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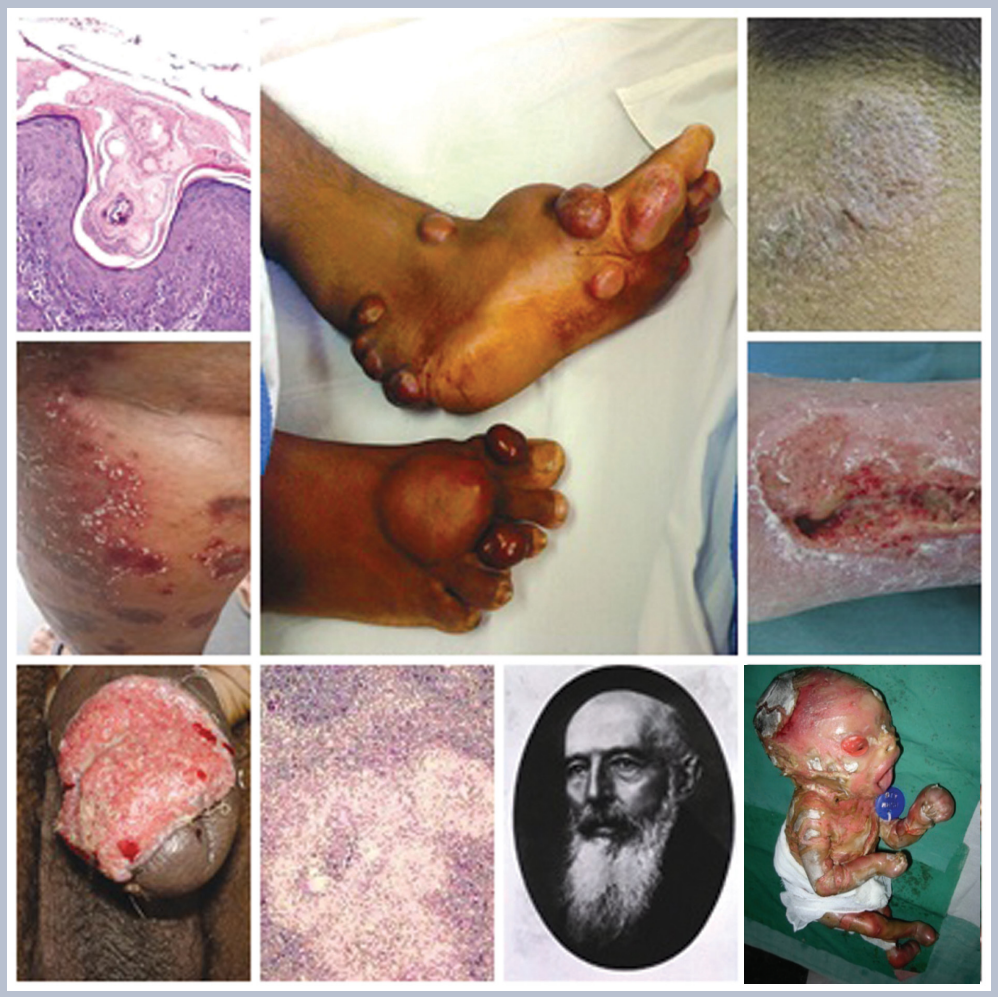

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DERMATITIS HERPETIFORMIS BODIES AND AUTOANTIBODIES TO NONCUTANEOUS ORGANS AND MITOCHONDRIA IN DERMATITIS HERPETIFORMIS

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Abstract
Introduction: The precise nature of the previously described dermatitis herpetiformis bodies remains unknown.
Aims: Our study was conducted to investigate the nature of dermatitis herpetiformis bodies in the skin in 7 cases of dermatitis herpetiformis, and to search for the presence of autoantibodies in other organs.
Methods: We utilized clinical, histopathologic, and immunologic methods to evaluate these patients.
Results: Dermatitis herpetiformis bodies were found to be comprised of an amalgamation of immunoglobulins A and M, as well as molecules reactive with antibodies to armadillo repeat gene deleted in velo-cardio-facial syndrome, desmoplakins 1 and 2, and plakophilin 4. In addition, we found immunologic colocalization with selected autoantibodies associated with mitochondria in the skin, heart, kidney, and peripheral nerves. The dermatitis herpetiformis bodies did not demonstrate immunologic colocalization with tissue/epidermal transglutaminase.
Conclusions: The complete biochemical nature of dermatitis herpetiformis bodies requires further characterization. Dermatitis herpetiformis bodies in these patients appear to be distinctly different than cytoid bodies. Further studies are required to determine if the antibodies to noncutaneous organs are pathogenic, and/or contribute to systemic morbility in dermatitis herpetiformis patients.

Key words: dermatitis herpetiformis; endomysium; mitochondria; plakophilins; p120 ctn molecules; desmoplakins

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Ana Maria Abreu Velez, Hong Yi, Julia Griffin Girard, Zhe Jiao, Mauricio Duque Ramírez, Luis F Arias, Bruce B Smoller, Samuel C Dudley Jr, Michael S.Howard: Dermatitis herpetiformis bodies and autoantibodies to noncutaneous organs and mitochondria in dermatitis herpetiformis. Our Dermatol Online. 2012; 3(4): 283-291

Introduction

Dermatitis herpetiformis (DH), previously known as hydroa or Duhring-Brock disease is an autoimmune, subepidermal blistering disease characterized by IgA deposits in the dermal papillae [1-2]. DH predilects females and Caucasians, and is a rare disease. The eye and oral cavity are very seldom affected. Immunoglobulin, complement and epidermal transglutaminase (eTG) deposition has been previously detected in the cutaneous blood vessels in dermatitis herpetiformis [3]. A gluten dependent enteropathy may accompany DH.

The mucosa of the small intestine is often atrophic in patients with DH, and autoantibodies to gliadin and endomysial antigens have been found in most patients, as well as antibodies to tissue transglutaminase (tTG) [3]. Moreover, DH is also associated against eTG; eTG represents a member of the same protein family as tTG. Further, tissue transglutaminase has been described as the primary autoantigen of celiac disease [3]. However, one study of 132 patients with celiac disease showed that only 15 of them were associated with dermatitis herpetiformis [4]. In another study of 22 patients with dermatitis herpetiformis, the authors searched for IgA antibodies against endomysial antigen (EmA) and tTG and only found these antibodies in 50% and 62.5% of their sera, respectively. Small intestinal biopsies confirmed the presence of celiac disease in only two patients [5].

Pruritus is the predominant DH symptom; the eruption is symmetric, with a predilection for the shoulders, buttocks, elbows, and thighs and extensor areas [1].

The most common dermatologic findings in DH are 1) weals, papules, vesicles or bullae (sometimes grouped), 2) scratch marks (often complicated by secondary pyogenic infections), 3) pigmented macules, and 4) occasional scars following primary lesion healing. The etiology of the disease remains obscure; sulfapyridine and dapsone are therapeutic drugs of choice [1]. The eruption will reappear promptly following complete suppression if therapy is discontinued.

Besides the granular and/or fibrillar deposits of IgA in the dermal papillary tips, the presence of dermatitis herpetiformis bodies (DHBs) in the papillary dermis of affected skin has been demonstrated; their nature remains unknown [6]. Previous studies using Gold conjugated immuno-electron microscopy have demonstrated the DHBs to be IgA positive, and identified amorphous clumps interpreted as immunocomplex aggregates scattered throughout the upper papillary dermis [7]. Dermatitis herpetiformis bodies were seen underneath the basement membrane zone (BMZ), sometimes along microfibrillary bundles, as well as adjacent to papillary collagen fibers and within the microfibrillar region of elastic tissue. Some dermatitis herpetiformis bodies, however, were described as not associated with any fibrillar components. Notably, the collagen and elastic fibers, microfibrillar bundles, anchoring fibrils, and elastic microfibrils per se were unlabelled. In our cases we searched for DH autoantibodies in the skin, in the dermatitis herpetiformis bodies and in other organs to further elucidate their nature.

Material and Methods

We studied 7 cases of DH whose diagnosis was established based on history, clinical and histological features, and immunological tests [1,2]. Before entering the study, all the patients and controls gave written informed consent; the study was approved by the local Ethics Committee. In all patients of the study, histologic examination revealed neutrophilic infiltrates and neutrophilic abscesses; in selected cases, subepidermal blisters were also noted. Classic papillary microabscesses were observed in 5 biopsies. Patients in the study demonstrated by direct immunofluorescence (DIF) the presence of granular deposits of IgA in skin dermal papillae. Indirect immunofluorescence testing was positive for IgA endomysium antibodies (Esophagus monkey IgA EmA, Medizinische Labordiagnostica, Denmark), in 6/7 patients (titer 1:10–1:320, median 1:40). Anti-tissue transglutaminase antibodies were measured using ELISA (Celikey, Pharmacia & Upjohn, Freiburg, Germany), and were present in 4 out of 7 cases (median 4.3 IU/mL). For each patient, we performed two lesional skin biopsies from clinical blisters. The first biopsy was fixed in 10% buffered formalin and submitted for hematoxylin and eosin (H&E) staining, as well as immunohistochemistry (IHC). The second biopsy was placed in Michel's transport medium, and submitted for DIF. Serum was obtained for IIF studies. Our DIF, IIF and IHC studies were performed as previously described [7-13]. As controls, we tested skin from seven healthy patients undergoing breast and/or abdominal aesthetic reduction surgeries. Biliary cirrhosis was ruled out in all the subjects of the study.

Colocalization of dermatitis herpetiformis bodies with known antibodies utilizing confocal microscopy:

We utilized standard 20 and 40X objective lenses; each photoframe included an area of approximately 440 x 330 μm. Images were obtained using EZ-1 image analysis software (Nikon, Japan). For colocalization experiments with the dermatitis herpetiformis serum autoantibodies, we used antibodies to desmoplakins 1 and 2, (DI-DPII), armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF) and anti-p0071 (Progen Biotechnik, Heidelberg, Germany). Our studies were performed as previously described [7-13].

Immunoblotting (IB):

IB testing was performed as previously described [12]. In brief, we used sodium dodecyl sulfate (SDS) extracts of human and bovine epidermis fractionated by 7% SDS polyacrylamide gel electrophoresis (SDS-PAGE) according to the Laemmli method [9,10,14]. Gels were transferred onto nitrocellulose membranes (5,10). As experimental controls, we utilized 1) an anti-desmoplakin multiepitope cocktail from Progen (Heidelberg, Germany), 2) the serum of a patient with bullous pemphigoid that recognized bullous pemphigoid antigens 1 and 2 (230 and 180 kDa, respectively), and 3) serum from a patient with paraneoplastic pemphigus. Our IB was performed as previously described [7-13].

Direct and indirect immunofluorescence (DIF and IIF):

For DIF and IIF, sera from all subjects were titrated in PBS IX buffer at 1:25 and 1:40 dilutions. We then incubated the substrate tissues with the serum. We next added the secondary antibodies; we utilized FITC conjugated rabbit anti-total IgG (Dako, Carpinteria, California, USA) and FITC conjugated rabbit anti-human IgG4 (gamma chain; Sigma Aldrich, Saint Louis, Missouri, USA) at dilutions 1: 20 and 1:40, respectively. For IIF, the antigen source was monkey esophagus (ME). The samples were run with positive DH control sera and a negative control serum. For the DIF, we used FITC conjugated rabbit antisera to human IgG, IgA, IgM, C1q, C3, fibrinogen and albumin. Anti-human IgA antiserum (alpha chain) and anti-human IgM antiserum (mu chain) were obtained from Dako.

Anti-human IgE antiserum (epsilon chain) was obtained from Vector Laboratories (Burlingame, California, USA). Anti-human IgD FITC-conjugated antibodies were also used (Southern Biotechnology, Birmingham, Alabama, USA).
The slides were counterstained with 4',6-diamidino-2-phenylindole Dapi (Pierce, Rockford, Illinois, USA). Mouse anti-collagen IV monoclonal antibody (Invitrogen, Carlsbad, California, USA) was used with a secondary donkey anti-mouse IgG (heavy and light chains) conjugated with Alexa Fluor 555 (Invitrogen).

Immunohistochemistry (IHC):
We performed IHC to differentiate between specific autoreactivity and non-specific intrinsic autofluorescence (produced by the physiological presence of autofluorescent molecules), using antibodies conjugated with horseradish peroxidase (HRP)-labelled secondary antibodies. We utilized multiple monoclonal and polyclonal antibodies, all from Dako (Carpinteria, California, USA). For all our IHC testing, we used a dual endogenous peroxidase blockage, with the addition of an Envision dual link (to assist in chromogen attachment). We applied the chromogen 3,3-diaminobenzidine, and counterstained with hematoxylin. The samples were run in a Dako Autostainer Universal Staining System. Positive and negative controls were consistently performed. Our studies were specifically performed as previously described [7-13].

Indirect immunoelectron microscopy (IEM):
Our technique was performed as previously described [7-13]. In brief, postembedding immunogold labeling was performed on samples of El Bagre-EPF sera and controls. Peripheral rat nerve was used as an antigen; the tissue was dissected, fixed in 4% glutaraldehyde with 0.2% paraformaldehyde, and embedded in Lowicryl® resin. The tissue was then sectioned at 70 nm thickness. The samples were blocked with a solution from Aurion™ (Electron Microcopy Sciences/EMS, Hatfield, Pennsylvania, USA). Our tissue grids were then washed with PBS-BSAC (Aurion™, EMS). The primary antibodies were incubated overnight at 4°C. The next day the grids were again washed, and a secondary antibody solution, specifically 10 nm gold-conjugated protein A PBS BSAC (Aurion, EMS™) was applied. The samples were then double-stained with uranyl acetate and lead citrate. The samples were observed under a Hitachi H7500 transmission electron microscope. Immunogold particles displaying any pattern of positivity were converted to TIF format.

Results

Histologic findings:
Examination of the H&E tissue sections demonstrated a focal, subepidermal blistering process in 6/7 of our biopsies. Specifically, multiple, punctuate subepidermal vesicles were present at the tips of the dermal papillae, with numerous neutrophils noted within the vesicular lumens in 7/7 cases. Occasional eosinophils were also present. In all biopsies, the papillary dermis contained a mild, superficial, perivascular infiltrate of lymphocytes, histiocytes and neutrophils; eosinophils were rare. No definitive evidence of an infectious, or a neoplastic process was observed. No dyskeratosis or acantholysis was noted. The control biopsy findings were negative for blisters and neutrophilic infiltrates.

Immunofluorescence studies:
DIF studies displayed the following positive results: IgG (+, in the dermatitis herpetiformis bodies and weakly positive granular staining at the BMZ) in 6/7 cases; IgG3 and IgG4 (+, diffuse positivity in the upper dermal papillae); IgA (+++, granular deposits at the BMZ in 7/7 cases, accentuated at the tips of dermal papillae; also in the DHBs); IgM, anti-kappa and anti-lambda light chains (++, positive in the dermatitis herpetiformis bodies, and granular deposits at the BMZ); IgD (-); IgE (++, several positive cells around dermal blood vessels); complement/C1q (+/-, granular deposits at the BMZ); complement/C3 (++, granular at the BMZ, and accentuated at tips of dermal papillae); albumin(+/-, granular at the BMZ) and fibrinogen (+++, granular at the BMZ, accentuated at tips of the dermal papillae and positive in the dermatitis herpetiformis bodies). The IIF utilizing monkey esophagus (ME) substrate (Oregon National Primate Center, Beaverton, Oregon, USA) showed positive endomysial antibodies, with both IgA and IgM in 6/7 cases. The dermatitis herperpetiformis bodies did not demonstrate colocalization with tissue/epidermal transglutaminase, which was positive in only 3/7 cases and in none of the controls

Immunohistochemical studies:
IHC demonstrated cells positive for Factor XIIIa in the papillary and reticular dermal interstitial tissue and around the upper dermal blood vessels in 3 biopsies. Several cells were also positive and displayed a similar dermal staining pattern with antibodies to myeloid/histoid antigen, mast cell tryptase (MCT) and c-kit (CD117). The CD1a marker was relatively normal, without evidence of a pathologic pattern (Fig. 1, 2). The figures display several representative photomicrographs showing von Willebrand factor (VWF) overexpression; antibodies to IgA, IgG, IgM, kappa and lambda light chains, fibrinogen, albumin, complement/C1q, complement/C3c, and complement/C3d were also positive in similar patterns. Of importance, the positive reactivity of these immunoglobulins and complement components was not only observed by IHC, but also confirmed via DIF and IIF.

Discussion

Given our data, we suggest that dermatitis herpetiformis bodies are complex structures composed of an agglomeration of several immunoglobulins (IgA, IgM and to a lesser extent, IgG). In addition, fibrinogen, complement/C3 and molecules that react with ARVCF [specifically, desmoplakins 1 and 2 and plakophilin 4 (p0071)] seem to be colocalizing with the dermatitis herpetiformis bodies. Previously, other authors have described deposits of fibrin within DHBs in some patients with DH [14,15].

It has been previously suggested that circulating IgA and IgG EmA and tTG antibodies are detected in almost all patients in the acute phase of dermatitis herpetiformis, and that these markers follow the clinical course of the disease. However, we were not able to colocalize these markers within DHBs. Other authors however have found an association between levels of IgA antibodies to tissue transglutaminase and gliadin-related nonapeptides in dermatitis herpetiformis [16].

We did find colocalization of desmoplakins 1 and 2, p0071 and ARVCF molecules with the dermatitis herpetiformis bodies. Several of these molecules are linked to neuro-vascular structures; perhaps these findings can explain the pruritus seen in DH patients. Of interest, several molecules of the armadillo repeat motif are necessary to maintain barrier function and intestinal homeostasis [17,18]. ARVCF, an armadillo repeat protein of the p120 catenin (ctn) family, associates with classical cadherins. Plakophilins 1-3 are also members of the p120 (ctn) family [17,18]. The plakophilins have been characterized as desmosomal proteins, while p120 (ctn) and the closely related delta-catenins ARVCF and p0071 associate with adherens junctions and play indispensable roles in stabilizing cadherin-mediated adhesion. Recent evidence suggests that plakophilins are essential components of the desmosomal plaque, where they interact with desmosomal cadherins as well as the cytoskeletal linker protein desmoplakin [17,18]. The three plakophilins exhibit distinct expression patterns, and although partially redundant in their function, mediate distinct effects on desmosomal adhesion. In our patients, we showed colocalization of several of these molecules [e.g. ARVCF, desmoplakins 1 and 2 and plakophilin 4 (p0071)] with the DH antibodies by both DIF and CFM. All of these molecules are present in the skin, heart, kidney, intestine and nerves.

Correlating our immunoblotting studies, our patients displayed autoantibodies with the same molecular weights (MWs) as the molecules we found to be colocalizing with the dermatitis herpetiformis bodies, including p0071 (135 kDa MW) ARCVF (97 kDa MW), and desmoplakins 1 and 2 (250 and 210 kDa MW, respectively). Therefore, we cannot exclude the possibility that patients with DH could have autoantibodies to these molecules. Similar reactivity has been recently described in patients with PNP that recognize plakophilin 3, a member of the p120 (ctn) family [19]. In addition, we showed that our patients displayed cytoid bodies. Cytoid bodies are predominately formed by IgM, and/or fibrin not colocalizing with the immunoglobulins, complement components and other molecules described above.

In addition, our and other authors' previously published articles suggest that our findings of autoantibodies to peripheral nerve axons may contribute to the clinical pruritus, metamerical grouping and flexoral distribution of DH lesions [20,21]. We can exclude that the neural reactivity was due to a side effect of dapsone [22], since this medication was initiated only after skin and blood samples were obtained from our patients. Recently, other authors also described the expression of selected neuropeptides in the pathogenesis of bullous pemphigoid and dermatitis herpetiformis [20]. Our findings using immunoelectron microscopy and immunogold antibodies clearly show deposits of autoantibodies in the peripheral nerves. We thus speculate that our findings may explain the metamerical, grouped and pruritic nature of DH lesions. Further studies are necessary to confirm our hypothesis.

In our patients, we also confirmed autoreactivity against the kidney; others have also described these associations [23,24]. Specifically, immunoreactivity to the kidney has been also previously documented in patients with DH exhibiting normal kidney function. Indeed, electron microscopy performed on some patients with DH who had no previous signs or symptoms of renal disease demonstrated mesangial deposits, and subsequent renal biopsy and DIF revealed IgA and complement deposits in the glomeruli. Renal involvement was not related either to the degree of jejunal villous atrophy, or to the deposition of IgA and complement in the skin. Glomerular deposits, however, were associated with a high frequency of circulating IgA and IgG subclass immune complexes and IgA subclass antigliadin and antireticulin antibodies [23,24].

Other authors have also found alterations within the heart associated with some patients suffering from DH [25,26]. We suggest that our findings may be pertinent in this context.

We also detected autoantibodies to heart and kidney mitochondria in the sera from patients affected by dermatitis herpetiformis. Other authors have described antimitochondrial autoantibodies in pemphigus vulgaris as a missing link in disease pathophysiology [27]. We also described antimitochondrial autoantibodies in a new variant of endemic pemphigus foliaceus in El Bagre, Colombia, South America [27].

Since DH is a rare disease, further studies with larger numbers of patients are needed to confirm our data regarding the nature of dermatitis herpetiformis bodies. Moreover, although transglutaminase has been described as a primary antigen for DH, it is possible that many other DH antigens remain to be discovered in the skin, other organs, and in mitochondria.

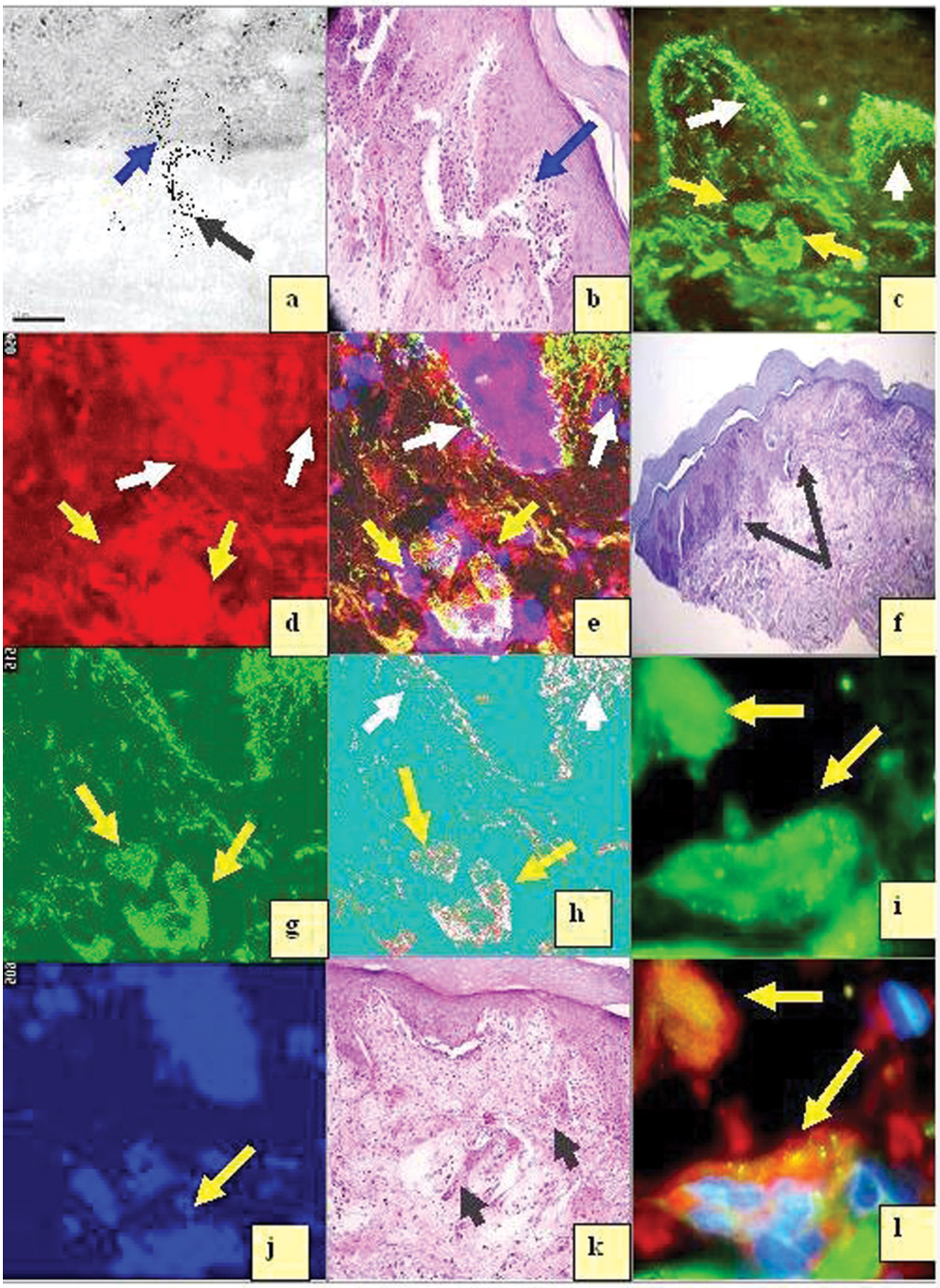

Figure 1. Dermatitis herpetiformis bodies detected using multiple test modalities

Figure 1. a IEM positive deposits of 10nm Gold particles near the BMZ of the skin; the black arrow highlights the staining at the BMZ, and the dark blue arrow shows staining in the upper papillary dermis. **b.** H&E staining demonstrating a DH subepidermal blistering process with dermal edema and multiple luminal neutrophils (blue arrow) (100x). **c.** DIF positive staining utilizing FITC conjugated anti-human IgA at the dermal papillary tip BMZ ("snow on the mountain" pattern; green staining, white arrows). Also note positivity on a DHB in the papillary dermis (green staining; yellow arrows). **d.** CFM utilizing Texas red conjugated anti-armadillo repeat deleted gene in velo-cardio-facial syndrome (ARVCF) antibody (Progen, Heidelberg, Germany) shows positive staining in the papillary dermis (white arrows) and in DHBs (yellow arrows). **e.** CFM confirming colocalization between FITC conjugated human IgA antibodies (green staining) and the Texas red conjugated ARVCF antibodies (red staining). The white arrows highlight colocalizations at the BMZ on the tips of the dermal papillae, and the yellow arrows highlight positivity in DHBs. **f.** PAS positive staining highlighted at the BMZ, where the primary inflammatory process is present (faint red staining; black arrows). **g.** CFM utilizing FITC conjugated anti-human IgA antibodies alone (green staining) showing positivity within dermal papillae on DHBs (yellow arrows). **h.** A CFM silhouette of e, showing colocalization of antibodies to IgA and ARVCF (white arrows at the BMZ, yellow arrows on DHBs). **i.** DIF showing staining of the DHBs using FITC conjugated anti-human IgA (green staining; yellow arrows) and in l, colocalizing this antibody with Texas red conjugated ARVCF (yellow arrows). In l, note the upper DHB contains no cell nuclear material, whereas the lower DHB contains blue nuclear material, counterstained with Dapi (4',6-diamidino-2-phenylindole). Note Dapi nuclear counterstaining of pertinent areas in **d, e, g,** and **h.** Please also note that some areas of the DHBs reveal no nuclear material, and other areas contain nuclear material. **j.** Same as g, with only Dapi staining. **k.** H&E shows eosinophilic material in the dermis where the DHBs are located (black arrows).

