out skin and irritate the area around the piercing.

It is mandatory to wash hands with an antibacterial soap. Then it is useful to use a cotton swab and the cleaning solution to gently wipe the area around belly button and the ring, nose or mouth or whichever part of the body.

Afterwards it is advisable to pat the area dry with a clean towel.

It i salso advisable to place a warm compress on the infected piercing. This can help the pus drain and cause the swelling to go down. Wet a compress, such as a warm washcloth, with the cleaning solution. Place the compress on the piercing. Gently dry the area with a clean towel after using the wet cloth.

Using an antibacterial cream — not an ointment — often clears up minor infections. Ointments are greasy and may block oxygen from getting to the wound, complicating the healing process.

Over-the-counter antibacterial cream exist too, but there is a risk for allergic irritation of the skin with this type of product. If you don't have an allergy with over-the-counter antibiotic cream, you can carefully clean the piercing site, and then follow the directions on the container.

Triclosan (restriction of use in cosmetics 0.3%, according to L.11.10.86 n 713 A V S1 P2 n 28 DM 24.1.87 n 91) could be the best solution, even if in case of infections caused by metals 0.3% of triclosan is unuseful.

Nowaday tricolosan effectively it is retrieved in most cosmetics even dentifrices and shampoos, even if 0.3% is a percentage excessively poor to disinfect infections caused by piercings.

Moreover some researchers of the Korea University showed the claimed antibacterial activity of triclosan onto 20 bacterial streamsis not appropriate, since its action begins after the sample toilette before to eat with naked hands (like Asians do).

In Europe the SSC (*Scientific Steering Committee of CE)* in 2002 [6] had declared that che triclosan is an useful ed biocide, confirming that has been used for

Table I: Quantities of brown mucus excreted by the nostril

At the beginning of the experiment	At 1st day	At 2nd day	At 3rd day	At 4th day	At 5th day	At 6th day	At 7th day	At 8th day	At 9th day	At 10th day
55	50	46	44	41	39	36	33	21	16	nil

35 years all over the world for preserving cosmetics and even for oral mucosae.

The Swedish Ministery of Health has banished it at all in food and cosmetics, since like all the chlorinated phenols can accuulate in all the human tissues and in maternal milk and so alterate the liver function, can cause lung distruption and induce sterility and alterate the immune system till complete paralysis.

Finally since 2016 triclosan has been banned by FDA in US.

Because of all these complications it is better not to employ soaps containing triclosan.

The othe ingredient I have chosen is quaternium 15, (hexamethylenetetramine chloroallyl chloride) that is a quaternary ammonium salt used as a surfactant and preservativein many cosmetics and industrial substances. It is an anti-microbial agent by virtue of being a formaldehyde releaser 4,6] however this can also cause contact dermatitis, a symptom of an allergic reaction, especially in those with sensitive skin.

For the fact that is reputed a formaldehyde releaser can be used at concentration of 0.2%, that is sufficient to guarantee a complete disinfection of the area where piercing must be removed and cleaned day after day.

MATERIALS AND METHODS

A girl (19 years old) desired to be visited since she showed a continuous brownish discharge from her nose and felt nausea and told to me that she had inserted a piercing (made of surgical steel) one week before, in her nostril.

After the preface, We directly have chosen the quaternium-15, instead low dosages of triclosan.

Quaternium-15 is not water soluble, but is only sluble in ethanol, ether and alkaline concentration.

We had prepared a 0.2% solution of quaternium-15 in white rubbing ethanol and We prayed her to remove the piercing twice a day and make all the operations generally physicians suggest.

To consider the results, We obtained We have kept on account only the secretion of the brown discharge, measuring exactly by the aids of an electronic scale.

The duration of the tratment lasted 10 days and We have measured since the very first day the quantity in mg of brown mucus the volunteer excreted day after day.

RESULTS

In Table I it is possibile to state how the quantity of brown mucus decreases day after day from the infected nostril of the volunteer. Measures are reported in mg.

CONCLUSIONS

One can notice that during the first 10 days after the application of a metal piercing (that had caused inflamation and infection) the usage of an ethanolic solution of quaternium-15 is very efficient.

There has been not any necessity to repeat the treatment.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Case Report

Remember the great imitator 'syphilis' in oral lesions

Funda Tamer

Department of Dermatology, Ufuk University School of Medicine, Ankara, Turkey

Corresponding author: Dr. Funda Tamer, E-mail: fundatmr@yahoo.com

ABSTRACT

Syphilis is an infectious disease characterized by various mucocutaneous and systemic findings. It can mimic many other diseases. Therefore, syphilis is known as 'the great imitator'. It remains a public health problem especially in developing countries. Treatment of the early stages of syphilis is fast, easy and effective. However, it can result in serious complications if left untreated. Therefore, early diagnosis is crucial. Hereby, a 30-year-old Caucasian female with an oral syphilis who had previously been misdiagnosed was presented. Syphilis can be easily misdiagnosed in patients with oral mucosal lesions. It should be considered in the differential diagnosis of other intraoral diseases.

Key words: Mouth mucosa, Penicillin G benzathine, Syphilis

INTRODUCTION

Syphilis is a systemic disorder caused by the spirochete Treponema pallidum. Syphilis remains a serious global health problem. However, Africa and low-income and middle-income countries have a high incidence and prevalence of the disease. Syphilis usually presents with several clinical manifestations. Local inflammatory response to the spirochete has been implicated as the cause of varied presentations of syphilis. The diagnosis is usually made based on clinical findings and serological tests. Dark field microscopy, immunohistochemistry, fluorescent antibody staining and polymerase chain reaction can be used as direct diagnostic methods [1].

CASE REPORT

A 30-year-old Caucasian female presented with a three-month history of an asymptomatic lesion on the oral mucosa. The patient was treated with nystatin oral suspension 500.000 units four times a day and 0.1% triamcinolone acetonide in orabase three times a day for two weeks previously. However, no clinical improvement has been achieved. Dermatological examination revealed a mucosa-colored, annular, infiltrated plaque and linear erythema on the left side of the hard palate (Fig. 1). The past medical history was unremarkable. Laboratory tests including complete blood count, chemistry panel, serum vitamin B12, folate, ferritin, zinc and thyroid-stimulating hormone levels were all in normal limits. Serum IgM antibodies for *Herpes simplex virus* type-1 (HSV-1) and HSV-2, serum levels of hepatitis B surface antigen, antibodies against hepatitis C virus, hepatitis B virus and human immunodeficiency virus were negative. However, serologic testing for syphilis revealed positive Venereal Disease Research Laboratory (VDRL) at a titer of 1:2560 and *Treponema pallidum* haemagglutination (TPHA). The patient was diagnosed with secondary syphilis based on clinical and laboratory findings. She was treated with a single dose of benzathine penicillin G (BPG) 2.4 million units (MU) intramuscularly. No adverse effects have been observed after therapy. The lesion started to regress within two days (Fig. 2). Therefore, the patient was advised to make a follow-up appointment four weeks later to evaluate the clinical and serological response to treatment.

DISCUSSION

Syphilis usually presents with an anogenital ulcer termed as chancre. Then the stages develop with various mucocutaneous and systemic findings in untreated infected individuals [2]. Dermatological symptoms

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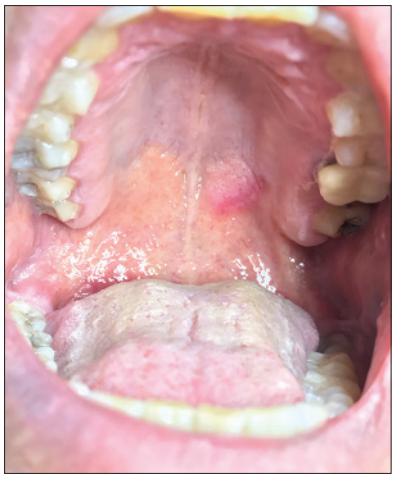

Figure 1: Erythematous plaque on the left side of the hard palate.

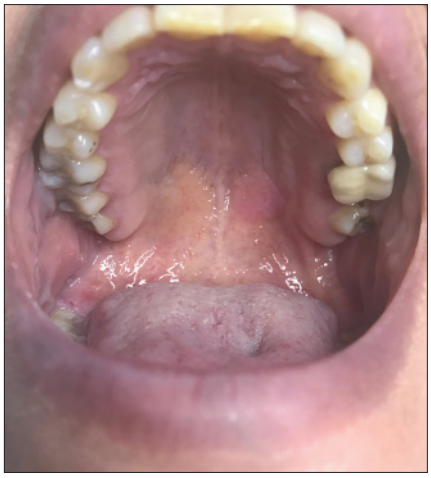

Figure 2: The lesion regressed in two days after penicillin injection.

include single, painless, indurated genital ulcer, regional lymphadenopathy, widespread maculopapular rash, palmoplantar rash, alopecia, buccal and lingual patches, condylomata lata and granulomatous lesions with central necrosis [3].

Oral manifestations of syphilis can also be various. Primary syphilis can present with ulceration of the tongue dorsum, erythema, edema, petechial hemorrhage and chancre. Secondary syphilis is characterized by mucous patches. They are slightly raised, oval ulcers with an erythematous border and overlying gray membranous exudates. Chronic, destructive lesions occur in tertiary syphilis. The tounge is usually atrophic, fissured and has a leukoplakic plaque over it [4]. Therefore, the diagnosis of syphilis is not always easy. It should be kept in mind in the differential diagnosis of other intraoral diseases like tuberculosis, histoplasmosis, squamous cell carcinoma, herpetic and fungal infections [4].

The new insights on the management of early syphilis have been reviewed through this case. 2016 World Health Organization guidelines for the treatment of *Treponema pallidum* advice a single dose of BPG 2.4 MU intramuscular injection as the first line therapy option for early stages [5]. United Kingdom national guidelines updated on 2015 recommend BPG since multiple injections of procaine penicillin is not convenient and cost-effective [3].

CONCLUSION

In conclusion, treatment of the early stages of syphilis is fast, easy, inexpensive and effective. However, the disease can be easily misdiagnosed in patients with oral mucosal lesions as a result of its various clinical presentations.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Actinomycetoma due to Actinomadura madurae: A therapeutic challenge. Case report

Ana Gabriela Fuentes-Nava[1], Leonel Fierro-Arias[1], Javier Araiza[2], Mariana Ivonne Benitez-Barradas[3], Hugo Eduardo Peláez González[3], Alexandro Bonifaz[1,2]

[1]Department of Dermatology, Hospital General de México. "Dr. Eduardo Liceaga", Mexico City, Mexico, [2]Department of Mycology, Hospital General de México. "Dr. Eduardo Liceaga", Mexico City, Mexico, [3]Department of Imagenology, Hospital General de México. "Dr. Eduardo Liceaga", Mexico City, Mexico

Corresponding author: Dr. Alexandro Bonifaz, E-mail:a_bonifaz@yahoo.com.mx

ABSTRACT

Mycetoma is a chronic granulomatous infection that develops after traumatic inoculation of the skin with either true fungi (eumycetoma) or aerobic actinomycetes (actinomycetoma). Can be found in geographic areas in close proximity to the Tropic of Cancer also known as "mycetoma belt", the predominant climate of this region is subtropical and dry tropical. Actinomycetomas caused by *Actinomadura* spp. occur in drier areas with low relative humidity. We report a case in a 45 years-old female, with a 9-years history of a progressive inflammatory tumor, sinuses tracts and granules on her left sole. She was treated with antibiotics and amputation without improvement. Actinomycetoma due to A. *madurae* was confirmed and successfully treated with a combination therapy that included streptomycin plus trimethoprim/sulfamethoxazol.

Key words: Mycetoma; Actinomicetoma; A. *madurae*; Streptomycin; Trimethoprim/sulfamethoxazole

INTRODUCTION

Mycetoma is a chronic, granulomatous, subcutaneous, inflammatory disease caused by true fungi (eumycetoma) or filamentous bacteria (actinomycetoma). Commonly affects adults, and the most common affected site are the feet. The characteristic clinical triad is tumefaction, draining sinuses and discharging grains or granules. It is caused by exogenous traumatic inoculation therefore, it is considered an infection by implantation. The global geographical distribution is 60% for actinomycetomas and 40% for eumycetomas [1,2]. It exists throughout the world, especially in intertropical countries like Asia, Africa and America. Eumycetomas predominate in Africa and Asia, and actinomycetomas in Latin America. In Mexico mycetomas are mainly actinomycetoma (98%); 86% are caused by *Nocardia spp.*, of which 71% are due to N. *brasiliensis*. A. *madurae* is observed in 10% [3].

CASE REPORT

45 years-old woman native of México and resident of Waukegan, Illinois. Without chronic degenerative diseases diagnosed. In her clinical history must be noted that she made annual family visits to the state of Guerrero (endemic state of mycetoma), where there were houses built with adobe with dirt floors. In her pathological personal history she had a 9 years history of a progressive inflammatory tumor associated with sinuses tracts and tumefaction on her left sole. A surgical amputation of the 5th metatarsal of the left foot in 2009 was made and she received previous treatments with trimethoprim/sulfamethoxazol [TMP/SMX] and diaminodiphenyl sulfone [DDS] for 2 years without clinical improvement (Figs. 1a and 1b).

She went to the dermatology service of the Hospital General de México in August 2017 where *direct examination* with potassium hydroxide [KOH] biopsy, image studies and microbiological cultures were made.

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In direct examination two large, multi-lobed grains with size of 3 mm were observed (Fig. 2). Skin biopsy showed a granulomatous suppurative process with basophilic grains (Fig. 3). Microbiological cultures were positive, and *Actinomadura madurae* was identified.

X-rays of the foot showed an increase in soft tissue volume and in bone structures, lytic lesions, thickening of the cortex and cavities (Fig. 4). Finally in a high resolution computerized axial tomography the lytic lesions were confirmed as well as total absence of the 5th metatarsian by previous amputation (Fig. 5).

With all the data obtained, the confirmed diagnosis was actinomycetoma due to *Actinomadura madurae*. We continue treatment with streptomycin 1 g three times a week to completing 50 g., plus TMP/SMX 160/800 mg. The audiometries previous, during and at the end of the treatment were normal.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

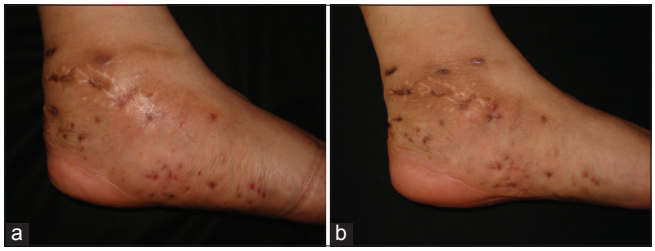


Figure 1: (a) Actinomycetoma baseline. (b) Actinomycetoma after 1 year and 8 months of treatment.

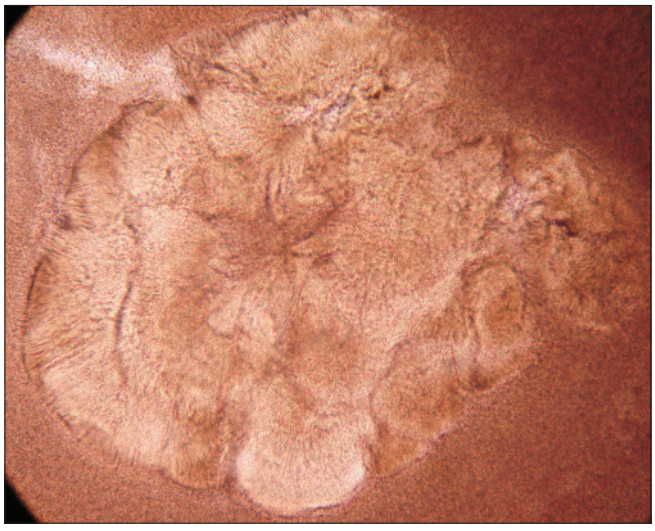
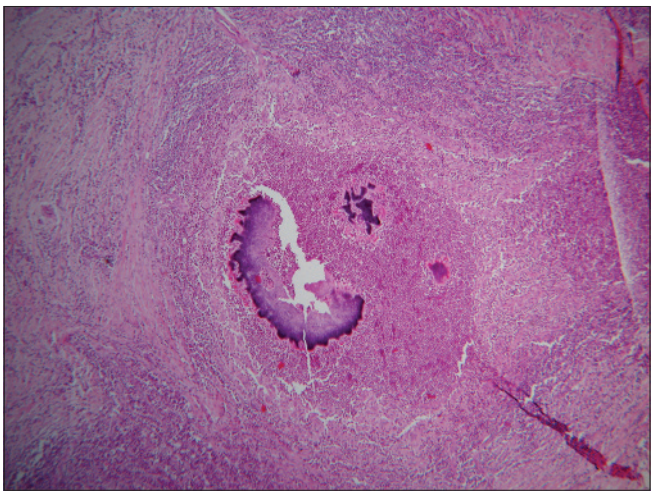


Figure 2: Large, multi-lobed grain with a caratographic, polylobulated and oval shape, characteristic of *A. madurae*. (KOH, 10x).

DISCUSSION

On 28th May 2016, mycetoma was recognized as a neglected tropical disease by the World Health Organization [3]. Mycetomas caused by A. *madurae* occur in drier areas with low relative humidity. Three main regions of A. *madurae* have been noted in México: The western center (Guanajuato, Michoacán, Jalisco and Querétaro), the southern center (Puebla, Oaxaca and northeast of Guerrero) and west of Hidalgo [1,2,4-7].

In 2016, the First Argentine Conference of Mycetomas was organized in Santiago del Estero, where a total of 159 thus far unpublished cases were presented. There was remarkable that actinomycetoma cases due to A. *madurae* are now slightly more frequent. It is important to mention that these cases are predominantly accounting for 55–70% of actinomycetoma cases; different from what is reported in Mexico [3,4].



Figures 3: Granulomatous suppurative process with basophilic grain. (H&E, 10X).

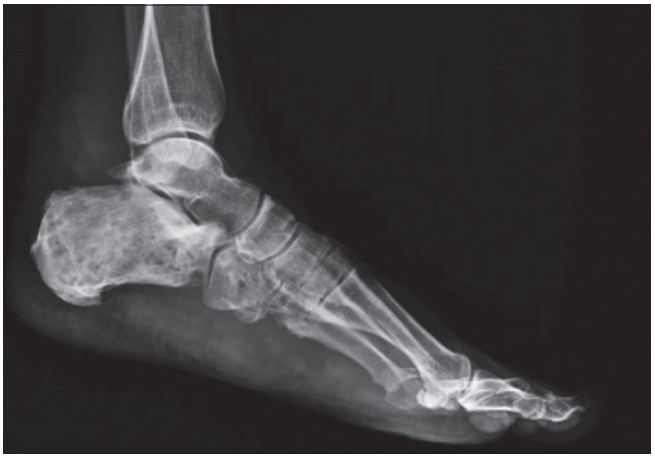


Figure 4: Radiographs of the foot showed lytic lesions, thickening of the cortex, cavities and mild soft tissue swelling.

One of the most notable difference between mycetomas by A. *madurae* and by N. *brasiliensis* or by others agents is the predominance of A. *madurae* in females, a hormonal influence has been suggested; while the other mycetomas are more commonly reported in males (4:1), in the case of A. *madurae* the relationship is 2:1 [1,6-8].

Mycetoma by A. *madurae* is located mostly in the middle part of the foot affecting mainly the plant, unlike the mycetomas by *Nocardia sp*. that generally affect the lower third of the leg and malleolar region [1,5,6]. Other locations are extremely rare. Two cases have been reported in oral cavity, possibly in relation to the use of wood sticks for brushing teeth in many Afro-Asian communities [9].

Clinically they are more voluminous, of hard consistency, with few sinuses, a woody appearance and can resemble tumor processes of another origin. Unlike those produced by *Nocardia spp*. present a more inflammatory aspect, with numerous fistulas that exude a serous or purulent fluid and are generally of greater extension [1,5,8].

A. *madurae* produces white and soft grains that can be identify through direct examination or with the naked eye, due to its large size and cartographic edges [1,8]. It grows slowly in about 1 month at 37°C on Sabouraud dextrose agar without antibiotics or in Lowenstein-Jensen agar. The colonies are folded or cerebriform, with waxy aspect and yellow, white, pink or red color [1,5,8].

The histopathology of mycetoma is very similar to the rest of subcutaneous mycoses, presents exulceration of the epidermis, pseudoepitheliomatous hyperplasia, fistula formation, dense inflammatory infiltrate composed of polymorphonuclears, lymphocytes, plasma cells and histiocytes with formation of giant cells, which give rise to a suppurative granuloma, with vascular proliferation, damage to the vessel walls and fibrous tissue. In the microabscesses of PMN are located the "grains". [8]

The grain of *Actinomadura madurae* measures from 1 to 20 mm, with a caratographic, polylobulated and oval shape; clear in the center, dense purple in the periphery with with irregular and eosinophilic edges [1,5]. The tissue may be very friable if the biopsy is taken in an exulcerated or fistulous area, and there is a risk of not finding the grain if it is taken in a fibrous zone [8,10,11].

There are some especially osteophilic agents, among them A. *madurae*, N. *brasiliensis* and M. *mycetomatis*. Most frequent alterations are periostitis, osteitis, osteofibrosis and osteolysis, with formation of cavities or osteophyte-holes "geodos" [6,12]. X-rays and tomographies are essential to indicate the degree of bone involvement. Computed helical tomography and MRI allows measuring the affected area and locating the specific damage (visceral and vascular). The recently described "dot in circle sign", a central tiny hypointense focus (Fig. 6) [13] on magnetic resonance imaging (MRI) is easy to recognize and specifc to this condition and establishes the role of MRI in early diagnosis [14].

The lytic lesions or cavities are due to replacement of bone tissue and marrow by masses of A. *madurae* grains. Those image findings are not specific and

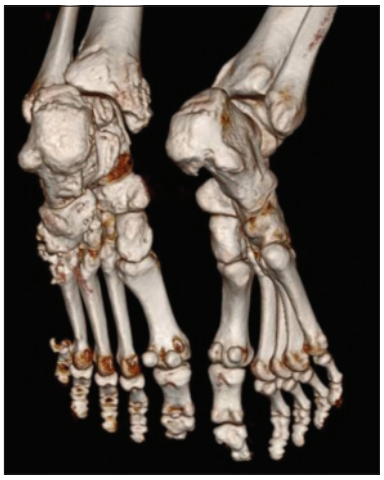


Figure 5: High resolution computerized axial tomography with many lytic lesions, thickening of the cortex as well as total absence of the 5th metatarsian by previous amputation.

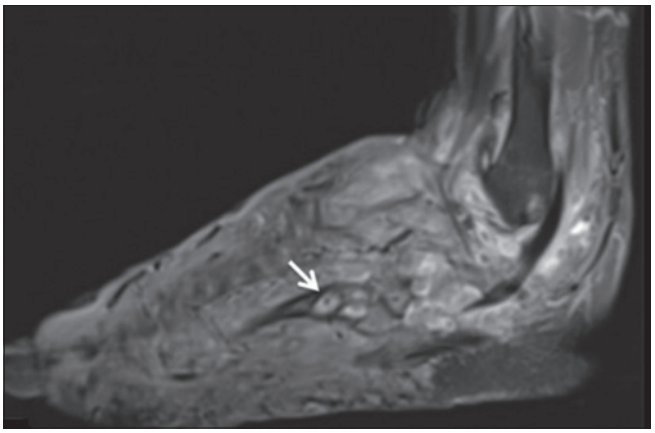


Figure 6: MRI T2 show inflammatory changes with multiple soft tissue and osseus small hyperintense lesions with peripheral hypointenserim corresponding to mycetoma grains (yellow arrows). Few of them showing "dot in circle" sign (thicker white arrow).

cannot differentiate mycetoma from chronic bacterial osteomyelitis, granulomas, soft tissue tumors, bone tuberculosis and cold abscesses. On the contrary, the small ovoid-shape, low-signal lesions that we observed on T1- and T2-weighted images are more helpful in the diagnosis of actinomycetoma, since they are present in 80% of the cases [12].

The studies of susceptibility in *Actinomadura madurae* are not standardized, although low activity to penicillin, cephalosporins and trimethoprim-sulfamethoxazole has been described. *In vitro A. madurae* is sensitive to amikacin, TMP-SMX, linezolid and ciprofloxacin [15]. Therefore, it has been suggested that treatment should be combined. The best results have been with streptomycin (1 g once daily in adults; 20 mg/kg once daily in children) until a total dose of 50 g. is reached in combination with TMP-SMX or DDS. During the treatment with streptomycin otic function should be monitored. Also good response has been reported with ciprofloxacin in resistant cases. Despite the efforts, a good number of cases do not respond to treatment [1,5,6,13]. Alternatives for A *madurae* include streptomycin plus oral clofazimine (100 mg once daily), oral rifampicin (300 mg twice daily), oral tetracycline (1 g once daily), oral isoniazid (300–600 mg once daily), and oral minocycline (100 mg twice daily; also effective for A *pelletieri*) [8,13,16].

Surgery is contraindicated in the actinomycetomas, since in most of these the process continues in the stump despite large surgical margins, and may even lead to lymphatic or hematogenous dissemination worsening the prognosis [4-6,13,17].

The criteria used to guide the discontinuation of initial therapy for any mycetoma include a decrease in the volume of the lesion, closure of sinuses, 3 consecutive negative monthly cultures, image studies showing bone regeneration, lack of echoes and cavities on echography, and absence of grains on examination of fine-needle aspirates. After the initial treatment protocol is finished, most experts recommend continuing treatment with DDS 100 to 300 mg once daily for several years to prevent recurrence [6,13,14].

We present one case of a woman who according to the clinical characteristics had an eumycetoma. She was previously treated with TMP/SMX plus DDS for 2 years without clinical improvement. In our Institution we extended the diagnostic protocol and actinomycetoma due by A. *madurae* was confirmed. So we added streptomycin 1 g per day and suspended DDS. Currently our patient has significant improvement with a decrease in volume of the lesion, no more sinuses and negative cultures. Thereby demonstrating the benefit of combination therapy with streptomycin in actinomycetomas due by *A. madurae*.

The authors have no grants or other assistance and declare that they have no conflict of interest.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Purpura Fulminans in an adult with Pseudomonas aeruginosa septicemia

Leah Ellis Wells[1], Alexander Kennon[2]

[1]Medical Student at Mercer University School of Medicine, [2]Dermatologist at Skin Care Physicians of Georgia in Macon, GA

Corresponding author: Leah Ellis Wells, E-mail: Leah.C.Ellis@live.mercer.edu

ABSTRACT

Purpura fulminans is a serious dermatological condition that can be a sequela of sepsis complicated by disseminated intravascular coagulopathy (DIC). This occurs most frequently in children with *Neisseria meningitis* or *Streptococcus pneumoniae* infection. Once diagnosed, treatment of the underlying infection, surgical debridement, and replacement of anticoagulation factors are recommended. Most patients suffer significant long-term morbidity, including amputations and sometimes death. We describe a rare case of an adult patient with Pseudomonal bacteremia leading to purpura fulminans. The patient's underlying infection was promptly treated and her lesions were debrided appropriately. However, correction of coagulopathy was not pursued. Despite this, amputations were avoided and the patient survived. This case demonstrates the need to be vigilant and open minded to the diagnosis of dermatological diseases with atypical presentations. Further, it highlights the chief importance of treating the underlying infection and providing proper wound care in septic purpura fulminans.

Key words: Purpura fulminans; Pseudomonas aeruginosa; Sepsis

INTRODUCTION

Purpura fulminans is a rapidly progressive thrombotic disorder characterized by hemorrhagic infarction of skin and disseminated intravascular coagulation. It is associated with high mortality and long-term morbidity in survivors, making recognition and treatment crucial. It most commonly occurs in infants and children in association with a heritable deficiency of protein C or protein S and/or an acquired deficiency secondary to an infection with *N. meningitis* or *S. pneumoniae* [1]. Purpura fulminans in an adult with Pseudomonal sepsis is not typical [2-4].