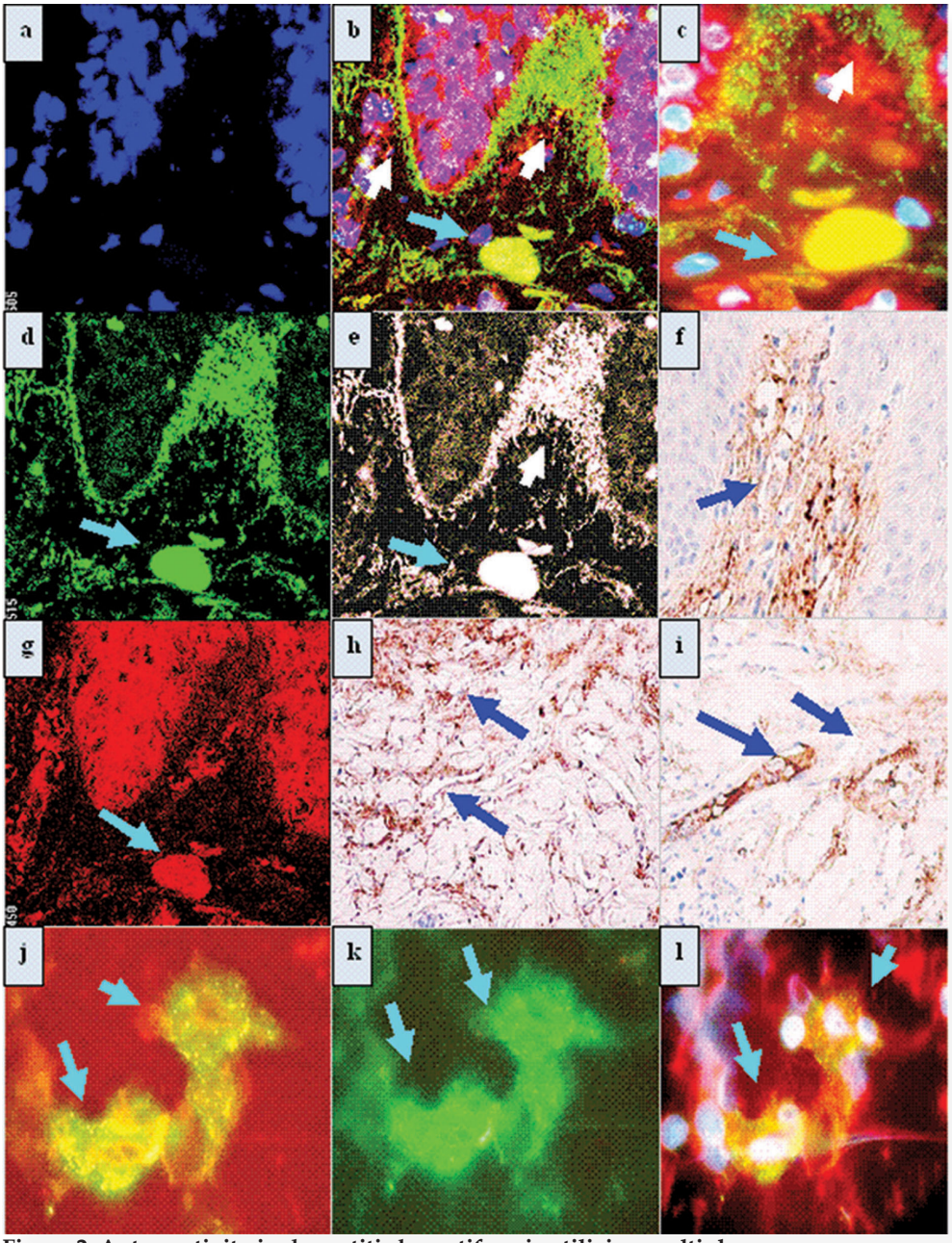

Figure 2. Autoreactivity in dermatitis herpetiformis utilizing multiple assays

Figure 2. Shows representative images demonstrating that both ARVCF antibody and an antibody against combined desmoplakins I and II (DPI-DPII) (Progen) stain the DHBs. Figures **a, b, d, e** and **g** represent CFM. **a.** Dapi counterstaining of epidermal keratinocyte nuclei in blue. **b.** Shows CFM colocalization of antibodies (FITC conjugated IgA in green, and Texas red conjugated DPI-DPII in red). The white arrows indicate positivity at the BMZ and dermal papillae; the light blue arrow to a DHB. **c.** DIF image of the IgA and DPI-DPII colocalization, showing similar results to **b. d** Positive CFM staining against the BMZ and dermal papillae, as well as to a DHB (light blue arrow) utilizing FITC conjugated anti-human IgG (green staining). **e.** A CFM silhouette of the overlapping antibodies in **b.** The white and light blue arrows are defined in **b. f** IHC staining with IgA on upper dermal blood vessels (brown staining, blue arrow). **g.** Positive CFM staining utilizing Texas red conjugated DPI-DPII (red staining); the light blue arrow points to a DHB. **h.** IHC staining of dermal blood vessels with anti-human IgM (brown staining; blue arrows); in **i,** similar IHC staining with anti-fibrinogen (brown staining; blue arrows). **j, k** and **l** demonstrate positive DHB DIF staining. In **j,** colocalized FITC conjugated anti human IgA (yellow-green staining) and Texas red conjugated anti-DPI-DPII antibodies (red staining) (light blue arrows). In **k,** DIF similar to the j image, utilizing only FITC conjugated anti-IgA (green staining; blue arrows); **l.** Similar to the **j** DIF image, but also including nuclear counterstaining with Dapi (white/blue staining, light blue arrows).

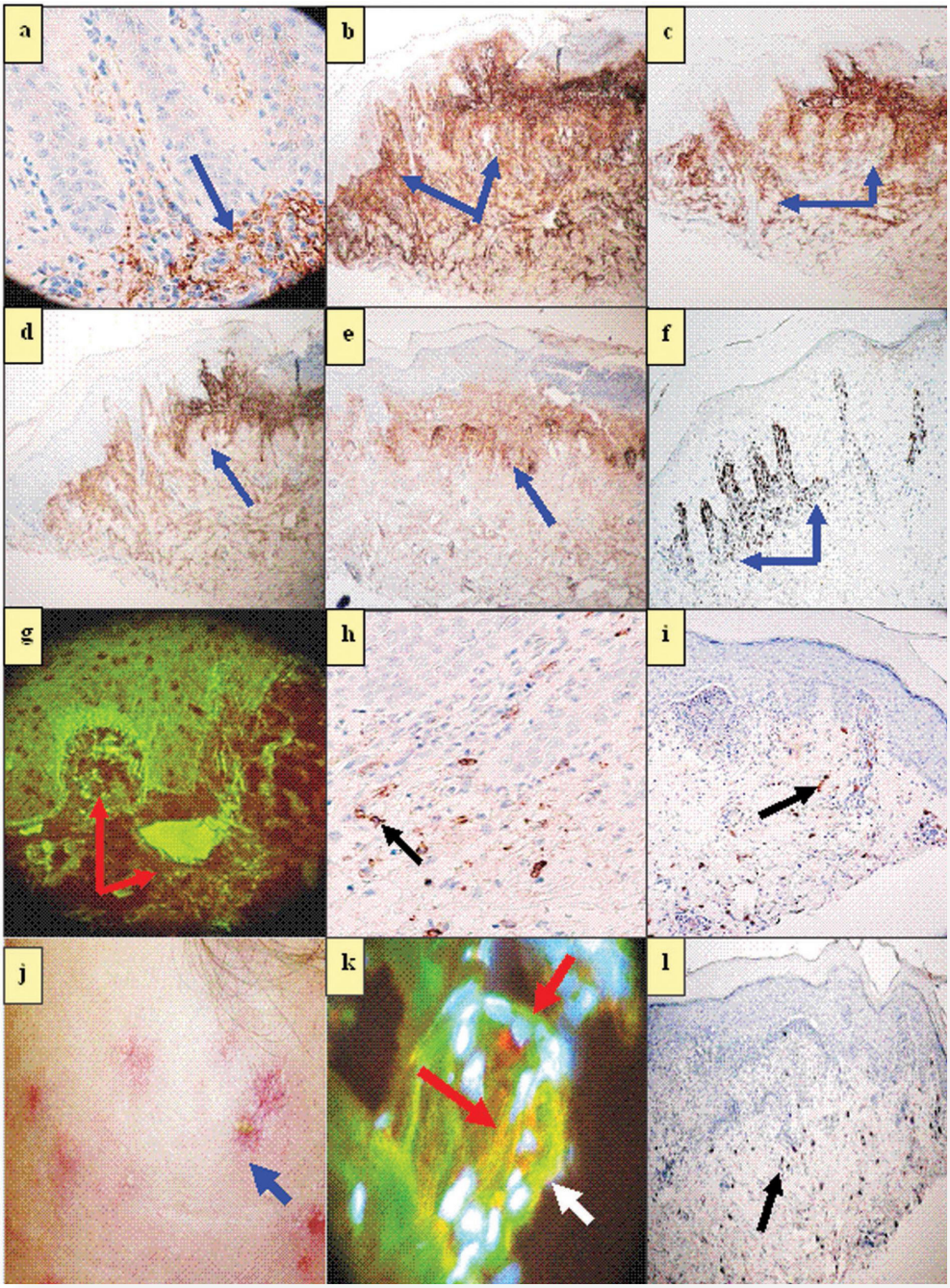

Figure 3. Clinical lesions, immunohistochemistry and immunofluoresence in dermatitis herpetiformis

Figure 3. a IHC positive staining for anti-human IgM around papillary dermal blood vessels (blue arrow, brown staining). **b.** Strong deposition of albumin detected in the dermis by IHC, in areas of the autoimmune reaction (brown staining, blue arrows). In **c,** strong IHC deposits of complement/C3c are noted in the same dermal areas as in **b** (brown staining, blue arrows); in **d,** robust IHC deposits of fibrinogen in these areas (following the pattern of positivity of IgM, C3c and albumin; brown staining, blue arrow). **e.** Shows that the highly reactive areas shown in **a** through **d** also have simultaneous IHC overexpression of von Willebrand factor (VWF) (brown staining, blue arrow). Please note that there is differential expression (or compartmentalization) of the VWF positivity; the expression is seen primarily in the papillary dermis, with a more delicate presence in the subjacent reticular dermis. **f.** IHC staining with compartmentalization of the autoimmune response, utilizing myeloid/histoid antigen antibody; concentrated staining is noted in the dermal papillae (black staining, blue arrows) **g.** DIF also shows positive staining for FITC conjugated anti-IgM (green staining) at the BMZ, as well as in the papillary dermis and on a DHB (red arrows). **h.** Positive IHC staining of multiple individual dermal cells with anti-IgE, especially around dermal blood vessels (brown staining, black arrow). **i.** We also detected several positively stained cells with anti-Factor XIIIa in the dermis by IHC (brown staining, black arrow). **j.** A classic clinical lesion, showing ruptured, punctate blisters on an erythematous, macular base (blue arrow). **k**. Colocalizing positive DIF staining against a dermal nerve subjacent to a clinical blister and inflammation. The colocalization is performed utilizing FITC conjugated anti-human-IgM (green staining, white arrow) and Cy3 conjugated monoclonal anti-glial fibrillary acidic protein (GFAP) (red-orange staining, red arrows). **l.** IHC staining with mast cell tryptase (MCT) around dermal blood vessels at the periphery of the primary autoimmune response (brown staining, black arrow).

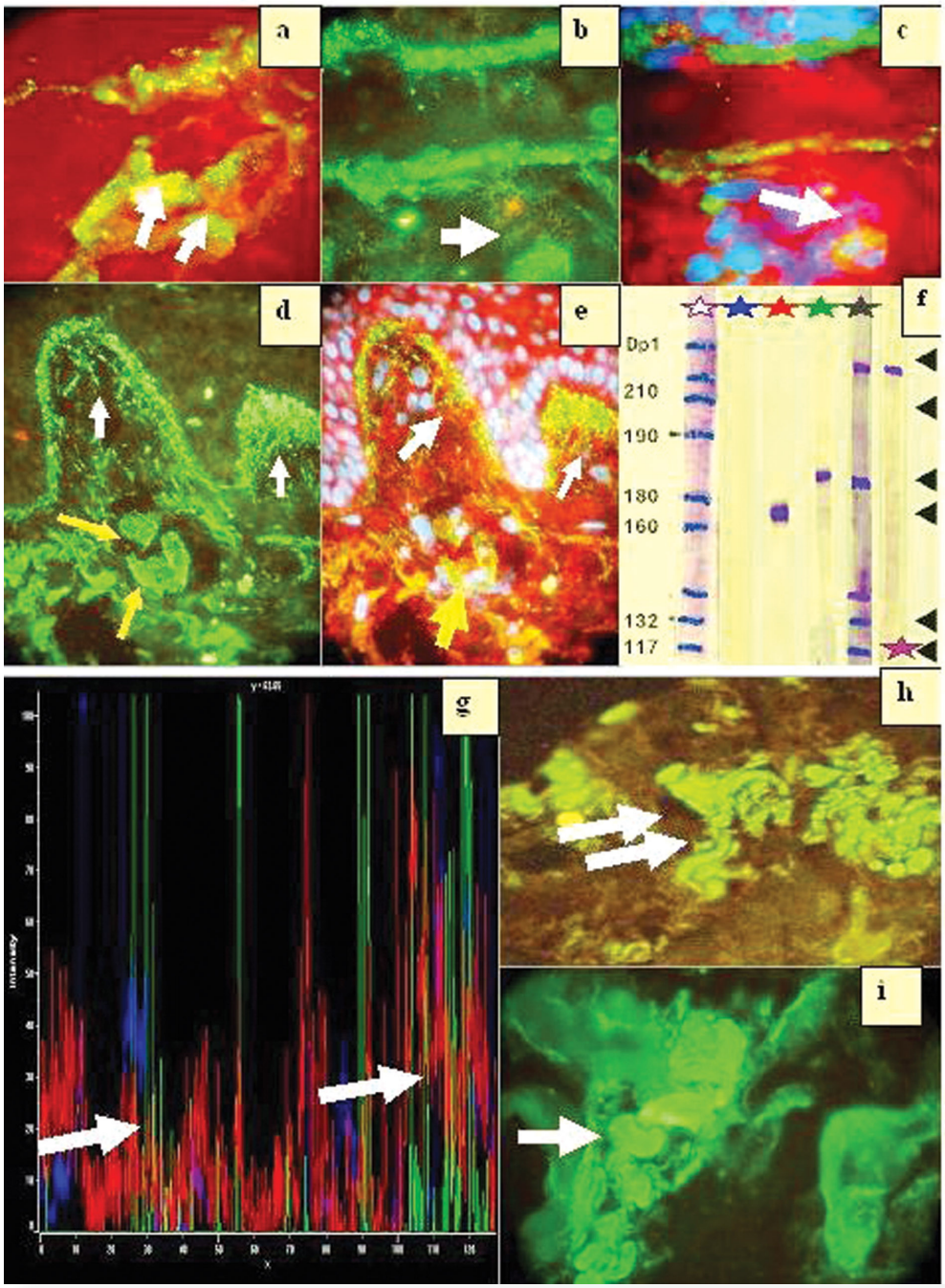

Figure 4. Immunologic findings, immunoblotting and confocal microscopy in dermatitis herpetiformis

Figure 4. Shows some representative pictures with colocalization of patient autoantibodies and p0071 antibodies, differentiating the DHBs from cytoid bodies. In **a,** DIF positive staining with FITC conjugated IgA at the BMZ and against a DHB (yellow-green staining) colocalizing with Texas red conjugated p0071 antibody (red staining) (white arrows). Note the staining within the DHB appears as multiple dots. **b,** Similar to **a,** but only with anti-IgA, without staining for p0071 (yellow staining; white arrow). **c.** Similar to **a,** but with additional nuclear counterstaining with Dapi (blue staining), demonstrating that the dermatitis herpetiformis bodies contain nuclear debris (white arrow). **d** and **e,** lower magnification images of **b** and **c,** respectively, showing that the dermatitis herpetiformis bodies (yellow arrows) represent discretely different staining structures vis-a-vis nearby staining to the papillary tips and BMZ (white arrows). **f.** Immunoblotting; the first lane (white star) shows the reactivity of a paraneoplastic pemphigus serum used as a positive control. Desmoplakin is represented by the highest band. The second lane (blue star) is a negative control. The third lane (red star) is a serum positive control, from a patient affected with pemphigus foliaceus (note positivity for the 160 kDa antigen, desmoglein 1). The fourth column (green star) is a positive control serum from a patient affected with bullous pemphigoid (note the bullous pemphigoid 2 antigen at 180 kDa). The fifth column (brown star) is one of the patient's DH serum; please note the presence of bands around 250-230 kDa; these bands represent desmoplakins, confirmed by the sixth column. In the fifth column, please also notice that three additional bands of 140, 132 and 117 kDa are present. The sixth column (bottom pink star) is a control monoclonal desmoplakin protein (Progen). **g.** CFM data, demonstrating precise colocalization of several peaks of the Texas red conjugated antibody to p0071 (red peaks) with FITC conjugated IgA (green peaks) (white arrows). The blue peaks represent Dapi nuclear counterstaining. **h** and **i** Globular cytoid body deposits of immunoglobulins; in **h,** FITC conjugated IgM (yellow staining, white arrows), and in **i,** FITC conjugated fibrinogen (green staining, white arrow). These cytoid body findings did not colocalize with other antibodies staining the DHBs (i.e., p0071, ARVCF, and IgA).

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A COMPARATIVE STUDY OF PSORIASIS AND PSORIASIFORM LESION ON BASIS OF CD4 AND CD8 CELL INFILTRATION

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Abstract
Introduction: Psoriasis is a chronic inflammatory skin disorder with immunological factors playing an important role in its pathogenesis. It is now regarded as a T cell mediated disorder in which lymphocytic infiltrates, mainly CD4 and CD 8 cells which provide a major contribution in the initiation and maintenance of psoriatic lesions.
Material and Methods: Skin biopsies from both psoriatic and psoriasiform lesions were stained with monoclonal antibodies against CD4 and CD8 and their percentage was calculated in the epidermis, upper dermis and lower dermis.
Results: The difference of mean value of percentage of CD4 cells, among psoriasis and psoriasiform lesion in the epidermis was statistically insignificant (p=0.228), while it was significant in the upper dermis (p=0.002) and in lower dermis (p=0.043). The difference in the value of percentage of CD 8 cells was statistically significant in the epidermis (p=0.007), upper dermis (p=0.005), and the lower dermis (p=0.043).
Conclusions: Both CD4 and CD 8 T cells are present in the appropriate anatomic locations to sustain lesional skin pathology in psoriasis and psoriasiform lesions.

Key words: psoriasis; psoriasiform; CD4; CD8

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Introduction

Psoriasis is a chronic, non-pruritic disease characterised by erythematous plaques, covered by fine silvery scales. It is a common chronic inflammatory skin disorder affecting approximately 1.5-2% of the population in western countries and 1.3% in general population [1]. Typically it involves extensor surfaces such as elbows, knees, back and scalp [2]. Histologically it is characterised by confluent parakeratosis,acanthosis with regular elongation of rete ridges, suprapapillary thinning, presence of spongiform pustules, diminished to absent granular layer and presence of Munro microabcesses. Dermis on the other hand shows elongation and edema of dermal papillae alongwith presence of dilated and tortuous capillaries.

Psoriasis is an autoimmune skin disease characterised by T-cell mediated hyperproliferation of keratinocytes. Immunological factors are known to play an important role in the pathogenesis of psoriasis. It is now regarded to be a T-cell mediated disorder with T-lymphocyte predominance in the inflammatory infiltrates, mainly CD4+ (helper/inducer) lymphocytes alongwith CD8+ (suppressor/cytotoxic) subsets are known to occur [3,4]. T-lymphocytes in psoriatic lesion are known to be in an activated state with expression of HLA-DR and IL-2 receptor. Pathologic collaboration between innate immunity (mediated by antigen presenting cells and NK-T lymphocytes) and acquired immunity (mediated by T-lymphocytes) results in production of cytokines, chemokines and growth factors that contribute to inflammatory infiltrate seen in psoriatic plaques [3,4]. CD4+ T-cells are important in initiating and maintaining the pathogenic process of psoriasis but that cross-primed CD8+ T-cells are the main effector cells [5].

The presence and potential importance of T-cells in the epidermis was emphasized in the pathogenesis of psoriasis. Mixtures of CD4+ T-cells and CD 8+ T-cells were found in papillary dermis and epidermis of psoriatic lesion [6].

More so, it has been suggested that spontaneous remission or fluctuation in the activity of disease is determined by balance within the lesion between effector and suppressor, CD4+ and CD8+ T-cells respectively.

Psoriasiform lesions on the otherhand have clinical and histological features similar to psoriasis (Fig. 1). Allergic contact dermatitis, seborrhoeic dermatitis, Atopic dermatitis, Pityriasis rubra, Lichen simplex chronicus are considered as psoriasiform lesions. T-cell play a role in the pathogenesis of psoriasiform lesions more so in atopic dermatitis. Studies have reported a high proportion of CD4+ T-cells in the dermis on immunohistochemical analysis [7].

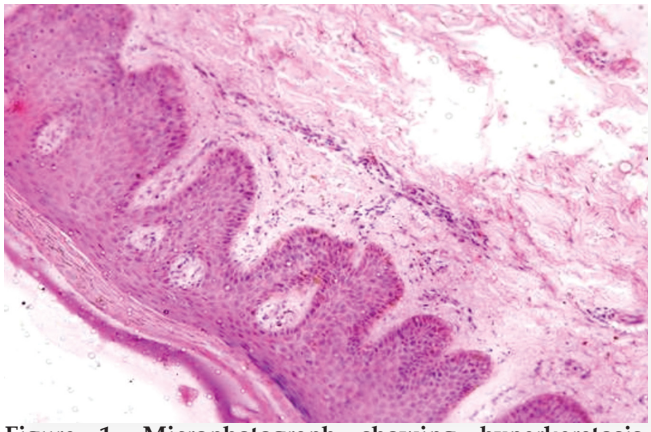

Figure 1. Microphotograph showing hyperkeratosis, parakeratosis and irregular acanthosis in psoriasiform dermatitis (20X, H&E)

The presentation in inflammatory cells in the skin is exceedingly heterogenous. By means of potent antigen presenting cells, cytokines and chemokines, lymphocytes, the skin is able to respond very efficiently to pathogens that threaten the individual. T-cell infiltration in psoriasis has recently been an important subject of investigation. Comparative analysis of lesional T- cell infiltrate in psoriasis and psoriasiform dermatitis has only been sparingly performed. Our study aimed at evaluating and comparing CD4 and CD8 cell distribution in psoriasis and psorisiform lesions.

Material and Methods

Skin biopsies from 25 cases each of psoriasis and psoriasiform lesions were included in the present study. The diagnosis of psoriasis was confirmed on the basis of clinical features (pink to red papules with fine silvery scales and positive Auspitz sign) in conjunction with classical histological changes. The psoriasiform lesions included in our study were endogenous eczema, hyperkeratotic eczema, seborrhoeic dermatitis, nummular eczema, allergic contact dermatitis, irritant contact dermatitis, Lichen simplex chronicus and pityriasis rosea.

The biopsies obtained were processed, sections cut and stained with Haematoxylin & Eosin (H&E).Stained sections were examined under light microscope for histopathological characterization of the lesion. The epidermis, upper dermis and lower dermis were examined for the presence of inflammatory infiltrate, the nature of infiltrate was categorised as neutrophils or lymphocytes. It was graded as: 0-no infiltrate, 1-mild infiltrate, 2-moderate infiltrate, 3-marked infiltrate.