Diagnosis is based on recognition of erythematous painful macules that develop central areas of necrosis as the disease progresses. Typical laboratory values include prolonged plasma clotting times, thrombocytopenia, and markedly reduced Protein C and Protein S levels [1]. Biopsy can be performed to confirm diagnosis, but empiric treatment should be initiated while waiting for the results [2]. Standard treatment of purpura fulminans includes antibiotic therapy for any underlying infection, surgical debridement to remove necrotic tissue, and correction of the various coagulation cascade abnormalities characteristic of the disease [1,5].

CASE REPORT

A female in her 60s was admitted to the intensive care unit for altered mental status. Upon arrival she was afebrile, tachycardic, tachypnic, and hypotensive, but able to follow simple commands. On physical examination, there was tenderness and erythema of the right lower extremity. Initial labs revealed a leukocytosis and lactic acidosis. An initial platelet count was 140 (10^3)/uL. Blood cultures were obtained, and the patient was started on empiric broad-spectrum antibiotics and pressors. When the blood culture was positive for *Pseudomonas* aeruginosa, antibiotics were tailored to sensitivities accordingly. Despite therapy, the patient began developing stellate dark necrotic lesions with bullae (Figs. 1 - 3). At this time, D-dimer, prothrombin time (PT), and partial thromboplastin time (PTT)

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Figure 1: Violacious purpuric stellate patches on right lower extremity.

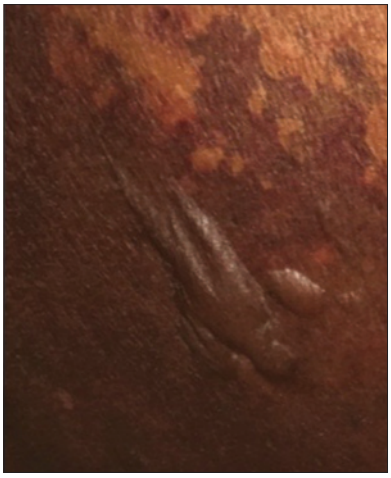

Figure 2: Large flaccid bullae within field of purpuric patches on right lower extremity.

were elevated and platelet count was 54(10^3)/uL. Given clinical presentation and laboratory findings, a diagnosis of purpura fulminans was made. Subsequent biopsy confirmed diagnosis. Appropriate antibiotics were continued and the patient underwent several surgical debridements. She did not receive heparin, fresh frozen plasma, protein C supplementation, antithrombin, or platelet transfusion. She was discharged to a rehab facility after a prolonged hospital stay.

DISCUSSION

Purpura fulminans is a rare, life threatening dermatological emergency with multiple etiologies, each typically seen in a certain population. Neonatal purpura fulminans is usually due to a heritable deficiency of Protein C or Protein S [1]. Post-infectious purpura fulminans may appear in children a few days to weeks after a febrile infectious illness. Affected children typically show a

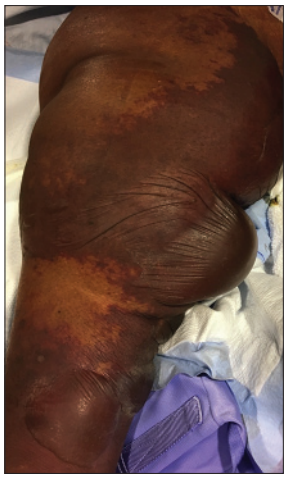

Figure 3: Right lower extremity displaying extensive involvement several days into antibiotic treatment, prior to surgical debridement.

severe acquired Protein S deficiency resulting from IgG autoantibodies that cross-react with Protein S, increasing its clearance and leading to a hypercoagulable state. Acute sepsis secondary to certain organisms, such as *Neisseria meningitis*, *Streptococcus pneumonia*, and *Haemophilus influenzae* can also precipitate purpura fulminans, most commonly in children [1]. The pathogenesis of acute infectious purpura fulminans is related to the systemic activation of coagulation and complement pathways, which commonly accompanies sepsis and DIC [2]. In adults, infectious PF is most commonly caused by sepsis from similar organisms as children. Purpura fulminans secondary to Pseudomonal sepsis is a more rare occurrence [3,4].

The initial cutaneous findings of purpura fulminans are painful areas of erythema that are often reversible with treatment of the underlying infection. As the condition progresses, the areas become characteristically stellate in shape as a result of intravascular thromboembolic events. Lesions may become bullous, and eventually necrotic. Once full thickness necrosis has developed, patients require more extensive treatment, longer recovery time, and have poorer outcomes, including amputation and death [1]. Thus, purpura fulminans is a hematological and dermatologic emergency that requires urgent diagnosis and intervention.

Diagnosis is primarily clinical, based on typical skin lesion appearance as well as laboratory findings (elevated D-dimer, decreased platelets, etc.) [1]. Skin biopsy can be performed to support the diagnosis, and would include the presence of thrombi in dermal vessels, extensive intravascular platelet aggregates, and massive vascular congestion [2]. However, empiric treatment should be started without delay.

Proper treatment for purpura fulminans in the context of sepsis includes antibiotics and surgical management to prevent further tissue death and decrease the likelihood of future amputations [5]. Both were utilized in the care of the described patient. Treatment targeting the coagulation cascade abnormalities found in purpura fulminans is also considered standard, including platelet transfusion for severe thrombocytopenia (platelet count $<50\times10^9$/dl) and replacement of coagulation factors [1]. The combination of thrombomodulin (a cofactor for thrombin) and fresh frozen plasma has also been found to be effective in contributing to the resolution of purpura fulminans [6]. Isolated protein C supplementation is a newer method used to successfully restore anticoagulant factors consumed in the disease process [7]. Despite the above array of options for reversing coagulation pathway abnormalities, and their shown benefits in purpura fulminans, none were used in the treatment of our patient. Yet, the patient survived and was discharged from the hospital.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Pemphigus vulgaris and renal amyloidosis: a new association?

Mansouri Siham[1], Sqalli Asmaa[1], Jean Pierre Dione[2], Alhamany Zaitouna[3], Senouci Karima[1], Hassam Badr[1], Ismaili Nadia[1]

[1]Department of Dermatology, University Hospital Ibn Sina Rabat, Morocco, [2]Department of Nephrology, University Hospital Ibn Sina Rabat, Morocco, [3]Department of Pathology, University Hospital Ibn Sina Rabat, Morocco

Corresponding author: Dr Mansouri Siham, E-mail: siham-mnsr@hotmail.fr

ABSTRACT

Pemphigus vulgaris (PV) is a life- threatening chronic autoimmune disease characterized by the formation of intraepithelial blisters on the skin and mucous membranes. The etiology of PV is still unknown. It results from an autoimmune process. There has been virtually no description of the relationship between pemphigus vulgaris and kidney disease. The case we report illustrates a special situation in which PV was associated with renal amyloidosis.

Key words: Pemphigus vulgaris; Renal amyloidosis; Autoimmune

INTRODUCTION

Pemphigus vulgaris (PV) is a bullous auto-immune disease affecting the skin and mucosa. It is characterised by acantholysis that results in the formation of intraepithelial bullous lesions [1]. There has been no description of the relationship between PV and kidney disease, even though the kidney is a frequent site of immune-mediated injury. Herein we report a case distinguished by its unusual clinical presentation.

CASE REPORT

A 61-year-old man came to our department with a 9 months history of two facial skin lesions treated with different topics but without improvement. Within 5 months, he presented painful oral ulceration. Within 07 month, he developed lower extremity edema.

Physical examination revealed multiple diffuse erosions and ulcerations in the entire oral cavity (Fig. 1), mainly in the tongue, palate and cheek mucosa; two bilateral hyperkeratotic plaques with hemorrhagic crusts were present in front of each mandible (Fig. 2); nails dystrophy and discoloration of the nail plate (Fig. 3); and edema of the lower extremities. In addition, Nikolsky's sign was positive in perilesional at the facial level. The rest of the clinical examination was normal.

The mycological nail tests were negative. Histological examination of two biopsy sample taken from the erosion of skin and the nail bed of one finger, the direct and the indirect immunofluorescence confirmed the diagnosis of PV.

After confirming the nephrotic syndrome (positive proteinuria 15,75g/24h, hypoalbuminemia, positive urine protein electrophoresis test and normal renal function), histopathology and immunofluorescence from a kidney biopsy specimen was performed and confirmed glomerular and vascular amyloidosis AA. The biopsy containing 15 glomeruli without cell proliferation, found massive amyloid deposits in the glomerulus and vessels with an important intertitial fibrosis. Congo red coloration was positive. The immunohistochemical marker SAA was positive (Fig. 4). No detectable gammapathy was found.

No acute infection was detected (Hemoculture, hepatitis, syphilitic and HIV serology were negative).

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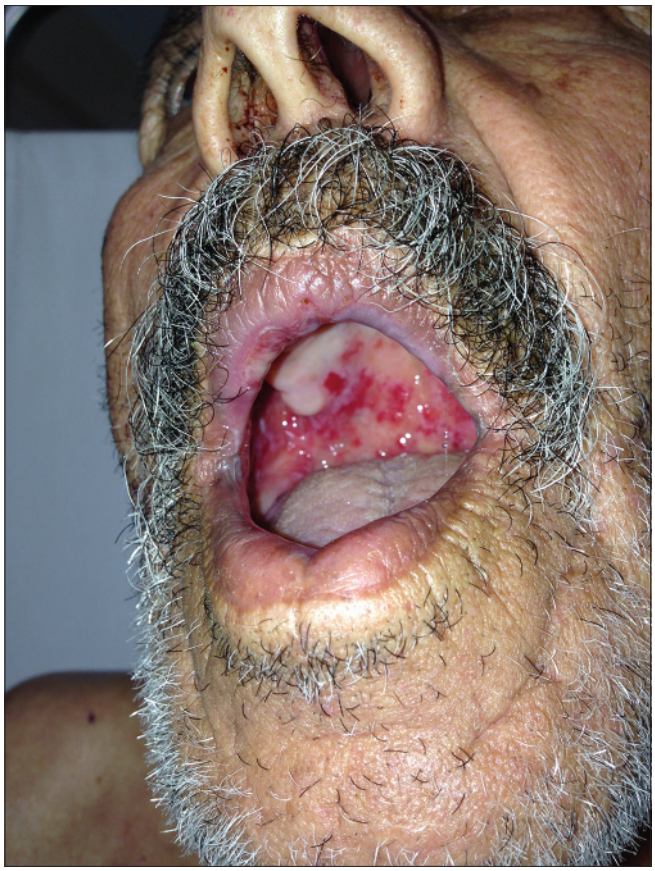

Figure 1: Multiple diffuse erosions and ulcerations in the entire oral cavity.

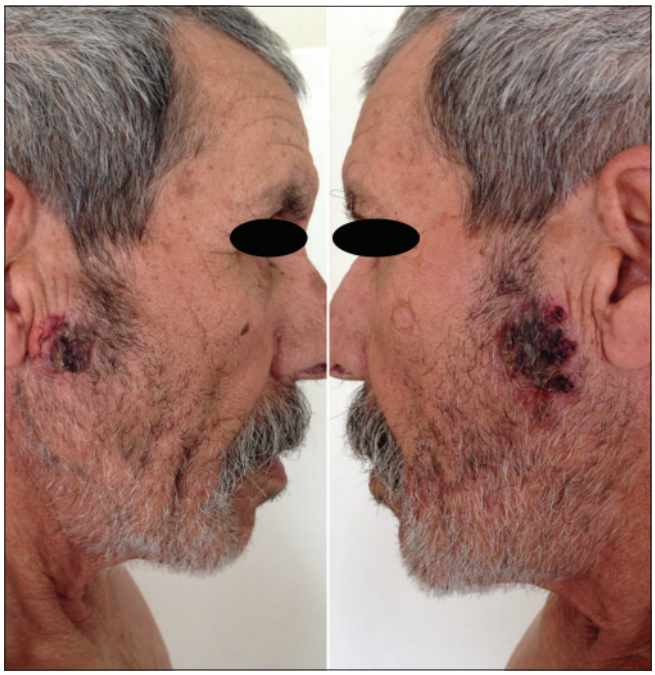

Figure 2: Two bilateral hyperkeratotic plaques with hemorrhagic crusts in front of each mandible.

Blood tumor markers, the oeso-gastroduodenal fibroscopy, colonoscopy, the cerebral, cavum, thoracic,

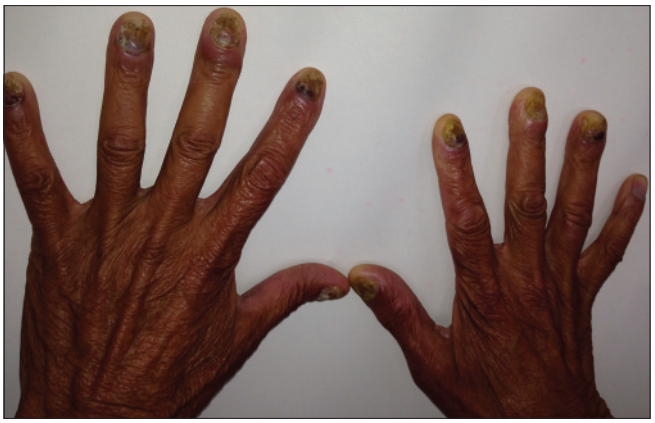

Figure 3: Nails dystrophy and discoloration of the nail plate.

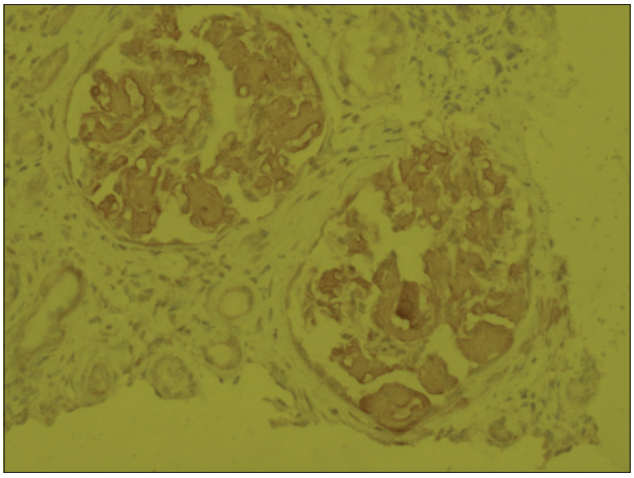

Figure 4: A histopathology and immunofluorescence from a kidney biopsy specimen found massive amyloid deposits with a positive immunohistochemical marker SAA.

abdominal and pelvic CT scan performed in search of a neoplastic etiology was normal.

The nephrologist advocated putting the patient under angiotensin-converting enzyme inhibitors, adding an anticoagulant given the low albuminemia and maintaining a hyposodic and hyperprotid diet.

Oral corticosteroid therapy was initiated consisting of prednisone 2 mg/kg per day. The oral hygiene was checked and maintained by a dentist. Improvement of the different lesions of PV occurred after three months of treatment. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

General practitioners and other medical professionals must be sufficiently familiar with the clinical

manifestations of PV to ensure early diagnosis and treatment. There has been no description of the relationship between PV and kidney disease, even though the kidney is a frequent site of immune-mediated injury. Our observation of renal amyloidosis and PV occurring simultaneously in a patient in the absence of offending agents or other clinically apparent disease processes represents a novel finding.

Glomerular involvement was also reported during acquired bullous dermatosis. The glomerular affections reported are varied but some associations appear: nephrosis with minimal glomerular lesions and pemphigus [2,3], extramembraneous glomerulonephritis and bullous pemphigoid [4], immunoglobulin A glomerulonephritis and dermatitis herpetiformis [5]. They are conceived in a context of autoimmunity, neoplasia, and even drug toxicity with D-penicillamide.

Amyloidosis, unlike dystrophic epidermolysis bullosa, is found only in an elderly patient with acquired epidermolysis bullosa [6].

One report describes an association of PV with renal disease, and, in this case, a clear offending agent (D-penicillamine) was identified [7].

Another observation of minimal change nephropathy and PV occurring simultaneously in a patient was reported [8].

Chronic inflammatory syndrome and recurrent skin infections are clearly the cause of amyloid glomerular complications.

The initial appearance of PV, followed by clinically apparent nephrotic syndrome, suggests the possibility of a causative effect of PV in the pathogenesis of renal amyloidosis. Otherwise, an unidentified process may have caused the simultaneous occurrence of the two disorders, although the absence of any other apparent disease makes this possibility speculative. Unfortunately, there are no data on which to address this issue: the small number of cases and the absence of a prospective study do not make it possible to retain one of the factors more specifically responsible for such a glomerular entity.

CONCLUSION

This study adds to the limited number of cases of PV associated to kidney disease. An important question is raised as to whether patients with PV and autoimmune bullous diseases should be screened for proteinuria. We suggest that performed prospective studies could help resolve this issue.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Rosacea infant: not always a benign dermatosis

Sabah Bazouti[1], Loubab Omahsan[1], Hanane Chahib[2], Rachid Sakhsoukh[2], Siham Dikhaye[1,3], Nada Zizi[1,3]

[1]Department of Dermatology, Mohammed VI University Hospital of Oujda, Medical School of Oujda, Mohammed First University of Oujda, Oujda, Morocco, [2]Department of Ophthalmology, Mohammed VI University Hospital of Oujda, Medical School of Oujda, Mohammed First University of Oujda, Oujda, Morocco, [3]Epidemiology Laboratory of Research and Public Health, Oujda, Morocco

Corresponding author: Dr. Sabah Bazouti, E-mail: Sabah.bazouti@gmail.com

ABSTRACT

Rosacea is a condition that is most often associated with adults; however, various forms exist in the pediatric population and must be taken into account when a child presents a rash to the face. We report a rare case of rosacea with severe ocular involvement in a 7-year-old child with discrete papules and pustules on both cheeks and chin with blepharitis and decreased visual acuity. The ophthalmologic examination confirmed a severe blepharitis with severe mibomitis associated with a stromal corneal ulcer. The diagnosis of rosacea with ocular involvement was made. Patient was put on oral azithromycin, topical metronidazole at the face and a photoprotection with good evolution. Early recognition and treatment of ocular rosacea in children can improve patient outcomes by limiting the progression of corneal pathology.

Key words: Pediatric rosacea; Ocular rosacea; Cutaneous rosacea

INTRODUCTION

Rosacea is a chronic inflammatory facial dermatitis. It mainly affects persons of middle age and a clear phototype, and it is considered rare in children [1]. Ocular involvement is the most serious complication requiring early diagnosis in order to preserve the visual function. We report a new case of ocular rosacea in a 7-year-old child.

CASE REPORT

A 7-year-old boy with a phototype III, and a family history of rosacea affecting his mother and maternal aunts, consulted the ophthalmic emergencies for a painful red right eye with significant photophobia. In the anamnesis, we find notion of flushes during temperature changes and repeated chalazion with a many similar episodes during the last two years wrongly treated as allergic conjunctivitis. Ophthalmological examination showed blepharitis with severe meibomitis associated with a stromal corneal ulcer (Fig. 1). A dermatological examination had objectified the presence of some erythematous papules, telangiectasias on a pink background of cheeks, chin and the palpébral edges (Fig. 2). The dermoscopic examination had shown the presence of arborizing vessels, sometimes polygonal, as well as pustules and erythematous background. The diagnosis of rosacea was retained and the patient was put on oral azitromycin, topical metronidazole in the face and photoprotection with a good evolution.

DISCUSSION

Rosacea is a fairly common chronic facial dermatitis, whose infantile forms are rare and often underdiagnosed. The cutaneous manifestations described in children, generally inconspicuous, seem identical to those observed in adults [2-3], with the exception of hypertrophic rosacea never reported in this age group [2]. Familial history of rosacea is often reported [1] as in our case which could support the diagnosis. Ocular signs, however, are not specific and can reach all levels of severity ranging from simple photophobia to blepharitis-meibomitis to blindness through a

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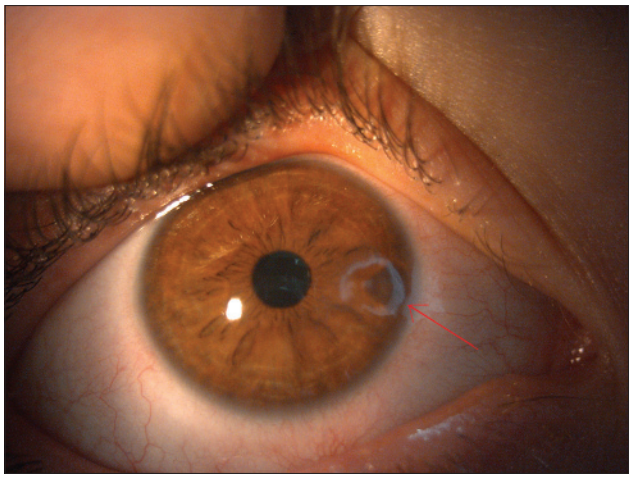

Figure 1: Clinical image showing a corneal ulcer.

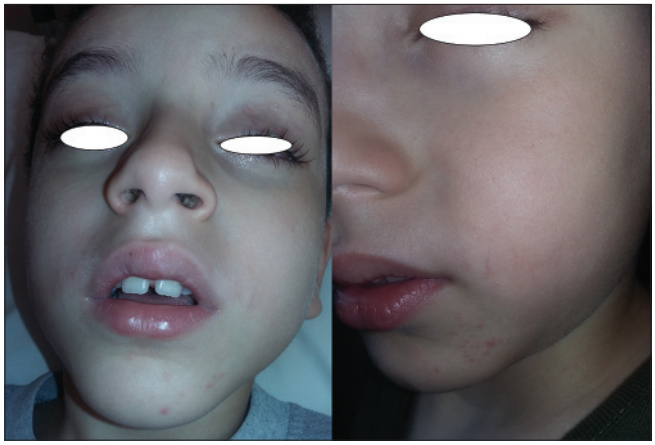

Figure 2: Papulopustular lesions associated with telangiectasia.

keratoconjunctivitis complicated sometimes by corneal ulcers [4] as was the case in our patient, imposing immediate care. There is no correlation between the severity of ocular rosacea and inflammatory cutaneous rosacea [5]. Although rosacea in children especially before puberty, is uncommon, ocular symptoms are often present at diagnosis [6].

The local treatment is identical to that of adult rosacea [1]. A systemic treatment is proposed in case of failure of topics or in case of severe ocular involvement. Systemic antibiotics, primarily the tetracyclines, are the drugs of choice for most individuals with rosacea. Tetracyclines should not be used in children younger than 8 years, because they can lead to discoloration of teeth and susceptibility to fracture by incorporation into bones and teeth. In this younger age group, macrolides are the preferred agents. Azithromycin can produce marked improvement, even when administered for only 5 days [7].

CONCLUSION

Infantile rosacea is a rare and potentially serious disease in its ocular form. Its presentation is not specific and can be confusing, especially in the absence of dermatological lesions. In front of a child with ocular signs suspicious of rosacea, the dermatological examination is an important step for making the diagnosis. Early management avoids serious complications such as keratitis and/or corneal ulcer. Only a multidisciplinary and effective management by dermatologist and ophthalmologist avoids the complications that can lead to blindness.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Zosteriform cutaneous squamous cell metastasis from carcinoma cervix - a rare case report

Romita Bachaspatimayum[1], Bishurul Hafi[1], Pradeepa Duraswamy[1], Th. Bipin[2]

[1]Department of Dermatology, Venereology and Leprosy, Regional Institute of Medical Sciences, Imphal, Manipur, India, [2]Babina Diagnostics, Imphal, Manipur, India

Corresponding author: Dr. Romita Bachaspatimayum, E-mail: dr.romita.bachaspatimayum@gmail.com

ABSTRACT

A 49 year old women presented in out-patient department with itchy, papulo-nodular lesions on the left side of the neck and upper trunk in dermatomal distribution of three months duration. She was earlier diagnosed with squamous cell carcinoma of cervix and was on follow-up for the past one year after completing chemo-radiation. A diagnosis of zosteriform metastasis was made and biopsy was taken from a representative sample which showed moderately differentiated squamous cell carcinoma. Majority of these cases in the past have been misdiagnosed as herpes zoster and were treated with antiviral drugs. Hence metastatic diseases might be considered as the differential diagnosis of zosteriform rash in known cases of squamous cell carcinoma cervix.

Key words: Cutaneous metastasis; Zosteriform pattern; Carcinoma cervix

INTRODUCTION

Carcinoma cervix is the most common gynaecological malignancy which usually metastasise to lungs and liver. Cutaneous metastasis is very rare in carcinoma cervix, ranging from 0.1-4.4% only [1]. Out of them a very few cases presented in linear or zosteriform fashion. To our best knowledge no cases of zosteriform metastasis from squamous cell carcinoma (SCC) of cervix has been published in English literature yet.

CASE REPORT

A 49 year old multiparous woman presented with itchy skin lesions over left side of root of neck and upper chest for the past three months (Figs. 1 and 2), which was aggravated on sweating and on exposure to sunlight. It started along the neck and gradually spread to upper chest. One year back she was diagnosed with squamous cell carcinoma of uterine cervix and had undergone chemo-radiation. Cutaneous examination revealed grouped shiny papules, nodules and plaques over left side of neck and upper chest, not crossing the midline in a dermatomal fashion along C4, T1 and T2. Stony hard, matted, mobile, non tender lymph nodes of 3cm x 2 cm were present in left upper cervical group. Hard, single, mobile lymph node of 1.5cm x 1cm was present in left lower cervical group. Left supra clavicular lymph node was also enlarged, two in number, 0.5cm x 0.5cm, hard and mobile. Right side of the neck and the trunk were normal. Clinical examination of breasts was normal. Oral cavity was also normal. A provisional diagnosis of zosteriform cutaneous metastasis was made. Chest and ENT consultation was done to rule out other primary sites. Her blood routines and radiological investigations including CT thorax were within normal limits. Skin biopsy of the representative sample taken from the neck lesion showed skin with dermis showing malignant squamous cells arranged in clusters and singles infiltrating the stroma with irregular margins. Overlying epidermis is uninvolved. Features were of metastatic squamous cell carcinoma (Fig. 3). Patient was advised Fine needle aspiration cytology (FNAC) of the enlarged cervical and supraclavicular lymph nodes and was referred to Radiotherapy department of the Institute but was lost to follow-up. Prior to the study,

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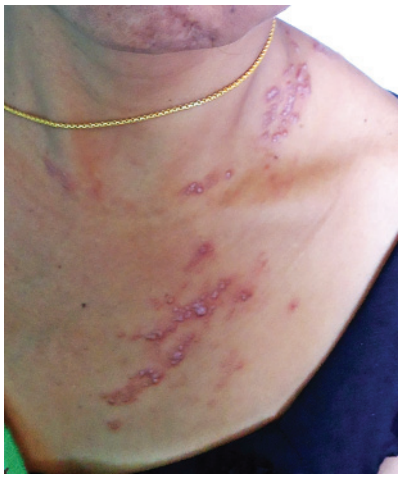

Figure 1: Grouped shiny papules, nodules and plaques over left side of neck and upper chest in a dermatomal fashion.

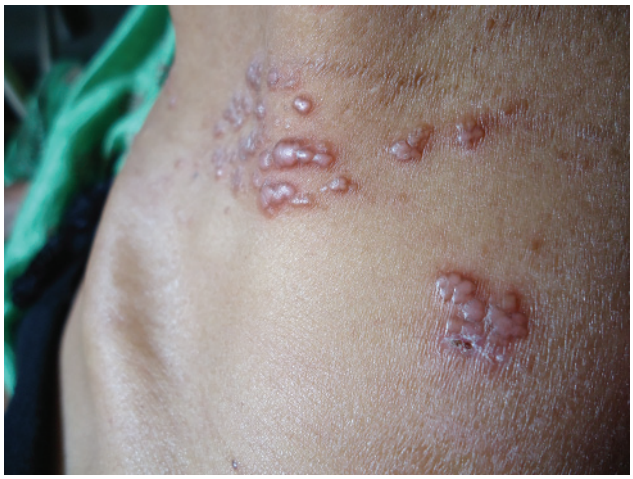

Figure 2: Close-up view of Figure1.