Sections were obtained and immunohistochemical staining for CD 4 and CD 8, (Bio Genex, USA) using the streptavidin biotin peroxidise method was performed. Simultaneously, CD4 and CD8 stained sections were examined and their percentage was determined among the lymphoid cells in epidermis, upper dermis and lower dermis. Statistical analysis was done. The data of grading of inflammation was categorical in nature, hence chi-square test was applied to study the difference between psoriasis and psoriasiform lesion. The data of CD4 and CD8 T-cell distribution was normally distributed, hence students t-test was applied to study the difference. A p value of $p<0.05$ was considered statistically significant.

Results

Grades of inflammation were assesed in both psoriasis and psoriasiform lesions on the H&E stained sections and results are as in Table I. The inflammation in the epidermis was present in 11 cases (44%) of psoriasis and all were of mild grade comprising of mixtures of polymorphs and lymphocytes. The mean of the percentage of polymorphs was calculated out of total inflammatory cells and among the positive cases, it was 67% (SD=16), whereas that of lymphocytes was 33% (SD=16). In the upper dermis (upper dermis), inflammation was evident in all the 25 cases (100%) and it was mostly of moderate grade. Polymorphs were seen in 21 cases (84%) with a mean percentage of 23% (SD=15.22) and lymphocytes in all the 25 cases (100%) had a mean of 83% (SD=16.4).

Inflammation in the lower (reticular) dermis was present in 18 cases, (72%) mostly of mild grade, with polymorphs in only 3 cases (12%) and the mean among positive cases was 23% (SD=23.10) while lymphocytes were evident in 18 cases (72%) with amean value of percentage of cells as 96% (SD=11.95). None of the case showed presence of only polymorphs. Polymorphs if seen in cases of psoriasis were associated with lymphocytes (Tabl. I).

In psoriasiform lesions the inflammation was present in the epidermis in only 2 cases (8%), both showing mixtures of polymorphs and lymphocytes. Mean value of percentage of polymorphs in positive cases was 50% (SD=0) whereas that of lymphocytes was 50% (SD=0). Within the upper dermis, all the 25 cases (100%) showed inflammation with grade 2 inflammation in maximum number of cases. In 22 cases (88%), polymorphs were seen with a mean value of cells in positive cases as 26.36% (SD=17.54), lymphocytes in all the cases (100%), mean 76.80% (S.D=18.59). Only four cases (16%) in the lower dermis showed inflammation, three having mild and one severe inflammation. One case (4%) had polymorphs with a mean value of 30% while 4 cases (16%) had lymphocytes with a mean value of percentage of cells as 92.50% (S.D=15.0) (Tabl. I).

Immunohistochemical staining was done and the distribution of CD4 positive cells was seen in psoriasis patients. In the epidermis only 5 cases (20%) were positive and the mean value of percentage of cells in the positive cases was 30% (SD=20). In the upper dermis, CD 4 cells were present in 23 cases (92%) with a mean value of 35% in positive cases (SD=21.24) (Fig. 2). In the lower dermis, 11 cases (44%) were positive for CD 4 cells with mean of 34% (SD=24.47) (Tabl. II).

CD 8 positive cells on the other hand were seen in the epidermis in 10 cases (40%) and the mean among positive cases was 82% (SD=21.50). In the upper dermis, all the 25 cases showed CD 8 positive cells with mean value of 65% (SD=21.70) (Fig. 3). In the lower dermis, CD8 positive cells were found in 17 cases (68%) with a mean value of 75% (SD=26.66) (Tabl. III), (Fig. 4).

Grade	Epidermis		Upper Dermis		Lower Dermis	
	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form
0 (nil)	14	23	0	0	7	21
1 (mild)	11	2	2	8	13	3
2 (moderate)	0	0	15	15	5	0
3 (severe)	0	0	8	2	0	1

Table I. Grades of inflammation in psoriasis and psoriasiform cases

% of CD 4 positive cells	Epidermis (No. of cases)		Upper Dermis (No. of cases)		Lower Dermis (No. of cases)	
	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form
0	20	23	3	1	14	21
1-10	2	1	6	1	3	2
11-20	0	0	3	3	1	0
21-30	1	0	4	0	2	0
31-40	0	0	1	2	1	0
41-50	2	1	3	3	2	0
51-60	0	0	3	5	0	0
61-70	0	0	1	5	0	0
71-80	0	0	1	1	0	2
81-90	0	0	0	4	2	0
91-100	0	0	0	0	0	0

Table II. Comparison of distribution of CD4 positive cells in psoriasis and psoriasiform cases

% of positive CD8 cells	Epidermis (No. of cases)		Upper Dermis (No. of cases)		Lower Dermis (No. of cases)	
	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form	Psoriasis	Psoriasi-form
0	15	23	0	0	8	21
1-10	0	0	0	4	1	0
11-20	0	0	2	1	0	2
21-30	0	0	0	5	0	0
31-40	0	0	3	5	0	0
41-50	2	1	3	3	4	0
51-60	1	0	2	2	1	0
61-70	0	0	6	0	1	0
71-80	2	0	5	3	2	0
81-90	0	1	2	1	1	2
91-100	5	0	2	1	7	0

Table III. Comparison of distribution of CD8 positive cells in psoriasis and psoriasiform cases

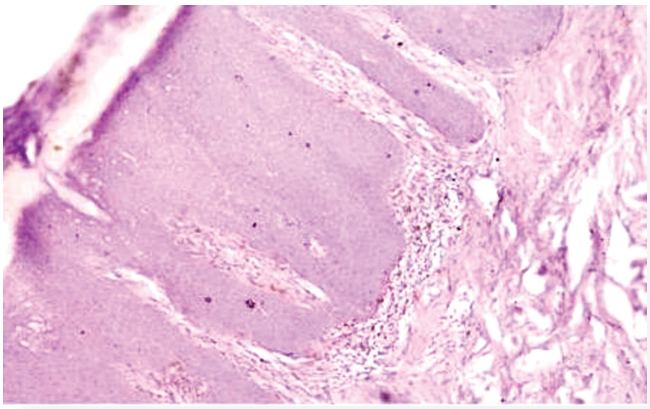

Figure 2. Microphotograph showing CD4+ T-cell in upper dermis of psoriasis case (20X, IHC)

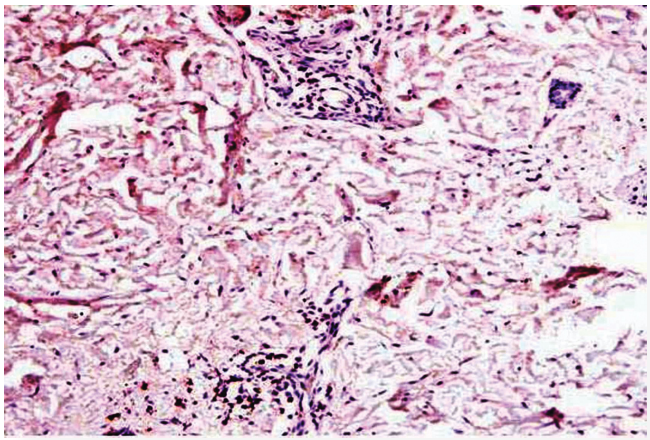

Figure 3. CD8+ T-cells in epidermis (arrow) and papillary dermis of psoriasis (20X, IHC)

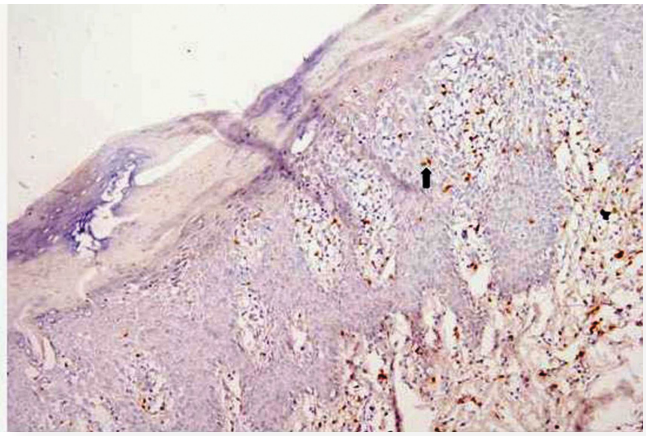

Figure 4. Microphotograph showing perivascular presence of CD8 +T-cells in deep dermis of psoriasis (20X, IHC)

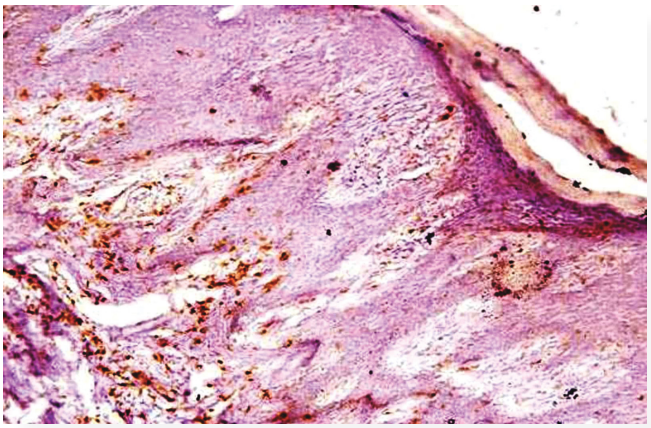

Figure 5. Microphotograph showing CD 8 + T-cells in upper dermis of psoriasiform case (20X, IHC)

On evaluating Psoriasiform lesions only 2 cases (8%) showed CD4 positivity in the epidermis of psoriasiform lesion. The mean value of percentage of cells was 30% of these positive cases (SD=28.28). In the upper dermis area, 24 cases (96%) showed positivity with a mean value of 55.6% (SD=25.8). In the lower dermis area, only four cases (16%) showed CD4 positivity with a mean value of 45% (SD=40.4) (Tabl. II). CD 8 positive cells in the epidermis were seen in 2 cases (8%) and the mean value among positive cases was 70% (SD=28.24). In the upper dermis area, all the 25 cases showed CD8 cells with a mean value of 44.4 (SD=25.8) (Fig. 5). Lower dermis region showed CD8 cells in 4 cases (16%) with a mean value of percentage of infiltrating cells as 55% (SD=40.4) (Tabl. III).

On comparing CD4 and CD8 cells infiltration in psoriasis and psoriasiform lesions, the difference in percentage of CD4+ T-cells in epidermis was not statistically significant (p=0.228,student t-test) between psoriasis and psoriasiform lesion. However, the difference in percentage of CD8 positive T-cells in epidermis between psoriasis and psorisiform lesion was statistically significant (p=0.007). There were more number of CD 8 + T-cells.

On analyzing the upper dermis for CD4 and CD8, the difference in percentage of CD4+ T-cells was statistically significant (p=0.002) between psoriasis and psoriasiform lesion. More so, the difference in percentage of CD8+ T-cells, in upper dermis between psoriasis and psoriasiform lesion was also statistically significant (p=0.005).

A statistically significant difference was drawn in percentage of CD4+ (p=0.043) and CD8+ (p=0.000) T-cells in lower dermis of psoriasis and psoriasiform lesion.

Discussion

Psoriasis is a chronic inflammatory relapsing disorder accompanied by an infiltration of activated T-cells. The presence and potential functional importance of these cells in the pathogenesis of psoriasis is emphasized [6]. An inflammatory infiltrate consisting mostly of lymphocytes is present in the upper dermis and the papillae [8], however in early lesions neutrophils may be seen. The expression of CD4+ lymphocytes as well as CD8 lymphocytes is increased significantly in the epidermis and the dermis of lesional skin as compared to healthy skin. This suggested that a cascade of cells and cytokines play an important role in the immunopathogenesis of psoriasis vulgaris [9]. Psoriasis is characterised by increased proliferative activity of normal slowly cycling epidermal progenitors that is followed by chronic accumulation of immunocompetent cells [10].

Normal skin lacks interferon ϒ (IF-ϒ) [11]. In lesional skin, however T-cell clones produce IF-ϒ, an important element for induction into the G1phase of cell cycle by psoriatic keratinocyte stem cells leading to hyperproliferation of T-cell clones of psoriatic origin release IFN-ϒ in vitro which together with growth factors (IL3, GM-CSF) [12] and fibronectin are necessary for cell cycle induction occurring in vivo among K1/K10 keratinocyte stem cells.

A study revealed elevated levels of CD4 and CD8+ T-cells in all compartments of psoriatic skin as compared to normal indicating both CD4 and CD8+ IF-ϒ + T-cells are present in appropriate anatomic locations in order to sustain lesional pathology [13]. Similarly, in the present study, inflammation was seen in all the compartments of lesional skin, it was of mild grade in the epidermis of 44% cases, while in upper dermis 100% of cases showed moderate grade and in the lower dermis, 72% cases had inflammation of mild grade.

T cell infiltration in psoriasis has recently been an important subject of investigation. Comparative analysis of lesional T-cell infiltrate in psoriasis and other psoriasiform dermatitis have been only sparingly performed [14]. Psoriasis is accompanied by an infiltration of activated T-cells in papillary dermis and epidermis. The presence of potential functional importance of T-cells was emphasised in the pathogenesis of psoriasis [6]. In the present study, CD8+ T-cells were present in the epidermis of 40% cases with a mean value of 82%. This is in concordance with previous studies [5,6,15,16] indicating CD8+ T-cells play a major effector role in psoriasis. CD8 T-cells are known to respond to specific antigens in the psoriatic lesions with help of CD4 T-cells that are also probably antigen specific [17].

Most studies emphasize the role of CD4 and CD8 cells in the pathogenesis of psoriasis [5,6,18,14]. CD4+ T-cells may be necessary for providing critical inductive and helper signals while CD8 are likely to be the principal effector agents in psoriasis. It should be reiterated that at least 80% of T-cell in chronic lesional epidermis are of CD8 phenotype associated with keratinocyte. Furthermore an increase in CD8 T-cells has been observed in the epidermis of uninvolved skin of psoriasis patients [19]. We found CD8+ cells in upper dermis in all the biopsies (100%) and CD4+ cells in most of the biopsies (88%). More number of CD8+ cells were reported as compared to CD4+ cells in upper dermis in the present study. This was in contrast to trends reported in literature where a higher percentage of CD4+ cells as compared to CD8+ cells have been observed in the upper dermis [5,15] alongwith mixtures of CD4+ and CD8+ cells [6]. However, it compared favourably with others, where CD8+ T-cells were distributed both in the epidermis and dermis but preferentially in the dermis, as seen in the present study [20]. On review of literature, no relevant data was available to the best of our knowledge which described percentage of CD4 and CD8+ cells in papillary and reticular dermis separately of psoriatic lesions. However, in our study, the percentage of CD4+ cells increased in lower dermis as compared to upper dermis. In the lower dermis region, 11 cases (44%) were positive for CD4 cells. CD8+ cells were found in 17 cases (68%). CD8+ cells secrete various cytokines affecting the epidermis and is also stimulated by cytokines secreted by epidermal, dendritic cells as well as CD4+ cells. Studies investigating the pathogenesis of psoriasis conclude the essential role of CD8+ cells in psoriasis [5,6,14,18,21,22]. T lymphocytes in lesional skin showed CD8+ cell figured more strongly than C cells [23].

Psoriasiform lesions on the other hand have morphological features similar to psoriasis. They are inflammatory diseases characterized by infiltration of lymphocytes and macrophages Allergic contact dermatitis, seborrhoeic dermatitis, Atopic dermatitis, Pityriasis rubra, Lichen simplex chronicus are considered as psoriasiform lesions. T-cell are known to play a role in the pathogenesis of psoriasiform lesions more so in atopic dermatitis.Studies have reported a high proportion of CD4+ T-cells in the dermis on immunohistochemical analysis [7]. An immunophenotyping of the inflammation of psoriasiform lesions was done in our study, CD4+ cells were seen predominantly in the upper dermis, 96% cases had CD4+ T-cells with a mean of 56.25%. Lower dermis area showed 16% cases having CD4+ cells with a mean of 55%. Psorisiform lesion such as atopic dermatitis is a multifactorial chronic inflammatory skin disease where CD4+ cells are considered to play an important role in its pathogenesis [24]. In a study, the patch test positive atopic dermatitis patients showed an infiltration of CD4+ T-cells. About 10% of the cells were CD8 positive ranging from 3-24% [24,25]. Immunophenotyping of the inflammatory cells performed in atopic dermatitis in other studies reveal a high proportion of CD4+ T-cells in dermis as well as in peripheral blood lymphocyte showing selective activation of CD4+ lymphocytes and a relative expansion of CD4+ cell subset [26,27].

Exact etiology of Pityriasis rosea, another psoriasiform lesion is still unknown. Cell mediated immunity may be involved in the pathogenesis [28] as activated helper–inducer T-lymphocyte (CD4+/HLA-DR+) are present in the epidermis and dermis. In our series of Pityriasis rosea, in the upper dermis area, 90% of the inflammatory cells were of CD4 and 10% were of CD8 type. Allergic contact dermatitis. represents a type IV cell mediated delayed type of hyper sensitivity reaction. Both CD4 and CD8+ T-lymphocytes participate in contact hypersensitivity reaction [22].

On comparing the immunophenotypic pattern between psoriasis and psoriasiform group CD4+ T-cells in the epidermis were evident in only 5 cases of psoriasis and in two cases among the psoriasiform group in our study which was statistically insignificant (p=0.228). Various studies, have shown that CD4+ cells are less frequent in psoriatic epidermis [5,6,14,18]. Moreso, CD8+ cells were seen in epidermis in 40% cases in psoriasis and 8% in psoriasiform lesions. The mean value of percentage of cells was 82% in psoriasis and 70% in psoriasiform group and this difference was statistically significant (p=0.007). These findings are in concordance with earlier studies which have shown CD8+ cells in abundance in psoriasis [5,6,14,18,27].

In the upper dermis positivity of CD4+ T-cells were found to be similar in both psoriasis and psoriasiform lesions in the present study. The mean value of percentage of cells was 35% in psoriasis and 55.6% among psoriasiform lesion and this difference was statistically significant (p=0.002). The CD8+ T-cells in this area were found to be similar in both psoriasis and psoriasiform cases. All the cases in both the groups were positive for CD8. The mean value of percentage of CD8+ T-cells among psoriasis cases was 75% while in psoriasiform group, it was 44.4%, a statistically significant (p=0.005) difference was drawn. In the upper dermis area, a slightly higher number of CD4+ cells as compared to CD8+ T-cells which were more sporadic in dermis in psoriatic [5,14]. One of the study [6] has shown mixtures of CD4+ and CD8+ T-cells were present in the upper dermis in psoriasis whereas studies done for psoriasiform group show that CD4 + cells are in abundance in the upper dermis area and play a major role in the pathogenesis [24,25,27,28].

On comparing the infiltration of the lower dermis by CD4+ T cells, a statistically significant difference (p=0.043) in the mean value of percentage of cells was seen between psoriasis and psoriasiform lesions. On the other hand,a statistically significant difference (p=0.000) was also drawn on the mean value of CD8+ T-cells present in the lower dermis. No relevant data to the best of our knowledge was available on the distribution of CD4+ and CD8+ T- cells in papillary and reticular dermis separately.

Conclusion

The histopathological features of psoriasis have many similarities with other psoriasiform lesions which cause diagnostic difficulties in acheiving a final diagnosis. Distinguishing the two lesions on the basis of immunophenotyping of T-cell infiltrate has emerged as a useful tool. We demonstrated a statistically significant difference in grades of inflammation between psoriasis and psoriasiform lesion. A statistically significant difference has been drawn in CD4 and CD8 T-cell infiltration in upper and lower dermis, and CD8 in epidermis however the difference was insignificant for CD4 cells in the epidermis. The difference in amount and pattern of CD4, CD8 T-cells in the various compartments may be helpful in differentiating between psoriasis and psoriasiform lesions especially in cases with borderline morphology.

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DERMATOLOGY IN THE INTENSIVE CARE UNIT

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Abstract
Introduction: The intensive care unit (ICU) represents a special environment for patients. We analyzed patients in the ICU/ high care unit (HCU) with respect to dermatology counselling and skin problems.
Setting: Academic Teaching Hospital over a 10 month period.
Material and Methods: The total number of patients of the ICU was 1,208 with a mean stay of 4.1 days. In the HCU the mean stay was 16 days. Diagnosis leading to admission were analyzed. All files of dermatological counselling were evaluated in detail.
Results: Fifty-five patients with dermatologic problems were identified: 19 women and 26 males. The age ranged from 22 to 90 years of life (mean ± standard deviation: 67.2 ± 17.4 years). The total number of consultations were 85. The range of repeated dermatological consultation ranged from two to ten. The major reasons were skin and soft tissue infections, adverse drug reactions, chronic wounds including pressure sores and skin irritation or dermatitis. Pre-existing skin conditions may complicate the treatment and care during ICU/HCU stay.
Conclusions: A tight collaboration between of the medical staff of ICU/HCU and dermatology department will ensure a rapid diagnosis and treatment of various skin conditions in the ICU, without increasing the costs significantly. Interdisciplinary education of nursing staff contributes to improved skin care in the ICU/HCU and helps to prevent acute skin failure.

Key words: Intensive Care Unit; dermatological counselling; skin diseases

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Introduction

Patients in intensive care units (ICU) represent a proportion of patients with most complex medical issues. Counselling of other specialities is a common procedure to avoid delay of diagnosis and specific treatment. Surprisingly not much has been published on interaction with and the role of dermatology in such a setting although skin diseases are quite common in the general population [1]. Data from burn centres suggest that an intense teamwork with dermatologists seem to be favourable for patients [2].

Skin diseases itself may lead to ICU admission in case of emergencies like severe adverse drug reactions including Stevens-Johnson syndrome [3], drug reactions with eosinophilia and systemic symptoms (DRESS) [4], toxic epidermal necrosis [5], serum sickness-like syndrome [6]. The incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis has been calculated as high as 1.89 per million inhabitants per year in western Germany and Berlin [7]. A survey from Britain identified the following big three dermatological admissions: infectious diseases, cutaneous malignancies and acute skin failure. The mortality rate for patients with dermatologic diseases in ICU was estimated as high as 27.5%, with 39.6% who died before ultimate discharge from the hospital [8].

In this study we would like to analyze skin problems in ICU patients in an Academic Teaching Hospital in the south-east of Germany. We will focus on those skin problems that need a dermatological counselling during the patient's stay in the ICU. We hope that such an analysis will better define the necessary for an optimal patient care and also that we appreciate the importance of team work which is vital in such an environment to avoid unnecessary misdiagnosis and treatments.

Material and Methods

Patients: We analyzed patients in the Intensive Care Unit (ICU) of our hospital treated from January to October 2010 including dermatological counselling.

The average annual number of dermatologic consultations in the whole Academic Teaching Hospital is 2,000 to 2,500. The patients were analyzed for diagnosis, treatment and diagnostics resulting from the dermatologic consultations.

Results

The total number of patients of the ICU was 1,208 with a median stay of 4.1 days. The Department of Anaesthesiology & Intensive Medicine, Emergency Medicine and Pain Management runs a specialized high care unit (HCU) with 16 places for assisted ventilation among other facilities. Table I summarized diagnoses for admission in this ICU.

Diagnosis	N
Intracerebral bleeding	16
Acute haemorrhagic anaemia	8
Respiratory insufficiency	8
Pancreatitis	5
Polytrauma	4
Peritonitis	3
Pneumonia	3
Fractures, spine	3
Renal insufficiency	2
Urosepsis	2
Ileus	2
Cardiac insufficiency	2
Abscess, intraspinal	1
Abscess, lower leg	1
Acute cholecystitis	1
Acute enteric ischaemia	1
Acute ischaemic enterititis	1
Acute mastoiditis	1
Anaphylaxis, drug-induced	1
Colon diverticulitis with abscess formation	1
Colon necrosis	1
Colon torsion	1
Collum phlegmonia	1
Discitis, lumbar	1
Endocarditis	1
Empyema, knee joint	1
Gut perforation	1
Haemato-pneumothorax	1
Hypopharyngeal malignancy	1
Infection due to joint prothesis	1
Larynx oedema	1
Noninfectious colitis	1
Oesophageal resection	1
Perforated aortal aneurysm	1
Reanimation	1
Rhabdomyolysis	1
Shot gun injury, lung	1
Thoracic abscess	1
Tracheostoma	1

Table I. Diagnoses leading to an admission to the HCU

The median time of stay for HCU patients was longer compared to the general ICU population, i.e. 16 days (standard deviation 35.4 Days). Among the HCU patients 47 patients suffered from sepsis, 12 patients died. The median time of assisted ventilation was 288 hours (standard deviation 783 hours). In the following we will focus on the HCU facility.

Fifty-five patients with dermatologic problems were identified: 19 women and 26 males. The age ranged from 22 to 90 years of life (mean ± standard deviation: 67.2 ± 17.4 years). The total number of consultations was 85. The range of repeated dermatologic consultation ranged from two to ten.

Two cases were excluded from further analysis: one patient had died before the bedside consultation was possible and another patient had no dermatologic symptoms at the time of consultation.

A major problem was communicating with the patients. This was due to patients on respirators or had impaired hearing function or dementia and others. The following analysis groups various patients into different categories of skin problems. Each patient could be further classified in more than one category.

Infestations and infections: Viral infections were most common (n = 8) including generalized and localized herpes zoster and herpes simplex. The usual treatment for herpes zoster was systemic acyclovir and astringent topical lotions. None of the ICU patients were hospitalized for the viral infections but they still had an impact on treatment and costs. Although septicaemia is an important indication for HCU treatment it was not a cause for the dermatological counselling.

However, some septicaemic patients were seen by the dermatologist for secondary problems such as skin irritation, adverse drug reactions, oedema and soft tissue infections.

Bacterial infections seen by the dermatologist in the HCU included five patients with erysipelas (n=2), phlegmonia (n=1), abscess formation (n=2), and there was a single case of suspected gas brand infection (Fig. 1).

The recommended treatment was either surgical, systemic antibiotics or a combination of both. Furthermore, bacterial infections can cause significant morbidity and mortality in the HCU. They are a major factor for increasing the costs by using newer classes of antibiotics due to bacterial resistance, instead of classical antibiotics which are cheaper.

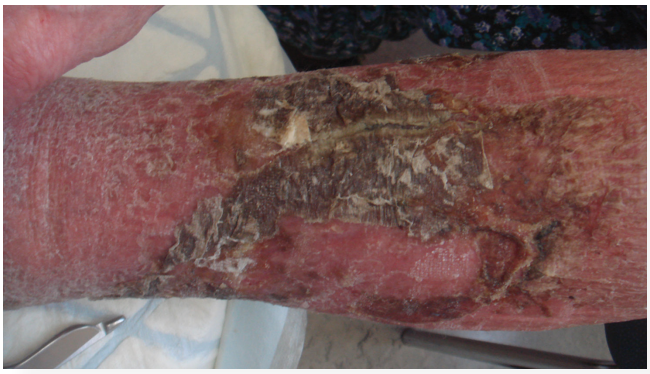

Figure 1. Vaselinoderma in chronic venous insufficiency, mimicking infection and erysipelas. There is no need for antibiotics but cleansing and skin care

Infestation with head lice was seen once during the observation period.

Skin irritation: The major age group was in their 7th and 8th decade of life. Xerosis cutis is often seen that can aggravate in an environment such as HCU, of which the major clinical symptoms are pruritus, excoriations, desquamation and redness are major clinical symptoms. The diagnosis of asteatotic eczema was confirmed in five patients (Fig. 2, 3). Skin care and treatment with emollients and sometimes topical corticosteroids were recommended.

One particular problem with obese patients in HCU was the development of intertrigo (n = 2). The disease can be aggravated with larger ulcerations which could lead to bacterial and mycotic infections. The topical treatment in these cases is more meticulous therefore requiring more attention.

Patients with sensitive skin can develop irritant contact dermatitis due to skin care products, wound dressings and disinfectants. We have seen one patient who developed contact dermatitis due to plasters.

Wounds: The dermatological consultation for problems with chronic wounds plays a significant role in the HCU (n = 8).

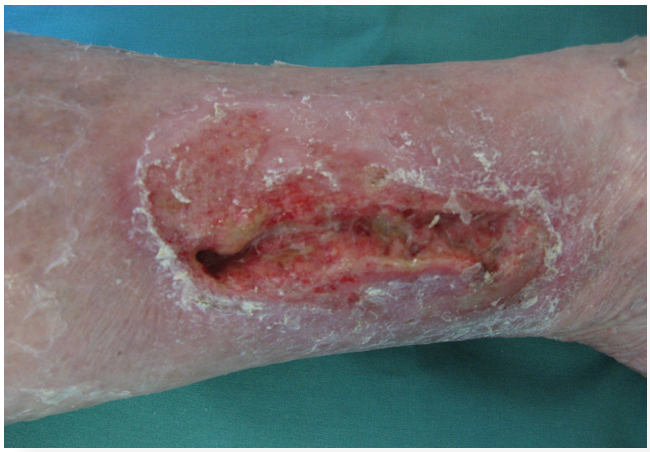

Figure 2. Atypical phlegmonia (no fever, very limited redness, limited pain, but general malaise) in a patient with treatment with anti-tumour-necrosis-factor alpha therapy

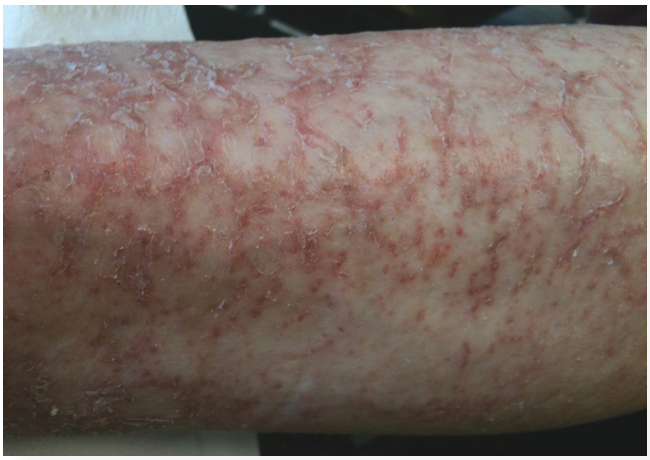

Figure 3. Asteatotic eczema (69-year-old male patient). This is a complex condition caused by intrinsic ageing, inadequate skin care, can be worsened by statins

These wounds may have developed before hospital admission or during the stay in the HCU. We did not come across any major wounds developing during the HCU stay. Some patients, however, suffered from large pressure sores (n = 1). Minor pressure sores (small ulcers mainly on the feet, grade I-II) were also seen as a result of prolonged immobilization, i.e. during respirator treatment after septicaemia or shock therapy (n = 3).

Patients with leg ulcers were examined by the dermatologist for further advice of good ulcer care (n = 2).

Sometimes post surgery wound problems develop, when the patient needs to be treated in the HCU for other severe conditions. There was one patient with limited skin flap necrosis and there was only one patient for follow-up after mesh-graft transplantation.

Adverse drug reactions: The major part of adverse drug reactions in the HCU consists of acute rash with macular, papular or urticarial lesions. We saw seven patients with drug rash ranging from very mild to life-threatening allergic shock. In all of these patients but one, systemic antibiotics was a suspected cause (Fig. 4). One patient had a drug rash after non-steroidal anti-inflammatory drug, while another patient developed steroid-acne due to systemic corticosteroid therapy. Although confirmation of suspected medical drugs by in vivo and in vitro allergy tests is most important, this cannot be investigated during stay in the HCU. In most cases topical corticosteroids, systemic antihistamines and cessation of the suspected drug therapy leads to complete remission, sometimes systemic corticosteroids and other measures may be needed. It is most important to mention the suspected drug allergy in all patient files and reports (allergy passport) to prevent a second exposure with the possibility of a fatal outcome. It was reported that irritant contact dermatitis due to electrodes or wound dressings can also occur (Fig. 5).

Pre-existing skin problems: Some patients were submitted to HCU with a pre-existing chronic skin disease (n = 4). Whereas atopic dermatitis and psoriasis could be expected since they are common, orphan diseases may need complex procedures and treatment and further dermatological consultations may become necessary. We have seen one patient with bullous pemphigoid who needed 10 consultations during his stay at HCU. Other skin diseases which were included were psoriasis (n = 2) and a basal cell carcinoma patient.

Diagnostics: Most cases could be confirmed by clinical examination with or without dermoscopy. Diagnostic excision was recommended in one patient in case treatment failed. Mycologic culture of skin scraps was suggested in two cases.

Additional costs: Early dermatological counselling will not have a negative impact on future costs of diagnosis or treatment but it is capable of preventing the increase of costs that arise after delayed diagnosis of severe skin conditions and diseases.

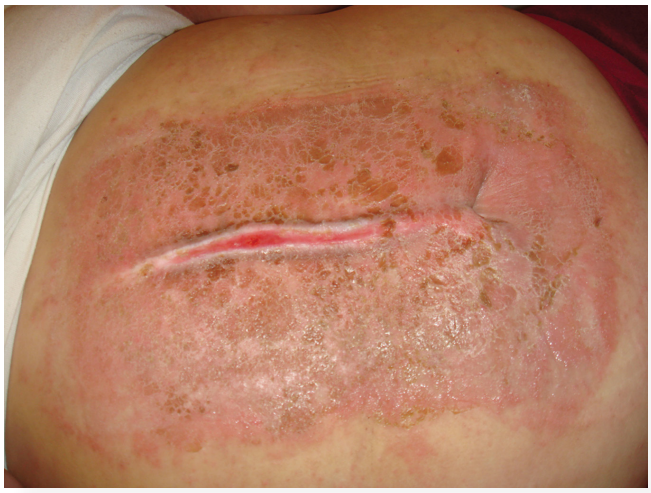

Figure 4. Subacute irritant contact dermatitis with sharp borders due to glue in wound dressing

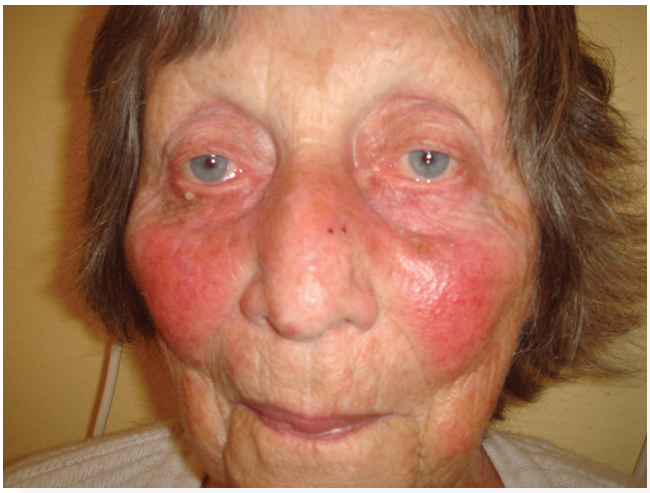

Figure 5. Butterfly-like rash caused by ampicillin

Discussion

The ICU/HCU is a special environment for critically ill patients leading to various skin conditions which could be detrimental to the health of the patient due to immobility, sweating and decreased perfusion. Non-invasive measurements of transepidermal water loss (TEWL) and skin surface pH, however, did not show generally a significant deterioration of skin barrier function in ICU patients [9].

Nevertheless asteatotic eczema and other irritant skin conditions were quite common among our mostly elderly patients. There is a need for improved skin care with moisturizers and avoidance of irritants. Untreated eczema (dermatitis) can become a cause of an acute skin failure as well as adverse drug reactions, bullous diseases and others. Since many of our ICU/HCU patients were elderly polypragmatic drug therapy is a risk for adverse drug reactions [10].

One of the most severe presentations of identified skin conditions in ICU is the risk of acute skin failure. Acute skin failure is defined as loss of temperature control with subsequent inability to maintain the core body temperature, loss of fluid, electrolytes and protein, and disruption of skin barrier function markedly increasing the risk of severe infections [11].

In such patients TEWL raises from 400 ml/day to > 1000 ml/d. TEWL is highest during scaling of skin, e.g. after toxic exanthema. Electrolyte imbalance (low sodium and high potassium) is often accompanied by hypophosphataemia what aggravates insulin resistance [12].

There is a loss of nutrients in particular by scaling. Peripheral oedema is commonly seen in long-standing cases due to hypoalbuminaemia, associated cardiac failure and inflammation form primary skin diseases. There is increased capillary leakage and shift of fluid to extracellular space. In erythroderma increased levels of vascular permeability factor and vascular endothelial growth factor have been detected in circulation [13].

Acute skin failure can give raise to pulmonary, immunological and vascular complications.

Therefore monitoring of these patients and care in an interdisciplinary team with well-skilled nurses is a must. Regular removal of crusts and skin cleansing, barrier-nursing and use of emollients to recover skin barrier function are recommended [14].

Skin and soft tissue infections (SSTI) can contribute to morbidity and mortality in ICU. In a population-based study from Taiwan covering almost 150,000 patients one third of ICU patients suffered from SSTI had also non-SSTI which where responsible for ICU admission. The three most common groups of SSTI were „other cellulitis or abscess", „decubitus ulcer" and „post-operation wound infection"; and they accounted for 76.5% of all hospitalized cases and for 72.9% of ICU ones, respectively. In addition, „infection caused by vascular device/implant", „gangrene" and „necrotizing fasciitis" comprised another 24.3% of the ICU cases. Among the six SSTI, the ICU admission rates were the highest in „necrotizing fasciitis" (23.8%), followed by „decubitus ulcer" (22.8%), „infection due to vascular device/implant" (21.2%), „post-operation wound infection" (17.8%), „gangrene" (15.4%) and „other cellulitis/abscess" (3.8%), respectively [14]. Others reported fatal SSTI in ICU in up to 59.1% reflecting the different social and ethnic background and triage policy [15].

An observational, cross-sectional cohort study was conducted in the United States in 2008 and 2009. The overall prevalence and facility-acquired pressure sore rates were 13.5% and 6% (2008, n = 90,398) and 12.3 and 5% (2009, n = 92,408), respectively. In 2008 and 2009, overall prevalence rates were highest in long-term acute care (22%). Facility-acquired rates were highest in adult ICUs and ranged from 9.2% to 12.1% in 2008 and from 8.8% to 10.3% in 2009 [16]. An analysis in a tertiary hospital with a pressure sore rate of 12% tried to define factors related to pressure sore development. Multivariate analysis showed that "emergency ICU/high care unit (HCU) patients" and "infrequent turning" were related to pressure ulcer development. Patients with pressure ulcers experienced significantly fewer turns and repositionings (OR = 0.452, 95% CI: 0.212-0.966], $p < 0.05$. Fewer pressure ulcers developed in scheduled ICU/HCU patients than in emergency ICU/HCU patients (OR = 0.041 [95% CI: 0.004-0.470], $p < 0.01$) [17]. This can explain why patients with prolonged assisted ventilation have a higher risk of pressure sore development [18]. Other risk factors for the development of pressure sores include age, length of stay, mobility, friction/shear, norepinephrine infusion, and cardiovascular disease explained a major part of the variance in pressure ulcers [19].

Skin diseases can markedly increase the time needed for treatment and care. They may also prolong the stay in ICU/HCU, in particular SSTI [8]. The control of skin diseases during ICU stay is related to the implementation of an interventional hygiene plan with standards of nursing, bathing, use of beds, skin care, and prevention of incontinence-related dermatitis [20]. In a recent report from a pediatric ICU the majority of skin problems resulted from an underlying illness responsible for admission to the ICU, e.g. infection, vasculitis, or adverse drug reaction. In 15 of 42 cases dermatological problems were related to the ICU care regimen, such as adverse drug reactions, pressure sores or catheter complications [21]. Although skin diseases can be a factor increasing the risk of mortality in the ICU, fortunately we did not observe any case in our analysis. We conclude that the intense cooperation between the staff and dermatology department in the management of the critically ill patients with skin problems is a necessity.

Another important issue is the interdisciplinary education of the nursing staff which has been practised in our hospital since many years. One of the topics in the continuous education of the prevention and treatment of chronic wounds like pressure sores.

Furthermore, in order to improve the patient care, the dermatology department should be strictly involved in this continous medical education for both the doctors and nurses. On the other hand, there is a need for better understanding the principles of intensive care by counselling dermatologists to improve further communication and select appropriate treatment.

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A STUDY ON NON VENEREAL GENITAL DERMATOSES IN NORTH INDIA

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Abstract
Non-venereal dermatoses of female external genitalia include a spectrum of diseases with varied etiology. The most common non-venereal dermatoses in males were scrotal dermatitis seen in 16.6% patients, vitiligo was seen in 14.3% patients, fixed drug eruption, scabies and pearly penile papules were seen in 10% patients each. Sebaceous cyst, tinea, psoriasis and lichen planus was seen in 6.6% patients each. Balanitis xerosus obliterans, squamous cell carcinoma and verrucous carcinoma and achrochordon were seen in 3.3% patients each. The most common genital dermatoses seen in females were lichen sclerosus (15%), vitiligo (15%) and vulval candidiasis in 15% cases. Other non venereal genital dermatoses in females were lichen simplex atrophicus (10%), bartholin cyst (10%), tinea (10%), psoriasis (10%), vulval lymphoedema (10%) and achrochordon in 5% patients.

Key words: genital; non venereal; female; male; dermatoses

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Introduction

Dermatoses involving female external genitalia are not always sexually transmitted. Those which are not sexually transmitted are referred to as non-venereal dermatoses. The various non-venereal dermatoses of female includes inflammatory cutaneous disorders (psoriasis, seborrheic dermatitis, lichen planus, lichen sclerosus), autoimmune (vitiligo), multisystem diseases (Behcet syndrome, Reiter syndrome, Crohn disease), exogenous (contact dermatitis, corticosteroid abuse, fixed drug eruption), and benign and malignant neoplasms (extramammary Paget disease) [1-3]. The non venereal dermatoses in males encompasses two group of disorders [4,5]. Group one consists of disorders that are seen only in the genitalia e.g. angiokeratoma of Fordyce, median raphe cyst), group two comprises of disorders that affect genitalia as well as other parts of the body. Because venereal and non-venereal dermatoses tend to be confused, the occurrence of these dermatoses may be associated with mental distress and guilt feelings in affected patients.

The non venereal dermatoses may be classified into five types based on pathogenesis. It includes inflammatory diseases, infections and infestations, congenital disorders, benign abnormalities, premalignant and malignant lesions. Since these groups include a wide variety of disorders, the identification and establishment of the nature of disease is a challenging venture.it is also important to distinguish between venereal and non venereal dermatoses, as venereal diseases are of primary concern to the patient.

Material and Methods

We selected 50 cases of non venereal genital dermatoses for the study from the department of dermatology and STD. Informed consent was taken from all the patients for the study and prior approval of the hospital ethical committee was taken for the study. Patients having venereal disease were excluded from the study. A detailed history including demographic data, chief complaints related to skin, presence of itching, skin lesions, onset, pregnancy status, menstrual status, and associated medical or skin disorders was elicited and recorded. Enquiry was made with regard to history of sexual exposure. Cases having venereal diseases were excluded from the study. The external genitalia were examined and findings were noted. A detailed physical examination was made to see any associated lesions elsewhere in the body. Investigations such as Gram stain and KOH mount were done as and when required to establish the diagnosis. Biopsy and histopathological examination of the specimen was done when required to confirm the diagnosis. VDRL and Elisa test for HIV were done in all the patients to exclude any sexually transmitted disease.

Results (Tabl. I, II)

A total of 50 patients with non venereal genital dermatoses were included in the study. The data was collected and the results were analyzed. The mean age of the patients in our study was 38 years and the commonest age group of the patients was between 30-40 years of age. The majority of the patients were married (96%) and 4% were unmarried. Males outnumbered females in the ratio of 1.5:1.

Sr no	Genital dermatoses	Number	Percentage
1	Vitiligo	4	14.3
2	BXO	1	3.3
3	Scrotal Dermatitis	5	16.6
4	Sebaceous cyst	2	6.6
5	Fixed drug eruption	3	10
6	Tinea	2	6.6
7	Pearly penile papules	3	10
8	Psoriasis	2	6.6
9	Lichen planus	2	6.6
10	Scabies	3	10
11	SCC	1	3.3
12	Verrucous carcinoma	1	3.3
13	Achrochordon	1	3.3
	TOTAL	30	100

Table I. Genital dermatoses in males (n=30)

Sr no	Genital dermatoses	Number	Percentage
1	LSA	3	15
2	LSC	2	10
3	Vitiligo	3	15
4	Vulval candidiasis	3	15
5	Bartholin cyst	2	10
6	Tinea	2	10
7	Psoriasis	2	10
8	Vulval lymphoedema	2	10
9	Achrochordon	1	5
	TOTAL	20	100

Table II. Genital dermatoses in females

Discussion

Genital diseases may be associated with severe psychological trauma and fear in the mind of patients. Majority of our patients belonged to age group of 21-40 years.The mean age of the patient was 32 years. Males (60%) outnumbered females (40%) and male : female was 1.5:1. The common presenting feature were itchy genitalia, white discoloration, swelling, pain, burning sensation, mass, dyspareunia, redness, exfoliation of skin, raised lesions over skin, oozing, constipation, burning micturition, ulceration, erosion and thickening of skin. Some patients had more than one complaint. In females, labia majora was the most common site of involvement, accounting for 87% cases followed by labia minora in 48% cases and mons pubis in 10% cases. In males, penis (52%) was the common site of involvement, followed by prepuce (32%) and scrotum in 20% cases.

The most common non-venereal dermatoses in males were scrotal dermatitis seen in 16.6% patients, vitiligo was seen in 14.3% patients, fixed drug eruption (Fig. 1), scabies and pearly penile papules were seen in 10% patients each. Sebaceous cyst, tinea, psoriasis and lichen planus (Fig. 2) was seen in 6.6% patients each. Balanitis xerosus obliterans, squamous cell carcinoma (Fig. 3) and verrucous carcinoma and achrochordon were seen in 3.3% patients each. The most common genital dermatoses seen in females were lichen sclerosus (Fig. 4) seen in 15% cases, vitiligo (15%) and vulval candidiasis in 15% cases. Other non venereal genital dermatoses in females were lichen simplex atrophicus (Fig. 5) in 10% patients, bartholin cyst (10%), tinea (10%), psoriasis (10%), vulval lymphoedema (Fig. 6) in 10% patients and achrochordon in 5% patients.

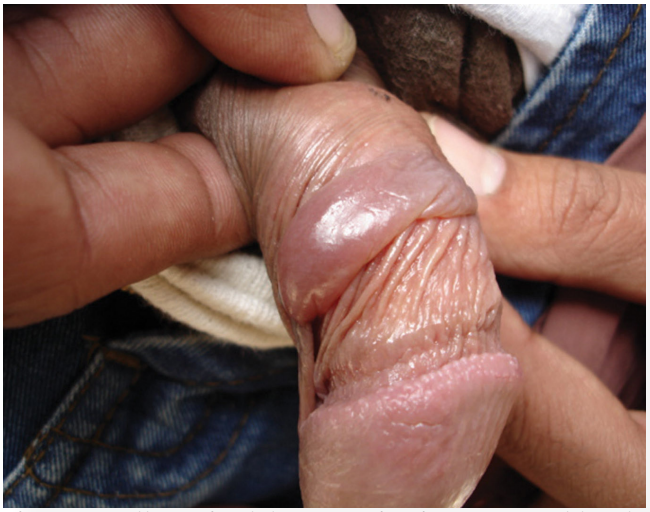

Figure 1. Bullous Fixed drug eruption in a 25 year old male

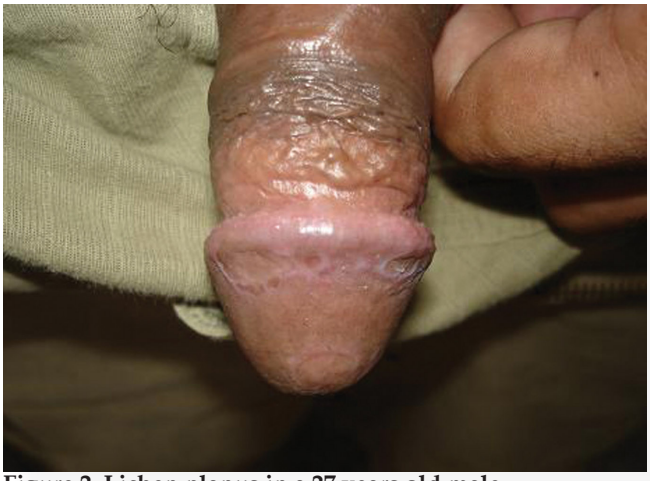

Figure 2. Lichen planus in a 27 years old male

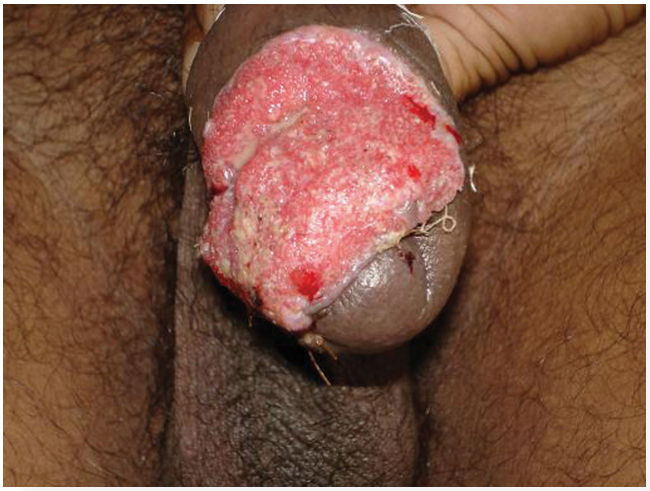

Figure 3. Squamous cell carcinoma in a 46 year old male

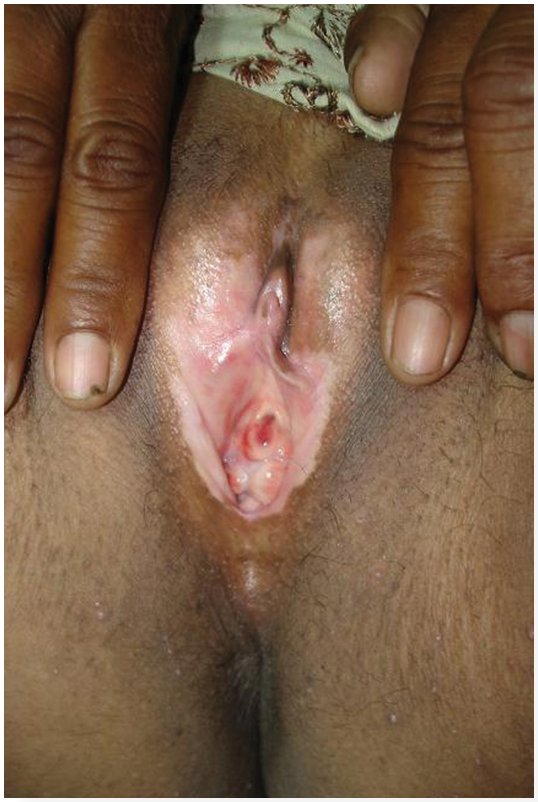

Figure 4. LSA in a 45 year old female

Figure 5. Lichen simplex atrophicus in a 48 years old female

Lichen sclerosus in females is chronic inflammatory dermatoses associated with substantial discomfort and morbidity [7,8]. Anogenital LS is characterized by porcelain white atrophic plaques that may become confluent extending around vulval and perianal skin in a figure-of-eight configuration. The resulting atrophic plaque may have a cellophane-paper-like texture, wrinkled and fragile surface associated with telangiectasia, purpura, erosions, fissuring or ulceration [9,10].