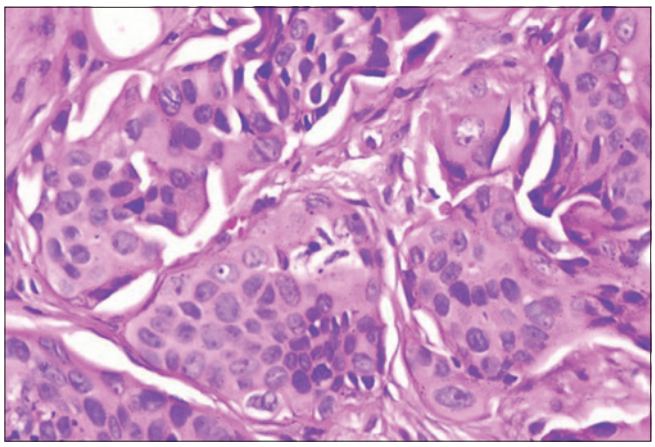

Figure 3: Moderately differentiated squamous cell carcinoma. H.P.E. (H&E, 10x).

patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Cervical cancer is one of the most common malignancy affecting women in India. It frequently metastasizes to lungs, abdominal cavity, gastrointestinal tract, liver, para-aortic nodes, supraclavicular nodes, inguinal nodes and spine [2]. Cutaneous metastases arising from cervical cancer are particularly rare even in the advanced stages of the disease, with its incidence ranging from 0.1% to 4.4% [1]. Mostly, they occur as a sign of disease recurrence and are associated with poor prognosis. SCC accounts for 80% of all cervical cancers but it metastasise to distant sites less commonly than adenocarcinoma [3].

There is enormous variability in clinical appearance of skin metastasis, with multiple nodules as the most common clinical appearance; less common forms include inflammatory or erysipeloid form, sclerodermoid form, alopecia neoplastica, or bullous form [4]. Cutaneous manifestations may herald the underlying disease process [5]. Zosteriform pattern is very rare type of cutaneous metastases with only a few reported cases. Many of the dermatomal metastases have been initially diagnosed as herpes zoster which is a common finding in immunocompromised cancer patients. Spontaneous pain mimicking herpes zoster has been observed in many patients with zosteriform metastases with many of them initially having been treated with antiviral drugs.[5] It manifested as a sign of relapse following definite treatment of the primary tumour in most reports, but it was the presenting complaint in a few cases [6].

Only 56 cases of zosteriform pattern have been reported in the English literature since 1970 as per a meta analysis published in 2009 [7]. In males the highest prevalence of primary malignancy was SCC (22.2%) and lung carcinoma (22.2%). In females the highest prevalence of primary malignancy was breast carcinoma (35%), followed by ovary carcinoma (25%). But it was also reported in patients with melanoma, carcinoma of prostate, bladder, colon, rectum and renal pelvis [8]. However, we could not find any case of the same occurring in patients of carcinoma uterus. According to a previous report, adenocarcinomas were the commonest histopathological pattern followed by transitional carcinoma [4]. Generally, the histological features of the metastases are similar to the primary tumor, although metastases may be more anaplastic

and exhibit less differentiation. The exact mechanism of zosteriform metastases is still speculative. It has been hypothesised that it might be due to: a) Koebner-like reaction at the site of prior herpes zoster infection ('locus minoris resistentiae'- site of lessened resistance); b) Perineural lymphatic spread; c) spread via fenestrated vessels of the dorsal root ganglion; d) Accidental surgical implantation [4].

Metastases from the uterine cervix to the neck lymph nodes are uncommon. With more recent improved treatment of cervical cancer, supraclavicular lymphadenopathy has emerged as a more common manifestation of recurrent disease [9]. Our patient probably had secondaries in the cervical and supraclavicular lymph nodes which could not be confirmed as she was lost to follow-up.

CONCLUSION

In patients with carcinoma cervix and lesions of zosteriform skin lesions, a differential diagnosis of metastasis may be considered to avoid inadequate diagnosis and treatment. A representative biopsy sampling should be taken if the lesions are unresponsive to antiviral agents.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Penile nodules revealing systemic amyloidosis associated with myeloma

Loubab Omahsan[1], Nassiba Zerrouki[1], Nada Zizi[1,2], Siham Dikhaye[1,2]

[1]Department of Dermatology, Mohammed 6 University Hospital of Oujda – University of Mohammed First – Faculty of Medicine and Pharmacy, Oujda, Morocco, [2]Laboratory of Epidemiology, Public Health and Scientific Research, Oujda, Morocco

Corresponding author: Dr. Loubab Omahsan, E-mail: oloubab@gmail.com

ABSTRACT

Amyloidosis is a rare disease. Nodular cutaneous amyloidosis is the rarest clinical form of cutaneous amyloidosis. It may be associated with a systemic disease. We report an exceptional case of amyloidosis associated with myeloma, with a double atypical localization: Well-defined papulo-nodules of the base of the penis; Vertebral amyloidosis causing spinal cord compression. The association of nodular skin lesions to a myeloma should evoke the diagnosis of amyloidosis.

Key words: Penile nodules; Amyloidosis; Spinal cord compression; Myeloma

INTRODUCTION

Amyloidosis is a rare disorder characterized by the deposition of insoluble proteins in tissues. Nodular cutaneous amyloidosis (ACN) is the rarest form of cutaneous amyloidosis. Only a dozen cases of skin amylosis of the glans of the penis have been reported until today [1]. We describe the case of systemic amyloidosis with atypical presentation.

CASE REPORT

A 57-year-old patient with no significant pathological history has been followed for two months for multiple myeloma retained on the presence of medullary plasmocytosis, monoclonal gammopathy type Lambda and two CRAB criteria (Hypercalcemia, renal failure, anemia <10g/dl, bone involvement), as well as positive Bence Jones proteinuria. Our patient was placed under a chemotherapy regimen Cylclophosphamide-Dexamethazone-Thalidomide (CDT), associated with bisphosphonates. He presented ten days after diagnosing his myeloma a medullary compression treated surgically and whose histopathological study had found asclerogenic fibrosis without individualized plasmocytic elements in the bone and cartilaginous tissues. He has reported for 20 days the appearance of some skin lesions slightly pruriginous sitting in the genital area. Clinical examination revealed multiple papulo-nodular lesions which are soft, fleshless, painless, resting on healthy skin and sitting at the base of the penis (Fig. 1). The remainder of the dermatological examination was without anomaly. The cutaneous biopsy revealed deposits of an anthropic eosinophilic substance, enhanced by the violet crystal (Fig. 2a) and the Congo red (Fig. 2b) with a yellowish green dichroism in polarized light evoking nodular cutaneous amyloidosis. The systematic assessment was without abnormalities, including: Renal and hepatic function, 24h proteinuria, thyroid biological examinations, chest x-Ray, abdominal ultrasound, CT scan of brain, chest, abdomen and pelvis as well as troponin, electrocardiogram and echocardiography. The histological study of the accessory salivary gland biopsy (ASGB) did not find amyloid deposits. Medullary compression secondary to amyloidosis was mentioned in the absence of plasmocyte elements at the vertebral level. A re-reading of the vertebral

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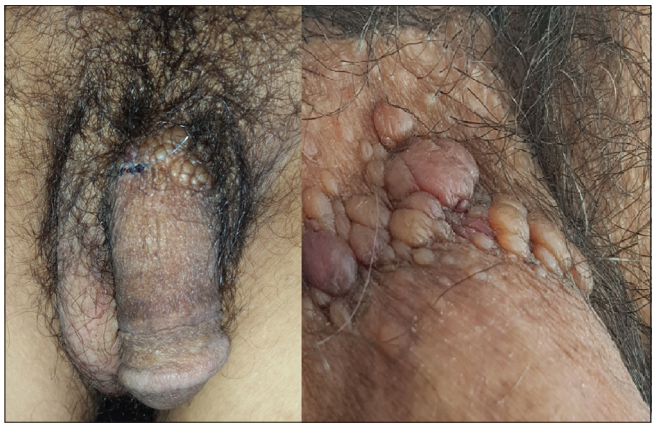

Figure 1: Multiple papulo-nodular lesions resting on healthy skin and sitting at the base of the penis.

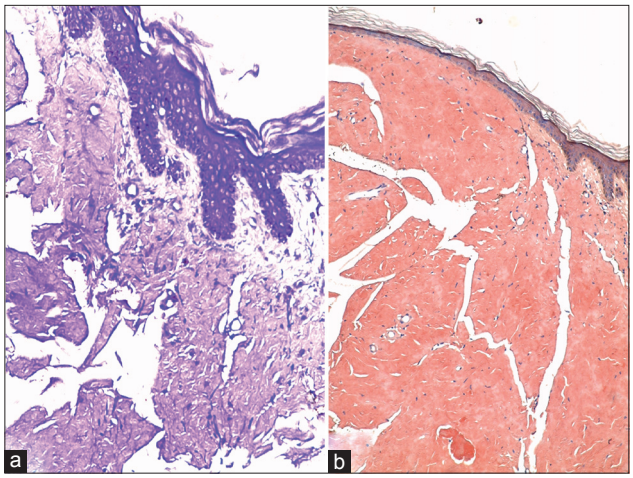

Figure 2: (a) Deposits of an anthropic eosinophilic substance, violet crystal + (b) Yellowish green dichroism in polarized light.

piece allowed us to retain the diagnosis of a double localization of amyloidosis associated with myeloma. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

In addition to macular and lichenoid forms, nodular cutaneous amyloidosis is the rarest clinical form, and about a hundred cases have been described in the literature [2]. The most common clinical form is a single or rarely multiple nodule sitting at the acral level, the face, scalp or extremities [3]. Penile localization remains rare, and 14 cases have been reported in the literature with localized involvement in the glans penis [1]. In our case, the lesions of cutaneous amyloidosis were found at the level of the base of the penis without damage of the glans.

Although rare, nodular cutaneous amyloidosis is often associated with a systemic disease including Sjogren's syndrome, or a multiple myeloma dysproteinemia such as the case of our patient. The risk of evolving to systemic amyloidosis is 10% [4]. Our patient has presented a second localization at the spinal level. The mechanism underlying spontaneous vertebral compression fractures in amyloidosis has not been identified [5]. Once the diagnosis of nodular skin amyloidosis is retained, anamnesis, a complete clinical examination, as well as a serum electrophoresis and urinary proteins, ASGB, rectal or abdominal fat biopsy must be performed In order to exclude an amyloid deposit at the extracutaneous level [1].

The treatment of systemic amyloidosis associated with myeloma is not standardized; it relies mainly on chemotherapy. The treatment of the vertebral impairment is also based on chemotherapy with a total excision of lesions [5].

CONCLUSION

Our case remains original by the exceptional double localization of amyloidosis, as well by nodules well individualized at the base of the penis as well as the vertebral localization causing a medullar compression. The association of nodular skin lesions to a myeloma should evoke the diagnosis of amyloidosis and perform a skin biopsy without restricting the systematization assessment that must be guided by the patient's history and physical examination.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Delayed diagnosis of radiation - associated cutaneous angiosarcoma

Nina Korsaga/Somé[1,2], Nayi Zongo[3], Thibault Kervarrec[4], Aurélie Sallot[5], Alexandre Penaud[6], Gonzague de Pinieux[4,7], Laurent Machet[1,7]

[1] Department of Dermatology, CHRU, Tours, France, [2]Faculty of Health Science of Ouaga 1 Pr Joseph Ki-Zerbo University, Burkina Faso, Burkina Faso, [3]General and Digestive Surgery, Yalgado Ouédraogo University Hospital, Ouagadougou, Burkina Faso, [4]Department of Pathology CHRU, Tours, France, [5]Department of Plastic surgery, CHRU, Tours, France, [6]Pôle de Santé Léonard de Vinci, Plastic Surgeon, Chambray les Tours, France, [7]Université François-Rabelais, Tours, France

Corresponding author: Dr. Nina Korsaga/Somé, E-mail: nessine2000@yahoo.fr

ABSTRACT

Angiosarcoma is most frequently occurring in patients treated for a previous cancer with radiation therapy. Our aim was to measure the time between the first signs found by the patient and the first biopsy, and the time before the final diagnosis of radiation-associated angiosarcoma (RAAS) and to analyse the reasons for delayed diagnosis. Four patients met the inclusion criteria. Three had cutaneous RAAS and one had suprapubic cutaneous RAAS after treatment for cancer. The intervals between the first cutaneous sign recorded by the patient and the diagnosis of RAAS were 9 to 37 months. The initial diagnosis by the non-specialist pathologist was a benign vascular lesion. Review of the initial biopsy was consistent with RAAS in 3 cases and with AVL in 1 case. Clinicians should alert pathogists when a vascular lesion is larger than 5 mm in the context of irradiated skin. Histology review by an expert should be recommended.

Key words: Angiosarcoma; Radiation; Pathology; Diagnosis; Atypical vascular lesion; Chemotherapy

INTRODUCTION

Angiosarcoma (AS) is a rare malignant tumour that develops from endothelial cells. In Europe, the annual incidence of AS is approximately 0.31 cases per 100.000 people [1].

Primary lymphoedema is known to be a contributory factor in the occurrence of cutaneous AS (Stewart-Treeves syndrome) [2]. Conservative treatment of breast cancer combining lumpectomy, radiotherapy and sentinel lymph node dissection, or more generally combined radio-surgery treatment of non-breast cancer, are also known risk factors for secondary lymphedema [3] and for the development of radiation-associated angiosarcoma (RAAS) [4]. It is difficult from both clinical and histology points of view to distinguish benign vascular lesions from atypical vascular lesions (AVL) and true AS of the skin [5-7].

We report four consecutive cases of cutaneous RAAS occurring in patients who had previously been treated with radiation therapy for cancer. Our aim was to measure the time between the first signs found by the patient and the first biopsy, and the time before the final diagnosis of RAAS and to analyse the reasons for delayed diagnosis.

CASE REPORT

This is a retrospective series of patients with cutaneous RAAS treated 1 January 2008 and 31 December 2014. The inclusion criteria comprised the development of RAAS located initially in the radiotherapy field that had appeared more than six months after radiotherapy and confirmed by a pathologist with expertise in sarcoma.

We gathered the following data: date of diagnosis of the first cancer, modalities of treatment for the first

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cancer and radiation dose, date of first clinical signs that alerted the patient to the appearance of vascular lesions that led to the diagnosis of RAAS, date of the first biopsy, and date of definitive diagnosis of RAAS. The existence of primary lymphoedema, or secondary lymphoedema induced by treatment for the primary cancer, the treatment modalities and response to treatment, and the date of death were also gathered. Histology slides were stained with a panel of autoantibodies including CD31, CD34, D2-40, Myc and Ki67.

Four patients met the inclusion criteria (Tables I and II). Three had cutaneous RAAS after treatment for breast cancer, and one had suprapubic cutaneous RAAS after treatment for uterine cancer (Fig.1). The interval between treatment of the primary cancer and the occurrence of RAAS ranged between 36 months and 72 months. The intervals between the first cutaneous sign recorded by the patient and the diagnosis of RAAS were 9 to 37 months. The pathogy and clinical diagnoses of AS were unambiguous in all 4 cases at the time of diagnosis (Figs. 1 and 2). First biospy from each patient was reviewed retrospectively by experts in dermatopathology in our centre. In 3 cases, the diagnosis of RAAS was made. In the remaining case, the diagnosis of atypical vascular lesion was made on the biopsy but the diagnosis of RAAS was established after total surgical removal. Initial treatment was wide surgery in two cases. Chemotherapy was offered to the other two patients who were deemed inoperable. They died 7 and 10 months after diagnosis of AS.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

In this series, the interval between the first clinical signs and diagnosis was longer than 1 year in two of four cases. In addition, at least two biopsies, and a second opinion

Table I: Patients characteristics

Patient	1	2	3	4
Age at diagnosis of AS (years)	84	85	78	53
Sex	F	F	F	F
Location	Suprapubic	Breast	Breast	Breast
Primary cancer	Uterus	Breast	Breast	Breast
Pre-existing lymphedema	None	None	None	None
Acquired lympoedema	Yes	Yes	Yes	Yes
Radical lymph node surgery	Yes	Yes	Yes	Yes
Radiation dose (Gray)	60	30	59.5	60
Chemotherapy for primary cancer	None	None	None	Paclitaxel and herceptine
Interval between radiation therapy and diagnosis of AS (months)	72	70	36	45
Interval between first clinical signs and diagnosis of AS (months)	15	10	9	37
Interval between first biopsy and diagnosis of AS (months)	0	6	25	35
Number of biopsies	1	3	2	2
Histology review of the first biopsy	AS	AS	AVL	AS
Treatment for AS	Chemotherapy Bevacizumab 3 months (PD) Paclitaxel 2 months (PD)	Chemotherapy Paclitaxel 3 months (PD) Doxorubicine 3 months (PR)	Mastectomy Paclitaxel 6 months (CR) Pazopanib (CR)	Mastectomy Paclitaxel 3 months (PD) Pazopanib (NE)
Overall survival since diagnosis of AS (months)	7	10	44	12
Alive	No	No	Yes	Yes

PD=progressive disease; PR=partial response; CR=complete response; NE=not evaluable

Table II: Main pathology findings

Patient	1	2	3	4
Histology of RAAS	Conventional angiosarcoma	Conventional angiosarcoma	AVL followed by conventional angiosarcoma	Epithelioid angiosarcoma
Grading	3	2	3	3
CD31	+	+	+++	+++
CD34	+	+	-	+
D2-40	+	+	+	+
Myc	few cells stained	+	+	+
Ki 67	20%	25%	AVL <1% AS >20%	>60%

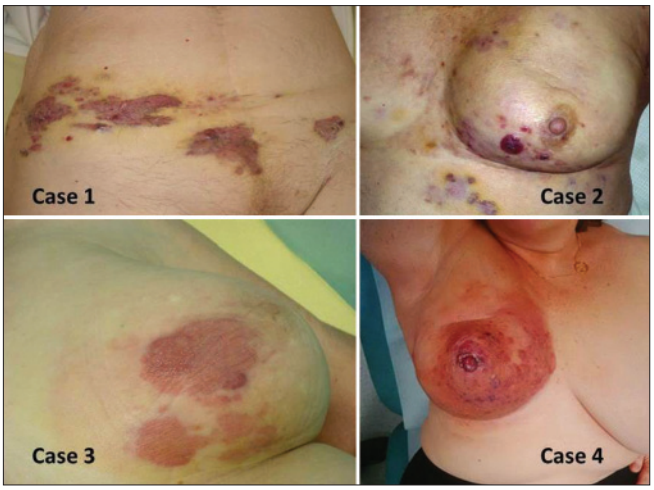

Figure 1: Clinical lesions. Case 1: infiltrated, papular lesions, purplish extended, seen at the level of the pelvic area, bounded by points of radiation, in a patient of 84, which occurred 6 years after radiation therapy for cancer of the cervix, in a patient of 84. Case 2: Nodular lesions, with vascular appearance on the left breast, diffused, bursting to the contralateral breast with a painful infiltration of the whole left breast, occurring 7 after radiation therapy for left breast carcinoma in a patient of 85. Case 3: Angiomatous erythematous plaque on the left breast took place 4 years after radiation therapy for infiltrating ductal breast carcinoma on the same treated breast, in a 78-year-woman. Case 4: Lymphedema and breast fibrosis, topped with an Erythematous cutaneous plaque, infiltrated, including lymphangiectasia, extended to the whole right breast, occurred 4 years after radiation therapy for cancer of the right breast, in a patient of 54.

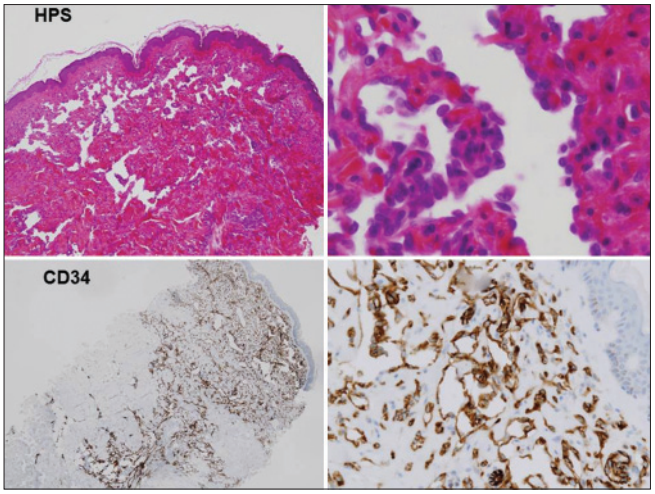

Figure 2: Histopathological lesions (a) Nodular Proliferation of fusiform cells delineating the vascular slots under an epidermal coating without atypia, after staining with HPS (Hematoxylin Phloxine Safran), and 4 x magnification. (b) Details at the highest magnification (10X) of image " a ", showing the slots bordered by atypical endothelial cells (c) Intensive and diffused immuno-marking of sarcomatous proliferation, with anti-CD34 antibody, 4X. (d) Details at the highest (10X) magnification of image " c ", showing an intensive marking of the membrane in tumor cells.

from a pathologist with expertise in sarcoma, were required in three of the four cases. Moreover, reviewing the initial biopsy by experts in dermatopathology allowed the diagnosis of RAAS in three of the fours cases. This strongly supports the need for systematic reviewing of any vascular lesions in patients previously treated with radiation therapy for breast cancer.

Increased risk of developing sarcoma after radiation treatment for cancer has been known for decades [8]. The interval between the treatment of the primary cancer and diagnosis of AS is usually long: 60 months in a metanalysis of 222 cases [9]. Due to the long latency period between radiation and the occurrence of AS, and due to the slow progressive development of vascular lesions and the rarity of the tumour, early recognition by both patient and physician may be difficult [7,8]. All the lesions were larger than 5 cm. The interval ranged from 0 to 36 months in another series [10]. Such an interval may be detrimental to patients and emphasises the difficulties for non-specialist pathologists in differentiating benign vascular lesions from atypical and malignant lesions. D2-40 immunostaining was believed to be helpful in one series, as it was positive in 11/12 AVL and negative in 15/21 AS [11]. However, D2-40 staining was positive in all of our four cases. AVL should be considered as a slow precursor to AS or slowly progressive AS [12]. MYC amplification by Fish analysis may help to separate the two entities, as in one study it was evidenced in all the cases of RAAS and absent from those with AVL [13]. More interestingly, one study reported that immunostaining with a commercial Myc antibody was strongly related to Myc amplification in 24 of 25 cases of RAAS and staining was negative in controls (including 16 AVL and one AS not related to radiation) [14]. More recently, Myc staining was found to be highly specific but poorly sensitive as it was negative in 12 cases of primary AS and 29 AVL, but positive in only 20 of 37 RAAS. Thus a negative Myc expression result does not rule out the diagnosis of RAAS [15].

Treatment of RAAS consists usually in mastectomy. Paclitaxel may provide clinical improvement as in one of our patients. More recently, pazopanib provided complete response in one patient and partial response in another patient and was used as maintenance therapy at low dose [16]. Complete response was also shown in one of our patient who is still in maintenance therapy.

CONCLUSION

The early diagnosis of post-radiation low grade AS may be difficult for both the clinician and the pathologist.

The clinician should alert the pathologist in cases where the lesion is larger than 5 mm, since AVL are often small lesions [17], and should ask for a second pathologist's opinion with expertise in sarcoma in every suspicious case.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Cutaneous epithelioid hemangioma mimicking infected Montgomery tubercle

Padmapriya Jaiprakash, Kanthilatha Pai, Vidya Monappa

Department of Pathology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India

Corresponding author: Dr. Padmapriya Jaiprakash, E-mail: padmapriya.j@gmail.com

ABSTRACT

Cutaneous epithelioid hemangioma is a vascular lesion of uncertain pathogenesis. Recurrences are common in cases with incomplete surgical excision. Histologically, it can be differentiated from other conditions by the presence of prominent endothelial lining and mixed inflammatory infiltrate in the background with predominance of lymphocytes and eosinophils. A 19 year old lady presented with a painful left breast swelling, which was clinically diagnosed as infected Montgomery's tubercle and excised. Histopathology showed features of cutaneous epithelioid hemangioma. Cutaneous epithelioid hemangioma can occur rarely in the breast, where it can mimic an inflammatory pathology.

Key words: Epithelioid; Hemangioma; Breast

INTRODUCTION

Cutaneous epithelioid hemangioma, also known as angiolymphoid hyperplasia with eosinophilia (ALHE), is an entity whose origin is controversial. It is said to be a neoplastic process or a reactive proliferation secondary to various stimuli, including trauma [1]. Most involve dermis, subcutaneous or deeper tissues. Sites commonly involved include external ear, occipital region and around temporal artery. Deeper tissues include head and neck region, arm, hands, axillae and inguinal region. Rare sites including oral cavity, tongue, lymph node, bone, testis and breast have been reported [2].

CASE REPORT

A 19 year old lady presented to the OPD with a pruritic and painful lesion in the left breast since 1 month. There was no history of similar lesions in the past or any other parts of the body. On examination, a single lesion was noted in the areola of the left breast with local raise in temperature. A diagnosis of infected Montgomery's tubercle was made and an excision biopsy done. The sections studied showed proliferation of small sized blood vessels (Fig. 1) with vague lobular architecture, lined by plump (epithelioid) endothelial cells (Fig. 2) surrounded by dense perivascular inflammatory infiltrate composed of lymphocytes and eosinophils (Fig. 3). A diagnosis of epithelioid hemangioma or ALHE was made. Reticulin stain done highlighted the vascular channels (Fig. 4). On follow-up, the patient was asymptomatic. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Epithelioid hemangioma affects females more than males and most commonly involves pre-auricular area and scalp. Systemic eosinophilia is seen in 20% of cases [2]. Grossly, they are circumscribed lesions measuring 0.5 to 2cms in size. Epithelioid hemangioma are characterized by a prominent proliferation of small, capillary-sized vessels lined by plump, epithelioid endothelial cells. The vessels typically have an immature appearance. Early lesions demonstrate a predominance of rapidly proliferating atypical vasculature [3]. Late lesions illustrate maturation of these blood vessels with prevalence of lymphoid follicles seen towards the

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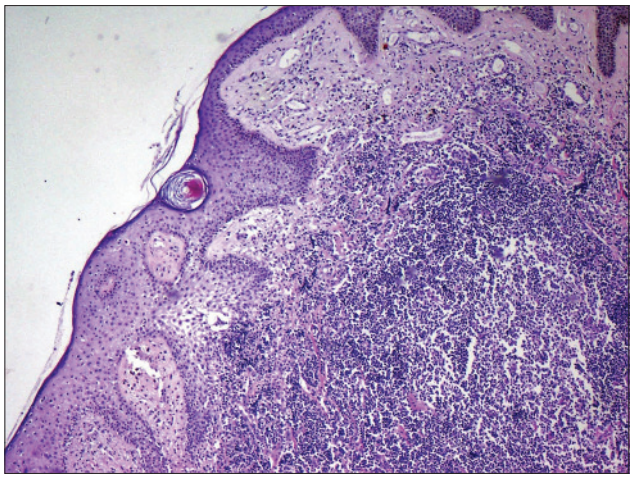

Figure 1: Epidermis overlying dermis showing a lesion composed of vascular proliferation surrounded by lymphocytic infiltrate with few eosinophils (H&E, 40x).