Vitiligo is an acquired pigmentary disorder characterized by loss of melanocytes resulting in depigmentation [11]. Approximately 0.1 percent to 4 percent of people worldwide are affected by vitiligo. Indian studies report 0.46 percent to 8.8 percent prevalence of vitiligo. Lymphedema is swelling attributed to accumulation of lymph in tissue. It is associated with inadequate lymphatic drainage. If it is from intrinsic abnormality of lymph conducting pathways, then it is called primary lymphedema.

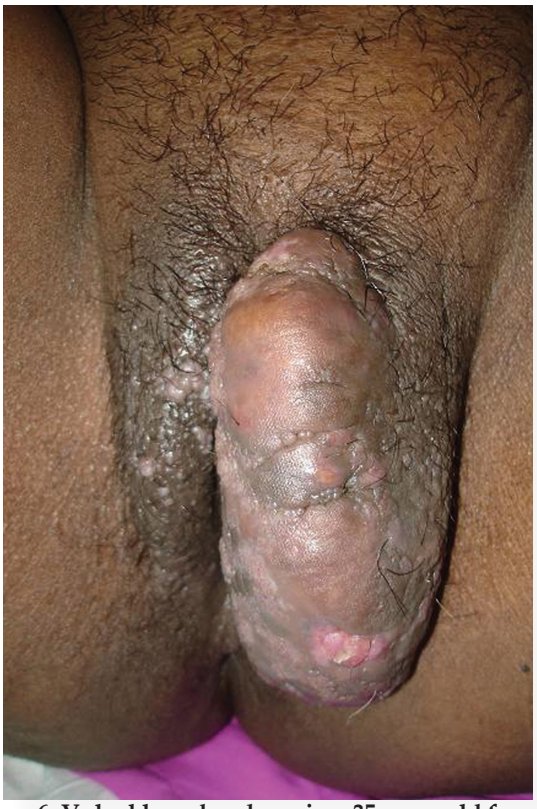

Figure 6. Vulval lymphoedema in a 35 years old female

Primary lymphedema usually involves the lower extremities. But if inadequate lymphatic drainage is from an acquired obstruction or obliteration of lymphatic channels, it is said to be secondary lymphedema. The common causes of secondary lymphedema are trauma (surgery, radiotherapy), infection (filariasis, tuberculosis), inflammation, and malignancy [12]. Vulval lichen planus usually presents as violaceous or erythematous papules or annular plaques or erosions with or without a lacy white border [13,14]. These lesions may ulcerate. If only vulval involvement is present, then disease is more likely to be erosive, with most lesions around labia minora, clitoris and clitoral hood [15].

Bartholin cysts are the most common cystic growths of the vulva [16]. Two percent women develop Bartholin duct cyst or gland abscess at sometime in life. Bartholin gland abscesses are almost three times more common than Bartholin duct cysts [17]. Gradual involution of the Bartholin glands occurs by 30 years of age. This is probably responsible for the more frequent occurrence of Bartholin duct cysts and gland abscesses during the reproductive years, especially between 20 and 29 years of age. It may start as an asymptomatic unilateral nontender cystic swelling, but it can cause pain and limitation of activity with increase in size.

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A STUDY ON NON VENEREAL GENITAL DERMATOSES IN NORTH INDIA

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Non-venereal genital dermatoses are a complicated group of illnesses because most of the patients that suffer from them feel embarrassed. They frequently think that all genital skin diseases are sexually transmitted, so they usually don't consult until the disease burden is unbearable. When that finally happens, some of these illnesses are already at an advanced stage that could endanger their lives. To make things worse, a lot of these patients get into serious troubles with their couples when they find about their disease.

Genital dermatoses are not easy to diagnose because their morphology is modified by the special environment of the genital area which produces heat, friction and occlusion [1]. For example, scales, a major finding in dermatoses like psoriasis, are less prominent than in other topographies. Fortunately, some of these dermatoses also affect other areas of the body, so examining extragenital areas aids in the diagnosis. A broad range of inflammatory, non-venereal dermatoses affect the genital skin. Some of them, like vitiligo, manifest as hypopigmented areas. But it is important to remember that lichen sclerosus (LS), lichen simplex chronicus and vulvar intraepithelial neoplasia (VIN) might also manifest as hypopigmented lesions [1]. Physicians should be aware of the diagnosis of LS, because this disease is associated with a risk of developing invasive squamous cell carcinoma (SCC) in both male (4-6%) and female (2-5%) patients [2,3]. Erythematous lesions of the genital area can be caused by tinea, candidiasis, psoriasis or dermatitis (atopic, contact or seborrheic). It is important not to underestimate the prevalence of contact dermatitis, especially the irritative type, which can be the primary cause of the patient's complaints or could be superimposed to other dermatoses [1-4]. Other entities that can manifest as erythematous or erythematosquamous plaques are Zoon's balanitis or vulvitis, VIN, extramammary Paget's disease, erythroplasia of Queyrat (EQ) and Bowen's disease (BD) [1-5]. Erosive genital lesions are not uncommon either. Lichen planus, pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, linear IgA bullous disease, Hailey-Hailey disease, Darier disease, lupus erythematosus, Behçet disease, Crohn disease and SCC can cause erosive disease. In many cases, biopsy is the only way to make the final diagnosis [1-5]. It is worth mentioning that physicians should be well familiarized with the anatomy of the genital region, so normal findings such as penile pearly papules do not end being treated as genital warts [2].

It is interesting that this study didn't find cases of VIN or SCC in female patients or cases of EQ or BD in male patients. That could be explained, at least in part, because most of their patients were relatively young. It is well known that penile carcinoma in situ (EQ/BD) and SCC typically affect uncircumcised men older than 60 years [2,4]. The same is true for most of the cases of vulvar SCC and differentiated VIN, the subtype of VIN with the highest malignant potential [5]. It is worrisome to notice that older patients were not seeking attention in this study because they are the ones at the highest risk of developing neoplastic diseases that might put their lives in danger if not treated on time. Older patients are probably not coming because, as it happens worldwide, this age group tends to be less educated. This highlights the importance that patient education also has in the prevention and early diagnosis of genital dermatoses.

Even though the number of patients included was small, I think that this study is very important because it draws the attention of dermatologists and other physicians to a group of diseases that has been neglected. Genital dermatoses are usually neglected because dealing with them means dealing with a lot of psychosocial factors that are time consuming for physicians. Most dermatologists don't routinely ask about genital problems until they are expressly told by the patient and most Gynecologists and Urologists usually concentrate their attention into other areas of the genitourinary anatomy. This study will certainly serve as an incentive for other researchers to direct their attention to these dermatoses. All these factors might contribute to a better diagnosis and treatment of non-venereal genital dermatoses.

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ROLE OF LEUKOTRIENE RECEPTOR ANTAGONIST MONTELUKAST IN THE TREATMENT OF CHRONIC URTICARIA: A HOSPITAL BASED STUDY

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Abstract
Introduction: Chronic urticaria is a disabling disease which may be refractory to standard therapies. Leukotriene receptor antagonists like montelukast have been tried in allergic diseases like asthma and find mention as a therapeutic option in chronic urticaria.
Purposes: A randomized single-blinded non-placebo controlled study to evaluate the role of montelukast, in addition to the adjunctive role of non-sedating antihistamine levocetirizine (H1), was conducted in patients with chronic urticaria.
Methods: Thirty-five patients with chronic urticaria were enrolled. Medication was given for a period of twelve weeks. Montelukast 10mg/day in an adult and 5mg in the age group 6-13 years, 4mg 2-6 years and levocetirizine 5mg once a day was added, if patient had new weals while on therapy. The improvement was monitored by estimating the episodes of wheals and pruritus in any two weeks period.
Results: Twenty-two patients showed a good response with occasional wheals at the end of 2 weeks and no weals at the end of 12 weeks. These included all 8 patients on non-steroidal anti-inflammatory drugs (NSAIDS). Four of these patients relapsed on discontinuation of therapy.
Conclusions: Montelukast is effective in chronic refractory urticaria especially in patients on non-steroidal anti-inflammatory drugs with occasional add-on use of a non-sedating anti-histamine.

Key words: chronic urticaria; montelukast; levocetirizine

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Introduction

Chronic urticaria is a disabling condition in which recurrent pruritic weals manifest on the body daily or for most days of the week for longer than 6 weeks. Pathophysiologically it is characterized by local vasodilatation and increased permeability of capillaries and small venules followed by transudation of plasma constituents into the papillary and upper reticular dermis. A large number of substances including kinins, prostaglandins, leukotrienes, proteolytic enzymes and the best-known histamine have been found to elicit the typical weal and flare reactions [1-4].

Anti-histamines are the first-line treatment for all patients with chronic urticaria. Chronic urticaria may however often be refractory to standard therapy. For patients with severe, unremitting urticaria who have failed to benefit from conventional therapies, other modalities have been tried. As urticaria symptoms can have a profound effect on a patient's quality of life (QoL) therefore treatment should address both relief of physical symptom and improvements in QoL. One such class of drugs is the leukotriene receptor antagonists (LTRA). Leukotrienes are derived from arachidonic acid, a constituent of the membrane phospholipid bilayer, and are produced by inflammatory cells (neutrophils, eosinophils, mast cells/basophils, monocytes/macrophages and lymphocytes). Much is known about the role of leukotrienes in asthma and allergic rhinitis. Leukotrienes promote microvascular leakage, airway mucus secretion and airway edema. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs. Leukotriene receptor antagonists like montelukast have been tried in chronic urticaria with variable results. A randomized single blinded non-placebo controlled study to evaluate the role of montelukast in addition to the adjunctive role of non-sedating antihistamine levocetirizine (H1) was conducted in patients with chronic urticaria [5-7].

Material and Methods

Thirty-five patients with chronic urticaria who attended the outpatient department were enrolled in the study. Informed consent was taken. Clearance was taken from the local ethical committee. A complete history including the patient's age, sex, marital status, residence and occupation; duration of urticaria; history of atopy (like asthma, rhinitis, hay fever); thyroid symptoms (heat/cold intolerance, sweating, sleep appetite, bowels); acid peptic disease or post-prandial distension, constipation; photosensitivity, arthralgia or arthritis, Raynaud's phenomenon; urinary symptoms; vaginal discharge; any drug intake; and exacerbating factors if any especially food or inhalant was recorded. Investigations included complete blood count with differential counts, erythrocyte sedimentation rate, peripheral blood film, renal function test, liver function test, blood sugar estimation, anti-nuclear antibody, stool examination and thyroid function test. Autologous serum skin test was done in all the patients. Montelukast in a dose of 10mg/day in adults, 5mg in the age group 6-13 years, 4mg in the age group of 2-6 years was administered for a period of twelve weeks and levocetirizine 5mg/day was added if patients developed new weals while on therapy. All medications like steroids or any other anti-histamines were withheld for a period of four weeks prior to the study.

The response at every 2 week interval and at the end of twelve weeks was noted as good (no weals in a 2 weeks period), moderate (occasional weals in a 2 weeks period) and nil (no response at all).

Results (Tabl. I)

The study group comprised of 35 patients of chronic urticaria. They included 21 females and 14 males with an age range of 14-80 years (average 35 years). Duration of urticaria ranged from 2 months to 20 years. Atopy in the form of allergic rhinitis, atopic eczema or asthma was seen in 4 patients and was associated with a longer duration of urticaria (maximum 20 years). Five patients, all females, had symptoms of and a biochemical profile of hypothyroidism. Photosensitivity was seen in 1 male. Ten female patients and 2 male patients gave a history of arthritis/arthalgias. Acid peptic disease and post-prandial distension was seen in 12 patients (8 females and 4 males) and constipation (habitual) in 12 (8 females and 4 males). Raynaud's phenomenon was seen in 1 female. Recurrent urinary tract infections or nephrolithiasis was seen in 6 patients. In 2 females, leucorrhea with smear positive for Trichomoniasis and Candidiasis was seen. Sixteen patients gave a positive drug history including non-steroidal anti-inflammatory drugs [9], anti-tubercular treatment [1], anti-depressants [5], Unani medicines [1], and benzathine penicillin [1]. Exacerbating factors included dust [2] and egg [1]. Associated diseases were lichen planus, hepatitis, sinusitis, vitiligo and rheumatic heart disease. Angioedema was seen in 2 patients. Autologous serum skin test was positive in 5 patients (4 males and 1 female) and these patients had a long duration of urticaria. Stool examination revealed *Giardia*/*Ascaris* infestation in 4.

All these patients were put on Montelukast. Out of 35 patients only 31 completed the study, 4 patients were lost to follow up. Response was judged at 2 weeks, 6 weeks, and 12 weeks. 22 patients showed a good response with occasional weals at the end of 2 weeks and no weals at the end of 12 weeks. These included all 8 patients on NSAIDs.

Four of these relapsed on discontinuation of therapy-1 just a week later and 3 after 4 months. A moderate response was seen in 4 patients. Five patients had persistent urticaria (response nil). They included patients with chronic urticaria of many years duration or with underlying atopy and/or ASST positive patients.

Associated features	Number of patients
Atopy	4
Hypothyroidism	5
Photosensitivity	1
Arthralgia or arthritis	12
APD or PPD	12
Constipation	12
Raynaud's phenomenon	1
UTI or nephrolithiasis	6
Leucorrhoea	2
Drug intake	16
Angioedema	2
ASST	5

Table I. The various factors present in the study group of chronic urticaria patients

Discussion

Chronic urticaria is defined as the appearance of pruritic weals on the body, daily or on most days of a week for a period greater than six weeks. The term chronic urticaria encompasses a variety of different disorders with diverse etiologies and presentations that share wealing as the most common clinical feature. These include the physical urticaria, autoimmune urticaria and chronic idiopathic urticaria (CIU). Co-existence of physical urticaria with CIU or autoimmune urticaria occurs frequently. Angioedema occurs concurrently with chronic urticaria in 87% patients with CIU and is also frequent in autoimmune urticaria. An overall average lifelong prevalence of chronic urticaria is estimated to be about 1-2%. Urticaria can be highly distressing and can cause personal, social and occupational disability [1-4].

Most patients with chronic urticaria have been found to have an endogenous rather than an exogenous cause of illness. There is a wide range of secondary external aggravating factors that can bring out weals and angioedema in patients with chronic urticaria especially pressure; friction; drugs eg NSAIDS; foods and food additives like tartrazine and other azo dyes; infections/infestations like intercurrent viral infections, intestinal parasites; inhalants like grass pollen, animal danders, house dust; implants like metal pin, metal dental prosthesis and systemic diseases especially connective tissue diseases [5-8].

A good number of cases may be idiopathic with auto immunity being recognized as an increasingly important cause. Sera of approximately 60% of patients with chronic urticaria cause a pink weal, probably due to histamine release, when injected intradermally into the patient's own skin (the autologous serum skin test). Infact sera of about 30-50% patients with chronic urticaria released histamine in vitro from basophils and skin slices obtained from healthy people implying presence of circulating serum histamine releasing factor. This activity has been found to be due to functional IgG antibodies directed against α-subunit of high affinity IgE receptors (FcεRI-α) or less frequently against receptor bound IgE. In some patients the histamine-releasing factor is mast cell specific and is a non-immunoglobin which is not inhibited by preincubation with FcεRI or IgE [9-13].

It has also been found that normal subjects with history of acute urticaria induced by several NSAIDs show a positive reaction to intradermal injection of autologous serum, a phenomenon observed in patients with CIU and suggests a possible common background in CIU and NSAID induced urticaria. A relation between these two conditions is further suggested by the fact that up to 30% of the patients with chronic urticaria have worsening of their skin disorder after ingestion of chemically unrelated NSAIDs. A study conducted in these normal subjects with NSAID intolerance revealed a propensity to develop chronic urticaria in 33% over a follow up period of 1-10 years [14].

The treatment of chronic urticaria can be quite challenging. Anti-histamines are the first-line treatment for all patients with chronic urticaria. Three main groups of anti-histamines used singly or in combination include the classical sedating H1, non-sedating second generation H1 and their derivatives and the H2 antihistamines. Second generation anti-histamines are preferred to first generation H1 anti-histamines in the treatment of chronic urticaria because of their lack of sedation, impairment of cognitive and psychomotor performance and other side effects. In a fraction of cases treatment is inadequate. In these patients with unremitting disease, non- conventional modalities are tried. These include dapsone, doxepin, epinephrine, prednisolone, sulfasalazine, thyroxine, montelukast, cyclosporine, intravenous immunoglobulins, plasmapheresis and immunosuppressants [15,16].

As urticaria symptoms can have a profound effect on a patient's quality of life (QoL); therefore, treatment should address both relief of physical symptoms and improvements in QoL. Erbagci Z. [17] conducted a randomized single-blind placebo-controlled study in 30 patients of chronic refractory urticaria. The medication was given in a cross-over manner over 12 weeks as adjunctive treatment to an anti-histamine (H1). After informed consent, 2 groups were made. Group A received montelukast 10 mg once a day for six weeks followed by crossover to 6 weeks on placebo and a non-sedating antihistamine as needed. In Group B administration was reversed. Urticaria activity score (UAS) and visual analogue score (VAS) was used to monitor the response. No side effects were noted. H1 antihistamine intake was significantly less frequent during montelukast period ($p<0.01$). Statistically significant difference in UAS and VAS ($p<0.01$, $p<0.05$) between montelukast and placebo periods was seen. Thus montelukast was found to be a safe and effective adjuvant to anti-histamines in urticaria.

In our patients montelukast was effective in majority of cases and the adjunctive intake of levocetirizine was reduced. Moreover the drug was well-tolerated with minimal side-effects. It was found especially useful in the patients on NSAIDS. Urticaria has been known to be caused by a number of pathophysiological mechanisms. These include immunological IgE and IgE-receptor dependent urticaria; urticaria mediated by complement and other effector systems; urticaria after direct mast cell degranulation; urticaria relating to abnormalities of arachidonic acid metabolism and idiopathic urticaria. Leukotrienes play a pivotal role in NSAID induced urticaria. Leukotriene receptor antagonists block the action of these and hence their benefit in aspirin sensitive urticaria.

In our study twenty-two patients had a good response, four showed moderate and five patients had no response. A quick relapse was seen in atopics and ASST positive patients indicating perhaps the need for a longer therapy.

In conclusion montelukast seems a promising option both in terms of safety and efficacy in chronic urticaria. It is well worth a trial in these patients.

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INTERFERON GAMMA GENE POLYMORPHISM AS A MARKER OF SOME ALLERGIC DISEASES (ALLERGIC SKIN DISEASES AND ALLERGIC CONJUNCTIVITIS) IN A SAMPLE OF EGYPTIAN POPULATION

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Abstract
Introduction: Allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur to normally harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid. Allergy is one of four forms of hypersensitivity and is called type I (or immediate) hypersensitivity.
Aim: To Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic skin diseases and allergic conjunctivitis.
Material and Methods: This study included 300 Egyptian individual, divided into 100 patients with allergic skin diseases, 100 patients with allergic conjunctivitis and 100 healthy individual were taken as controls. Eosinophil count was estimated, Total IgE level was measured by ELISA technique, Nuclear DNA extracted from peripheral leukocytes and interferon gamma gene polymorphism 874A>T detected by Amplification Refractory Mutation system (ARMS-PCR).
Results: In the Skin allergic group, the (AT) genotype and the (TT) genotype were the most common (both are 45%), while in the Conjunctivitis group and the normal control groups the (TT) genotype was the most common (60% and 90% respectively). Moreover, there was statistically significant difference in the distribution of the IFN-γ genotypes at position 874 among the studied groups as compared all together.
Conclusions: The IFN-ɤ gene polymorphism at position +874 increases susceptibility to atopic diseases, and the identification of variants of the IFN-ɤ gene and their role in the development of atopic diseases provides a focus for the development of novel diagnostic and therapeutic strategies.

Key words: allergic skin diseases; allergic conjunctivitis; interferon gamma; gene polymorphism

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Introduction

Allergy is a hypersensitivity disorder of the immune system [1,2]. Allergic reactions occur to normally harmless environmental substances known as allergens; these reactions are acquired, predictable, and rapid [2,3]. Strictly, allergy is one of four forms of hypersensitivity and is called type I (or immediate) hypersensitivity [1,4]. It is characterized by excessive activation of certain white blood cells called mast cells and basophiles by a type of antibodies known as IgE, resulting in an extreme inflammatory response [3,5]. Common allergic reactions include eczema, hives, hay fever, asthma attacks, food allergies, and reactions to the venom of stinging insects such as wasps and bees [6,7].

Interferons (IFNs) are proteins made and released by the cells of most vertebrates in response to the presence of pathogens - such as viruses, bacteria, or parasites or tumor cells [8,9]. They allow communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors [10-15].

IFNs belong to the large class of glycoproteins known as cytokines [16,17].

Although they are named after their ability to „interfere" with viral replication within host cells, IFNs have other functions: they activate immune cells, such as natural killer cells (NK) and macrophages, they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus [18-20]. Certain host symptoms, such as aching muscles and fever, are related to the production of IFNs during infection [21-26].

The aim of the work is to Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic diseases (allergic skin diseases and allergic conjunctivitis) and to study the relationship of the allele with markers of allergy (serum IgE level and absolute Eosinophil count).

This study included 300 Egyptian individual, divided into 100 patients with allergic skin diseases, 100 patients with allergic conjunctivitis and 100 healthy individual were taken as controls. The patients selected from the ophthalmology and dermatology outpatient clinic of the main University Hospital, Faculty of Medicine, University of Alexandria.

Informed consent was taken from all patients participating in the study; The study was approved by the Alexandria Faculty of Medicine, Research Ethics Committee.

Methods

All the studied individuals (allergic skin diseases, allergic conjunctivitis and control groups) were subjected to the following:

I. Full history of:

- Onset of symptoms.
- Previous history of the same symptoms.
- Aggravation of symptoms by some types of food.
- Past history of other allergic conditions as atopic asthma, eczema and rhinitis.
- Drug history.
- Family history of allergic diseases.

II. Clinical examination:

Symptom of allergy:

a. Ophthalmologic examination

b. Dermatological examination

III. Laboratory investigations:

- Eosinophil count was estimated.
-Total IgE level was measured by ELISA technique.
- Nuclear DNA extracted from peripheral leukocytes and interferon gamma gene polymorphism 874A>T was detected by Amplification Refractory Mutation system (ARMS-PCR).

1. Absolute Eosinophil Count.

Complete blood count (CBC) were performed on a 3 differential automated cell counter sysmex KX-2IN (Sysmex, Kobe, Japan) and Absolute Eosinophil Count was estimated.

2. Total IgE level by ELISA technique.

Total IgE level was assayed using DRG International Inc., [27] USA ELISA kit.

3. Detection Of Interferon Gamma Gene Polymorphism 874a>T

- Genomic DNA extraction

Genomic DNA was extracted from peripheral blood leucocytes. Venous blood was collected from each subject into EDTA tubes withdrawn under complete aseptic technique. Genomic DNA was isolated using illustra blood genomicPrep Mini Spin Kit (GE Healthcare, United Kingdom) using column extraction technique.

Gamma interferon gene polymorphism detection using polymerase chain reaction - Amplification Refractory Mutation system [28]

Genotyping for 874AT polymorphisms in IFN-γ was performed and genes were typed using the refractory mutation system-polymerase chain reaction (ARMS-PCR). To assess the success of PCR amplification in both reactions, an internal control was amplified using a pair of primers designed from the nucleotide sequence of the human growth hormone (HGH).

- Primers used:

a. Common primer (antisense) of IFN- γ 5'-TCA ACA AAG CTG ATA CTC CA-3'

b. Allele-specific sense primer T 5'-TTC TTA CAA CAC AAA ATC AAA TCT-3'

c. Allele-specific sense primer A 5'-TTC TTA CAA CAC AAA ATC AAA TCA-3'

d. Control primer (HGH) (sense), 5'-CCTTCCAAC CAT TCC CTT A-3'

e. Control primer (HGH) (antisense), 5'-TCA CGG ATTTCT GTT GTG TTTC-3'

Results

The results of the present study showed that in the Skin allergic group, the (AT) genotype and the (TT) genotype were the most common (both are 45%), while in the Conjunctivitis group and the normal control groups the (TT) genotype was the most common (60% and 90% respectively). Moreover, there was statistically significant difference in the distribution of the IFN-γ genotypes at position 874 among the studied groups as compared all together.

The results also revealed statistically significant association between genotype and the allele frequencies of the +874T/A gene polymorphism in patients with skin allergy compared with controls and show the A allele frequency was 32.5% and the T allele frequency was 67.5%, also revealed statistically significant association between genotype and the alleles frequencies of the +874T/A gene polymorphism in patients with Conjunctivitis group compared with controls and show the A allele frequency was 27.5% and the T allele frequency was 72.5%, and showed that there was statistically significant difference in the serum IgE level and absolute Eosinophil count among the studied groups with elevated values of both parameters in allergic groups compared to control group, but higher values in Skin allergic group than in the Conjunctivitis group.

We found that the relation between genotype with absolute eosinophil count and serum IgE level in skin allergy group show that there was no statistically significant relation

between AA and each other genotypes but there was statistically significant relation between AT and TT genotype, in conjunctivitis group show that there was no statistically significant between AA and AT genotype as regarding to the absolute eosinophil count of, but there was statistically significant between AA and AT genotypes as regarding to the Serum IgE level, and also there was statistically significant between AA and TT genotypes and when we compared AT and TT genotypes we founded that there was statistically significant between this two genotypes, when we compared AT and TT genotypes in control group we founded that there was statistically significant between this two genotypes.

Discussion

Allergic diseases are common illnesses that have been increasing in prevalence in our surroundings which could be due to increased environmental exposure to allergens or genetic predisposition [1,2].

Studies of allergic diseases have traditionally used allergy skin test reactivity, serum IgE levels or peripheral blood eosinophilia to identify atopic subjects. Although the diagnostic value of specific IgE levels against definite allergens is well accepted, there are conflicting results about predictive value of total serum IgE levels [10,11]. Population studies have shown an association between prevalence of different allergies and serum total IgE levels independent of specific reactivity to common allergies or symptoms of allergy [29,30].

This study was undertaken to Analyze the allelic distribution of interferon gamma gene polymorphism 874A>T in some allergic diseases (allergic skin diseases and allergic conjunctivitis).

In the current study we found that, the frequency of allele A874 of INF- ɤ gene was greater in allergic patients than in control subjects [31]. This is consistent with the finding of other studies; Hussein et al. [31] who found the same results. Grewe et al. [32] stated that IFN-ɤ gene polymorphism is correlated with the allergic skin diseases (his study was conducted in allergic skin diseases only), he mentioned that the correlation may be related to the capacity of IFN-ɤ to enhance Eosinophil viability and activate vascular endothelial molecules, which in turn increases infiltration by eosinophils and induces allergic diseases.

However Hoffmann et al. [33] who conducted his study in 329 normal volunteers and patients he reported that there is no association between allergic disease and IFN-ɤ alleles.

This discrepancy could be due to differences in population and age groups; in other words, each analysis may identify the allele or haplotype responsible for the phenotype in that specifi c population.

In our study there was a significant increase in eosinophil count in both allergic skin and allergic. Conjunctivitis groups compared with the control group. Other authors have found similar results [34,35]. When we compared between allergic skin and allergic conjunctivitis groups as regards peripheral blood eosinophil count we found statistically significant differences which mismatch with Winther et al. [36], who found no statistically significant differences between the two groups as regards peripheral blood eosinophil count, this mismatch may be due difference in environment, population or season in which both studies were conducted.

In clinical practice, peripheral blood Eosinophil counts are widely used to demonstrate the allergic etiology of disease, to monitor its clinical course and to address the choice of therapy [37]. Therefore, peripheral blood eosinophil count can be useful for observing the association of host factors and environmental determinants as indicators of allergy prevalence [38].

In the current study we found that, the frequency of allele A874 of INF- ɤ gene was greater in allergic patients than in control subjects, and that is correlates with markers of atopy (increased IgE levels and eosinophil count). This agreed with Hussein et al. [31] who reported significant association between genotype and the frequency of the A allele of the +874T/A polymorphism in atopic patients. However, Ohly [39] revealed that there was no significant association between the +874T/A polymorphism and IgE level in atopic German newborns. Also in a study conducted in a Chinese population by Chang et al. [40], there was no association between short tandem repeats at the first intron of IFN-ɤ gene and allergic diseases.

In our study we also found that total IgE was higher in allergic patients (allergic skin diseases and allergic conjunctivitis) than in control patients. These results matching with Hussein et al. [41] and Kawai et al. [42] who reported a significant correlation between the allergic diseases and total IgE levels. Johansson et al. [43] found that the total serum IgE in allergic conjunctivitis was higher than that of the control patients in addition to Staikuniene et al. [44] who reported an elevation of serum IgE level by a more than 2-fold in allergic skin patients.

However, other studies question the role of total IgE as a useful indicator of allergic skin diseases. Kaliner et al. [45] found that 40% of allergic patients had normal total IgE levels. Wüthrich and Schmid-Grendelmeier [46] mentioned that the overlap IgE levels made it suggestive but not diagnostic of allergic diseases and explained it by the presence of non–IgE mediated inflammatory mechanisms which may play a significant role in the mechanism of allergic diseases.

The present study revealed a significant correlation between peripheral blood eosinophil count, and total IgE levels in the all studied groups. This consistent with A Japanese study conducted by Yoshizawa et al. [47] to evaluate the role of eosinophils in allergic diseases, by correlating eosinophil count and IgE level and revealed a positive correlation between the number of peripheral blood eosinophils and IgE level [48], and matched with Hussein et al. [31] who reported a positive correlation between peripheral blood eosinophil count, and total IgE levels in his studied groups and finding that there was a negative correlation between peripheral blood eosinophil count, and total IgE levels with the serum level of IFN-ɤ ,and mentioned that his finding may simply reflect the fact that IFN- ɤ expression in this situation is a surrogate marker of TH1 cell activation and reflects its down regulation in blood eosinophilia and serum IgE levels and also mentioned that his data support the hypothesis that a normal level of IFN-ɤ synthesis regulates disease severity in allergic diseases, as activated B-cell clones could remain active (perhaps for years) and produce IgE.

Nevertheless, IgE-mediated local release of mast cells in atopic areas could lead to acute exacerbations of atopic manifestations after acute allergen exposure, although this does not imply an obligatory role for IFN- ɤ /IgE in the pathogenesis of chronic atopic diseases.

Cline et al. [49] reported the highest total IgE levels were seen in the age group 8-14 years. In the presented study no significant relationship of serum Total IgE levels with any age group was observed. Interestingly no association was found with either sex, however many studies have reported males to have raised IgE levels [49].

According to Toma et al. [50], infants suffering from severe allergic diseases have significantly higher number of eosinophils and eosinophilic nuclear lobes, platelets, and total serum IgE level.

Studies over the past 2 decades have shown that eosinophils play a major role in allergic diseases, characterized by activated eosinophils in the peripheral blood and in the lesional skin [51]. Interestingly, immunological response to allergens represents an important trigger for the increase of eosinophil counts in the peripheral blood and serum IgE level [52].

A Japanese study found that the eosinophil levels correlated with the allergic diseases, high blood eosinophil levels in atopic diseases [53]. They found that both the absolute eosinophil count and the IgE level showed significant increase with allergic diseases. The distribution of the absolute eosinophil count and the IgE level were reflected in the large range and higher standard deviation.

A study carried out in Egyptian atopic patients showed a significant association of IFN- ɤ gene polymorphism at position +874 A/T [31]. Study from China reported a significant association of IFN-ɤ +874 A/T gene polymorphism and severe acute respiratory syndrome [54,55].

A significant association was observed between interferon-ɤ gene polymorphisms and systemic lupus erythematosus suggesting that elevated interferon-ɤ is associated with increased systemic erythematosus susceptibility [56]. Lai et al. reported that genetic polymorphism of IFN-ɤ gene is associated with individual susceptibility to cervical carcinogenesis [57].

Feher et al could not find any association between IFN-γ +874 A/T gene polymorphism and Alzheimer disease [58]. Other study found a significant association of 'TT' genotype of IFN-γ +874 gene polymorphism and ischemic stroke in South Indian population [54].

In about 80% of adult patients with allergic skin diseases, the disease is associated with increased serum IgE levels (>150 IU/mL) [59,60]. In contrast, 20% of adult patients with allergic skin diseases have normal serum IgE levels. This subtype of allergic skin diseases often has a late onset (>20 years of life) and a lack of IgE sensitization against inhalant or food allergens [59,60]. However,some of these patients might have IgE sensitization against microbial antigens, such as *Staphylococcus aureus enterotoxins* and *Candida albicans*.

From this study it was concluded that:

The IFN-ɤ gene polymorphism at position +874 increases susceptibility to atopic diseases, and the identification of variants of the IFN-ɤ gene and their role in the development of atopic diseases provides a focus for the development of novel diagnostic and therapeutic strategies. Elevation of total IgE level and absolute eosinophil count in the atopic patients, and positive correlation between these parameters supports their effect, either directly or indirectly, in the atopic diseases and make them are strong predictors of atopic diseases.

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ANTINUCLEAR ANTIBODY LEVELS IN POLYMORPHIC LIGHT ERUPTION AND THEIR RELATION TO THE SEVERITY OF DISEASE

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Abstract
Introduction: PLE is an idiopathic photodermatosis characterised by a polymorphic eruption ranging from papulo-vesicular lesions to large plaques, located predominantly in a photoexposed distribution. It is an acquired disease and is the most common idiopathic photodermatosis. It is characterised by recurrent abnormal delayed reaction to sunlight. PLE is the most common idiopathic photodermatosis, the prevalence of which has been estimated to be around 10-20% in USA, England and Ireland. Previous studies have shown elevated levels of ANA in 2.9-19% of patients with PLE.
Aim: The aim of our study was to determine the frequency of ANA positivity in a cohort of patients of ethnic kashmiri origin with Polymorphic light eruption and to examine whether there is any relation of their levels with the severity of disease.
Methods: Patients with Polymorphic light eruption clinically who attended the Outpatient Deptt. of Dermatology GMC Srinagar were referred to the Deptt. of Biochemistry GMC Srinagar where patients blood samples were analysed for ANA index by ELISA method (BRIO SEAC ITALY).
Results: Our study consisted of 36 patients (with 23 males and 13 females with age group ranging between 15-65 years) presenting with typical clinical features of PLE without associated autoimmune connected tissue diseases like discoid lupus erythematosus or systemic lupus erythematosus and 20 healthy age and sex matched controls. Two patients (1 male and 1female) showed positive results and 1 patient (female) showed equivocal results. Among the control group one patient showed ANA positivity. Thus total frequency of ANA positivity of of 5.55% was observed among the cases and 5% among the controls with frequency of 4.34% in males and 7.69% in females.
Conclusions: ANA levels were found in 5.55% of patients with PLE, however there is no relation between the levels of ANA in PLE and with the severity of disease (p value >0.05).

Key words: antinuclear antibodies; polymorphic light eruption; discoid lupus erythematosus; ANA index

Abbreviations and acronyms: ANA (antinuclear antibodies), PLE (polymorphic light eruption), DLE (discoid lupus erythematosus), AI (ANA index).

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Iffat Hassan, Peerzada Sajad, Sabiya Majid, Hamid Bashir: Antinuclear antibody levels in Polymorphic Light Eruption and their relation to the severity of disease. Our Dermatol Online. 2012; 3(4): 318-320

Introduction

PLE is an idiopathic photodermatosis characterised by a polymorphic eruption ranging from papulo-vesicular lesions to large plaques, located predominantly in a photoexposed distribution. It is an acquired disease and is the most common idiopathic photodermatosis. It is characterised by recurrent abnormal delayed reaction to sunlight ranging from erythematous papules, papulovesicles and plaques to erythema multiforme like lesions on light exposed areas. Within any one patient only one clinical form is consistently manifested [1-3].

The condition is seen most commonly in parts of the world with four seasons and it is most commonly triggered by springtime sun exposure. The rash occurs on the sun exposed parts of the body, usually 1-4 days after exposure.

The sensitivity of the skin and sensitivity of the rash gradually lessens as the spring changes into summer and skin becomes adjusted to light. PLE affects men and women, adults and children equally however the problem typically begins between the age of 20-35 years. (Native Americans have a high rate of PLE and there is some evidence of genetic predisposition) [4,5]. Previous studies have shown elevated levels of ANA in 2.9-19% of patients with PLE [6,7]. The prevalence of autoimmune diseases in PLE has been found to be as high as 15% in some studies and even higher (22%) if hypothyroidism and non-toxic goitre were considered as the autoimmune processes. This is more than the estimated prevalence of 5-7% of the autoimmune diseases in the general population and indicates that the patient's with PLE have an increased risk of contracting an immunological disorder, although cases of lupus erythematosus didn't outnumber those of any other autoimmune disease [8]. Epstein has postulated that PLE is a cell mediated, delayed type hypersensitivity response to a sunlight-induced neoantigen. Another pathogenic pathway postulated is immunosuppression by ultravoilet radiation (due to genetic predisposition) resulting in increased recognition of antigens. This could be either due to resistance of Langerhan's cells to depletion by very intense ultravoilet radiation exposure and a reduced capacity to handle free radical insult through genetically determined glutathione depletion [9,10].

Material and Methods (Fig. 1, 2)

Our study consisted of 36 patients and 20 healthy age and sex matched controls who attended the outpatient Department of Dermatology, STD and Leprosy an associated hospital of GMC Srinagar. Out of 36 patients; 23 were males and 13 were females. Their age group ranged between 15 – 65 years (2). The method used to measure ANA index was ELISA BRIO SEAC (ITALY).The patients having classical clinical features of PLE and without other criteria suitable to the diagnosis of lupus erythematosus were regarded as having PLE and were included in the study. All the patients were ethnic kashmiris. An assessment of the patients present history, and personal history included questions about photosensitivity, allergy, autoimmune diseases, drug intake and a detailed analysis of the individual PLE lesions (Morphology, symptoms, latency period between sun exposure and beginning of skin rash, duration of the disease and resolution with or without scarring. Particular attention was paid to any symptoms of collagen vascular disorders in particular lupus erythematosus. In Addition, the patients were examined for any physical signs of Lupus erythematosus as defined by the 1982-revised ARA criteria.

Exclusion criteria:

1. The patients having clinical manifestation of lupus erythematosus or other autoimmune diseases were excluded from the study.
2. Non-kashmiris:

Controls: Control population consisted of 20 individuals (12 males, 8 females) without clinical features of PLE.

The limitations of the study were low patient number and the basis of the diagnosis of PLE was clinical. Informed consent was obtained from each patient.

The statistical method used for drawing the inferences was one -sample t-test.

The study was approved by the ethical committee of the hospital.

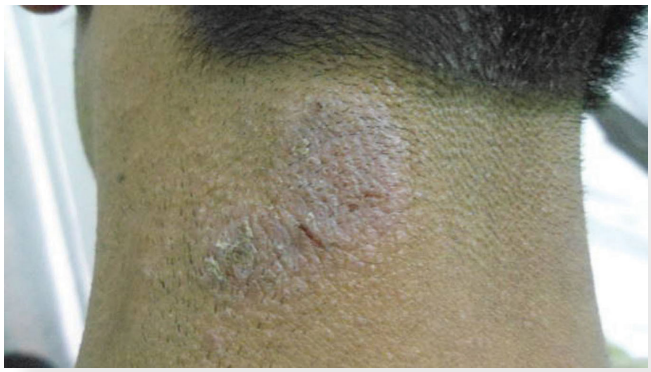

Figure 1. Plaque type PLE lesions on the nape of neck

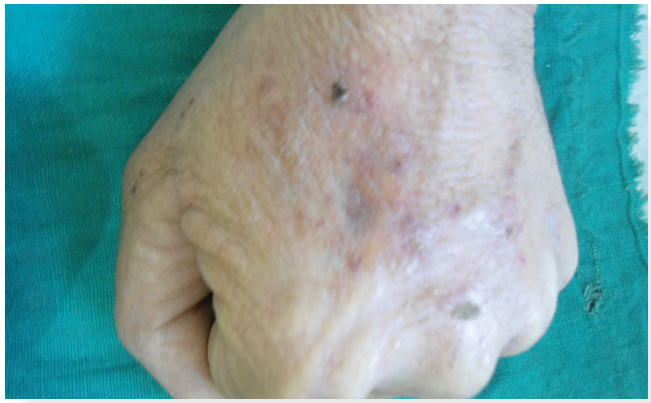

Figure 2. Erythema multiforme-like lesions and voilaceous papules over the dorsum of hands

Results

Two patients (1 male and 1 female) showed positive results and 1 patient (female) showed equivocal results. Among the control group one patient showed ANA positivity. Thus total frequency of ANA positivity of of 5.55% was observed. Among the cases and 5% among the controls with frequency of 4.34% in males and 7.69% in females (Tabl. I).

Disussion

PLE is an idiopathic photodermatosis characterised by a polymorphic eruption ranging from papulo-vesicular lesions to large plaques, located predominantly in a photoexposed distribution. It is an acquired disease and is the most common idiopathic photodermatosis. It is characterised by recurrent abnormal delayed reaction to sunlight ranging from erythematous papules, papulovesicles and plaques to erythema multiforme like lesions on light exposed areas. Within any one patient only one clinical form is consistently manifested [1-3]. Our study consisted of 36 patients who were clinically diagnosed as cases of polymorphic light eruption who were compared with 20 healthy age and sex matched controls. The most common type of clinical presentation was the micropapular type of lesions followed by the plaque, erythema multiforme and eczematous type of lesions.

	Total	M	F	+ives	-ives
CASES	36	23	13	3	33
CONTROLS	20	12	8	1	19

Table I. Incidence of toe and finger nail infections (n= 75)
Total cases studied=36
Normal range: ELISA METHOD
<1.0AI- NEGATIVE; 1.0-1.1AI=EQUIVOCAL; >1.1AI = (+IVE)
AI=ANA INDEX (Ratio of sample observance with cutoff)

The severity was clinically assessed on the basis of extent of involvement of photoexposed areas, time taken to resolution, intensity of pruritus and frequency of recurrences. All the patients were ethnic kashmiris. An assessment of the patients present history, and personal history included questions about photosensitivity, allergy, autoimmune diseases, drug intake and a detailed analysis of the individual PLE lesions (morphology, symptoms, latency period between sun exposure and beginning of skin rash, duration of the disease and resolution with or without scarring. Particular attention was paid to any symptoms of collagen vascular disorders in particular lupus erythematosus. In Addition, the patients were examined for any physical signs of Lupus erythematosus as defined by the 1982-revised ARA criteria. There was no significant difference in the ANA positivity rate between cases and controls and also of the levels of ANA with the severity of disease.

Conclusion

Positive ANA levels were found in 5.55% of patients with PLE, which is consistent with the results of earlier studies, however there is no relation between the levels of ANA in PLE and with the severity of disease.

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EXPECTING THE MOST UNEXPECTED – A HARLEQUIN BABY! A CASE REPORT AND LITERATURE ANALYSIS

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Abstract
Twenty eight years old primi gave birth to an amazing live baby by vaginal delivery – a Harlequin. The child was born with massive, diamond-shaped scales which limit the child's movements. The term harlequin comes from the baby's facial expression and diamond-shaped pattern of the scales like the 17th century entertainers, harlequins. As the skin cracks at places of movement the protective function of the skin is lost. Till now the prenatal diagnosis was based on biopsy of fetal skin carried out in an advanced stage of pregnancy. The most important indication of fetal cutaneous biopsy is the diagnosis of genodermatosis and hereditary diseases including Harlequin ichthyosis. It is predictable that for Harlequin Ichthyosis the prenatal test based on DNA will replace the fetal biopsy made before tenth week of gestation by chorionic villus sampling, or even before, with non-invasive analysis of the DNA of fetal cells in maternal circulation. Advances in neonatal intensive care along with scaling being made easier by the use of systemic retinoids has led to improved survival and the use of the name "Harlequin baby" to "Harlequin fetus", "World's Largest Baby" or "World's Smallest Baby". The mortality rate for harlequin ichthyosis is high. With neonatal intensive care and the advent of retinoid therapy, some babies have survived the newborn period. They are still at risk of dying from systemic infection. It's the world's most unconquired medical challenge.

Key words: harlequin; ichthyosis; eclabium; ectropion; ABCA12; lipid transport

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Introduction

The term harlequin comes from the baby's facial expression and diamond-shaped pattern of the scales like the 17th century entertainers, harlequins. As the skin cracks at places of movement the protective function of the skin is lost. Till now the prenatal diagnosis was based on biopsy of fetal skin carried out in an advanced stage of pregnancy. The most important indication of fetal cutaneous biopsy is the diagnosis of genodermatosis and hereditary diseases including Harlequin ichthyosis. It is predictable that for Harlequin Ichthyosis the prenatal test based on DNA will replace the fetal biopsy made before tenth week of gestation by chorionic villus sampling, or even before, with non-invasive analysis of the DNA of fetal cells in maternal circulation. Advances in neonatal intensive care along with scaling being made easier by the use of systemic retinoids has led to improved survival and the use of the name "Harlequin baby" to "Harlequin fetus", "World's Largest Baby", "World's Smallest Baby", „Polymelia", „Diphallia", „Anencephaly", „Ectopia Cordis", „Harlequin ichthyosis", „Craniopagus parasiticus", „Cyclopia".
Diprosopus are the world`s ten most amazing babies.
The mortality rate for harlequin ichthyosis is high. With neonatal intensive care and the advent of retinoid therapy, some babies have survived the newborn period. They are still at risk of dying from systemic infection. It's the world's most unconquired medical challenge.

Case Report

A 28-year-old non consanguineous married woman ,a primi, delivered a full term live male baby at term per vaginum, weighing 2450 g, with APGAR scores of 6, 7 and 8 at 1, 5, and 10 minutes respectively. I was called to examine the baby which was abnormal. When I went there, to my amazement, the baby was a Harlequin. The infant had characteristics typical of Harlequin Ichthyosis (HI) (Fig. 1, 2) a parchment-like appearance of the skin, ectropion, eclabium and low-set dysplastic ears. There was flexion deformity of all joints of the limbs. The hands and feet were swollen.
There was no prenatal identification of Harlequin Ichthyosis and there was no family history of the disease. Prenatally Ultrasound examination revealed no evident fetal abnormalities, except mild oligohydraminos.An optimal anomaly screening could not be performed due to oligohydramnios. Despite the oligohydramnios, the fetal movement pattern appeared grossly unrestricted.
The infant was transported to the neonatal intensive care unit and an umbilical vein catheter was inserted.

Figure 1. Harlequin Baby immediately after delivery - lateral view

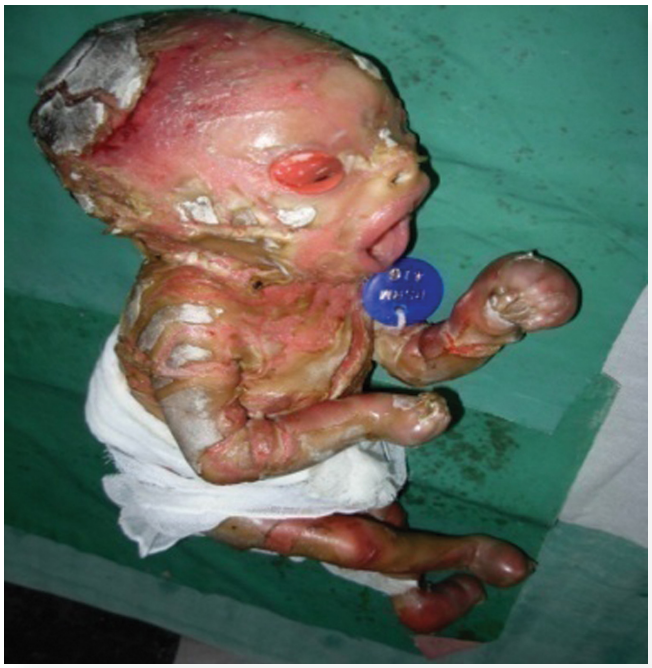

Figure 2. Harlequin Baby - anterolateral view

Fluids were given intravenously as partial parenteral nutrition and protection from dehydration. After appropriate cultures were taken, prophylactic antibiotic treatment was started and intensive skin care involving moisturizing and oiling with baby olive oil. Ophthalmic lubricants were used to protect the conjunctivae. Despite this intensive care, respiratory insufficiency and anuria began on the fourth day of follow-up. Culture of skin swabs revealed *Candida* and *Staphylococcus*. Despite optimum treatment with catecholamine, antibiotics and ventilator support, and neonatologist`s care the infant died due to sepsis on the fifth day.

Discussion

In Harlequin infants, premature birth is typical, leaving infants at risk for additional complications from early delivery. These infants are also at high risk for difficulty breathing, infection, low body temperature, and dehydration. Constriction and swelling of the mouth may interfere with the suck response and infants may need tube feeding. Medical monitoring is difficult because of the abnormal skin; electrodes cannot be placed effectively and blood vessels cannot be seen under the skin. Placing lines in the artery and vein of the umbilical cord can aid in monitoring the infant and delivering fluids and nutrition. These infants may have problems maintaining normal levels of electrolytes, especially sodium in their blood. They are particularly prone to develop hypernatremia (high sodium levels in the blood). The baby's corneas need to be lubricated and protected if the eyelids are forced open by the tightness of the skin. A high humidity environment in a heated incubator is necessary to help maintain body temperature and to prevent the skin from cracking.

Antibiotic treatment may be necessary to prevent infection at this time. Administration of a retinoid such as oral etretinate1 (1 mg/kg body weight) may accelerate shedding of the thick scales. Most Harlequin infants will need one-on-one nursing care for the first several weeks of life.

In the past, Harlequin infants rarely survived the first few days of life. However, with recent advances in neonatal care and perhaps with the administration of etretinate,1 Harlequin infants can survive. Several surviving children with Harlequin ichthyosis are now young adults. The surviving children display dry, reddened skin, which may be covered by large thin scales, and sparse hair. Physical development may be delayed by the enormous calorie needs their skin function demands, but their mental and intellectual developments are expected to be normal. Harlequin ichthyosis demands a meticulous ongoing skin care regimen to keep the skin moisturized and pliable and to prevent cracking and fissuring that may lead to infection.

Harlequin ichthyosis is a recessively inherited genetic disorder. In order to express (show) the disorder, individuals must inherit two recessive genes, one from each parent, but the parents (the „carriers") show no signs.

Recently, the cause of harlequin ichthyosis was traced to the ABCA12 gene. The ABCA12 gene is believed to encode a transporter protein involved in the transport of epidermal lipids across cell membranes. Identification of this gene has made DNA-based prenatal diagnosis of harlequin ichthyosis possible.

Harlequin ichthyosis (HI) - the most severe form of keratinizing disorders, often lethal in the neonatal period is characterized by a profound thickening of the keratin skin layer, a dense "armor"-like scale that covers the body, and contraction abnormalities of the eyes, ears, and mouth. Akiyama et al. [21-25] report that mutations in ABCA12 caused defective lipid transport that significantly impacted normal development of the skin barrier. Lipid secretion was recovered after corrective ABCA12 gene transfer into patient keratinocytes. These results should allow for early prenatal diagnosis of HI and lend hope to the possibility of a specific treatment for this devastating disorder.