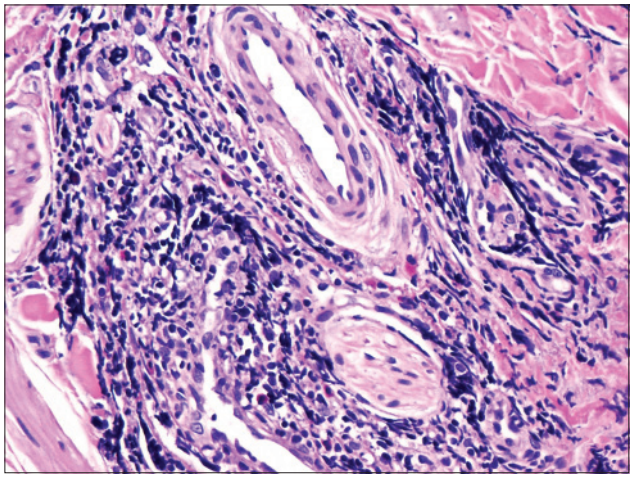

Figure 2: Vascular channels lined by plump epithelioid cells, surrounded by lymphocytes with few eosinophils (H&E, 100x).

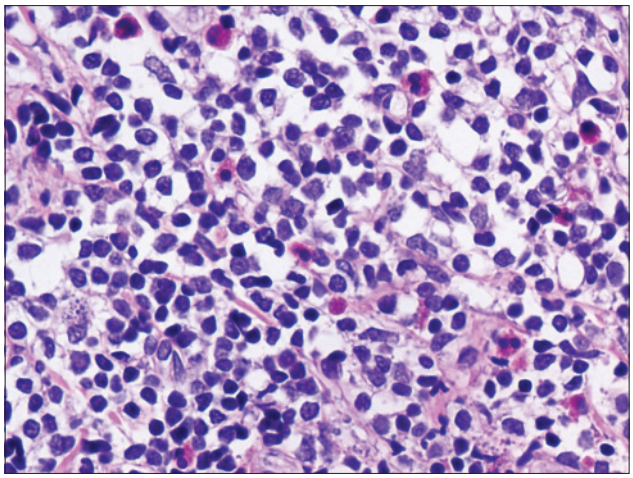

Figure 3: Polymorphous population of lymphocytes with interspersed eosinophils (H&E, 200x).

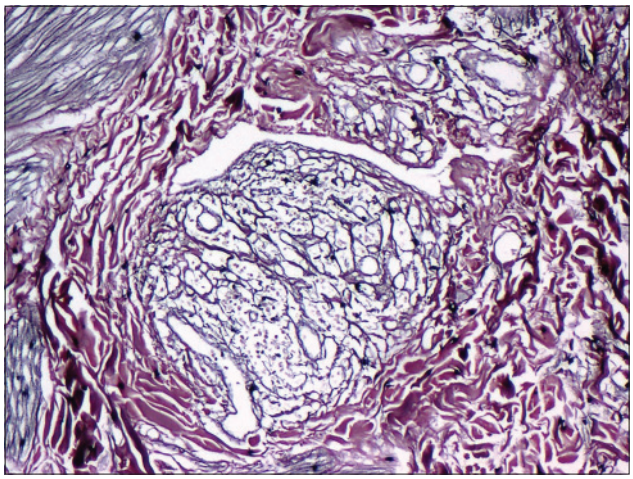

Figure 4: Reticulin fibres highlighting the vascular channels surrounded by the lymphocytes (Reticulin stain, 100x).

periphery of the lesion. Complete local excision and follow-up are optimal management for epithelioid hemangioma. Local recurrence is reported to occur in up to one-third of patients.

Amongst the differential diagnosis, first is Kimura disease [3,4]. Though used as synonyms previously, Kimura disease typically presents as a subcutaneous nodule in young male, in the preauricular or submandibular region.[1] Microscopically, it has characteristic eosinophilic microabscesses and lacks epithelioid cells seen in ALHE. The other ominous differentials include epithelioid angiosarcoma and epithelioid hemangioendothelioma (EHE). Angiosarcoma shows obvious malignant nuclear features, along with anastomosing vascular channels. EHE shows the presence of cords of vacuolated endothelial cells in a myxoid matrix, along with the absence of the lymphoid aggregates [5].

Clinical differentials include Kaposi sarcoma and pyogenic granuloma, both of which show characteristic vascular channels and are not microscopic mimics [5].

CONCLUSION

This case is being presented for involvement of a rare site, mimicking an infective lesion.

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Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

A pregnancy pilomatricoma: an uncommon dermatologic benign neoplasm

Ouiame El Jouari, Salim Gallouj, Zakia Douhi, Selma Benkirane, Hanane Baybay, Fatima Zahra Mernissi

Department of Dermatology and Venereology, University Hospital Hassan II, Fez, Morocco

Corresponding author: Dr. Ouiame EL Jouari, E-mail: eljouariouiame@gmail.com

ABSTRACT

Pilomatricoma is a relatively rare tumour of the skin. It derived from primitive basal cells of epidermis that differentiate into hair matrix cells. It usually arises from the lids and eyebrows. Tumour appear as solitary, firm nodules, exhibiting a normal to pearl white epidermis. A 25-year-old female in her third month of pregnancy, presented with an asymptomatic erythematous nodule 7 weeks. Examination revealed an erythematous nodule, measured approximately 1, 5 cm in diameter firm, with yellowish zones and dotted with telangiectasia. Dermoscopy demonstrated yellowish lobules surrounded by crown-like branching vessels. Patient underwent surgical excision. Microscopic examination revealed a pilomatricoma. After a follow-up of 10 months, the evolution was favorable without recurrence. We report the clinical, dermoscopic, therapeutic and evolutionary characteristics of a case of pilomatricoma in order to help clinicians to better diagnose this entity and decrease the rate of misdiagnosis, especially in pregnant women.

Key words: Pilomatricoma; Periocular; Pregnancy; Dermoscopy

INTRODUCTION

Pilomatricoma is a relatively rare tumour of the skin derived from primitive basal cells of epidermis that differentiate into hair matrix cells. It comprises approximately 1% of all benign skin tumours. Pilomatricoma is an uncommon lesion of the periocular tissues, it usually arises from the lids and eyebrows. Tumour appear as solitary, firm nodules, exhibiting a normal to pearl white epidermis. We describe an interesting case of a pregnancy pilomatricoma arising from the left medial canthus.

CASE REPORT

A 25-year-old female in her third month of pregnancy, presented with an asymptomatic erythematous nodule. The patient reported that the lesion started as a small 3-mm papule and grew significantly to a 15 mm lesion in 7 weeks. Examination revealed an erythematous nodule, measured approximately 1, 5 cm in diameter, Limited, with regular contours, firm, with yellowish zones and dotted with telangiectasia (Fig. 1). There was no palpable lymphadenopathy. Dermoscopy demonstrated yellowish lobules on an erythematous background, surrounded by crown-like branching vessels (Fig. 2). Patient underwent surgical excision of the lesion, out under local anaesthesia (Fig. 3). Microscopic examination revealed a regular squamous epithelium which has deep epithelial proliferation mummified cells with a very pale eosinophilic aspect, without having seen any nuclei. Presence of granulomatous reaction giganto-cellular with a foreign body and calcifications (Fig. 4). After a follow-up of 10 months, the evolution was favorable without recurrence (Fig. 5). Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Pilomatricoma or calcifying epithelioma of Malherbe is a benign skin tumor. It can occur at any age;

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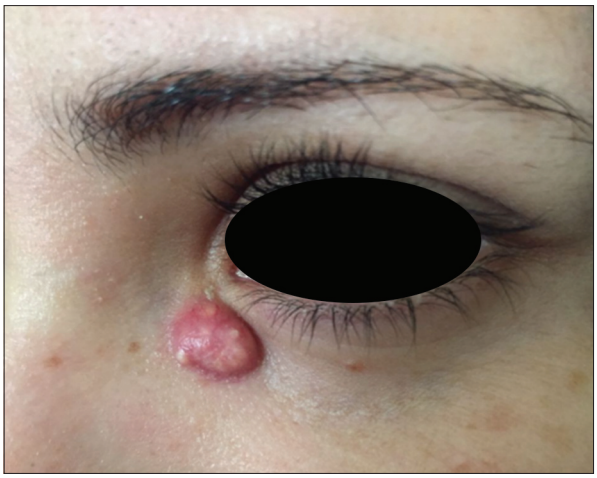

Figure 1: An erythematous nodule, measured 1, 5 cm in diameter, Limited, with regular contours and yellowish zones and dotted with telangiectasia.

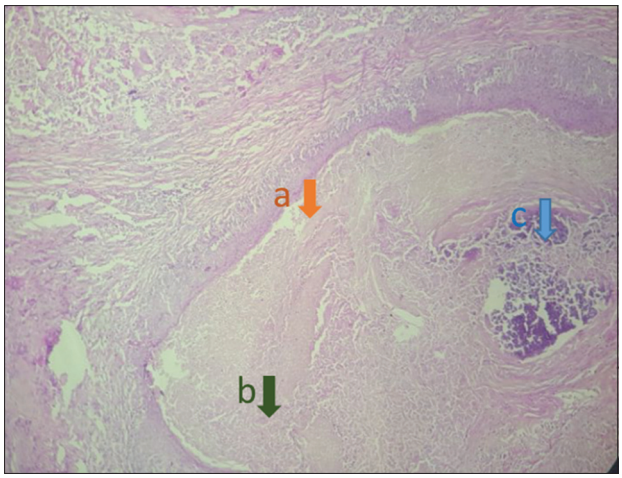

Figure 4: Histological section with coloration HE G x 50, presence of basaloid cells (a) and mummified cells (b) with abrupt transition between the two and presence of calcifications (c).

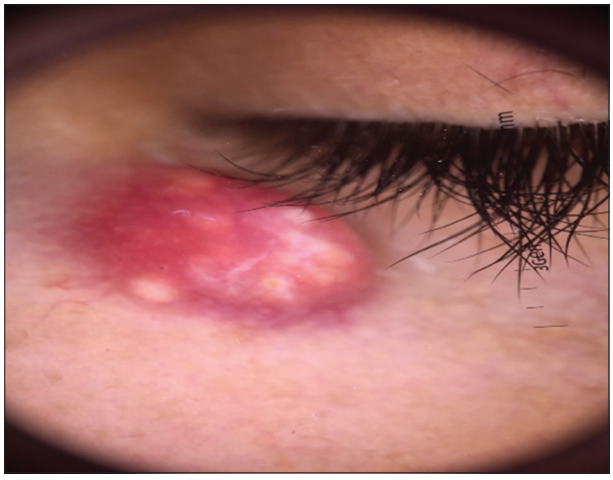

Figure 2: Yellowish lobules on an erythematous background, surrounded by crown-like branching vessels.

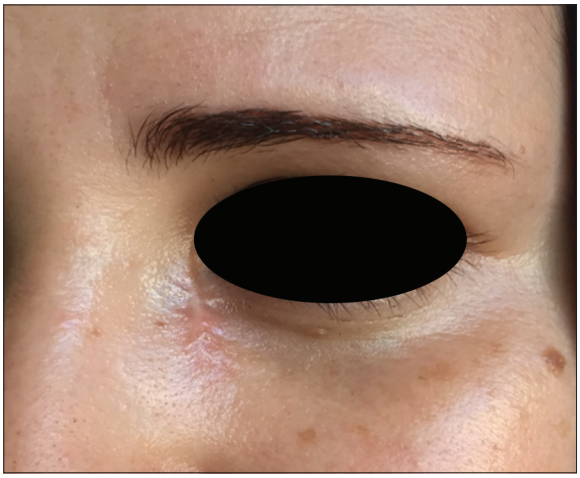

Figure 5: After a follow-up of 10 months.

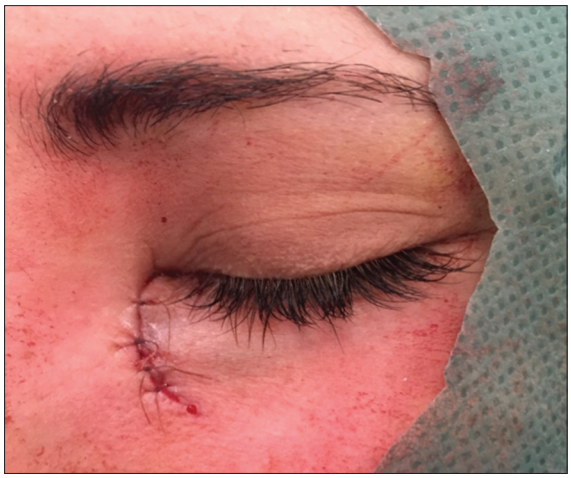

Figure 3: Image after resection of the tumor.

congenital forms have been reported. It affects women particularly with a sex ratio of 1.5 [1]. No identified risk factor for the occurrence of pilomatricoma, including pregnancy. The typical clinical aspect of the pilomatricoma is an irregular round or oval asymptomatic subcutaneous nodule of hard or firm consistency. The skin facing the lesion is often bluish. The tumor adheres to the superficial plane, while it is relatively mobile to the deep plane. The most common locations are the head, neck, and upper extremities. There are different clinical forms, perforating, ulcerated, anetodermic with an erythematous skin facing the lesion or pigmented [2].

Dermoscopy help to make the diagnosis, dermoscopic findings of pilomatricoma reported in the literature are yellowish-white structures together with streaks, linear irregular vessels and hairpin like vessels [3,4]. However Confirmation of diagnosis is histological.

Histopathologic examination reveals the tumor to be grossly well circumscribed and firm to gritty in consistency. Microscopic examination shows numerous islands of epithelial cells with characteristic arrangement of basophilic cells in the periphery and shadow cells in the center. As the tumor matures the number of basophilic cells loses their nuclei and becomes shadow cells. Calcification is seen in 75% of the cases. Sheets of intensely eosinophilic keratinous material is seen within necrotic areas, and this may induce a foreign body giant cell reaction [5]. The histopathologic findings of the case described in this reported are similar.

The reference treatment of the pilomatricoma is complete surgical excision, to avoid the risk of recurrence. The prognosis of the pilomatricoma is good [6].

CONCLUSION

Because of the low incidence and variable clinical presentation, pilomatricoma is a tumor not commonly suspected preoperatively. This presentation may help clinicians to better diagnose this entity and decrease the rate of misdiagnosis. Especially in pregnant women.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Case Report

Eruptive syringomas - a diagnostic challenge: Resistant to oral isotretinoin

Shashank Bhargava

R. D. Gardi Medical College, Ujjain, India

Corresponding author: Dr. Shashank Bhargava, E-mail: shashank2811@gmial.com

ABSTRACT

A syringoma is an appendageal neoplasm which is benign and commonly affects adolescent females. A 23-year-old female presented with multiple asymptomatic, skin-colored lesions of 4 months duration which were progressive in nature. Lesions started from face which later spread to neck and chest. Cutaneous examination revealed multiple skin-colored papules over the face (infra-orbital and above the upper lip) neck and chest with few discrete papules over both the upper limbs and abdomen. Histopathological examination revealed normal epidermis with benign adnexal neoplasm composed of small-island and duct-like structure embedded in collagen in the upper dermis. Small ducts were lined with a double row of flattened epithelial cells which form a comma-like projection (tails) and gave them the appearance of tadpole. Patient was started on oral isotretinoin 20mg for 4 months but she did not show any improvement. Finally, she underwent ablation using CO_2 laser.

Key words: Eruptive; Syringoma; Isotretinoin; CO_2 laser

INTRODUCTION

The word syringoma is derived from Greek language syrinx meaning a tube. A syringoma is an appendageal neoplasm which is benign and commonly affects adolescent females. Clinically, they appear as multiple small papules which are skin colored or slightly brown in color. They are symmetrically distributed and usually involve periorbital area and neck. The other sites like axillae, abdomen and extremities are also involved. Four major variants as proposed by Friedman and Butler [1] are localized, familial, generalized including eruptive and multiple and associated with Down syndrome [2-4].

CASE REPORT

A 23-year-old female presented with multiple asymptomatic, skin-colored lesions of 4 months duration which were progressive in nature. Lesions started from face which later spread to neck and chest up to the suprasternal area. There was no similar history in any of the family members. No significant medical or surgical history was present. She refused any use of medication prior to development of lesion. Cutaneous examination revealed multiple skin-colored papules over the face (infra-orbital and above the upper lip) neck and chest bilaterally (Figs. 1 and 2) of varying size from 1 to 4 mm. There were few discrete papules over both the upper limbs and abdomen. Palms and soles, mucous membrane, nails and scalp were spared. They had smooth surface and were non-indurated. Systemic examination was insignificant. Biopsy sample was taken from one of the papules over the chest keeping syringoma, verruca plana, acrokeratosis verruciformis of Hopf and sebaceous hyperplasia as clinical differentials. Histopathological examination revealed normal epidermis with benign adnexal neoplasm composed of small-island and duct-like structure embedded in collagen in the upper dermis. The tumour cells were monomorphic and had round-to-vesicular nuclei with eosinophilic cytoplasm. Small ducts were lined with a double row of flattened epithelial cells which form a comma-like projection (tails) and gave them the appearance of tadpole were

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seen (Fig. 3). Findings were consistent with the clinical diagnosis of syringoma. Patient was started on oral isotretinoin 20mg for 4 months but she did not show any improvement. Finally, she underwent excision using CO_2 laser.

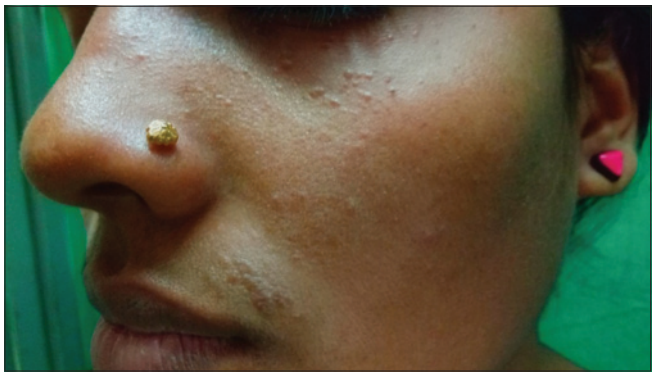

Figure 1: Multiple skin colored papules over the lower eyelid and above the upper lip.

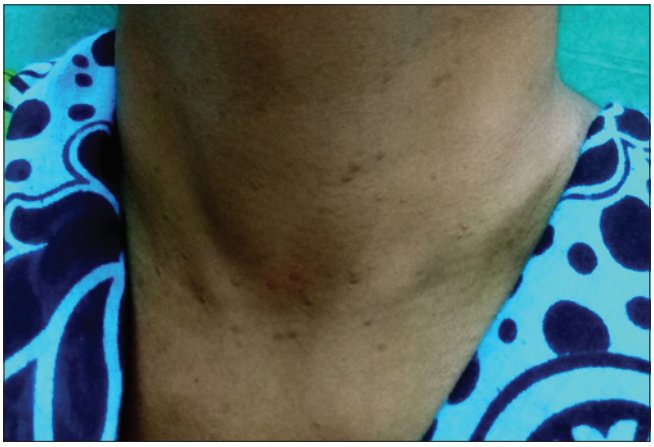

Figure 2: Multiple hyperpigmented papules over the anterior part of neck extending till the supra-sternal area.

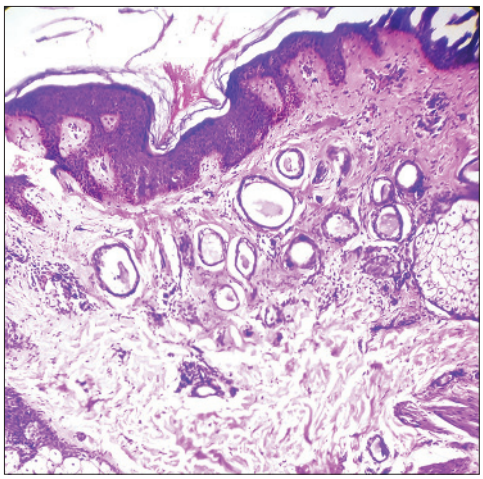

Figure 3: Histopathology shows normal epidermis with benign adnexal neoplasm composed of small-island and duct-like structure embedded in collagen in the upper dermis. Small ducts are lined with a double row of flattened epithelial cells which form a comma-like projection (tails), giving appearance of 'tadpole'. (H & E stain, 10x).

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Syringoma is a common benigh adnexal tumor composed of small solid and ductal elements embedded in a stroma and by convention located in the upper to mid dermis. They are commonly observed in adolescent females as multiple skin to brown colored lesions on the lower eyelids and cheeks. A rare type of syringoma is the eruptive or disseminated one. It was first described in 1887 by Jacquet and Darier. Eruptive syringomas are characteristically seen as rapid development of hundreds of small (1–5 mm), ill to well defined, smooth surfaced, skin-colored, pink, yellowish, or brownish papules typically involving the face, neck, trunk, genitalia and extremities. They have both follicular and non-follicular involvement. The pathogenesis of eruptive syringoma is still unknown. Garrido-Ruiz et al support that eruptive syringomas are due to hyperplastic response of the eccrine duct to an inflammatory reaction like contact dermatitis, shaving, laser hair removal, alopecia areata, radiation dermatitis etc. [5]. Chandler and Bosenberg presented evidence that eruptive syringomas are a resultant of autoimmune damage to acrosyringium and proposed the term autoimmune acrosyringitis with ductal cysts [6]. Recently, a systematic review by Williams and Shinkai, it was proposed that the strongest association of syringomas was with Down's syndrome (22.2%), diabetes mellitus (2.1%), Ehlers–Danlos syndrome, Marfan's syndrome and hyperthyroidism. Cases of syringomas in association with milia cysts and atrophoderma vermiculata are referred to as the Nicolau–Balus syndrome [7]. Eruptive syringomas often create significant cosmetic concern for patients. The treatment options include excision, dermabrasion, cryotherapy, chemical peels especially trichloroacetic acid, topical atropine, lasers like carbon dioxide laser and pulsed dye laser. All the modalities are associated with post-treatment adverse events such as scarring and dyspigmentation [8]. Oral isotretinoin was reported as a successful treatment in two cases with cumulative doses of 9 and 11 g isotretinoin over a 5–6-month period with significant improvement in reduction of number and size of syringomas [9]. There have been few reports with no improvement with Isotretinoin [10].

CONCLUSION

Eruptive syringomas are very rare and require early diagnosis with prompt treatment as they are of cosmetic concern for patients to face the society.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Lichen planus occurring on radiotherapy site: a case report

Imene Ben Lagha, Sana Mokni, Amina Aounallah, Marwa Guerfala, Wafa Saidi, Lobna Boussofara, Colandane Belajouza, Mohamed Denguezli, Rafiaa Nouira

Dermatology department, Farhat Hached University Hospital of Sousse, Tunisia

Corresponding author: Dr. Imene Ben Lagha, E-mail: imenebenlagha@gmail.com

ABSTRACT

Lichen planus (LP) is an inflammatory skin condition characterized by the presence of pruritic, polygonal, purple flat-topped papules and plaques typically symmetrically distributed. The occurrence of these lesions could be attributed to the isomorphic response of koebner occuring regularly in LP. A 38-year-old woman developed pruritic purplish papules spread on a brown lichenoid patch over the left chest area 3 months after radiation therapy for an invasive carcinoma of the left breast. These lesions were confined to the radiation therapy site. Almost any type of irritant can provoke the isomorphic response including traumatisms, friction, infection and ultraviolet light. Only few cases of LP confined to radiation site have been described so far.

Key words: Lichen planus; Radiation therapy; Koebner phenomenon

INTRODUCTION

Lichen planus (LP) is an inflammatory skin condition characterized by the presence of pruritic, polygonal, purple flat-topped papules and plaques typically symmetrically distributed [1]. The response of Koebner is a common phenomenon of LP in areas prone to trauma or irritation [2]. This phenomenon occurs in multiple dermatoses including LP. However, only few cases of LP confined to radiation site have been described. Herein, we report a case of a radiation-induced LP.

CASE REPORT

We report the case of a 38-year-old diagnosed with a bifocal invasive ductal carcinoma of the left breast with left axillary lymph nodes damage. The patient underwent a radical left mastectomy with axillary node dissection. External radiation therapy (RT) of the left breast area and supraclavicular nodal area was performed. The dose given was 52,2 Gy in 1.6 Gy dose per session over 5 sessions/week for 6 weeks. Three months after the last session of RT, she presented to our department with multiple pruritic purplish papules spread on a brown lichenoid patch over the left chest area, limited to the radiation site (Fig. 1). The contralateral side, the rest of skin, mucous and nails were free of any skin lesion. The histological findings confirmed the diagnosis of LP (Fig. 2). Further investigations excluded any use of medications or other trigger factor and serology for hepatitis B and C were negative, leading to the diagnosis of radiation-induced LP. The lesions resolved gradually after 3 months of treatment with topical betamethasone.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Lichen planus (LP) is an inflammatory dermatosis touching the skin and mucosae. It affects 0.5 to 1% of the population. Clinically it is characterized by pruritic violaceous polygonal papules with a shiny surface [1].

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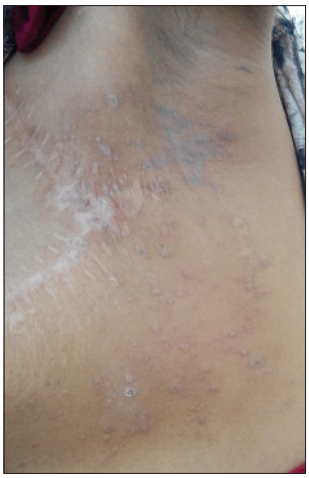

Figure 1: Hyperpigmented papules and plaques on a brown lichenoid patch located on the left chest radiated area.

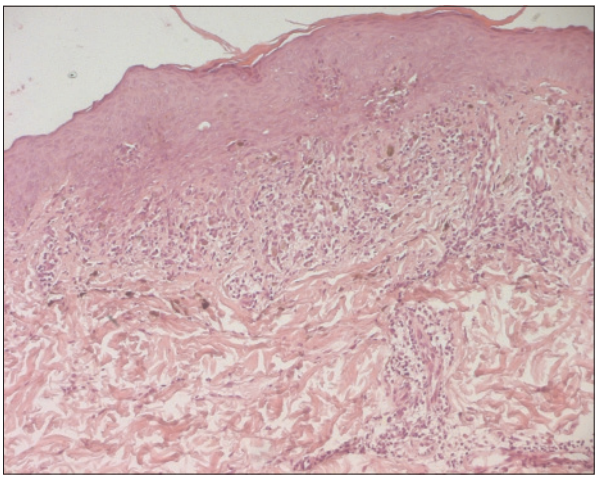

Figure 2: Histopathology: HE x 100: The epidermis showed mild acanthosis with basal vacuolar change. Ocassional civatte bodies are present in the basal layer. The papillary dermis showed a band like infiltrate of lymphocytes with exocytosis. There is prominent melanin incontinence.

Only a few cases of localized or generalized cutaneous LP occurring or re-appearing under radiation therapy have been reported [2-7]. Six cases were described to be confined to radiation field. While in other two cases the lesions were spread over the entire body. It has been suggested that an autoimmune process in which the damaged keratinocytes promote the elaboration of cytokines and therefore the activation of lymphocytes, causing the disease [3]. Other authors attributed the occurrence of lesson an isomorphic or Koebner response due to radiation injury [2,3]. The isomorphic response of Koebner occurs regularly in LP. Almost any type of irritation can provoke the isomorphic response including traumatisms, friction, infection and ultraviolet light. Koebnerization generally occurs within weeks of the trauma [6]. Shurman D and al. proposed the term "isoradiotopic response" to characterizethe phenomenon of secondary dermatoses occurring on radiationsites and to distinguish it from Koebner phenomenon. In fact, they noted two different points between the two phenomena: the variable time interval before eruption ranging from a few weeks to many years and the fact that other dermatoses not known to be involved in Koebner's phenomenon have been reported to appear after radiation (comedonal acne, folliculitis, erythema multiforme, scleroderma) [2].

In most of the cases reported in the literature, there was no history of LPand the lesions appeared for the first time after RT. The total given dose of radiation ranged from 18 Gy 7 to 60Gy 5 with an average of 46Gy. In majority of the cases, the lesions appeared within 1 to 3 months after treatment [2,4,5,7]. In one case of generalized generalized lichen ruber planus, the lesions appeared during the RT. In another case of lichen planopilaris after brain irradiation, the delay was about 10 years [6].