Waring pointed to what is believed to be the first harlequin fetus described in the US in the diary of Reverend Oliver Hart in 1750 [1].

Pathogenesis

Lipid processing in the skin is essential for the protective function of the stratum corneum, the most external layer of the epidermis. Corneocytes, attached to each other by corneo-desmosomes and embedded in intercellular lipid lamellae, form a cornified layer that acts as a barrier between the internal and external environment for bodily defense. The lipid lamellae are derived from lamellar granules, the major lipid-rich organelles present in epidermal granular cells, which originate from the trans-Golgi network.

At the granular layer–stratum corneum interface, the lamellar granules fuse with the cell membrane and discharge their content into the intercellular lamellae. Complex enzymatic reactions lead to modifications of the lipid composition of the intercellular space (cholesterol, ceramides, and free fatty acids) that provide a very effective water-permeability barrier. Corneocytes detach from each other in the superficial layers of the stratum corneum as a result of finely regulated proteolytic cleavage of corneo-desmosomes. In the skin of HI patients, the absence of ABCA12 prevents the transfer of lipids into lamellar granules, which themselves are abnormally shaped, reduced in number, or absent. As a result, exocytosis of lamellar granule content is reduced and intercellular lipid lamellae are absent. Abnormal lipid-containing vacuoles form in the cytoplasm of the corneocytes. The stratum corneum is remarkably thickened and does not desquamate.

In a previous study, electron microscopy in HI patients revealed that lamellar granules are either absent or abnormal and that no intercellular lamellae are present. These data suggest that this defect in the lamellar granules results in thickening of the stratum corneum and the accumulation of armor-like scales in HI. However, the genetic basis for these events had not been elucidated.

This discovery of the role of ABCA12 in HI reveals a major role of lipid transport in the formation of the skin barrier and its function. This involves two closely related lipid transporters, ABCA3 and ABCA12, which are essential for the production of alveolar surfactant and lipid lamellae in the stratum corneum, respectively. At birth, while ABCA3 prevents the lungs from collapsing, ABCA12 protects the skin from external aggressions and water loss. Loss of ABCA12 expression results in the most severe dysregulation of cornification in humans, covering the newborn infant in a lethal type of armor. Not only will these findings dramatically improve our ability to offer mutational screening and early DNA-based prenatal diagnosis of HI, but they will also allow for the development of new and specific therapeutic approaches.

Genetic correction of ABCA12 deficiency by gene transfer in patients' keratinocytes restored normal glucosylceramide cell distribution and lamellar granule formation. This result raises the possibility of HI treatment using systemic administration of functional peptides with ABCA12-like properties or ABCA12 gene delivery approaches undertaken either prior to or after birth [10-12].

Differential Diagnosis

Gaucher's disease – beta glucocerebrosidase defect [13].
X linked recessive ichthyosis – Steroid sulfatase defect [9].
Niemann - Pick disease – Sphingomyelinase defect [14].
Sjogren-Larsson syndrome – Fatty aldehyde dehydrogenase defect [15].
Autosomal recessive congenital ichthyosis - Lipoxygenase-3 and 12R- lipoxygenase defect [16].
Dorfman - Chanarin syndrome - CGI-58 defect [17].
Tangier disease – Defect in cholesterol transport between liver and other tissues [2-5].
Stargardt disease – Abnormal accumulation of retinoid [6-8].
Neu-Laxova syndrome - Autosomal recessive disorder with severe IUGR, extreme microcephaly, ichthyosis, marked edema with skin restriction, cranio facial anomalies, limb deformities and CNS malformations.

Conclusion

HI is a rare and extremely severe form of congenital ichthyosis, with an incidence of about 1 in 300 000 births. Prenatal diagnosis is usually difficult because of non-specific signs in the ultra sonographic examination and rareness of the disorder. Delivery of a child with congenital ichthyosis identifies a family at risk, and for subsequent pregnancies prenatal diagnosis can be offered. This report is a typical example of all of these issues.

<u>The ten most amazing babies in the world medical literature are:</u>
1. World's largest baby
2. World's smallest baby
3. Polymelia
4. Diphallia
5. Anencephaly
6. Ectopia cordis
7. Harlequin ichthyosis
8. Craniophagus parasiticus
9. Cyclopia
10. Diprosopus.

According to the literature survey the most constant sonographic findings are: a large gaping mouth; dysplastic or swollen hands and feet; aplasia of the nose; and bulging eyes. The "snowflake sign" reflecting skin particles floating in the amniotic cavity, intra-amniotic debris or floating membranes might be another indirect sign (Tabl. I) [18-20].

Polyhydramnios has been proposed as a marker of congenital ichthyosis [18]. However, we detected oligohydramnios in our case, and oligohydramnios was also present in the cases reported in the literature. In the first half of the pregnancy, the contribution of water transport across the highly permeable skin of the fetus to the amniotic fluid volume is a major mechanism of amniotic fluid dynamics. At 22 to 25 weeks of gestation, keratinization of the skin occurs; it is generally accepted that significant amounts of water and solute are not transferred across this membrane after keratinization. We could not demonstrate the cause of oligohydramnios in our case; neither any abnormal Doppler result nor any structural malformation or preterm premature rupture of membranes was detected. Definite prenatal diagnosis of HI is based upon the examination of fetal skin biopsy samples obtained after 19-23 weeks' gestation. Samples taken from the scalp will give a surer early diagnosis but are more difficult and more risky [20].

Constant sonographic findings
Persistent large gaping mouth
Dysplastic or swollen hands and feet
Aplasia of the nose
Bulging eyes
Indirect signs
"Snow flake sign"
Intra- amniotic debris
Floating membranes
Non specific ultrasonographic signs
Polyhydramnios
Oligohydramnios

Table I. Most constant ultrasonographic signs of Harlequin ichthyosis

The use of three-dimensional ultrasound diagnosis does not appear to have been widely adopted, though useful.

In HI mortality is very high that most affected neonates die within a few days due to sepsis, respiratory failure, infections, poor nutrition, and electrolyte imbalances. In 2003, Berg et al. could find only nine reported cases of prolonged survival of HI cases. Prolonged survival with better neonatal care is possible with developments of neonatal care and targeted oral retinoid therapy. Isotretinoin, etretinate, and acitretin were used for treatment of HI to achieve survival up to 8 years. Sing et al. successfully treated neonate with 1mg/kg/day (started 10 days after birth) up to 30 months. Though survival rates appear to be increasing, the severity of the persisting dermatosis results in a lifetime of suffering for the saved individuals. This makes early prenatal diagnosis to allow appropriate counseling that is highly desirable for the parents.

Prenatal diagnosis of HI remains difficult and is still usually only feasible in cases where there has already been an affected child. Better prenatal diagnostic procedures are needed.

UNANSWERED QUESTIONS

1. Do we have the technical knowhow and skills to diagnose prenatally/intrauterine of HI?
2. Do we have medical technology to give treatment intrauterine for HI? Is it feasible? Is it advisable? What sort of research going on regarding this condition?
3. Is it possible to make sustainable correction of dermatological defects soon after birth or neonatally?
4. As this case is an interdisciplinary approach, is the role of the dermatologist defined?
5. Is it medico legally accepted or any legislations executed for MTP if diagnosed prenatally?
6. What is the possibility of another child having same disease? Is there any medical records highlighting the same?
7. What sort of medical counseling should be given?

Finally there are many questions than answers for this condition….!!!

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PUSTULAR PSORIASIS RESPONDING TO PROBIOTICS – A NEW INSIGHT

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Abstract
Probiotics exhibit widespread effects on homeostasis and immunomodulation of both mucosal and systemic immunity. Probiotics counter weight aggressive commensals in the body and reinforce the barrier function of the epithelium while also contributing to the regulation of innate and adaptive immune responses of the host under healthy or pathogenic conditions. Probiotics could be used for prevention or treatment of chronic allergic and inflammatory diseases, such as inflammatory bowel disease (IBD) and atopic dermatitis. We describe a case of pustular psoriasis where probiotics were used for the treatment successfully.

Key words: psoriasis; pustular psoriasis; probiotics

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Introduction

Probiotics exhibit widespread effects on homeostasis and immunomodulation of both mucosal and systemic immunity. Probiotics counter weight aggressive commensals in the body and reinforce the barrier function of the epithelium while also contributing to the regulation of innate and adaptive immune responses of the host under healthy or pathogenic conditions. Probiotics could be used for prevention or treatment of chronic allergic and inflammatory diseases, such as inflammatory bowel disease (IBD) and atopic dermatitis. We describe a case of pustular psoriasis where probiotics were used for the treatment successfully.

Case Report

A 47yr old female, presented with crops of pustules all over her body since 20 days. The rashes started over the leg and rapidly progressed to the whole body. The rashes were associated with pain. Patient had fever and arthritis of both knees. There was no photosensitivity. Patient was a known case of psoriasis since 15 years. She was on treatment with different medications both topical and systemic. She was given Methotrexate 2yrs back for 6 months and since then she was on irregular treatment. The patient was anxious, looked very ill and was febrile. General physical examination showed bilateral pedal edema. On cutaneous examination there was diffuse erythema with areas of pustules over extensor aspect of upper and lower limbs, abdomen and chest (Fig. 1, 2). Multiple scaly plaques were present over the scalp. Axilla and groins had no lesions. Nails showed pitting with subungual hyperkeratosis. Palms and soles were normal. Systemic examination was within normal limits.

Her random blood sugar was 220mg/dl, triglycerides were 344mg/dl, C-Reactive Protein was positive, total protein was 5.6g/dl and albumin was 3g/dl. Ultrasonography of the abdomen did not show any significant abnormality.
On the basis of history, clinical examination a diagnosis of pustular psoriasis was made. The patient was admitted and put on steroids, dapsone and as she was already on methotrexate, it was continued with supplementation of analgesics and antipyretics. But even after two weeks she did not respond and her lesions kept increasing and her blood sugar increased. She started developing signs of steroid toxicity. We were forced to withdraw steroids. As she could not afford biologics we had to look for alternative medicines.

With anecdotal reference [4] of probiotics helping palmoplantar pustular psoriasis and their usefulness in atopic dermatitis, we thought of trying the regimen after obtaining consent from the patient. The patient was put on *Lactobacillus*, one sachet thrice daily with biotin 10mg once daily. All the other drugs were stopped forthwith. In fifteen days the fever subsided, lesions started involuting and no new lesions appeared (Fig. 3, 4). The patient's general condition also showed improvement. Blood sugar level dropped. She was continued with the same treatment and after six months follow up she is free of lesions and she is being followed up for possible recurrence. Her plaque psoriasis is also under control with only salicylic acid and coal tar.

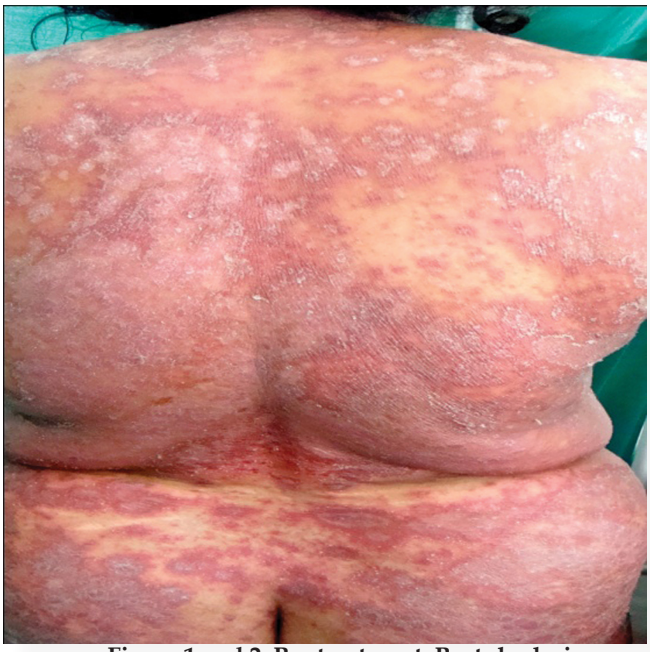
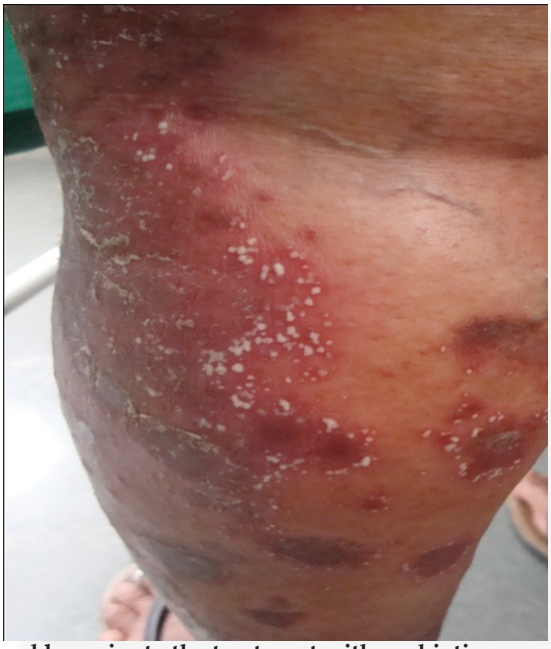

Figure 1 and 2. Pre-treatment: Pustular lesions over the back and leg prior to the treatment with probiotics

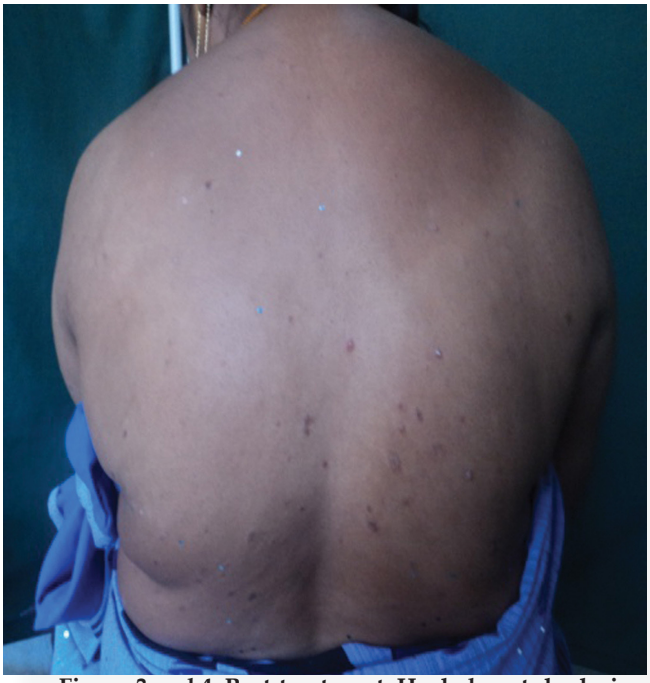
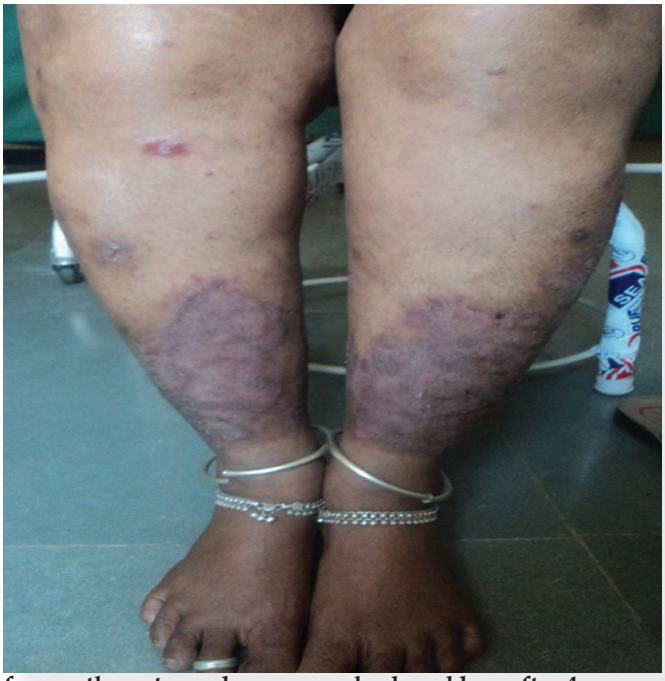

Figure 3 and 4. Post-treatment: Healed pustular lesions with few erythematous plaques over back and legs after 4 weeks of treatment

Discussion

Administration of probiotic *Lactobacillus strains* (a mixture of *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 12246) to children with atopic dermatitis has been shown to result in a moderate improvement in the clinical severity [5].

It is being reported that most of the probiotics containing lactic-acid producing bacteria (LAB) strains are nonpathogenic and nontoxigenic microorganisms. Over 70 clinical studies have been conducted over food containing microbial ingredients to investigate potential probiotic-side effects. None have shown any adverse effects [6]. The rationale of usage of such probiotics is furthered by its potential multi-pronged action. Though unclear the proposed mechanisms of action include modulation of immune response in the gut which can directly affect the development of inflammatory disease mechanisms in systemic sites of disease, such as the skin [7]. However, the mechanisms by which intestinal immune responses translate to systemic anti-inflammatory effects remain to be established. In our case *Lactobacillus Sporogenes* was used as it was the only available lactobacilli in the market along with biotin.

However, to date, the overall clinical evidence on the benefits of probiotics in the management of systemic inflammatory diseases is inconclusive. It is likely that quantity and time of administration, as well as the interaction with specific components of the host's microflora, will heavily influence the immunomodulatory effects of probiotics. The situation is complicated by the fact that different probiotic strains have different immunomodualtory patterns. Our treatment success in this case though forlorn can act as a catalyst in further evaluation of this exciting prospect in the management of psoriasis.

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SOLITARY POROKERATOSIS OF MIBELLI AT AN UNUSUAL SITE

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Abstract
Porokeratosis is an assorted group of five genetic disorders. These include porokeratosis of Mibelli, DSAP, punctate porokeratosis, porokeratosis palmaris et plantaris disseminata, and linear porokeratosis. They are disorders of abnormal keratinization characterized by the appearance of atrophic patches. Porokeratosis of Mibelli is referred to the more localized form of this disorder usually manifesting as solitary or a small group of lesions. It was first described by Mibelli in 1893 who described atrophic patches surrounded by a clinically and histologically unique ridge like border termed the cornoid lamella. The cornoid lamella is formed by rapidly proliferating atypical keratinocytes that expands peripherally to form a raised boundary at the junction of abnormal and normal cells. These lesions are most commonly found on the extremities, but can also be found on genitalia, face, oral mucosa and cornea. Though the patches are generally asymptomatic they can often lead to ulcerative, verrucous, giant, and malignant lesions. We describe a case of Porokeratosis of Mibelli at an unusual site in a 22 yr old male. The presenting history, clinical findings, biopsy results and available literature are reviewed.

Key words: porokeratosis of mibelli; ala nasi; solitary

Cite this article:
Nithya Raghunath, Metikurke Vijayashankar: Solitary Porokeratosis of Mibelli at an unusual site: A hospital based study. Our Dermatol Online. 2012; 3(4): 329-331

Introduction

Porokeratosis is an assorted group of five genetic disorders. These include porokeratosis of Mibelli, DSAP, punctate porokeratosis, porokeratosis palmaris et plantaris disseminata, and linear porokeratosis [1]. They are disorders of abnormal keratinization characterized by the appearance of atrophic patches. Porokeratosis of Mibelli is referred to the more localized form of this disorder usually manifesting as solitary or a small group of lesions. It was first described by Mibelli in 1893 who described atrophic patches surrounded by a clinically and histologically unique ridge like border termed the cornoid lamella. The cornoid lamella is formed by rapidly proliferating atypical keratinocytes that expands peripherally to form a raised boundary at the junction of abnormal and normal cells. These lesions are most commonly found on the extremities, but can also be found on genitalia, face, oral mucosa and cornea [2]. Though the patches are generally asymptomatic they can often lead to ulcerative, verrucous, giant, and malignant lesions [3].

We describe a case of Porokeratosis of Mibelli at an unusual site in a 22 yr old male. The presenting history, clinical findings, biopsy results and available literature are reviewed.

Case Report

A 22 year old male patient came with complaints of a white rash over his nose since 6 months. It was confined to the left ala of the nose (Fig. 1). The lesion started as a small papule and gradually spread peripherally. There was central clearing with hypo pigmentation and a raised border. The patient's history was otherwise insignificant. There was no similar history in the family. He was born of a non consanguineous marriage. There was no history suggestive of photosensitivity. His systemic examination was within normal limits. The differential diagnosis of Discoid Lupus Erythematoses, Basal Cell Carcinoma, Lupus Vulgaris and Porokeratosis were considered. Routine blood investigations were normal. HIV 1 and 2 was non reactive.

A full depth skin biopsy was taken from the outer part of the lesion with a 2mm disposable skin biopsy punch and subjected to histopathology. The histopathology revealed foci of epidermal invagination filled with keratin and parakeratotic coronoid lamella. Dermis showed a mild to moderate infiltrate of lymphocytes (Fig. 2). On the basis of history, clinical examination and histopathology, a diagnosis of Porokeratosis of Mibelli was made. Topical tretinoin was prescribed for the management of the lesion.

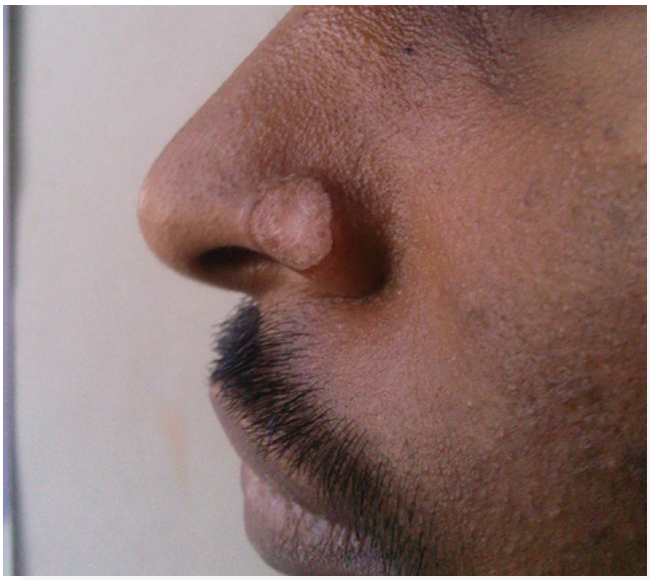

Figure 1. A single plaque with central clearing and a raised border over left ala of nose

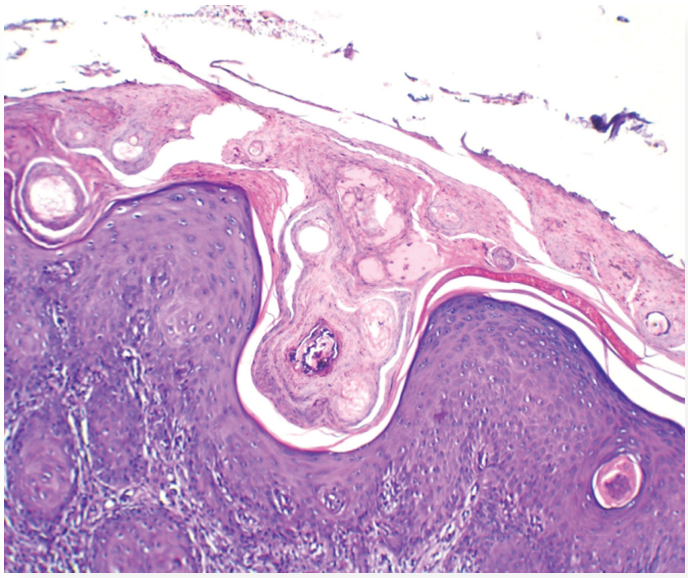

Figure 2. Histopathology (H&E 45x) shows foci of epidermal invagination filled with keratin and parakeratotic coronoid lamella. Dermis shows a mild to moderate infiltrate of lymphocytes

Discussion

Porokeratosis of Mibelli may be familial, inherited as an autosomal dominant disorder with the onset in childhood or sporadic with later onset. Risk factors include immunosuppression, genetic inheritance, and UV radiation. The common underlying pathway in all forms of porokeratosis is a clonal hyperproliferation of atypical keratinocytes resulting in the characteristic cornoid lamella [4]. Histopathologic examination of a skin biopsy specimen from the area of suspicion is essential for diagnosis.

Porokeratosis of Mibelli is the most characteristic and distinctive variant of the five described forms of porokeratosis. The classical form of Mibelli consists of a single plaque, or a small number of plaques, of variable size and can affect any part of the body. Common areas involved are palms, soles and mucous membranes. Other areas of involvement reported include labial commisures, lips [5]. Histologically, the invaginations of the epidermis in Porokeratosis of Mibelli are wider and deeper, and there is prominent adjacent papillomatosis when compared with the other variants. All variants show a diminution of the granular layer, dilated superficial plexus capillaries, and a nonspecific superficial chronic infiltrate. Dermoscopy is also used in the diagnosis of porokeratosis [6].

The management of such lesions includes many options. The approach to treatment is individualized and based on many factors, such as lesion size and location, risk of malignant transformation, and functional and aesthetical considerations. Sun protection, emollients, and observation for signs of malignant degeneration are mandatory. Medical modalities focus on inhibiting cell growth and proliferation of the rapidly proliferating keratinocytes. Various modalities used include oral and topical retinoids, 5-fluorouracil cream, vitamin D3 analogues, diclofenac gel, imiquimod cream cryotherapy, dermabrasion and surgical excision. Recently photodynamic therapy has been shown to be an effective and safe alternative [7].