In our case, the radiotherapy induced the appearance of the LP lesions with a 3-month latency period from the moment radiotherapy was completed to the appearance of LP. We suggest the external radiation therapy to be considered as a cause of koebnerization in our patient. Reporting more similar cases could be helpful to determine if there are factors associated with an increased risk of developing LP after RT, such as the total given dose, treatment period and modalities.

CONCLUSION

Only a few cases of lichen planus provoked by radiotherapy have been reported. We present one more case of LP strictly restricted to radiation site therapy.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Nail lichen planus: a patient with atypical presentation

Ahu Yorulmaz, Pelin Demirel Bulut, Basak Yalcin

Ankara Numune Research and Education Hospital, Department of Dermatology, Ankara, Turkey

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

ABSTRACT

Lichen planus is a common chronic inflammatory dermatosis characterized by small, violaceous, flat-topped polygonal papules mostly seen on the flexural wrists and ankles. Several variants of lichen planus have been described based on either morphological appearance, configuration of the lesions or site of the involvement. Moreover, lichen planus is a distinctive dermatosis, in which mucosal or nail involvement may develop in the absence of cutaneous involvement. It has been estimated that nails are affected up to 10% of all patients with lichen planus. The most specific and unique nail finding of lichen planus is the pterygium formation. Pterygium unguis also known as dorsal pterygium refers to a V-shaped extension of the proximal nail fold over the nail plate, which eventually produces permanent onychatrophy. Here, we describe a patient with pterygium unguis, who also manifests atypical mucosal and cutaneous lesions of lichen planus.

Key words: Lichen planus; Nail; Pterygium; Onychatrophy; Oral

INTRODUCTION

Lichen planus is a common disease affecting up to 1% of the population. Lichen planus is a chronic inflammatory dermatosis with characteristic clinical and histopathological features. Classic lichen planus typically characterized by small, violaceous, flat-topped polygonal papules mostly seen on the flexural wrists and ankles. A unique feature of lichen planus is superimposed, lacy, reticular pattern of crisscrossed whitish lines, termed "Wickham's striae", of which visualization is accentuated by application of a drop of immersion oil. Other than classic lichen planus, several variants of lichen planus, which differ in morphology and localization have been described. Moreover, lichen planus is a particular disease, in which mucosal or nail involvement may develop in the absence of cutaneous lesions. Although several nail changes are observed in lichen planus, one of the most distinguishing nail finding is the formation of dorsal pterygium [1-3]. Here, we report a case with dorsal pterygium, who also manifests atypical mucosal and cutaneous lesions.

CASE REPORT

A 62-year-old man came to our outpatient clinic with a several-month history of purplish red lesions over his trunk. While his family history was unremarkable, past medical history revealed diagnoses of bronchiectasis and atherosclerosis. He had gone through bypass surgery seven years earlier. The main complaint of the patient was two purplish red lesions, one of which was on the proximal end and the other was on the distal end of the thoracotomy incision scar. The patient also had dystrophic nails for twenty years. Medication history revealed he had been receiving metoprolol 50 mg, aspirin 100 mg and clopidogrel 75 mg daily for the previous seven years. Upon dermatological examination, we observed two violaceous patches located both ends of the thoracotomy incision scar. The one on the proximal end had a darker peripheral rim and the one on the distal end had a scale, which was centrally adherent (Fig. 1). Dermatological examination also revealed adhesion between the epidermis of the dorsal nail fold and the nail bed on the right third, fourth and fifth, also left first, third and fourth fingers. Complete

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anonychia of the left fourth fingernail was also detected (Figs 2-4). Oral mucosal examination demonstrated a slightly elevated whitish annular lesion (Fig. 5). Based on the clinical findings we made a diagnosis of lichen planus with pterygium formation. We suggested the patient to perform skin and oral mucosal lesion biopsy. However, the patient did not want any invasive procedure. Laboratory studies including complete blood count and differential, erythrocyte sedimentation rate and a complete serum chemistry profile revealed no abnormalities. Serologic tests for hepatitis B, C, and human immunodeficiency virus were negative with positive results for anti-HBs antibody. We prescribed topical corticosteroids for skin lesions and suggested intralesional injections of corticosteroids for nail involvement. On the other hand, the patient only accepted topical treatment and lost follow-up.

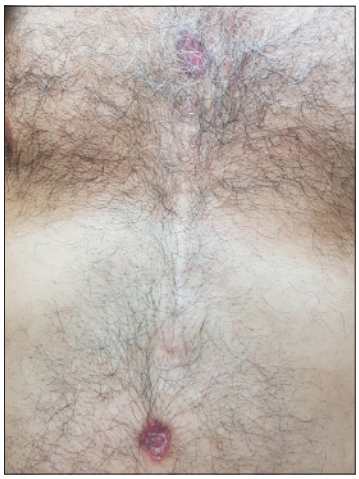

Figure 1: Violaceous patches located both ends of the thoracotomy incision scar. The one on the proximal end had a darker peripheral border and the one on the distal end had a scale, which was centrally adherent.

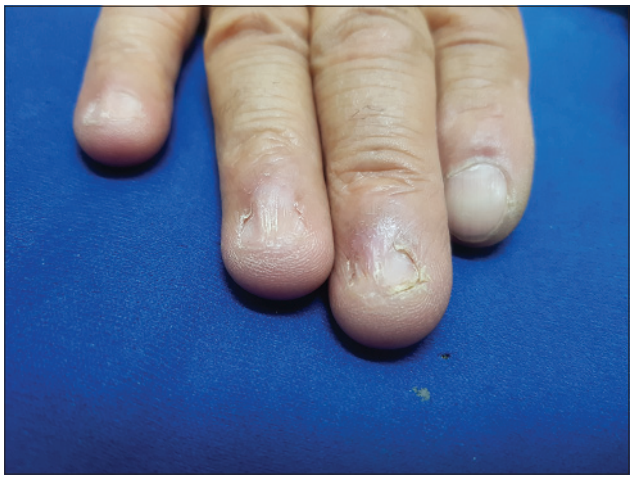

Figure 2: V-shaped extension of the proximal nail fold epidermis over the nail plate causing partial destruction of the right third, fourth and fifth fingernails.

DISCUSSION

It has been estimated that nails are affected up to 10% of all patients with lichen planus. Lichen planus has been associated with several nail findings, including lateral

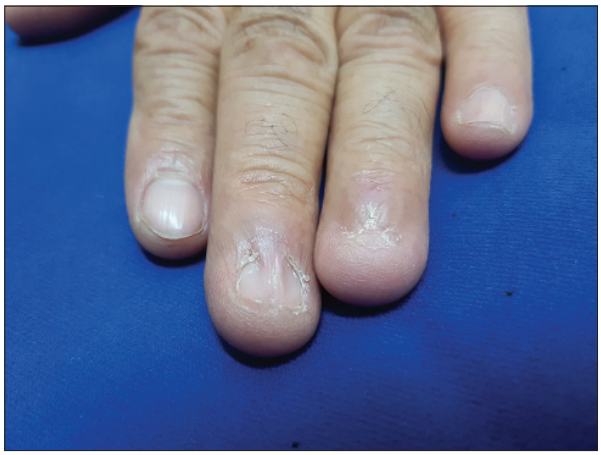

Figure 3: Adhesion between the epidermis of the dorsal nail fold and the nail bed on the left third digit and onychatrophy of the left fourth fingernail.

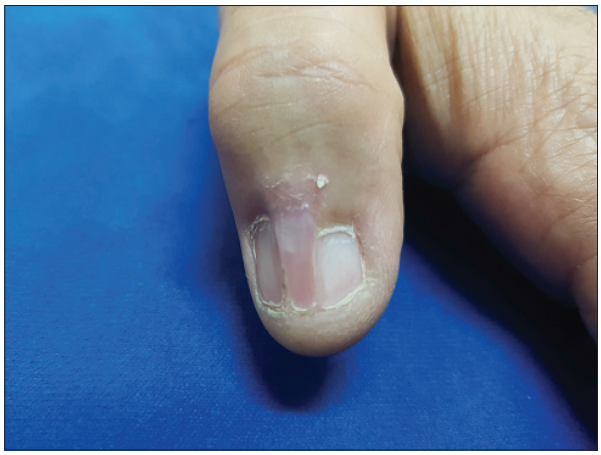

Figure 4: Extension of the proximal nail fold over the nail plate creating split portions on the nail plate on the left thumb.

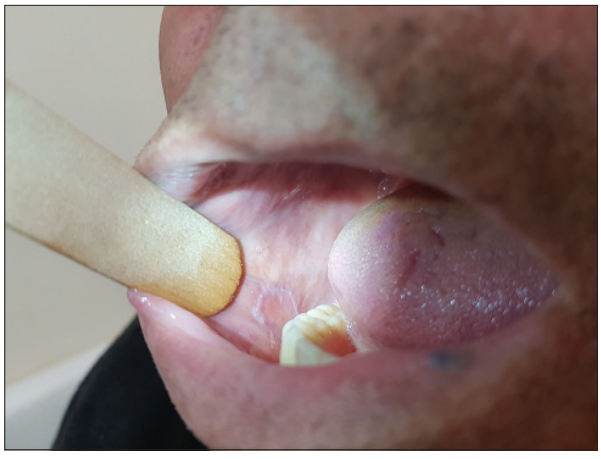

Figure 5: An annular lesion with a slightly elevated whitish rim located on the right buccal mucosa.

thinning, longitudinal ridging and striations, fissuring, distal splitting, subungual hyperkeratosis, onycholysis, trachyonychia and erythematous patches of the lunula. Pterygium unguis is the most specific and unique nail finding of lichen planus. It has been defined as wing-shaped scar formation, which is a result of severe nail matrix damage. Lichen planus is a chronic inflammatory disease. If the entire lenght of the nail matrix is involved in the inflammatory process, permanent destruction of the nail matrix eventually gives rise to pterygium formation. This specific sign is typically characterized by a V-shaped extension of the proximal nail fold fusing with the nail bed. Subsequently gradual destruction of the nail causes onychatrophy [2,4-8].

In lichen planus, fingernails are affected more commonly than toenails. The number of involved nails differs in every single patient. Although it is known that in most of the patients nail lesions develop simultaneously in all involved digits, it is quite interesting that the severity of the disease may vary in degree from nail to nail and within the same nail. In some patients, though initially only few digits are affected, subsequent involvement of other digits is frequently observed. Most of the nail findings of lichen planus are not exclusively seen in lichen planus. Ridging and splitting, for instance, quite common in the elderly without any dermatological disease [5]. However, pterygium is the most specific finding for nail lichen planus. Although it can be seen in other conditions, including trauma, Raynaud phenomenon, peripheral vascular disease, radiotherapy and immunobullous diseases, pterygium has been accepted as the almost pathognomonic clinical sign for nail lichen planus [8]. When differentiating nail lichen planus from other diseases causing pterygium, simultaneous involvement of several digits is the key point for the diagnosis, since in other diseases contemporaneous involvement is unexpected [5,8].

Our patient represents typical pterygium formation. Although nail biopsy remains the gold standard for the diagnosis of nail lichen planus, simultaneous involvement of several digits with V-shaped extension of the proximal nail fold over the nail bed and anonychia spontaneously directed us to the diagnosis of pterygium. We have presented our patient not only because pterygium is the most specific and almost pathognomonic nail finding of lichen planus, but also mucosal and cutaneous features of our patient were atypical. Configuration of the mucosal lesion, which was annular with slightly elevated whitish interlacing keratotic lines and localization of the violaceous patches, which were both ends of the thoracotomy incision scar were exceptionally interesting. The patient told that nail lesions had begun twenty years earlier, cutaneous lesions began several months ago and he did not know when the oral mucosal lesion had begun. It is known that pterygium does not necessarily correlate with the duration of the disease [5]. Thus, we think that in our patient lichen planus had begun twenty years ago but tended to be chronic, with fluctuations in signs and symptoms over time. Moreover, in our opinion, medications of the patient, which were metoprolol, acetylsalicylic acid and clopidogrel might have played a role in aggravating the condition, since these drugs are potential triggers for lichen planus [1,9,10]. On the other hand, the main limitation of our case report is that, we could not prove the diagnosis of lichen planus with histopathology. We suggest further case reports to be presented to enlighten atypical presentations of lichen planus with histopathological findings.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

A case of vitiligo with hypertrophic lichen planus – an autoimmune association

Mohanraj Madhumitha, Srinivasan Sundaramoorthy

Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India

Corresponding author: Prof. Srinivasan Sundaramoorthy, E-mail: hamsrini@yahoo.co.in

ABSTRACT

Vitiligo is a common autoimmune dermatological disorder characterized by depigmentation of the skin and mucous membranes. It has been associated with a variety of autoimmune disorders. A 54 years old male patient presented with depigmented patches over the legs for 30 years and itchy hyperpigmented plaques over the forehead for past 2 months. Patient had history of recurrent oral ulcers and history of psychological stress. Cutaneous examination revealed two well defined depigmented patches over the shin of both legs, and over lower lip. There were multiple hyperpigmented violaceous plaques over the forehead, right side cheek and scalp. White streaks were present over the buccal mucosa. Biopsy report for the hyperpigmented plaques was consistent with hypertrophic lichen planus and depigmented patch was consistent with vitiligo. Though the aetiology of vitiligo and lichen planus is not known with certainty, its coexistence has been scarcely reported in the literature suggesting a common autoimmune aetiology.

Key words: Vitiligo; Lichen planus; Depigmentation; Autoimmune

INTRODUCTION

Vitiligo is an acquired pigmentary disorder of the skin of unknown aetiology. Its prevalence ranges from less than 0.1 to more than 8% in various parts of the world [1]. It is characterised by presence of depigmented patches occurring over the skin and mucosa. Various theories like autoimmune hypothesis, neurogenic hypothesis, and self destruct theory of Lerner have been proposed in its aetiology [2]. Lichen planus is a chronic inflammatory condition of the skin characterised by plane topped purplish polygonal pruritic papules and plaques. About 0.5 to 1% population is affected by lichen planus among which the hypertrophic lichen planus constitutes about 4.7% of the cases [3]. The commonly affected age group affected is 20 to 49 years [4]. Although these two entities are encountered commonly in practice, their coexistence in the same patient is relatively rare, and also suggests a common autoimmune aetiology.

CASE REPORT

A 54 years old male patient presented with depigmented patches over the legs for 30 years and itchy hyperpigmented plaques over the forehead for past 2 months. Patient had history of recurrent oral ulcers and history of psychological stress. Cutaneous examination revealed two well defined depigmented patches over the shin of both legs, and erythematous patches over lower lips (Figs. 1a and 1b). There were multiple hyperpigmented violaceous plaques over the forehead, right side cheek and over the scalp (Figs. 1c – 1e). White streaks were present over the buccal mucosa (Fig. 1f).

Biopsy from the hyperpigmented plaque showed pseudoepitheliomatous hyperplasia, follicular plugging, civatte bodies, dense mononuclear cell infiltrate in the papillary dermis. Pigment incontinence is also seen (Fig. 1g). Impression was hypertrophic lichen planus. Depigmented patch

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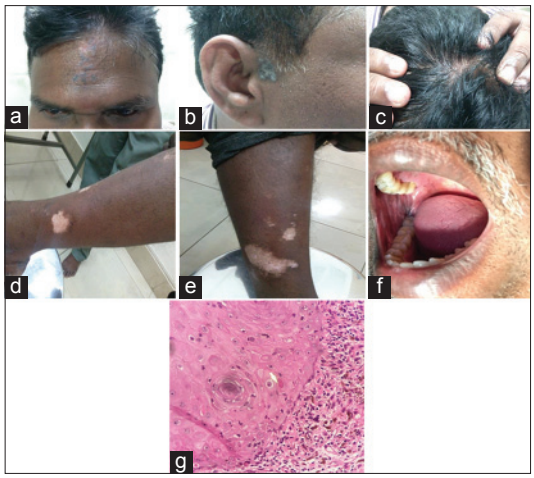

Fig. 1(a): Multiple depigmented patches over the left leg. (b) Multiple depigmented patches with few areas of perifollicular repigmentation over the right leg. (c) Multiple hyperpigmented violaceous plaques over the forehead (d) Hyperpigmented hyperkeratotic plaque over right pre auricular area (e) Hyperpigmented hyperkeratotic plaque over the scalp (f) Whitish streaks over the right side buccal mucosa (g) Histopathology picture showing pseudoepitheliomatous hyperplasia, civatte body and pigment incontinence

showed absence of melanocytes and was consistent with vitiligo. Dental opinion was obtained for the oral lesions and a diagnosis of oral erosive lichen planus was made. Patient was prescribed with topical tacrolimus 0.1% and clobetasol propionate for lichen planus and vitiligo lesions respectively. For oral lesions, triamcinolone acetonide (0.1%) for topical application 3 to 4 times a day for 2 weeks half an hour after food was prescribed. Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

DISCUSSION

Vitiligo is a common chronic autoimmune disorder affecting the skin and mucous membranes. The depigmentation is due to marked absence of melanocytes and melanin in the epidermis. They can begin at any age but 50% cases develop before age of 20 years. Its exact aetiology is not known but autoimmunity is one of the proposed theories. It has been associated with other autoimmune disorders like diabetes mellitus, thyroid disorder, alopecia areata, pernicious anaemia, myasthenia gravis, addison's disease and morphoea [2]. In addition, there is presence of melanocyte-specific antibodies detected in vitiligo patients and a higher frequency of organ specific antibodies compared with the general public is observed in such patients [5].

Lichen planus is a chronic inflammatory disorder involving cutaneous and mucosal surfaces, characterized by a T-cell-mediated immune response against epithelial cells, with persistent accumulation of T lymphocytes and epithelial cell damage [6]. The mechanism involved is largely unknown but there is a paucity of immune complexes present in the lesions of lichen planus [7]. There are several variants of lichen planus among which the classical type is the most common followed by the hypertrophic lichen planus and actinic lichen planus. About 30 to 70% of the patients have mucosal involvement [8]. Histologically hypertrophic lichen planus differs from other types by presence of pseudoepitheliomatous hyperplasia of the epidermis and the infiltration being less band like. Direct immunofluorescence shows globular deposits of IgM, and occasionally IgG and IgA, representing apoptotic keratinocytes at the dermoepidermal junction.

Other cases like - actinic lichen planus coexisting with vitiligo; oral lichen planus with vitiligo; becker's nevus with both vitiligo and segmental lichen planus – has been reported in the literature [9,10].

CONCLUSION

Hypertrophic lichen planus and vitiligo are commonly encountered dermatological entities, but their coexistence is scarcely reported in the literatures. Though the aetiology of both vitiligo and lichen planus is not known with certainty, their coexistence suggests a common autoimmune aetiology.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Cutis marmorata telangiectatica congenital: two case reports

Imene Ben Lagha, Soumaya Youssef Zaara, Sarra Harbaoui, Kahena Jaber, Mohamed Raouf Dhaoui, Nejib Doss

Dermatology Department, Military Hospital of Tunis, Tunisia

Corresponding author: Dr. Imene Ben Lagha, E-mail: imenebenlagha@gmail.com

ABSTRACT

Cutis marmorata telangiectatica congenita (CMTC), or Van Lohuizen syndrome, is a rare vascular malformation of the skin of unknown cause. We report here two cases of CMTC. We report 2 cases. Case 1: A 3 year old child had since 4 month old purple reticulated lesions with a peripheral halo of pallor, located on the limbs and the left side of the trunk. The center of the lesions became progressively atrophic and the livedo disappeared after the age of 5. Case 2: A young man of 16 year old had CMTC since he was 14 months. The lesions were located on the left side of the body. At the age of 16, he developed a venous insufficiency of the left lower extremity. It was complicated with a chronic leg ulcer above the lateral malleolus. A detailed examination and a thorough follow-up plan must be set-up in patients presenting with CMTC.

Key words: Congenital vascular malformation; Cutis marmorata telangiectatica congenital; Van Lohuizen syndrome

INTRODUCTION

Cutis marmorata telangiectatica congenita (CMTC), also called Van Lohuizen syndrome, is a rare vascular malformation of the skin of unknown cause. It is defined by the presence, mostly since birth, of localized or generalized fixed skin lesions of reticulated cutaneous vascular network. Other associated anomalies have been described like limb hypertrophy or atrophy and coexistence of ulcerations. The diagnosis is based on clinical findings. We report here two cases of CMTC.

CASE REPORT

Case 1

We report the case of a 3 year old child, born from a second degree consanguineous marriage. There was no particular family history. He was followed up in our department since he was 4 month old for purple reticulated lesions with a peripheral halo of pallor, located on the limbs and the left side of the trunk. Otherwise, no extra cutaneous abnormalities were observed. Anthropometric measurements were within the normal average and there was no asymmetry of limbs growth. The center of the lesions became progressively atrophic and the livedo disappeared after the age of 5 (Fig. 1).

Case 2

A young man of 16 year old had been followed up in our department since he was 14 months for CMTC. He was born of a non-consanguineous marriage. Birth and development history were normal. There was no history of trauma or infection or similar cases in family. The patient presented since birth fixed deep purple reticulated skin lesions with underlying atrophic changes. These lesions were located on the left side of the body: on the scalp, the forehead, the trunk and the left limbs, with an extension to the right side of the abdomen. Palms, soles and mucosa were spared. At the age of 16, the patient developed a venous insufficiency

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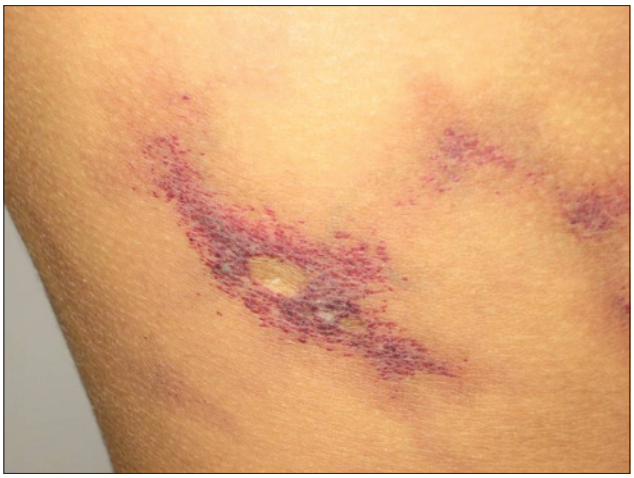

Figure 1: Red-purple vascular network with atrophic center.

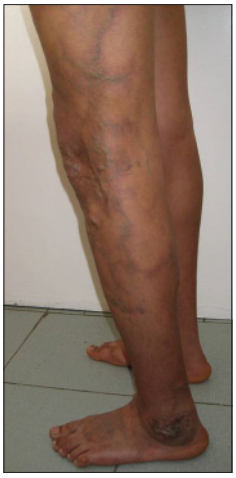

Figure 2: Varicose veins of the left leg with an ulceration above the lateral malleolus.

of the left lower extremity. It was complicated with a chronic leg ulcer above the lateral malleolus (Fig. 2).

DISCUSSION

First described by the Dutch pediatrician Van Lohuizen in 1922, CMTC is a rare congenital vascular malformation. About 300 cases have been described so far [1].

The pathogenesis is not obvious. It is considered as a sporadic disease even though a genetic etiology has been proposed in some cases. Multiple hypothesis have been suggested for the pathogenesis of this condition, such as autosomal dominant transmission with variable expressivity [2], a lethal gene surviving by mosaicism [3], a functional nervous defect [4], or a functional malformation of the terminal blood vessels [5]. A female predominance have been noticed in the literature with a more likely generalized distribution in female [1]. Our cases were both male and with a localized disease since the lesions covered less than 50% of the skin.

Clinical features are typical and the accurate diagnosis of CMTC can be made based upon a careful physical examination. Mostly, the lesions are present at birth, as it was described in our cases. Cutaneous findings in CMTC include a purple reticulate vascular network, similar to physiologic cutis marmorata. However, these lesions are persistent in CMTC and do not disappear with local warming [6]. Other skin changes include phlebectasia, telangiectasia and hyperkeratosis. Atrophy and ulceration may be present at first or appear later [1]. In our first case, atrophy appeared progressively. Our second case developed a leg ulcer at the age of 16. The distribution of lesions may be generalized or localized. They involve especially the legs and the trunk. A demarcation at the midline of the abdomen is very commonly observed [7]. Additional vascular anomalies were frequently reported such as port-wine stains, angiokeratoma and hemangioma [6].

Extracutaneous anomalies have been reported in more than 50% of patients with CMTC [1]. Asymmetric limb hypertrophy or atrophy is the most common anomaly associated with CMTC [4]. Skeletal defects such as hip dysplasia, club foot, syndactyly may be observed. Ocular anomalies may also be associated, particularly glaucoma [3]. Neurological concomitant abnormalities have also been reported. Particularly worthy of mention here is macrocephaly which was oft-times described in CMTC patients. This fact led to the individualization of a CMTC subtype called macrocephaly-cutis marmorata telangiectatica congenital in 1997 [8].

CMTC can be confused with several disorders which present with a reticular vascular network. The most common one is physiological cutis marmorata mentioned earlier. Other differencial diagnoses are Adams Oliver syndrome, klippel Trenaunay syndrome and Bockenheimer's syndrome [1]. Neonatal lupus erythematous can present with lesions similar to CMTC or be revealed with CMTC. Some authors proposed the CMTC to be part of the cutaneous findings in neonatal lupus erythematous [9]. Persisting cutis marmorata in children with Down syndrome, de Lange syndrome, Divry-Van Bogaert syndrome and homocystinuria must also to be ruled out [3].

Capillary malformation can be difficult to distinguish from CMTC. However, the association of underlying atrophy and the fading color with time are observed only in CMTC [6].

Diagnostic criteria for CMTC have been suggested by Kienast and Hoeger in 2009. They proposed that the presence of three major criteria (congenital reticular erythema, Absence of venectasia and unresponsiveness to local warming) and two of five minor criteria (Fading of erythema within two years, telangiectasia, port wine stain, ulceration and atrophy within affected area) is sufficient for diagnosis [10].

The prognosis is usually good with improvement during the first years of life [1]. In our first case, we noted a regression of the reticular pattern within 5 years. However, in the second case, the evolution was marked by the onset of a venous insufficiency and a chronic ulcer of the affected leg. Thus, in case of non-regressive lesions, we suggest that a Doppler ultrasound should be performed every 3 to 4 years in patients with CMTC. Furthermore, patients with facial CMTC lesions should have an ophthalmological examination. Other investigations should consist on skeletal and neurological examination and screening for developmental delay and macrocephaly.

CONCLUSION

Even though CMTC is a benign cutaneous disease with good prognosis, we should be aware of the association of more serious anomalies. Thus, a detailed examination must be performed and a thorough follow-up plan must be set-up.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Case Report

Erythema annulare centrifugum preceding carcinoma larynx

Piotr Brzezinski[1,2], Masaoud Sousak[3], Cesar Bimbi[4]

[1]Institute of Biology and Environmental Protection, Pomeranian Academy, ul. Arciszewskiego 22A, 76-200 Slupsk, Poland, [2]Department of Dermatology, Provincial Specialist Hospital in Slupsk, ul. Mickiewicza 12, 76-270 Ustka, Poland, [3]General Surgery Department, Paluckie Health Center, Znin, Poland, [4]Institute of Dermatology Centro Historico, Dermatology, Porto Alegre, Brazil

Corresponding author: Dr. Piotr Brzezinski, E-mail: brzezoo77@yahoo.com

ABSTRACT

Erythema annulare centrifugum (EAC) is characterized by annular, erythematous plaques with trailing scale. The skin lesions may be indurated or soft and may be static or spread centrifugally. It is considered to be a reactive condition with a wide variety of inciting causes but unclear pathophysiology. We describe a 62-year-old man with EAC. Since no association of EAC with concomitant bacterial or viral infections, we started diagnostics in the direction of systemic disease or cancer. Investigations confirmed carcinoma of larynx. We want to emphasize that EAC can appear many years before the onset of carcinoma. This is the first description of the ECM and carcinoma of the larynx with a long list of co-existing cancers.

Key words: Erythema annulare centrifugum; Erythema; Erythematous plaques; Carcinoma larynx; Carcinoma planoepitheliale

INTRODUCTION

Erythema annulare centrifugum (EAC) initially described in 1881. The term erythema annulare centrifugum first was used 1916 (Darier/Darier-Lipschütz). It includes erythema perstans, erythema gyratum perstans, erythema marginatum perstans, erythema exudativum perstans, erythema microgyratum perstans, erythema figuratum perstans, and erythema simplex gyratum. EAC is characterized by annular, erythematous plaques with trailing scale. The skin lesions may be indurated or soft and may be static or spread centrifugally [1].

It is considered to be a reactive condition with a wide variety of inciting causes but unclear pathophysiology [2].

Although its etiology is not known for certain, it is assumed to be hypersensitivity reaction to malignancies, infections, and drugs. Inciting factors may include viral (Epstein-Barr virus), bacterial (Streptococcal infections, E. coli), or fungal infections (dermatophytes), parasites, arthropod assault, medications (spironolactone, amitryptiline, ampicillin, cimetidine, hydrochlorothiazide, salicylates), malignant conditions or other systemic diseases, and foods. The eruption clears with cessation of the drug or treatment of the associated disease. However, in the majority of cases no underlying cause is identified [3-5].

The prognosis for EAC is excellent, except when associated with an underlying malignancy and other systemic disease. A diagnosis of EAC should be followed by diagnostic workup because it may result in discovery of an underlying disease.

The coexistence of EAC and cancer is used determine: Paraneoplasticerythema Annulare centrifugum eruption (PEACE) [6]. PEACE is speculated to be a result of a cytokine or other tumor-associated factors.

We describe a 62-year-old man affected by EAC who upon further examination was diagnosed carcinoma larynx.

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DOI:10.7241/ourd.20184.23

CASE REPORT

A 62-year-old male patient was admitted to our clinic with erythematous, annular, polycyclic plaques with indurated borders, without desquamation and rarely itching, on the limbs (Fig. 1).

Skin lesions was for more than 2 years. Clinical lesions was suggested EAC.

Skin punch biopsy revealed focal epidermal spongiosis and focal parakeratosis with eosinophils (Fig. 2).

The patient was diagnosed as EAC based on histopathologic and clinical findings.

The patient was excluded fungal infections (PAS stains for exclusion of fungi and wet mount microscopy for mycosis - negative); parasites; medications and started diagnostics in the direction of systemic disease or cancer.

Routine laboratory findings were within the normal ranges, Borrelia serology were negative.

The patient was referred to a specialist in internal medicine.

The patient came to the dermatology clinic only for six months (it was during radiotherapy due to carcinoma larynx). Histopathological diagnosis carcinoma of larynx was a carcinoma planoepitheliale (G2) (Fig. 3).

On the interview with the patient, otolaryngological and videolaryngostroboscopic examinations we diagnosed hypertrophic changes in the whole length of the right vocal fold with the fold mobility preserved.

The skin lesions decreased skin and reduce (but not resolved completely).

Currently you are finished radiotherapy. Skin lesions not occurs (three-month observation).

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

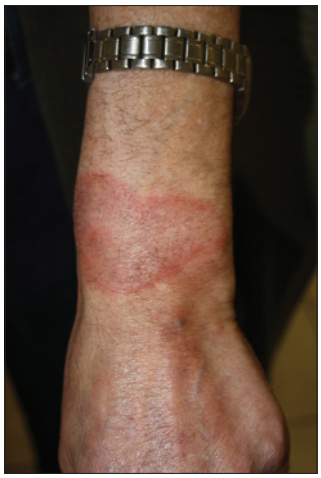

Figure 1: Erythematous, annular, polycyclic plaques with indurated borders on the forearm.

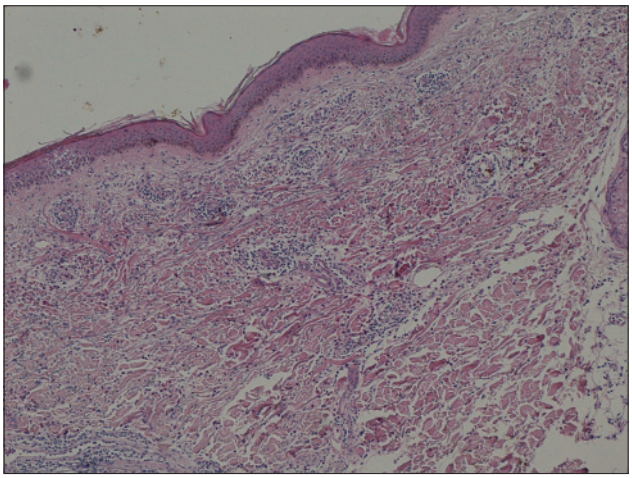

Figure 2: Histopathology: Focal epidermal spongiosis and focal parakeratosis with eosinophils.

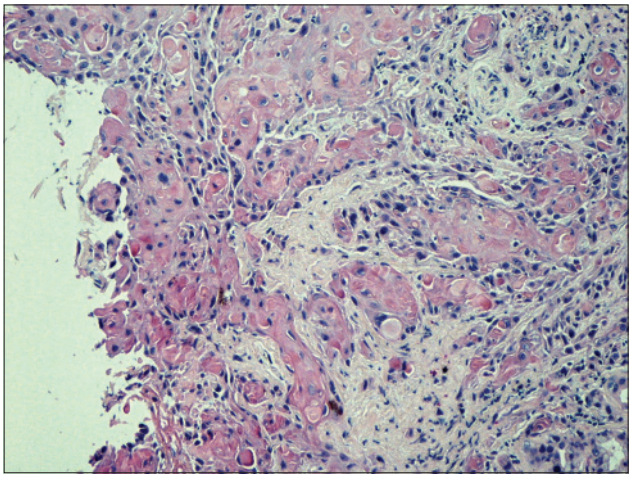

Figure 3: Histopathology: No features of differentiation, a large cellular atypia, numerous mitotic figures and invasive tissue infiltration.

DISCUSSION

There are two types of EAC (by Ackerman): a deep type with indurated borders, without desquamation and rarely itching. A superficial type with desquamation following the advancing border and itching is more

frequent. It is not clear whether these represent two separate diseases or a continuous range [4].

A review of medical literature reveals that malignancies related to EAC are acute myelocytic leukemia, Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, malignant histiocytosis [5] and internal organs cancers: nasopharyngeal carcinoma, peritoneal carcinomatosis, primary bronchial carcinoid, prostate carcinoma, mucinous ovarian carcinoma, breast cancer, metastatic gastric carcinoma [1,2].

One study of 66 cases identified cutaneous fungal infection as the most important etiologic factor (72%), while other causes included benign internal neoplasm (13%), skin diseases (18%) and internal diseases (21%) [6]. A study involving 73 EAC patients revealed neoplasia in 7% of deep type EAC cases [7].

Laryngeal cancer may also be called cancer of the larynx or laryngeal carcinoma.

Incidence is five in 100,000 (12,500 new cases per year) in the USA. The American Cancer Society estimated that 9,510 men and women (7,700 men and 1,810 women) would be diagnosed with and 3,740 men and women would die of laryngeal cancer in 2006.

Each year, about 2,200 people in the U.K. are diagnosed with laryngeal cancer [8].

Most laryngeal cancers are squamous cell carcinomas, reflecting their origin from the squamous cells which form the majority of the laryngeal epithelium. Cancer can develop in any part of the larynx, but the cure rate is affected by the location of the tumour.

Smoking is the most important risk factor for laryngeal cancer. Heavy chronic consumption of alcohol, particularly alcoholic spirits, is also significant. Some other quoted risk factors are low socioeconomic status, male sex, and age greater than 55 years.

Our patient was a hoarseness and persistent cough (he smoked cigarettes).

Ayca Alan Atalay at al described 52-year-old man affected by EAC, who upon further examination was diagnosed with squamous cell carcinoma of the lung (SCCL) [9]. The plaques had been present for more than 3 months.

Authors from Bulgaria describe recurrence of breast cancer after 10 years in a 73-year-old Caucasian female patient presented for three annular erythematous lesions on the left leg and buttock, persisting for two months [10].

CONCLUSION

Long-term, recurrent, non-specific cutaneous lesions are the most frequent cutaneous manifestation in patients with cancer. Our patient was a smoker, had a hoarseness and persistent cough and so EAC.

Although the EAC recurred since two years, carcinoma of the larynx was diagnosed in a "good" period (non-metastatic).

We want to emphasize that EAC can appear many years before the onset of carcinoma.

This is the first description of the ECM and carcinoma of the larynx with a long list of co-existing cancers.

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Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Review Article

Perspectives in psoriasis, psoriatic arthritis, non-alcoholic fatty liver disease and atherosclerosis in psoriasis

Iqbal Bukhari[1], Mona Ismail[2], Manal Hasan[2], Abdulaziz Alzahrani[3]

[1]Dermatology Department, Imam Abdulrahman Bin Faisal University and King Fahd Hospital of the University, Dammam, Saudi Arabia, [2]Internal Medicine department, Imam Abdulrahman Bin Faisal University and King Fahd Hospital of the University, Dammam, Saudi Arabia, [3]Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany

Corresponding author: Prof. Iqbal Bukhari, E-mail: ibukhari@iau.edu.sa

ABSTRACT

Psoriasis is a disease of chronic systemic inflammation that involves not only the skin, but also internal organs. The frequency of Non-alcoholic fatty liver disease was found to be significantly greater in psoriasis patients with increased risk of atherosclerosis and cardiovascular disease. A large number of immunes is found in Psoriatic skin and this immune produce chemokine's, cytokine and inflammatory molecules. The exact role of genetics in psoriasis is still unclear and an overlap between some psoriasis loci and those identified in other autoimmune or inflammatory diseases has been reported.

Key words: Psoriasis; Genetics; Arthritis; Fatty liver; Atherosclerosis; Obesity

INTRODUCTION

Psoriasis affects 2–3% of the European population. It is common found less in an individual of Asian descent (0.1% or less) and is exceedingly rare in Africa [1]. Large number of immunes is found in Psoriatic skin and this immune produce chemokine's, cytokine and inflammatory molecules. The genetics basis of psoriasis has been unclear yet, whether they reflect defects of the immune system or of the skin. It has been reveal by Genome-Wide association that genetic susceptibility factors which play a role in the formation of immune cell found in psoriasis or in the proliferation epidermal cell and skin barrier formation. Furthermore, as many as 10 - 30% of patient with psoriasis develop an inflammatory arthritis which causes the destruction of joints if it is not properly treated in aggressive manner. It is now universally acknowledged that psoriasis and Psoriatic arthritis are consistent with a multifactorial pattern of inheritance.

Pre-Genome Wide Association Studies in Psoriasis Genetics

The earliest genetic studies revealed association with human leukocyte antigen (HLA) class 1 alleles, and the strongest association was with the HLA-C allele. Approximately 10 genome-wide linkage scans, primarily with polymorphic microsatellites, led to the identification of over 20 possible linked regions. Some of which are: PSORS1 on 6p21.3 [2], PSORS2 on 17q [3], PSORS3 on 4q [4], PSORS4 on 1cenq21 [5], PSORS5 on 3q21 [6], PSORS6 on 19p [7], PSORS7 on 1p [8], and PSORS9 on 4q31 [9].

Psoriasis genetic associations

Inflammatory genes

GWAS studies have been performed primarily in populations of European and Asian till date, and the most highly significant associations that are found in both population are with SNPs from the MHC class I region that encodes the HLA molecules HLAA, HLAB and HLAC. The psoriasis-associated with SNPs are nearly to the gene encoding HLAC [10-12] and this have form several risk Gene that are HLAC [10-12], IL12B [13], IL23A, IL23R, TNFAIP3, TNIP1 [11], IL2\IL21 [10], SLC12A8 [14], ZNF313 [5], HBD [15] and LCE [12]. Additional two independent MHC locihave also confer the risk of psoriasis in both European and Chinese populations. One of the Mhc

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loci is found within the chromosome 6 open reading frame 10 (c6orf10),and the second locus is 30kb in size centromeric of HLAB and 16 kb telomeric of the MHC class I polypeptide related sequence A gene, MICA [16].

Barrier development genes

There is a new evidence that skin barrier functions may also plays a role in susceptibility to develop psoriasis. The Epidermal Differentiation Complex lies on human chromosome 1q21, spans 2 Mb and encodes at least 45 genes that play a role in the generation or maintenance of the epidermis. Many genes of the Epidermal Differentiation Complex are upregulated in psoriatic lesions suggesting the underlying alterations in coordinate regulation of genes of this complex [17,18].

Psoriasis risk factors shared by other autoimmune or inflammatory diseases

To date only one genome-wide scan has been completed in psoriatic arthritis (PsA), and this study localized a candidate region on chromosome 16q. Association of psoriasis and PsA with alleles in the MHC region has been recognized for over three decades, and presently there are plethora of association studies for both of these disorders with HLA alleles. Overlap between some psoriasis loci and those identified in other autoimmune or inflammatory diseases has been reported. The same variant of IL23R is associated with Crohn's disease, PsA, and ankylosing spondylitis [10,19,20]. This is consistent with the role of IL23R in Th17 cell activation and with the fact that these cells have a pathogenic role in several other inflammatory diseases including Crohn's disease and multiple sclerosis [21].

Genetics of Psoriatic Arthritis

Approximately 25% of patients also develop psoriatic arthritis (PsA), a common, debilitating auto-immune disease belonging to the family of spondyloarthritides [22]. HLA alleles have been associated with both psoriasis and PsA [23]. were described as being [24]. TNF-α -238 polymorphism and PsA [25] on psoriasis subjects of European ethnicity [10].

Genetics of Psoriatic Arthritis

Approximately 25% of patients also develop psoriatic arthritis (PsA), a common, debilitating auto-immune disease belonging to the family of spondyloarthritides [22]. Different number of studies base on association on a candidate-gene approach has been conducted to identify genes underlying susceptibility to PsA. Since the PSORS1 locus within the MHC region on 6p provides the strongest linkages with psoriasis in Genome wide linkage scan, also candidate gene within this region have been investigated. The number of genes for a gene dense region code are important in the immune response, including HLA and non -HLA genes. HLA alleles have been associated with both psoriasis and PsA [23]. It is not clear whether the associate HLA described are with psoriasis or with PsA, or both because most of the patient with PsA have psoriasis. HLA alleles that are peculiar to PsA are HLA-B27, B7, B38, and B39.HLA-B13, -B16, and its splits -B38 and -B39, B17 and Cw6 were described as being psoriasis associated arthristis or not [24]. The possible biologic significance that are assciated with psoriasis is recognize to be nine genes and this genes include HLA-B, HLA-C, PSORS1C3, OTF3, HCR, SPR1, SEEK1, corneodesmosin (CDSN), and TNF-α [25-31]. Genomic DNA sequences and recombinant haplotypes suggested that HLA-Cw*0602 is the allele diseases at PSOR1. It has been noted that gene within this region have been investigated with PsA [32]. A study from a metaphysis shows that there is an association between TNF-α -238 polymorphism and PsA [33]. A recent fine mapping of gene in MHC region has been observe the association of PsA with SNP rs11507 [34-35].Therefore, susceptibility locus for PsA may lie more centromeric to that of psoriasis and these is closer to HLA-B. PsA associated studies has recognized that a numbers of genes outside the chromosome 6p are IL-23R, IL-1, and killer-cell immunoglobulin like receptor genes [33,35,36]. The study of GWAS on PsA has not been formally shown. However GWAS on psoriasis subjects of European ethnicity, there were three loci that is associated with PsA when compared to normal controls (HLA-C, IL-12B, and TNIP1). it has been shown that between PsA and psoriasis alone, there is a statistical significant differences at three loci (HLA-C, IL-12B and IL-23R). The loci that more strongly associated with psoriasis alone are HLA-C and IL-23R, and IL-12B with PsA [11]. Another GWAS identified a novel PsA locus on chromosome 4q27 that harbors the interleukin 2 (IL-2) and interleukin 21 (IL-21) genes [10].

Psoriasis, Non-alcoholic Fatty Liver Disease and Obesity

Obesity is a significant and growing problem worldwide and it has also been linked to the onset of psoriasis. In the Nurses' Health Study II, increased body mass index (BMI) correlated with an increased incident rate of psoriasis, and hip circumference and waist-

to-hip ratio were all associated with a higher risk of incident psoriasis [37]. The psoriasis that are associated with metabolic syndrome and increase risk of cardiovascular disease are non-alcoholic fatty liver disease (NAFLD) and chronic plague. NAFLD is the hepatic manifestation of metabolic syndrome, with its key component being visceral obesity [38]. The prevalence of NAFLD is 10–24% of the general population worldwide, increasing to 57.5–74% in obese individuals. The mortality was increased in patients with NAFLD compared with the general population and in the National Health and Nutrition Examination Survey (NHANES III) study, the NAFLD cohort had both increased overall mortality and liver-related mortality compared with individuals without liver disease [39]. While in most patients, NAFLD does not progress beyond simple steatosis, it may progress to Non-Alcoholic Steato-Hepatitis (NASH). The prevalence of NASH also correlates with obesity, with waist-to-hip ratio and abdominal obesity reported to be predictors of NASH. Diagnosing patients with NAFLD and identifying those with NASH is challenging, as they are generally asymptomatic. Clinical presentation and current radiological modalities may not be reliably to diagnose NASH, while non-invasive biomarkers remain to be fully established. The frequency of NAFLD was found to be significantly greater in psoriasis patients (47%) vs. matched controls (28%). Indeed, the relationship strengthened with increasing psoriasis severity [40]. Collectively, these observations support the early recognition of NAFLD in psoriasis patients, the results of which may dictate treatment regimens to avoid potentially liver toxic therapies, such as methotrexate. Positive correlations have been reported among cumulative methotrexate dose, risk factors (e.g. obesity) and progression of NAFLD. Gram for gram, psoriasis patients are also twice as likely to develop hepatic complications from methotrexate as a patients with rheumatoid arthritis (RA). The prevalence of obesity and being overweight are increasing in Saudi Arabia reaching 35.5% [41]. Thus, reduction of weight are of considerable importance to public health [42].

Psoriasis Inflammation and Endothelial Dysfunction

Psoriasis inflammation may act independently in promoting an accelerated atherosclerosis by eliciting endothelial dysfunction and oxidative stress similarly to other chronic inflammatory systemic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease [43]. Psoriasis inflammation is characterized by high levels of TNF-a, IFN-a, IFN-g, IL-1, IL-6, and IL-17, which are released by keratinocytes and inflammatory cells infiltrating skin and joint tissues [44]. These cytokines could also boost several proatherogenic functions of the liver, adipose tissue, and skeletal muscle, including liver production of C-reactive protein (CRP), dyslipidemia, production of proinflammatory adipokines, and insulin resistance, generating lipid abnormalities and culminate in the development of NAFLD and resulting in endothelial dysfunction. Cytokines can also mediate several metabolic effects that can in short term result to inappropriate response to injury or infection, but on a chronic basis, its prove detrimental by accelerating the development of atherosclerosis and predisposing to thrombosis. Endothelial dysfunction is the critical early step in the process of atherogenesis, and it is commonly investigated by measuring arterial stiffness. Arterial stiffness has been found increased in psoriasis patients independently of the other cardiovascular risk factors [45,46].

NAFLD and Cardiovascular Disease

Giving the fact that NAFLD is usually an asymptomatic disorder, it is often unrecognized in everyday clinical practice. Therefore, patient with NAFLD have no symptoms, and aminotransferase levels which are used as a marker of liver damage, are within normal values in almost half of all patients. Type 2 diabetes (T2DM) is strongly associated with NAFLD and has been linked to increased cardiovascular disease (CVD) risk. It is characterized by insulin resistance and mitochondrial dysfunction[6]. Indeed, there is a gradual increase in the severity of insulin resistance in the range of NAFLD which may contribute to the evolution of liver damage. Also, it is associated with an increased risk of kidney disease in subjects with multiple CVD risk factors and tends to be considered as an independent CVD marker [47]. Diabetes, dyslipidemia, hypertension and CVD coexist more frequently in individuals with NAFLD [48]. Hepatic steatosis has been linked to visceral adiposity, low serum HDL, high serum triglycerides, and pro-inflammatory biomarkers such as CRP and has been shown to be associated with an increased risk of cardiovascular events independent of these other variables in diabetic patients [49].

PNPLA3 Gene polymorphism and Carotid Atherosclerosis

Identifying the underlying genetic factors for any disease locus relies intimately on data collected through

genome-wide association (GWA) initiatives. These studies survey genotypic-phenotypic associations among large population based cohorts [50]. Recent GWAs have isolated a number of single nucleotide polymorphisms (SNPs) linked to either increased hepatic fat content or elevated liver enzymes or coronary heart disease [50-52]. The patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene locus on chromosome 22 indicate one of the most investigated polymorphism in fatty liver diseases. Heterozygote carriage of the I148M minor allele in particular is associated with more hepatic triglyceride levels in 2 mixed population studies conducted in North America and Europe [51,53,54]. PNPLA3-148M homozygotes showed an even greater propensity for hepatic fat accumulation; triglyceride levels were two-fold higher in this group compared to non-carriers [1]. The variant allele surfaced most frequently in Hispanic persons, followed by those of European descent and least often in African Americans. On the contrary, a minor variant referred to as PNPLA3-S4531 was commonly detected in African Americans and furthermore associated with a lower hepatic fat burden in these individuals. The exact mechanism by which the PNPLA3-148M variant exerts its effects remains largely unknown. In humans PNPLA3 expresses most abundantly in the liver and to a larger extent in obese individuals [55]. Evidence from *in vitro* experiments suggests that PNPLA3 displays both lipolytic and lipogenic activity [56,57]. The PNPLA3-148M variant may promote fat accumulation by limiting triglyceride hydrolysis [55]. However, to what degree PNPLA3 participates in triglyceride hydrolysis remains controversial [55,57-59]. Targeted PNPLA3 deletion for example did not influence triglyceride hydrolysis or metabolic functions in animal models [57]. A marked up-regulation of PNPLA3 in response to feeding has led investigators to alternatively propose a function for PNPLA3 in lipid remodelling rather than catabolism [60]. Further functional studies should help assess the precise physiological role of PNPLA3 in hepatic lipid metabolism. Despite the strong association between fatty liver and both insulin resistance and glucose intolerance both studies which evaluated a Southern European population failed to find an independent association between PNPLA3-148M and features of metabolic syndrome including fasting serum insulin, HOMA-IR, triglycerides, total cholesterol, or HDL-cholesterol [14,17]. The Dallas Heart Study reported a similar finding [51].

Different lines of evidence, including cross sectional and prospective studies, showed that NAFLD patients are at high risk of cardiovascular dysfunction/events, identifying conventional cardiometabolic alterations and the extremity of liver damage as risk factors [61,62].

GCKR Functional Gene Variants and Atherosclerosis

Glukokinase (GCK) is the most overriding glucose enzyme (phosphorylating enzymes) that is present in the liver and Pancreatic islets, is also known as islets of Langerhans, which have small clusters of cells scattered throughout the pancreas. Pancreatic islets contain several types of cells, including beta cells that produce the hormone insulin which act as physiological glucose-sensor. This regulatory protein (Glukokinase regulatory protein) present in pancreatic islets and the liver form an inactive heterodimer. The GCKR that is 27 kb is located on chromosome 2p23 that contain encodes a 68 kDA protein 19 exons. The association study of wide genome has showed that the common functional variants of the GCKR gene are associated with insulin levels, fasting plasma glucose, and both serum triglycerides and low/high-density lipoprotein cholesterol levels, thus, single nucleotide polymorphisms [63-65]. The variant that is common in GCKR gene has been reported to be in association with increase in more CRP levels, which indicates a good atherosclerotic marker [66].

IN CONCLUSION

Psoriasis is a disease of chronic systemic inflammation, it therefore recommended to reduce the risk of associated co-morbidities such as psoriatic arthritis, NAFLD and CVD by early recognition and diagnosis. Chronic inflammation, mediated by either proinflammatory adipokines or skin-derived cytokines, may contribute to fatty liver disease development by increasing insulin resistance which in turn promotes hepatic lipid accumulation in patients with psoriasis and CVD risk. Further studies are needed to better understand the role of genetics and inflammatory markers. It is also essential to screen for comorbidities and hepatic ones in patients with psoriasis.

ABBREVIATIONS

HLA: Human leukocyte antigen
GWA: Genome-wide association
SNP: Single nucleotide polymorphisms
MHC: Major histocompatibility complex
PS: Psoriasis
PsA: psoriatic arthritis

CDSN: Corneodesmosin
IL: Interleukin
BMI: Body mass index
NAFLD: Non-alcoholic fatty liver disease
NHANES: Nutrition Examination Survey
NASH: Non-alcoholic steatohepatitis
CRP: C-reactive protein
T2DM: Type 2 diabetes mellitus
CVD: Cardiovascular disease
HDL: High density lipoproteins
PNPLA3: Patatin-like phospholipase domain-containing protein 3
GCK: Glucokinase

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Our Dermatology Online

Clinical Image

The Buschke-Loewenstein tumor

Ouiame EL Jouari[1], Anas Zaougui[2], Ghita Senhaji[1], Salim Gallouj[1], Moulay Hassan Farih[2], Fatima Zahra Mernissi

[1]Department of Dermatology, University Hospital Hassan II Fez, Morocco.[2]Department of Urology, University Hospital Hassan II Fez, Morocco

Corresponding author: Dr. Ouiame EL Jouari, E-mail: eljouariouiame@gmail.com

A 26-year-old patient had a verrucous lesion on the genital region. She reported a progressive growth of this lesions during the last 3 years and prurit. Clinical examination revealed a 6 cm tumor of the vulva with a verrucous surface, irregular contours and non-infiltrated base and no palpable adenopathies (Fig. 1). The diagnosis of Buschke-Loewenstein tumor was clinically retained and the patient was referred to the urology department for surgical excision.

The Buschke-Loewenstein tumor is a rare sexually transmitted disease. It is caused by subtypes 6 and 11 of the human papillomavirus (HPV) and characterized by excessive growth of verrucous lesions on the genitals and/or perianal region. The risk of recurrence and degenerescence is very important. the main treatment is surgical excision.

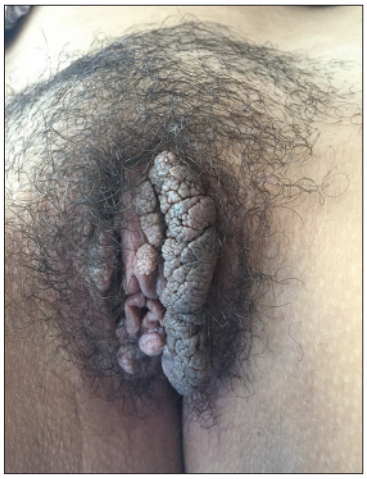

Figure 1: A 6 cm skin color tumor of the vulva with a verrucous surface and irregular contours.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

Source of Support: Nil, **Conflict of Interest:** None declared.

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A historical misleading case of erythema ab igne in a young female patient

Ghita Senhaji, Ouiame El Jouari, Zakia Douhi, Fatima Zahra Mernissi

Department of Dermatology, University Hospital Hassan II, Fez, Morocco

Corresponding author: Dr Ghita Senhaji, E-mail: ghitasenhaji88@gmail.com

Erythema ab igne is a persistent, chronic skin condition resulting from extended exposure to low grade heat [1]. It's usually asymptomatic, though some patients report itching or burning at the site [2]. Clinically, it is characterized by reticular, brownish pigmented, often telangiectatic lesions on the areas of heating exposure, commonly mistaken for livedo reticularis [3]. The prognosis is good with removal of the offending heat source typically resulting in a gradual regression of the hyperpigmentation [1]. Herein we present a historical case of erythema ab igne in a young female patient with history of chronic leg exposure to radiator heat.

A 29 year old female patient with history of hypertension and chronic renal failure, presented to the nephrology department for a surge of her disease requiring a hemodialysis session. She reported a history of painless and non-pruriginous hyperpigmented networked discolorations over her antero internal leg faces, which have been persistent for 1 year, with no functional signs. Clinical examination revealed a large, hyperpigmented, dark brown, reticular patch without telangiectasias nor erythema, spread diffusely over her internal leg faces (Figs. 1a and 1b). The patch was non infiltrated and non purpuric.

Dermoscopy examination found a diffuse brown hyperpigmetation without telangiectasias or erythema (Fig 2). There was neither pruritus nor pain. After meticulous questioning, the patient confirmed the area of hyperpigmentation corresponded to the area of heating exposure. Given this history and the physical findings with lack of systemic inflammation on biological testings, an underlying livedo reticularis was excluded and the diagnosis of erythema ab igne was made. The patient was then educated to avoid close and prolonged exposure to the offending heat source.

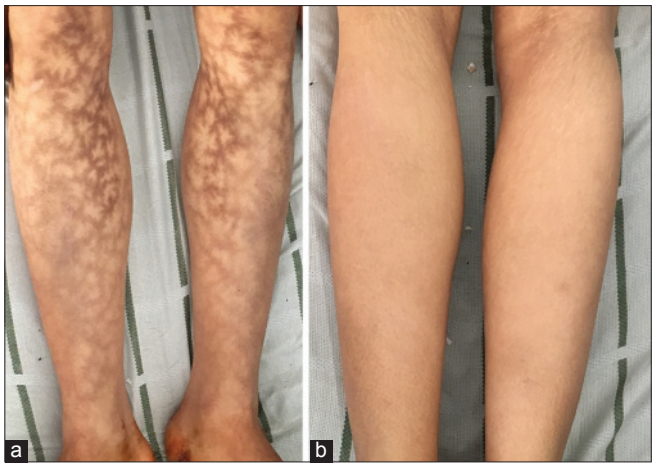

Figure 1: Erythema ab igne. (a): Clinical image showing a large, hyperpigmented, dark brown, reticular patch, localized over the internal leg faces. (b): Normal clinical aspect of posterior faces of the legs.

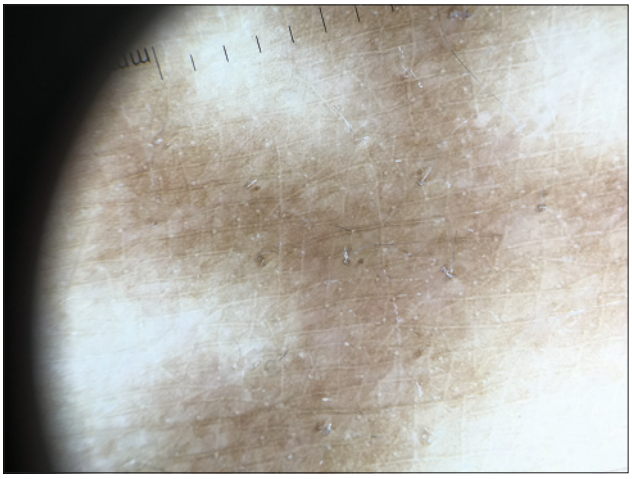

Figure 2: Erythema ab igne. Dermoscopic image showing a diffuse brown hyperpigmentation without purpura or telangiectasias.

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CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Disseminated herpes zoster infection in a splenectomized patient

Zarif Tuce Ozkara Duman, Gulsen Akoglu

Dermatovenereology Clinic, Ataturk Training and Research Hospital, Ankara, Turkey

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

Sir,

Disseminated herpes zoster infection is usually observed in patients with HIV infection, malignancy, or during immunosuppressive treatments and is very rare in immunocompetent patients [1]. Herein, we report a patient with disseminated HZ after splenectomy due to trauma.

A 51-year-old male patient presented to our outpatient clinic with painful eruption on his face, neck, and trunk. He had type 2 diabetes mellitus and was on oral antidiabetic treatment. He had a splenectomy operation due to a trauma 18 years ago. Dermatological examination showed grouping papulovesicules and some crusts located on the V1 dermatome over right forehead and on the C3-C4 dermatomes over left supraclavicular region. Leukocytosis (WBC: 13250/ml) and high C-reactive protein levels (19.4 mg/dl; normal range: 0-5 mg/dl) were detected in laboratory analyses. Liver and renal function tests and urinalysis were all within normal limits. Anti-HIV antibody was negative. He was diagnosed as having disseminated herpes zoster and put on acyclovir treatment with a dosage of 3x10 mg/kg/d intravenously. In the follow up, impairment of renal function was detected on the third day of acyclovir therapy. Treatment was stopped due to acute renal failure caused by acyclovir and the patient was treated with intravenous hydration. After five days, renal functions improved markedly and skin lesions healed.

Varicella zoster virus (VZV) is a double-stranded DNA virus belonging to herpes virus family. The virus remains latent in sensory root ganglions after recovery from primary VZV infection, acute varicella or chickenpox. Intact VZV specific cellular immunity blocks the reactivation. Upon decline in cell mediated immunity caused by natural aging, trauma, stress, T cell defects, HIV infection, chemotherapy, or bone marrow transplantation, the virus reactivates and reaches to the related dermatomal skin region through the sensorial nerve axon, presenting as herpes zoster infection [1,2]. The involved dermatomes are usually adjacent and unilateral in immunocompetent patients and dissemination is very rare [1-3]. Development of 20 or more vesicular lesions of HZ extending outside the main involved dermatome is called disseminated HZ infection. Dissemination is extremely rare except for the patients with HIV infection, malignancy, and who are on immunosuppressive treatment [1]. *Mazur and Dalin* reviewed 107 cases of HZ during a 20 year period and reported cutaneous dissemination in 15 % of patients, which most frequently occurred in splenectomized patients with Hodgkin's disease and in patients having systemic corticosteroid therapy [4]. *Manning et al.* reported only 3 patients with HZ, two of which were associated with generalized cutaneous dissemination, among 102 patients who had undergone splenectomy for non-malignant disease such as trauma, surgical complications, and hematologic indications. They suggest that splenectomy does not predispose to HZ; however, may involve in cutaneous dissemination [5].

Spleen is an important lymphoid tissue involved in both humoral and cellular immunity. Many immunological mechanisms such as T and B cell maturating processes,

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production of specific antibodies against circulating bacteria, and phagocytosis of cells opsonized with antibodies take place in the spleen. Therefore, spleen has an essential and important function in protecting the host from infections. Splenectomized patients have immunological defects including altered immunoglobulin levels, lower activation in alternative pathway of complement system, lack of opsonizing proteins in serum, and defective function of T helper cells [6]. We suggest that the defect in immune system depending on splenectomy caused reactivation of VZV infection and disseminated cutaneous HZ in our patient. In conclusion, herpes zoster may present as disseminated form in patients with splenectomy. Patients with diagnose of disseminated HZ infection should be questioned for history of splenectomy.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Telangiectasia macularis eruptive perstans under the dermoscope in the skin of color

Subrata Malakar[1], Samipa Samir Mukherjee[2]

[1]Department of Dermatology, Rita Skin Foundation, Kolkata, India, [2]Department of Pediatric Dermatology, Cloudnine Hospitals, Bengaluru, India

Corresponding author: Dr. Samipa Samir Mukherjee, E-mail: drsamipamukherjee@gmail.com

Sir,

Cutaneous mastocytosis is characterized by the proliferation and accumulation of mast cells in the skin and is characterized by five subtypes including urticarial pigmentosa, diffuse cutaneous mastocytosis, bullous mastocytosis, solitary mastocytoma and Telangiectasia macularis eruptive perstans (TMEP). TMEP is a rare disease, found in less than 1% of patients with cutaneous mastocytosis [1]. It affects predominantly adults and is characterized by erythematous and/or yellow-brownish macules with telangiectasias, preferably located on the trunk and upper limbs. Darier sign (urticaria after the friction of a lesion) is absent in most cases. Dermoscopy reveals a characteristic vascular pattern in TMEP thereby aiding in diagnosis.

A 34 year-old male patient presented with erythematous skin lesions on the upper chest, back and upper limbs of 3 years duration (Figs. 1 and 2). He denied any itching in the lesions. Cutaneous examination revealed erythematous-brownish macules ranging from 0.5 to 5.0 cm in diameter, confluent, distributed in the chest, back and upper limbs, and few residual hyperchromic macules. Darier sign was negative. History and systemic examination was not contributory. Dermoscopy of the erythematous-brownish lesions revealed thin and tortuous linear vessels in a reticular pattern, yellow brown background, mild erythema and delicate pigment network (Fig. 3). Histopathological examination showed dilated vessels with moderate inflammatory reaction around, mainly composed of mast cells, best visualized with Giemsa stain. Thus the diagnosis of TMEP was established.

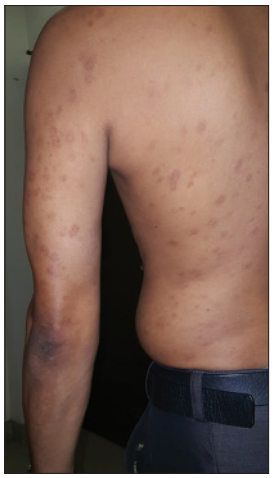

Figure 1: Erythematous brownish macules on the back and arm.

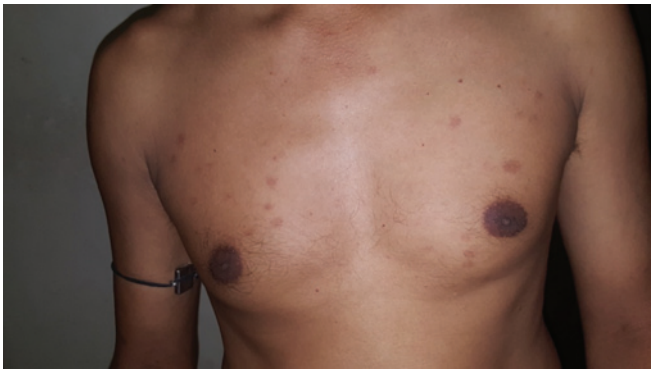

Figure 2: Erythematous brownish macules on the upper chest.

In 2009, Akay et al studied the dermatoscopic pattern in 6 patients with different forms of cutaneous mastocytosis and described the pigmented network and reticular vascular pattern. The pigmented network was observed predominantly in patients with maculopapular mastocytosis and urticaria pigmentosa and the reticular vascular pattern in patients with TMEP [2].

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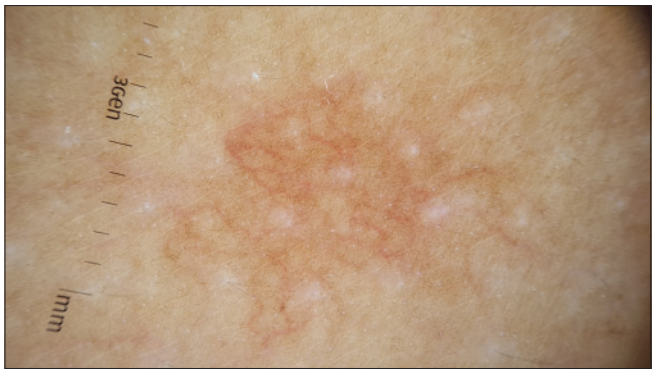

Figure 3: Mild erythema, thin and tortuous linear vessels, delicate pigment network, yellow-brown background.

Further in 2011,Vano-Galvan et al evaluated the dermoscopic findings of 127 patients with cutaneous mastocytosis and characterized four distinct patterns comprising of pigmented network, yellow-orange amorphous area, brown amorphous area and telangiectasia with reticular pattern [3].

In 2013 Unterstell et al reported similar dermoscopic findings of thin and tortuous linear vessels, mild erythema and fine pigment network in their report [4].

The Dermoscopic findings of the characteristic reticular vascular pattern, corresponds to dilatation and vascular proliferation associated with the presence of mast cells in the dermis. The mild erythema reported on dermoscopy reported in few cases in the literature may be difficult to appreciate in the skin of colour.

To the best of our knowledge this is the first report of dermoscopic findings in TMEP from the Indian subcontinent and we believe that dermoscopy can serve as an important adjunct in the effective diagnosis of this entity.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

A case of palmoplantar lichen planus

Orhan Şen[1], Seray Külcü Çakmak[1], Emine Tamer[1], Başak Yalçın[1], Ayşe Yılmaz Çiftçi[2]

[1]Dermatology Clinic, Ankara Numune Education and Research Hospital, Ankara, Turkey, [2]Pathology Clinic, Ankara Numune Education and Research Hospital, Ankara, Turkey

Corresponding author: Dr. Orhan Şen, E-mail: eru2017@gmail.com

Sir,

Lichenplanus (LP) is an idiopathic, inflammatory skin disease which may occur in various location sand morphologies [1]. Palmoplantar lichen planus (PPLP) is an uncommon, localized variant of LP which shows atypical clinical features [2,3]. PPLP presents classically with pruritic, erythematous, scaly and/orhyperkeratotoic plaques with well-definededges [3].

A 62-years-old female patient was admitted to our outpatient clinic with the complaint of a pruritic rash on her palmsandsoles for one year. The patients family and pastmedical history was not significant. Dermatological examination revealed multiple erythematous papules with scaling on the palmoplantar surfaces and dorsum of feet (Fig. 1). The oral and genital mucosas and nails of the patient were normal. The histopathological examination of the punch biopsy from the lesions revealed hyperkeratosis and acanthosis, thickening of granular layer, lichenoid infiltation in the dermoepidermal junction and few apopitotic keratinocytes in the epidermis which was consistent with LP (Fig. 2). Laboratory examinations including full blood count, routine biochemistry profile, hepatitis B and C serology were within normal limits, screening for human immunodeficiency virus infection and syphilis infection yielded negative results. The patient was diagnosed as PPLP and therapy with topical corticosteroid was started.

PPL is are rare form of LP which does not have the classically described clinical morphology of LP which makes the diagnosis difficult [4]. While typical LP is most common in women and between third and sixth decades, PPLP is more common in men between second and fifth decades [2,5].The lesions commonly involve the internal plantar arch and thenar and hypothenar eminence of palms with out involvement of fingertips [2,4]. PPLP may have multiple clinical presentations. While the erythematous scaly form with or with out hyperkeratosis is the most common, vesicular, petechiea -like, umblicated, pigmented macular,and ulcerative forms may also be observed [3]. While PPLP may be presentonly on the palms and/or soles, it may also be associated LP lesions on the other sites including mucosa land nail involvement in some patients [6].Our patient also had lesions on the dorsum of the hands. The histopathological features of PPLP is similar to classic LP. However parakeratosis, which is not a classical feature of classical LP has been described over half of the cases in a case series [7]. PPLP

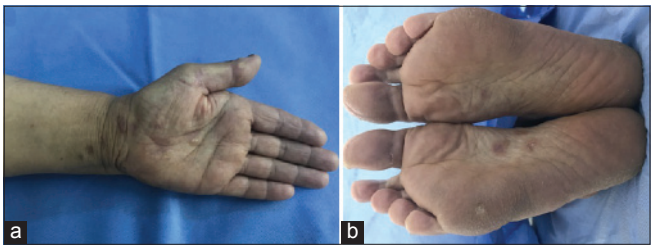

Figure 1: (a and b) Multiple erythematous papules with scaling on the palmoplantar surfaces.

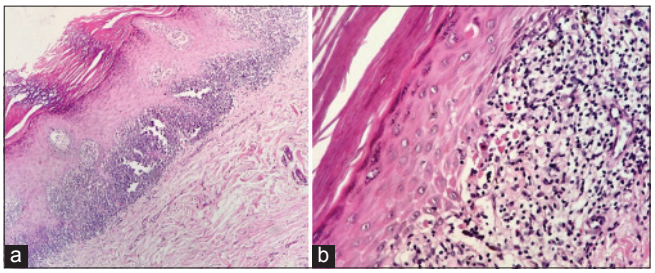

Figure 2: (a) Hyperkeratosis and acanthosis of epidermis, and distinct granular layer lichenoid infiltration in the dermoepidermal compartment (x10 H&E). (b) Intraepidermal and basal apoptotic keratonocytes (Civatte Bodies) (x40H&E).

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might be difficult to diagnose as it resembles many dermatoses that involvespalmoplantarareasincluding psoriasis,tineamanum/pedis,keratoderma, dyshidrotic eczema, mycosis fungoides, verruca vulgaris, and secondary syphilis [2,3].The duration of the lesion sranges between 1 month and 8 years with the avarage of 11 months [6]. PPLP may be resistant to treatment and topical and intralesional corticosteroids, acitretin, tacrolimus, tazarotene, cyclosporine, methotrexate and dapson have been used with variable results in the treatment [4,5,7].

Inconclusion we want to emphasize that PPLP is a rare form of LP and as it does not present with the classical, violaceous, flattopped papules the diagnosis may be challenging even for the dermatologists.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Our Dermatology Online

Letter to the Editor

A case of bilateral ear pyogenic granuloma following ear piercing

Suvashis Dash, Rakesh Kain

Department of Burns, Plastic and Maxillofacial Surgery, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Corresponding author: Dr. Suvashis Dash, E-mail: suvashis.dash@gmail.com

Sir,

We are reporting a case a pyogenic granuloma of bilateral ear following piercing of ear. An 18 year old student who has undergone piercing of her ears in a piercing parlor 2 months back. This patient underwent aesthetic piercing of her bilateral superior helix. After 2 weeks of piercing she developed slight swelling and pain. She stopped using her gold ornaments in the pierced holes. She visited her general practitioner who prescribed some antibiotics and analgesic but the symptoms did not subsided. Gradually the area becomes raw. Fleshy red colored wet granulation tissue about 3-5 mm of size present on both side of pierced surface, which bleeds on touch. The patient presented to us after 2 month of piercing. We have planned excision of the granuloma. Excision of lesions along with 2 mm margin of surround cartilage was done on both sides. Wound was closed primarily. On histopathology report it was found lobular pattern of vascular proliferation with signs inflammation resembling granulation tissue. There was ulceration with loss of epidermis. Stroma has dilated budding capillaries, surrounded by endothelial cells. The histopathology was suggestive of pyogenic granuloma. Wounds have healed without any complications.

Pyogenic granuloma – first described by Antonin Poncet and Dor, in 1897, who named it *botryomycosis hominis*. It is also called as lobular capillary hemangioma. The name is a misnomer as it is not pus producing or granulomatous; mostly it is seen in children and young adults on head, neck and extremities as a solitary red fleshy lesion that prone to ulceration and bleed on touch. PG is also very common in pregnant women (tumor of pregnancy) usually in oral cavity. Various factors are associated with the development of these lesions, like physical trauma irritation, hormonal factors and medications like oral contraceptives, retinoid and anticancer agents [1].

Post piercing pyogenic granuloma is common in nose but it is a rare presentation in ear. There are few cases of post piercing ear granuloma reported, but bilateral presentation is rare. The cause of pyogenic granuloma post piercing in this case may be continuous irritation or unknown. Prognosis is usually good, with recurrence rate of 16%. On gross feature these are fleshy exophytic lesions, which easily bleed on touch. On microscopy there is lot of capillary and venule with inflammatory stroma. The overlying epithelium is thinned with ulceration. Mature lesion often shows fibromyxiod stroma which separates the lesion in to lobes. Hyperkeratosis and acanthosis may be present. There may be mitotic activity present. In around 10% of pyogenic granuloma extramedullary hematopoiesis can occur. Presence of myxoid structures in the pyogenic granuloma may be the main cause of recurrence. Differential diagnosis includes-inflammatory granulation tissue, other vascular tumors like hemangioendotheliomas, hemangiopericytomas reactive angioendotheliomatosis and Bacillary angiomatosis.

Electrocauterization and curettage (excision), and laser treatment can be used. There are several differential diagnoses for the ear swellings which mimics pyogenic granuloma. Pyogenic granuloma post piercing is one of the uncommon diagnoses [2-4].

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Consent

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Letter to the Editor

Hypohydrotic ectodermal dysplasia: a case report

M. M. Aarif Syed[1], Bibush Amatya[1], Shagufta Parween[2]

[1]Department of Dermatology and Venereology, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal, [2]Department of Periodontology, Krishnadevaraya College of Dental Sciences, Bengaluru, India

Corresponding author: Dr. M. M. Aarif Syed, E-mail: syedmmaarif@gmail.com

Sir,

A 23 years old girl walked into our clinic with the complaint of sparse hairs over the scalp since childhood (Fig. 1). She revealed that consultation with various doctors from different streams could not be of any help to her till date. The scalp hairs were dull looking and lustreless and eyebrows were scanty with the outer third completely missing (Fig. 2). However, the eyelashes were normal. Hair in the axilla, pubic region and extremities were also sparse. The skin was dry looking. Further questioning revealed that she sweats very meagerly and was also intolerant to heat. However, she had never suffered stroke in the past. There were no scaling or peeling of skin noted. Periorbital hyperpigmentation with fine wrinkles around the eyes were evident. Nails were normal on examination. Her lower lips were slightly everted (Fig. 2). Oral examination found lower set of teeth completely missing. She did not have the mandibular teeth from birth. She had delayed dentition with only 8 maxillary deciduous teeth appearing which later got replaced with the same number of permanent teeth. She was a girl of normal intelligence. Her systemic examination was within normal limits. She had reached puberty on time with normal breast development and her menstrual cycles were regular. Her two siblings and parents were healthy without any similar complaints. A diagnosis of hypohydrotic ectodermal dysplasia (HED) was made based on clinical features.

Ectodermal dysplasia (ED) is defined as a large heterogeneous group of conditions, characterized by congenital defects in two or more ectodermal derivatives such as hair, teeth, nails or sweat glands. The classification of 2014 include 163 defined ED syndromes [1]. The most common EDs are X-linked recessive hypohydrotic ED (Christ Siemens Touraine Syndrome) (HED) and hydrotic ED (Clouston Syndrome). HED is characterized by the triad of hypotrichosis, hypodontia and hypohydrosis. Our case classically demonstrated this triad. It is inherited as an X-linked disorder; however autosomal dominant and recessive forms have been described [2]. Defect in three genes: Ectodysplasin A (EDA), EDA receptor (EDAR) and EDAR associated death domains (EDARADD) are implicated [3]. Females have generally partial manifestation of the disease unlike males who have more generalized features [4]. Beside the triad as described above, other clinical features may include nail disorders, craniofacial abnormalities, respiratory infections, eczema, and others. However, clinical manifestations are highly variable among individuals.

Hypohydrosis especially during infancy and childhood may cause thermoregulatory issues. In fact, in anhydrotic ectodermal dysplasia, heat stroke has been the most common cause of death in first year of life.

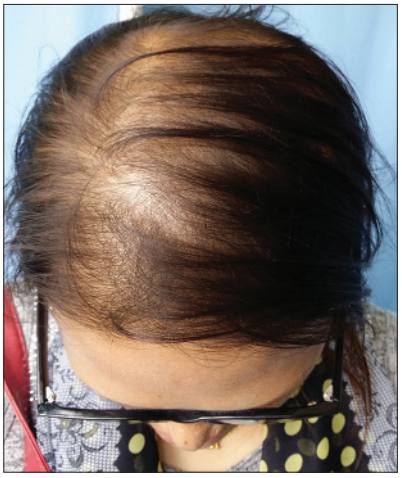

Figure 1: Sparse hairs over the scalp.

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Figure 2: Scanty eyebrows with the outer third missing, periorbital hyperpigmentation with fine wrinkles, and everted lips.

Thermal imbalance can be countered by drinking cold fluids, wetting the skin and preferring cooler place to live and work. The sparse hair is cosmetically unacceptable, more so among female patients. This was evident in our case as well. The alopecia is rarely total. Recently, topical application of 3% minoxidil for a year has achieved good results [5]. Delayed dentition is perhaps the first symptom that makes the parents seek medical advice. Dental issues range from anodontia to hypodontia, widely spaced to conical/pegged shaped teeth. Both temporary as well as permanent teeth are affected. My patient too did not have lower set of teeth. Immediate dental attention is warranted which is often challenging. A combined surgical, pedodontic and prosthodontic approach is prescribed. Nail changes could include onychodysplasia.

The diagnosis of HED may not be very difficult. However, it requires multidisciplinary approach to manage such patients. Counselling, prosthodontic treatment and dermatological consultation must be offered to every patient.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Drug-induced hypersensitivity syndrome in a patient with systemic lupus erythematosus and psoriasis

Takako Miura, Toshiyuki Yamamoto

Department of Dermatology, Fukushima Medical University, Fukushima, Japan

Corresponding author: Prof. Toshiyuki Yamamoto, E-mail: toyamade@fmu.ac.jp

Sir,

Co-existence of systemic lupus erythematosus (SLE) and psoriasis is relatively rare. We herein describe a rare case of drug-induced hypersensitivity syndrome (DIHS) in a patient with SLE and psoriasis vulgaris, induced by an anticonvulsant.

A 39-year-old man was diagnosed with SLE at the age of 28. Seven years later, he developed psoriasis (Figs. 1a and 1b), and was treated with topical corticosteroids and vitamin D3 ointment. Moreover, he had aortic regurgitation (AR), and underwent aortic valve replacement. After the operation, he developed convulsions, and carbamazepine (Tegretol^{R}; 200 mg/day) was administered. Four weeks later, he developed itchy eruptions on the trunk and extremities, with a fever reaching up to 40°C. On physical examination, erythema multiforme-like lesions were spread on the trunk and extremities (Fig. 1c). Tegretol^{R} was discontinued, but one week later, erosions of the oral mucosa appeared (Fig. 1d), and the erythema on the trunk coalesced with purpura. Inguinal lymphadenopathy was observed. Laboratory data showed a normal white blood cell count (6300/μl), with a differential count of 58% neutrophils and 21% eosinophils, elevated AST (66 IU/l) and ALT (116 IU/l) levels. Serum anti-nuclear antibody was positive (1:320, homogenous), whereas anti-DNA antibody was within normal ranges and hypocomplementemia was not detected. A biopsy specimen from the abdomen revealed apoptotic keratinocytes and perivascular inflammatory cell infiltration composed of mononuclear cells and eosinophils in the edematous upper dermis (Fig. 2). Before the onset of drug eruption, the patient's SLE was treated with oral prednisolone (12.5 mg/day); however the eruption was improved by escalating the dose of prednisolone to 25 mg/day. A lymphocyte transformation test using Tegretol^{R} was weakly positive (S.I. 188%), and HHV-6 IgG titer (1:10) was elevated (1:640) six weeks later. HLA-A and -B genotyping revealed HLA-A*1101, A*3101, B*1501, and B*3501.

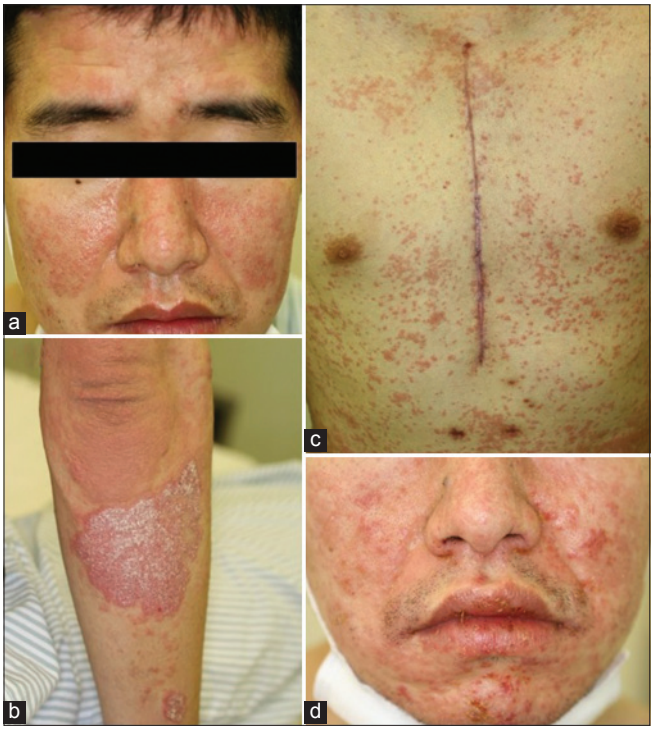

Figure 1: Clinical pictures at initial visit to our department showing malar rash and keratotic plaques on the forearm (a, b). Drug eruption showing erythema multiforme-like erythemas scattered on the trunk (c), facial erythema and mucosal erosion (d).

The co-existence of psoriasis and SLE is sometimes seen, and both diseases share some common pathogenesis, such as Th1/Th17 type-dominant cytokine imbalance, plasmacytoid dendritic cell activation *via* Toll-like

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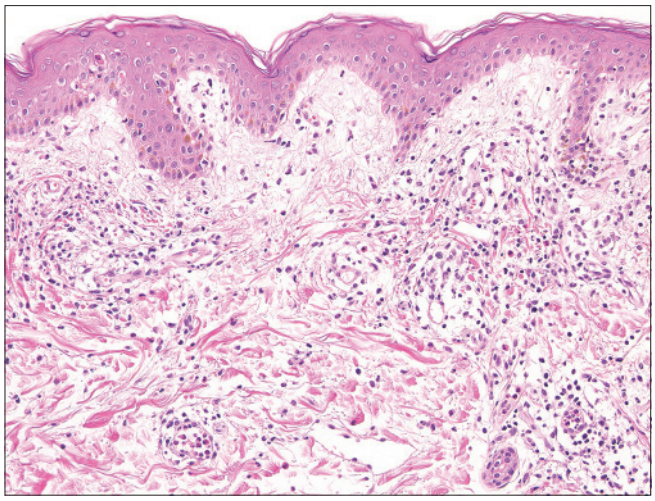

Figure 2: Histological features showing apoptotic cells in the epidermis and cellular infiltrates composed of mononuclear cells and eosinophils in the upper dermis.

receptors, and interferon-α release. Our patient developed psoriasis seven years after the diagnosis of SLE. Furthermore, he had AR and received operation at the remission phase of SLE. Four weeks after administration of an anticonvulsant drug, he developed DIHS, which fulfilled the Japanese criteria, without exacerbation of either SLE or psoriasis. It is known that several autoimmune disorders, including SLE, are induced after DIHS was improved [1,2], possibly due to functional defects of regulatory T cells (Tregs) [3]. However, our case developed SLE before the occurrence of DIHS, and thus the development of SLE was unassociated with DIHS. Patients with SLE have an increased risk of developing adverse cutaneous drug eruption [4], and cases such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) rarely occurs in patients with SLE [5].

To date, only one suspected case of SLE has been reported to develop drug reaction with eosinophilia and systemic symptoms [6]. HLA-A*3101 is significantly associated with susceptibility to carbamazepine-induced adverse drug reactions in Japanese population [7]. Our case also had HLA-A*3101, therefore may have developed DIHS unassociated with SLE itself.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Letter to the Editor

Urethral caruncle in a young pregnant woman: an uncommon cause of urethral overgrowth

Shailja Chauhan, Vikas Sharma, Vikram K. Mahajan

Department of Dermatology, Venereology & Leprosy, Dr. R. P. Govt. Medical College, Kangra (Tanda)-176001 (Himachal Pradesh), India

Corresponding author: Dr. Vikram K Mahajan, E-mail: vkm1@rediffmail.com

Sir,

Urethral caruncle is a benign fleshy overgrowth arising from the mucosa of posterior lip of distal urethra affecting postmenopausal women more often than premenopausal or perimenopausal women and men [1,2].

A 23-year-old woman in 9th month of her second pregnancy was referred from surgery clinic for evaluation of a *hematoma-like mass* protruding in the vaginal introitus. She had consulted at a peripheral centre for urinary frequency, dysuria and one episode of mild hematuria 2weeks back. She was treated as a case of infected hematoma with amoxiclavunate 625mg three times daily for 5 days without benefit. Her first pregnancy/parturition and postpartum period 3 years back, and medical history were unremarkable. She had no lower abdominal pain or vaginal discharge and antenatal examination was normal. Genitourinary examination showed solitary, fleshy, painless, brownish-black, soft to firm sessile mass with uneven lobulated surface arising from posterior lip of the urethra and protruding in the anterior introitus (Fig. 1). No excoriations, bleeding, or ulceration/crusting were noted. She did not consent for biopsy. With a diagnosis of urethral caruncle she was counselled about its benign nature, advised Sitz bath and follow up after delivery.

The exact etiopathogenesis of urethral caruncle remains obscure and its development is imputed to distal urethral prolapse due to urogenital atrophy from estrogen deficiency. The possible role of autoimmunity remains uncertain [3]. Chronic irritation of the exposed urethral mucosa only contributes to the growth, hemorrhage, and necrosis of the lesion. Clinically, it usually appears as a small to about 1 cm sized pink or reddish mass at the urethral meatus while purple or black color indicates thrombosis. When present in premenopausal women it may enlarge during pregnancy. Being mostly asymptomatic it is usually a chance finding during pelvic examination. However, pain, and dysuria may occur and few patients may seek consultation for bleeding from the lesion after noticing staining of undergarments. Urinary retention has been reported but storage or voiding abnormalities are not observed in urodynamic studies [4]. Tumors occur in about 2% of urethral caruncles and intraepithelial squamous cell carcinoma has been reported arising within the urethral caruncle [5]. The diagnosis is clinical but histopathological features of granulation tissue covered by either mixed hyperplastic urothelial, squamous or transitional epithelium infolding into papillary architecture, stromal fibrosis, edema, and/or inflammation will differentiate it from other simulating lesions of urethral melanoma, tuberculosis, intestinal ectopia, lymphoma, and urethral leiomyoma [1,6,7]. Urinalysis will exclude urinary tract infection and cystoscopy may be needed to ascertain origin of hematuria or to diagnose bladder and urethral abnormalities such as urethral prolapse, carcinoma, diverticulum, or periurethral abscess.

Most cases are treated conservatively with warm Sitz baths and topical estrogen creams or anti-inflammatory drugs despite their uncertain efficacy. Excisional biopsy is only needed for enlarging or large symptomatic lesions, atypical morphology, failure of conservative treatment, or when the diagnosis is uncertain.

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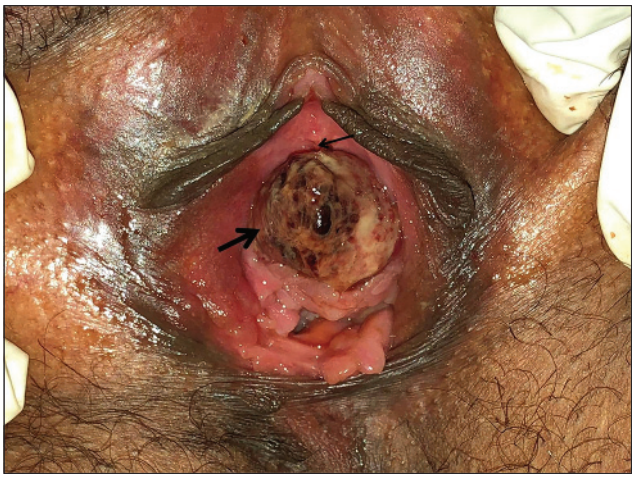

Figure 1: A solitary, fleshy, sessile mass in the anterior introitus (thick arrow) sized about 2x1 cm with lobulated uneven surface around lower part of urethral meatus (thin arrow). The brownish-black color is because of thrombosed vessels.

CONSENT

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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Historical Article

Dermatology Eponyms – sign –Lexicon (S). Part II

Piotr Brzeziński[1], Uwe Wollina[2], Leonardo Espinoza-Benavides[3], Patricia Chang[4], Mariem Mohamed[5], Stephen A. Geller[6,7]

[1]Institute of Biology and Environmental Protection, Department of Cosmetology, Pomeranian Academy, Slupsk, Poland, [2]Department of Dermatology and Allergology, Städtisches Klinikum Dresden, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany, [3]Dermatology Resident at Pontificia Universidad Católica de Chile, Chile, [4]Department of Dermatology, Hospital General de Enfermedades IGSS and Hospital Ángeles, Guatemala, [5]Dermatology Department, Fattouma Bourguiba University Hospital, Monastir 5000, Tunisia, [6]Department of Pathology and Laboratory Medicine – David Geffen School of Medicine – University of California, Los Angeles/CA, USA, [7]Department of Pathology and Laboratory Medicine – Weill Cornell Medical College, New York/NY, USA

Corresponding author: Dr. Piotr Brzeziński, MD PhD, E-mail: brzezoo77@yahoo.com

ABSTRACT

Eponyms are used almost daily in the clinical practice of dermatology. And yet, information about the person behind the eponyms is difficult to find. Indeed, who is? What is this person's nationality? Is this person alive or dead? How can one find the paper in which this person first described the disease? Eponyms are used to describe not only disease, but also clinical signs, surgical procedures, staining techniques, pharmacological formulations, and even pieces of equipment. In this article we present the symptoms starting with (S) and other. The symptoms and their synonyms, and those who have described this symptom or phenomenon.

Key words: Eponyms; Skin diseases; Sign; Phenomenon

Short Neck Sign

Sign seen in Klippel-Feil or Turner's syndromes [1].

Shrinking Dark Sign

Horrible rapid dehydration associated with a form of cholera in India, in which victims appeared to shrink and their capillaries burst, coloring the skin black and blue [2].

Shrunken Skin Sign

The lower jaw tremors and whole skin appears shrunken with dark rings under the eyes. A sign of malarial infection with *Plasmodium falciparum* [3].

Shuster's Sign

Scarring of the concha due to lesions of discoid lupus erythematosus is called as Shuster's sign and it can be present in 30% of the cases [4].

Shwartzman's Sign

A severe hemorrhagic reaction with necrosis, observed in rabbits which are first injected with 0.25 ml. of typhoid or certain other culture filtrates into the skin of the abdomen and which then twenty-four (eighteen to thirty-two) hours later are injected intravenously with 0.01 ml. of the same filtrate. The site of the later injection turns blue at the center and red at the periphery, the skin is glossy, smooth, and edematous, the blood vessels below the surface are ruptured and the numerous leukocytes are dead [5].

Gregory Shwartzman

Russian bateriologist, 1896-1965.

Siberian Sign

North Asian zoonotic tickborne rickettsiosis. Found in the Chinese, Mongolian, and Siberian wild rodent populations [6].

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Silex's Sign

Furrows radiating from the mouth. A sign seen in inherited syphilis (congenital syphilis) [7].

Paul Silex

German ophthalmologist, 1858-1929 (Fig. 1), is known for contributions made involving war-related blindness. He studied medicine at the Universities of Halle, Berlin and Breslau, obtaining his doctorate in 1883. Afterwards he served as an assistant to ophthalmologist Ludwig Laqueur in Strasbourg, followed by several years as an assistant to Karl Ernst Theodor Schweigger in Berlin. He received his habilitation in 1890, becoming an associate professor in 1897. In Berlin he opened a private clinic at St. Maria Victoria-Krankenhaus [8].

Silver Eye Sign

A blue deposit of silver in the skin, caused by exposure to silver dusts or salts. Often appears as a gray blue haze in the white of the eye. Also known as Argyria sign [9].

Sinbis Sign

Fever with a rash that can progress to hemorrhagic, as well polyarthritis and niuscle pains. Caused by a zoonotic alphavirus spread by the bite of infected mosąuitos [10].

Sister Marie Joseph Sign

This is a metastatic umbilical lesion secondary to a primary malignancy of any viscera, stomach and colon being most common in men, and ovary in women (Fig. 2) [28].

Sisto's Sign

Constant erying as a sign of congenital syphilis in infancy [11,12].

Genero Sisto

Argentinean paediatrician, 1870-1923, although some sources say that Genero Sisto was a Chilean Pediatrician and only more mentions a Dr Sisto being from Spain. But the vast majority of informations reveals that Genaro Sisto was actually from Argentina. His name can also be written "Jenaro Sixto".

He graduated from Medical School in 1985, presenting a thesis about Poliomyelitis. He then specialized as a

Figure 1: Paul Silex.

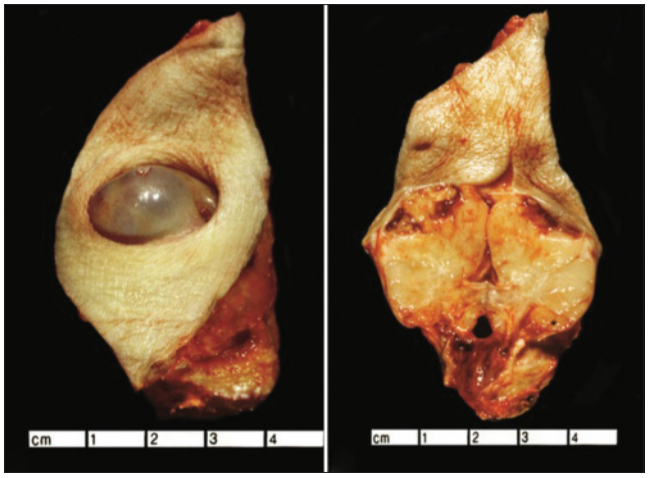

Figure 2: Sister Marie Joseph sign.

Pediatrician in Europe. As he returned to his country of origin, he became professor of his specialty at the Medical Faculty. Concurrently, he joined the "Cuerpo Médico Escolar" (Unit of School Physicians) where he had a renowned career that culminated with his appointment as Director. His actions regarding Schools' Health moved him to implement highly developed measures as they showed their effective results. Some of these measures were: the improvement of children's nutrition by the "gota de leche" ("drop of milk") provision and the school cafeterias, clothing for the students in need, the creation of Cooperative Associations, the inauguration of new doctors' school practices with medical specialties, vaccination campaigns, the expansion of the "aldea sanitaria" ("healthy village") concept, as well as special teaching methods and the treatment of "feeble kids". He was recognized by the Parisian Medical Academy and kept assisting international congresses related to his specialty (Sánchez, 2007, p. 517-518).

Currently, the Medical School of the University of Buenos Aires awards the Genaro Sisto Award triennially to the best original work about Children and Adolescent pathology or hygiene. A primary school in Buenos Aires carries his name [13].

Skimmer Sign

Sign in Kerion Celsi (Fig. 3), which consists in observing the exit of pus for each of the orifices of the hair follicles when doing lateral pressure on the area [29].

Skoptzy Sign

A sign of horrific religious castration of both men and women in Russia and Romania, which can include applying fire to the breasts as well as amputation of the breasts [14].

Skunk Boil Sign

Leptospirosis infection. Also known as Possum sign [15].

Slate Grey Sign

Slate grey colouration of the skin secondary to melanin and haemosiderin deposition. A sign of haemochromatosis [16].

Smith's Teeth Sign

The teeth are often inerusted with a brownish matter, which adheres to them closely near the gums. A sign indicating typhous fever [17].

Smith's Tongue Sign

The tongue in the commencement of this fever is covered with a white fur, which as the disease advances assumes a yellow tinge, and from that gradually changes to a brown, which eventually becomes almost black. Arrived at this State, it cracks and peels off, leaving the tongue smooth, dry and very red. It is then again renewed and again comes off, making these changes, in severe cases, several times in the course of the disease. A sign indicating typhous fever [17].

Nathan Smith

American physician, 1762-1828 (Fig. 4). One of New England's best-known and respected physicians. He was a skilled surgeon, teacher, writer, and practitioner. He single-handedly founded Dartmouth Medical School, and co-founded the University of Vermont College of Medicine, the medical school at Bowdoin College, and the Yale School of Medicine. Smith decided to study medicine at age 24, after seeing an operation performed by Dr. Josiah Goodhue. Smith spent three years with Dr. Goodhue at Putney, Vermont, then opened his own practice at Cornish, New Hampshire. He later went to the Harvard College's medical department where he obtained his MB in 1790. In 1803 Smith had gone to the University of Edinburgh where he attended medical classes for a year.

Smith founded the medical department at Dartmouth College. Initially the only member of the Dartmouth Medical School faculty, Smith taught anatomy, chemistry, surgery, and clinical medicine. He essentially served as dean and treasurer of the medical school, also. Smith emphasized experience rather than theory, and he largely eschewed bleeding and purging, favoring support of the body's own healing powers and attentiveness to the patient's comfort. Using these principles, he was a consultant on the child Joseph

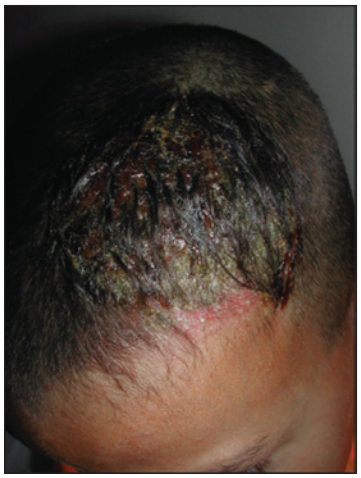

Figure 3: Skimmer sign.

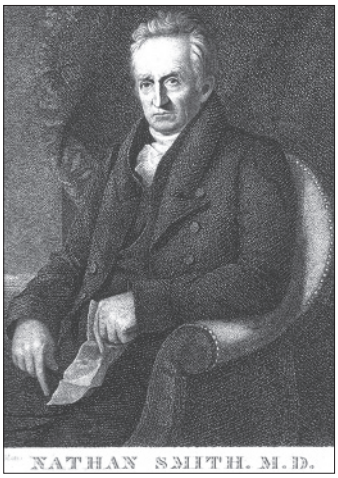

Figure 4: Nathan Smith

Smith, the future founder of the Latter Day Saint movement, saving his leg from amputation.

At Yale Smith was the first professor of physic, surgery and obstetrics [18].

Sodoku Sign

Japanese rat bit fever [19].

Spargana Sign

Nodular, cystic skin lesions that may be inflamed and itchy, can have eye and CNS involvement. Caused by exposure to cat or dog faeces containing eggs from the zoonotic Spirometru tapeworm. These pseudophyllidean cestodes can have many hosts including monkeys, snakcs, frogs, pigs, and weasels [20].

Spedalskhed Sign

Leprosy.

Spark plug Sign

Brocq methodically scraping is a clinical diagnostic method of psoriasis and is scraping by a teaspoon of plaque psoriasis with what you get initially the formation of small white flakes in the form of chips.

Sign of the spark plug or wax stain, because of its similarity to the material obtained by scratching a wax candle

Spider Sign

The spider angioma of liver eirrhosis [21].

Spoon Nail Sign

Spoon-shaped finger nails, dysphagia, and glossitis. A sign of Plummer-Vinson syndrome, iron deficiency anaemia, and hepatic disease (Fig. 5). Also called koilonychia [22].

Henry Stanicy Plummer

American physician, 1874-1937.

Henry Stanley Plummer, M.D. (1874-1936), was a prominent internist and endocrinologist who, along with William Mayo, Charles Mayo, Stinchfield, E. Starr Judd, Christopher Graham, and Donald Balfour founded Mayo Clinic (Fig. 6).

Plummer's work in internal medicine and endocrinology led to several advances important advances in the specialty, including: Plummer-Vinson syndrome, Plummer's nails, treatment of goiters with iodine, Plummer's disease, and Plummer's sign (used for diagnosis of Graves' disease).

He also directed the development of Mayo's clinical laboratories, as well as bringing in Louis B. Wilson in 1907 to develop and manage the diagnostic and research labs, and was the first to utilize X-ray machines as a diagnostic tool at the Clinic. Will Mayo called Plummer "a pioneer in the development of X-ray diagnosis and therapy". But, perhaps one of his greatest contributions to medicine was the development and implementation of the integrated private medical group practice.

Plummer is considered by many to be the "architect of the modern medical practice." His innovative contributions to medical systems and building designs, as well as his early understanding of the importance of the diagnostic and research aspects of the clinical practice, allowed for the creation of the integrated group practice, as well as medical specialization [23].

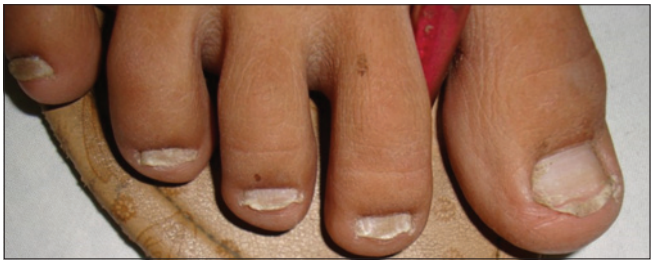

Figure 5: Spoon Nail sign.

Figure 6: Henry Stanicy Plummer.

Porter Paisley Vinson

American physician (1890-1959), was a surgeon at the Mayo Clinic. He was a doctor of Bronchoscopy. Vinson is best known for his contribution to medicine in the study of Plummer–Vinson syndrome. There is an award given in his name to promising students in Chemistry at Davidson College, NC [23].

Stairs Sign

Difficulty in descending a stairway. A sign found with locomotor ataxia or tabes dorsalis [11,24-27].

Stafne's Sign

Stafne's sign is seen in progressive systemic sclerosis. Widening of the periodontal ligament space secondary to increase in the collagen synthesis and increase in the bulk of the ligament, this is accommodated at the expense of alveolar bone, thus causing an increase in the width of the periodontal ligament space [30]. The sign was described by Edward C *Stafne*.

Steinhausen' Sign

Ichthyosis, morbid development of the papillae and thickening of the epidermic lamellae [26]. Also called Porcupine sign.

Sticker's Sign

Synonim of erythema infectiosum [31].

Georg Matthias Martin Josef Sticker

German physician (Fig. 7), 1860-1960. He was a German internist, epidemiologist and medical historian.

From 1880 he studied medicine at the Universities of Strasbourg, Bonn and Göttingen. In late March 1884, he received his doctorate in Bonn with a topic in the field of anatomy (description of a skull with obsolete traumatic unilateral mandibular dislocation). From 1884 to 1887 he worked as an assistant to the internist Franz Riegel at the University of Giessen, was already in 1886 initially in Weilburg and then from 1887 to 1895 settled in Cologne as a practicing physician. From 1895 Sticker was the assistant professor for medical history at the University of Giessen as a polyclinic assistant. In 1895 he habilitated there for the subject of internal medicine. In Gießen he was also appointed in 1898 as an associate professor.

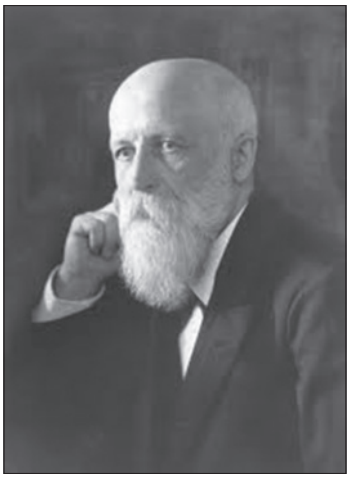

Figure 7: Georg Matthias Martin Josef Sticker.

In 1897 he had been one of the participants in the German expedition led by Georg Gaffky and Robert Koch, which had been sent to Bombay to investigate the bubonic plague that had erupted there. Sticker was able to identify flea and rat as intermediaries of the epidemic.

In 1899 he was the first to describe the Ringelröteln. From 1920 he taught as a full honorary professor at the University of Münster. In 1922 he became a successor to Friedrich Helfreich (1842-1927), who had taught 1896-1919 as Extraordinarius "History of Medicine, Medical Geography and Medical Statistics", full professor of the history of medicine at the University of Würzburg [32].

Straus' Sign

The injection of pilocarpine in facial paralysis due to a central lesion does not cause any difference in the perspiration of the two sides; but if the paralysis be of peripheral origin, the secretion of the paralyzed side is markedly affected [33]. Te sign was described by Isidore Straus (1854-1896) who was a French physician

Strawberry Tongue Sign

The surface of the tongue is coated with a thick white fur, through which protrude bright scarlet red papillae. A sign indicating scarlet fever. Also known as White Strawberry Tongue.

String of beads Sign

Synonim of Linear IgA Bullous Disease. In this disease round or oval blisters filled with clear fluid may arise

from normal-looking skin or from red flat or elevated patches. The blisters may be small (vesicles) or large (bullae). Typically, the blisters are arranged in rings (annular lesions) and they may form a target shape. The tendency for new blisters to arise in a ring around an old one is called the string of beads sign, and groups of small blisters may be described as a cluster of jewels [34,35].

Strychnine Sign

Feeling of suffocation, tetanic convulsions with arched back and blueness of the face, accompanied by raised eyebrows and an evil open grin, called risus sardonicas [35]. A sign indicating poisoning with strychnine. This presentation is similar to signs of a tetanus infection caused by the anaerobic bacterium Clostridium tetani, an important differential is the time between infection and showing the first signs in tetanus is at least five days, whereas strychnine poisoning shows signs ten to twenty minutes after exposure. Also known as Nux Vomica sign after the evergreen tree it is derived from named Strychnos nux vomica.

Sudden whitening of the hair Sign

Marie Antoinette syndrome designates the condition in which scalp hair suddenly turns white. The name alludes to the unhappy Queen Marie Antoinette of France (1755-1793), whose hair allegedly turned white the night before her last walk to the guillotine during the French Revolution. She was 38 years old when she died. Although the actual incidence is rare, this stigmatizing phenomenon, which has captured storytellers' imagination like few other afflictions, occurs to protagonists as a sign of grave sorrow in religious texts as early as the Talmud. History also records that the hair of the English martyr Sir Thomas More (1478-1535) turned white overnight in the Tower of London before his execution. More modern accounts refer to the turning white of hair in survivors of bomb attacks during World War II. In 1957, an American dermatologist witnessed a 63-year-old man's hair turn white over several weeks after he had fallen down some stairs. The patient noticed loss of hair but no bald patches and 17 months later had extensive vitiligo. The term canities subita has also been used for this disorder. Today, the syndrome is interpreted as an acute episode of diffuse alopecia areata in which the very sudden "overnight" graying is caused by the preferential loss of pigmented hair in this supposedly immune-mediated disorder. This observation has led some experts to hypothesize that the autoimmune target in alopecia areata may be related to the melanin pigment system [37].

Sulphuric Sign

Burning pains in mouth and throat with vomit containing white lumps of mucous and altered brown or black blood. Stains on skin and mucous membranes appear bright white, brown or black and stains clothing brown [38]. A sign of sulphuric acid poisoning.

Summer Sign

Characterized by several of the following abnormalities: lack of sweat and sebaceous glands, distress in warm weather, total or partial anodontia, defective hair, and saddle-type nose [39]. Signs of ectodermal dysplasia, an X-linked recessive trait.

Sunbed suntan sacroscapular sparing Sign

Rowland Payne described this sparing sign in connection with the use of sunbeds. The patients are usually young females having a distinct type of uniform tan on body that spares a palm sized area over sacrum and smaller symmetrical areas over the scapular regions on back. The reason is said to be due to skin blanching by vitropression, while lying on transparent tanning bed surface. Since UVA-induced delayed pigmentation is an oxygen-dependent process, the pressure sites are spared of the tan [40].

Sutton Sign

Halo nevi or Sutton nevi are common benign skin lesions that represent melanocytic nevi in which an inflammatory infiltrate develops, resulting in a zone of depigmentation surrounding the nevus [41,42]. Sutton originally described the lesion in 1916 as leukoderma acquisita centrifugum.

Richard Lightburn Sutton

American dermatologist (Fig. 8), 1878-1952. He is known as the namesake for Sutton's disease, also known as aphthous ulceration, or canker sores. He worked as a physician in Kansas City from 1905 until his retirement in 1940 [43].

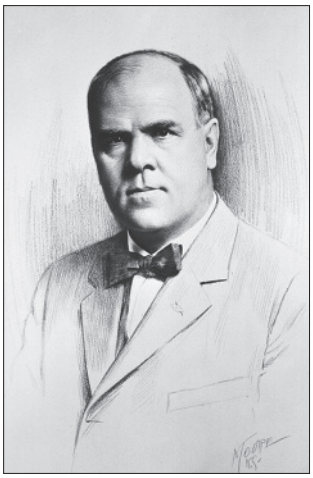

Figure 8: Richard Lightburn Sutton.

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