Conclusion

A solitary Porokeratosis of Mibelli over the nose is uncommon. Such lesions may not always be clinically diagnosed, hence it requires histopathological examination. Hence Porokeratosis of Mibelli should be a differential diagnosis for any such plaques over nose.

Our case presented with a single lesion over the nose. This is a rare presentation. There are only two such cases which have been reported [8,9].

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UNILATERAL LATEROTHORACIC EXANTHEM IN A PREGNANT WOMAN - CASE REPORT

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Abstract
Unilateral laterothoracic exanthem (ULE) (also termed asymmetric periflexural exanthem of childhood APEC) has been linked to viral infection, in particular parvovirus B-19, citomegalovirus and Ebstein Barr virus. Its prevalence is higher during spring and winter, most published reports involve white people. The diagnosis is clinical, the virusological tests, in most of the cases, are negative. The exanthem is self-limited, it resolves in four-six weeks, it requires only symptomatic treatment. Our case is particular by the appearance in a pregnant woman to whom we have not succed to identify any virus involved, with wonderful clinical results under no medication. We follow the evolution of the pregnancy.

Key words: exanthem; unilateral laterothoracic exanthem; pregnancy

Cite this article:
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Introduction

Unilateral laterothoracic exanthem (ULE) (also termed asymmetric periflexural exanthem of childhood APEC) was first described in 1962 in the United States, but the name was given in 1992 by Bodemer-de Prost [1].
It usually manifests as unilateral erythematous papules surounded by white halo, without systemic symptoms.
ULE has been linked to viral infection, in particular parvovirus B-19, citomegalovirus and Ebstein Barr virus [2]. While ULE most commonly occurs in children, ULE can occur in adults, we describe a typical case, appeared in a pregnant woman (Vth month of pregnancy) with a 2 weeks favorable evolution [1,3].

Case report

A 32 year-old woman presented in our Department with an asymptomatic 2-day history of a unilateral erythematous macular eruption on her left side of the trunk, scatered lesions on the hips, no systemic symptoms, no palpable lymph nodes. She was in good health state. She was pregnant in Vth month with her first baby.
She denied any drug intake, no previous ilness, no symptoms before the onset of the eruption.
The lab investigations showed a slight anemia, leucocytosis with neutrophilia and the virusology results were negative for Parvovirus B19, Ebstein Barr virus and citomegalovirus.
We did not recommend any therapy, just daily control and the lesions fadded and dissapeared in 15 days, with minor hyperpigmentation.

Discussion

Unilateral laterothoracic exanthem is also known as asymetric periflexural exanthem in children (APEC) and it is mainly described in children between one and five years old, although adults can be affected too. Its prevalence is higher during spring and winter, most published reports involve white people [1,3].
The diagnosis is clinical, the virusological tests, in most of the cases, are negative, although ULE is linked to viruses: parvovirus B-19, citomegalovirus and Ebstein Barr virus [2].
The exanthem is self-limited, it resolves in four-six weeks, it requires only symptomatic treatment.
Our case is particular by the appearance of ULE in a pregnant woman to whom we have not succed to identify any virus involved, with wonderful clinical results under no medication. We follow the evolution of the pregnancy.

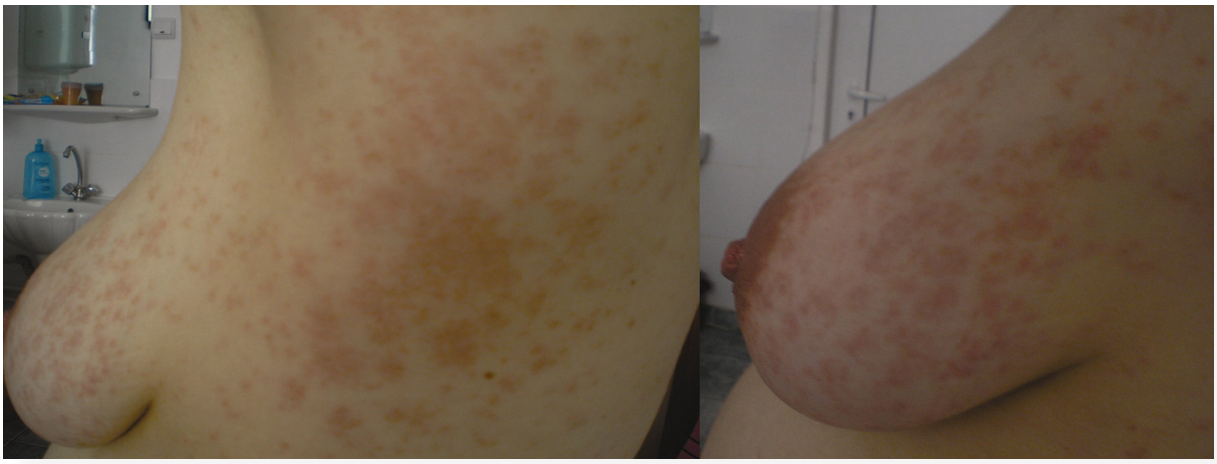

Figure 1. Erythematous macular eruption on the left side of the trunck

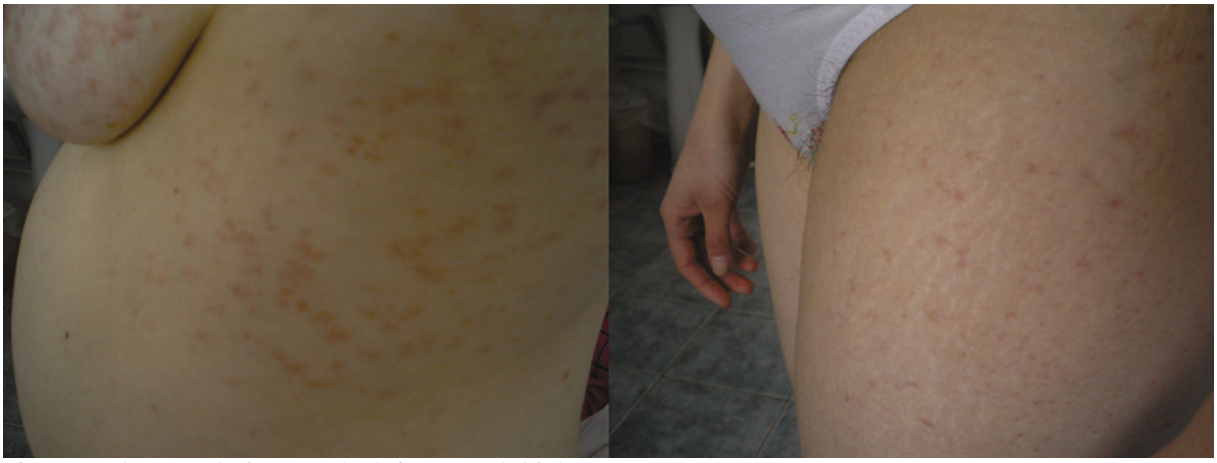

Figure 2. The same lesions on the left arm and thigh

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We read with admiration the report by Chiriac et al. on the normal pregnancy outcome of a 32-year-old lady in Romania with unilateral laterothoracic exanthem (ULE) at the fifth month of her first pregnancy. Virological investigations revealed insignificant findings.

We wish to make three comments. Firstly, we have also reported two pregnant ladies with an exanthem which might be caused by viruses, namely pityriasis rosea (PR) [1]. Maternal and foetal outcomes were good on both occasions. However, a case series report followed 38 women with PR [2]. Nine had premature delivery, and five miscarried. Six neonates showed hypotonia, weak motility, and hyporeactivity [2].

We should therefore clearly document, and report if possible, maternal and foetal outcomes when pregnancy is complicated by exanthems which may be related to viral infections, not only ULE and PR, but also Gianotti-Crosti syndrome (papular acrodermatitis in adults), papular purpuric gloves and socks syndrome, eruptive pseudoangiomatosis, and other similar exanthems.

Secondly, the authors stated that "virological results were negative for *parvovirus B19*, *Epstein-Barr virus*, and *cytomegalovirus* (CMV)". We hope they meant that IgG against CMV was positive, for such conferred some reassurance that primary infection during the exanthematous period was less likely.

The seroprevalence against CMV in young ladies in developed countries is relatively low. For a pregnant lady to have an exanthem for which CMV infection is known to be associated with, no test exists to exclude primary CMV infection definitely. Serial IgG to document seroconversion (preferably performed in parallel in a reference laboratory), and IgM can be arranged, but the interpretation of results is difficult [3]. Serial ultrasound scans can monitor intrauterine growth and detect markers of foetal abnormalities, but the sensitivity is low [3]. If amniocentesis is being considered, such should be done at least seven weeks after presumed time of maternal infection and after 21 weeks of gestation [4].

The paediatrician might be informed of the history of the paraviral exanthem during pregnancy. However, clinical detection on the neonate is insensitive. Where clinically indicated, the blood, urine, and saliva of the neonate can be tested for CMV within the first three weeks of life [3].

However, we have no information on the seroprevalence of CMV in Romania. CMV infection is not strongly associated with ULE [5], and there exists no licensed active intervention for congenital CMV infection. We thus hesitate on how far one should proceed in clinical settings independent of academic discussions and speculations.

Thirdly, we have previously reported two patients with the reversed version of ULE – namely unilateral mediothoracic exanthem. The eruption occurs mainly on the anteromedial aspect of the chest, reaching but not crossing the midline of the thoracic cage [6]. Readers of your prestigious journal coming across similar syndromatology might consider reporting such to the journal.

We once again congratulate the authors for their successful outcome of their patients and for their outstanding case report.

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LESIONES TUMORALES MÚLTIPLES EN UN PACIENTE ADOLESCENTE
MULTIPLE TUMORAL LESIONS IN AN ADOLESCENT PATIENT

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Resumen
El xantogranuloma juvenil (XGJ) es una histiocitosis de células no Langerhans, benigna, autocurativa, que afecta con mayor frecuencia a lactantes y niños, que se caracteriza por pápulas amarillentas asintomáticas y/o nódulos situados en la piel y otros órganos y que consisten en un infiltrado de macrófagos con un variable grado de lipidización en ausencia de un trastorno metabólico. Presentamos el caso de un varón, adolescente, de 14 años de edad, con múltiples lesiones tumorales gigantes en brazos y pies, limitadas a la piel y que no requirieron tratamiento alguno.

Abstract
Juvenile xanthogranuloma (JXG), a non-Langerhans cell histiocytosis, is benign and self-healing disorder, that affects most often infants and children, characterized by asymptomatic yellowish papules and/or nodules located in the skin and other organs consisting of an infiltrate of macrophages with a variable degree of lipidization in the absence of a metabolic disorder. We report the case of a male teenager of 14 years old, with multiple giant tumoral lesions in the arms and feet, limited to the skin and who did not require any treatment.

Palabras clave: xantogranuloma juvenil; histiocitosis de células no Langerhans; nevoxantoendotelioma
Key words: juvenile xanthogranuloma; non-Langerhans cells histiocytosis; nevoxanthoendoteliomais

Cite this article:
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Introducción

El XGJ se encuentra dentro de las histiocitosis de células no Langerhans o tipo II [1,2]. Recientemente, con el advenimiento de técnicas de inmunohistoquímica y estudios ultraestructurales, la Sociedad del Histiocito propuso reclasificar a las histiocitosis según el tipo celular predominante en 3 grupos:
1) Desórdenes derivados de células dendríticas (el cual incluiría a la histiocitosis de células de Langerhans y al XGJ entre otros),
2) Desórdenes derivados de macrófagos y
3) Enfermedades histiocíticas malignas.
El XGJ es una entidad tumoral, benigna y autolimitada que comienza típicamente en la infancia o juventud temprana con lesiones solitarias o múltiples.

Caso Clínico

Adolescente de 14 años de edad de sexo masculino, proviene de una zona rural del Paraguay. Consulta por lesiones sobre-elevadas en piel de brazo derecho y pies, de 7 años de evolución, que aumentan progresivamente de tamaño, no dolorosas, ni pruriginosas.
Antecedentes patológicos personales y familiares: sin datos de interés.
Examen Físico: Lesiones nodulares/tumorales de tamaños comprendidos entre 1.5 a 4.5 cm. de ejes mayores, de bordes regulares, y límites netos, cubiertas por piel normal, ligeramente amarillenta-anaranjada que afectan el brazo derecho (Fig. 1) y ambos pies (Fig. 2), donde se observan incluso algunas lesiones agrupadas. A la palpación son móviles, no adheridas a planos profundos y no son dolorosas. Algunas presentan telangiectasias en superficie (Fig. 3).

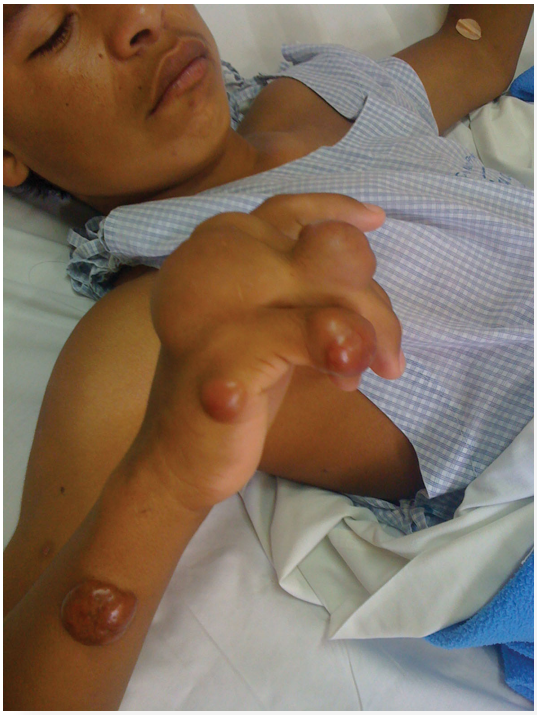

Figura 1. Clínica. Lesiones nodulares de tamaños comprendidos entre 1.5 a 4.5 cm. de ejes mayores, de bordes regulares, y límites netos, cubiertas por piel normal , ligeramente amarillenta-anaranjada que afectan el brazo derecho.

Figure 1. Clinic. Nodular lesions ranging in size from 1.5 to 4.5 cm. major axis, regular edges, and net limits, covered by normal skin, pale yellow-orange affecting his right arm.

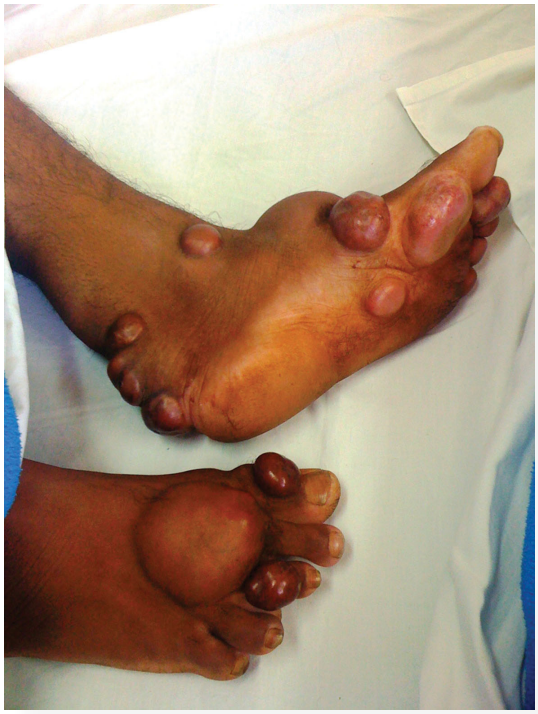

Figura 2. Clínica. Lesiones en ambos pies, donde se observan algunas agrupadas. A la palpación son móviles, no adheridas a planos profundos y no son dolorosas.

Figure 2. Clinic. Nodules in both feet, where there are agminated. On palpation are mobile, not attached to deeper layers and are not painful.

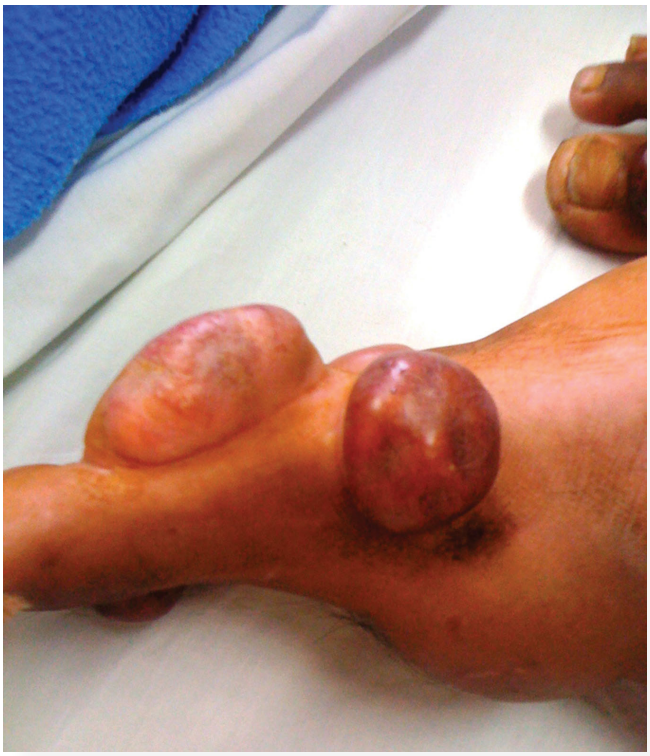

Figura 3. Clínica. Algunas presentan telangiectasias en superficie.

Figure 3. Clinic. Some have telangiectasias on the surface.

Auxiliares del diagnóstico:

· Hemograma, orina simple, perfil lipídio y perfil hepático: normales.

· Radiografías simples de miembros superiores o inferiores: afectación exclusiva de partes blandas. Ninguna afectación ósea.

· Examen oftalmológico: normal.

· Ecografía abdominal: normal.

Se efectúa extirpación quirúrgica de una lesión situada en el brazo y se remite a anatomía patológica, fijada en formol neutro tamponado al 10% y se procesa de manera rutinaria.

Anatomía patológica:

· **Macroscopía:** se recibe un fragmento cutáneo en cuña de 3 x 2.5 x 1.5 cm. de ejes mayores, sobre la que asienta una lesión nodular, de bordes netos y límites precisos, cubierta por piel no erosionada ni ulcerada. Al corte, se observa una tumoración amarilla homogénea, sin áreas de necrosis o hemorragia y es de consistencia sólida (Fig. 4).

· **Microscopía:** denso infiltrado dérmico, que respeta la epidermis de cual se halla separado nítidamente, compuesto por células espumosas, células gigantes de tipo cuerpo extraño y gigantes de Touton (Fig. 5), distribuidas principalmente en la porción más superficial de la lesión y en los bordes. No se encontraron linfocitos, eosinófilos, neutrófilos ni células plasmáticas dispersas a lo largo de la lesión. No se encontró fibrosis, y los lípidos no están presentes extracelularmente. La epidermis por encima de la lesión mostraba cierta atrofia con pérdida de redes de crestas e hiperpigmentación de la capa basal.

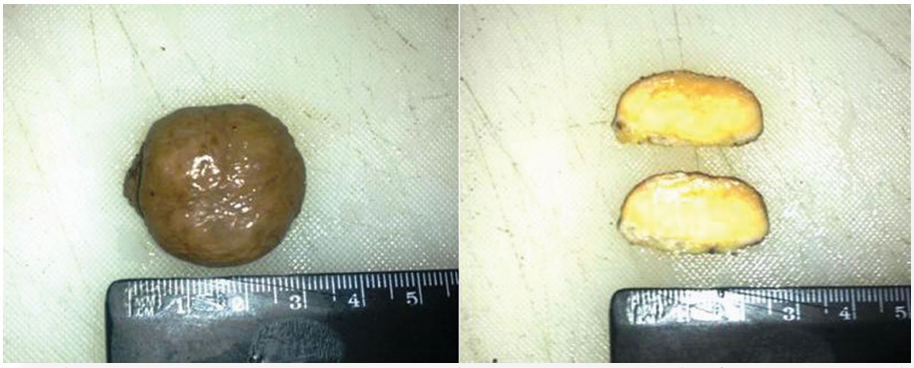

Figura 4. Histopatología. Fragmento cutáneo en cuña de 3 x 2.5 x 1.5 cm. de ejes mayores, sobre la que asienta una lesión nodular, de bordes netos y límites precisos, cubierta por piel no erosionada ni ulcerada (izquierda). Al corte, se observa una tumoración amarilla homogénea, sin áreas de necrosis o hemorragia y es de consistencia sólida (derecha).

Figure 4. Histopathology. Skin fragment of 3 x 2.5 x 1.5 cm. major axis, on which sits a nodular lesion of net edges and precise limits, covered by not eroded or ulcerated skin (left). Cut surface, yellow homogenous tumor without areas of necrosis or hemorrhage and solid consistency (right).

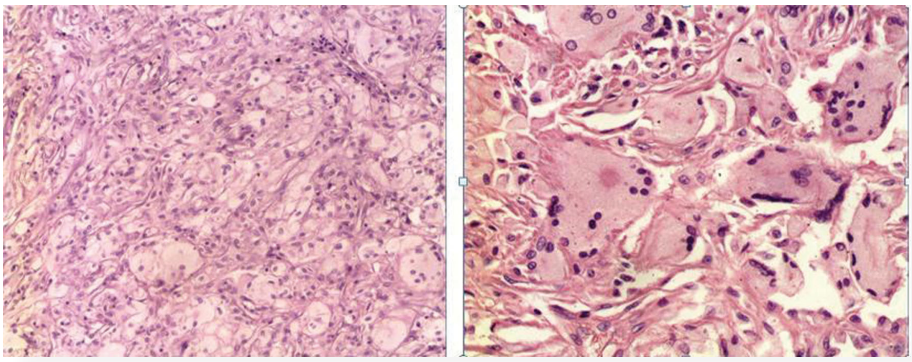

Figura 5. Histopatología. Denso infiltrado dérmico, compuesto por células espumosas (izquierda), células gigantes de tipo cuerpo extraño y gigantes de Touton (derecha).

Figure 5. Histopathology. Dense dermal infiltrate composed of foam cells (left), giant cells of foreign body and Touton type (right).

Diagnóstico Final: Histiocitosis de células no langerhans (Tipo II): forma nodular gigante de xantogranulomas juveniles en fase proliferativa.

Conducta terapeútica asumida tras el diagnóstico anatomo-patológico: conservadora con observación clínica.

Comentarios

El xantogranuloma juvenil (XGJ) fue descrito por Adamson [1] en 1905, quien lo llamó xantoma congénito múltiple. En 1954, Helwing y Hackney demostraron el origen fibrohistiocitico de la lesión y la denominaron xantogranuloma juvenil, término con el que se la conoce desde entonces.

Las Histiocitosis tipo II o histiocitosis de células no Langerhans incluyen un grupo muy variado de enfermedades por proliferación de histiocitos cuyo fenotipo es diferente de la célula de Langerhans. Clínicamente se dividen en 3 grupos, las que afectan predominantemente la piel, otras que afectando la piel presentan una afectación sistémica predominante, y el tercer grupo de enfermedades que son principalmente extracutáneas. El prototipo del primer grupo es el xantogranuloma juvenil, y del tercer grupo la linfohistiocitosis hemofagocítica.

Con el advenimiento de técnicas de inmunohistoquímica y estudios ultraestructurales, la Sociedad Internacional del Histiocito [3] propuso reclasificar a las mismas según el tipo celular predominante en 3 grupos: 1) Desórdenes derivados de células dendríticas (el cual incluiría a la histiocitosis de células de Langerhans y al XGJ entre otros), 2) Desórdenes derivados de macrófagos, y 3) Enfermedades histiocíticas malignas. Las clasificaciones se muestran en las tablas I y II.

El XGJ tiene múltiples denominaciones:

nevoxantoendotelioma, xantoma múltiple, xantoma juvenil, xantoma múltiple de la infancia, xantoma tuberoso congénito de la infancia, xantoma neviforme y granuloma juvenil de células gigantes.

Su etiología es desconocida. Se sugiere que se produce aumento de la biosíntesis de colesterol intracelular y de la unión de colesterol a lipoproteínas de baja densidad (LDL) en ausencia de trastorno metabólico. Los resultados de algunos autores sugieren que los histiocitos en las lesiones XGJ tienen diferenciación macrofágica, que probablemente representa un proceso reactivo a un estímulo desconocido [11].

La incidencia es desconocida. Es más frecuente en caucásicos. La relación en lactantes es V:M=1,5:1 y en adultos V=M, para los XGJ solitarios. Para los XGJ múltiples la relación V:M=5:1.

Histiocitosis tipo I: Histiocitosis de células de Langerhans
Histiocitosis tipo II: Histiocitosis de fagocitos mononucleares distintos a las células de Langerhans - Histiocitosis cefálica benigna, Xantogranuloma juvenil, Xantoma disseminatum, Xantoma papular, Xantoma eruptivo generalizado, Reticulohistiocitoma. - Linfohistiocitosis hemofagocítica (familiar y reactiva). - Histiocitosis sinusal con linfadenopatía masiva (enfermedad de Rosai-Dorfman).
Histiocitosis tipo III: Histiocitosis malignas. - Leucemia aguda monocítica (FAB M5). - Histiocitosis maligna. - Linfoma histiocitario verdadero.

Tabla I. Clasificación de las histiocitosis (Sociedad del Histiocito)

Table I. Classification of Histiocytosis (Histiocyte Society)

ENFERMEDADES DE COMPORTAMIENTO BIOLÓGICO VARIABLE
Enfermedades de células dendríticas
- Histiocitosis de células de Langerhans - Enfermedades secundarias de células dendríticas - Xantogranuloma juvenil y enfermedades relacionadas - Histiocitoma solitario de fenotipo dendrítico
Enfermedades de los macrófagos
- Síndromes hemofagocíticos. - Linfohistiocitosis hemofagocítica primaria (formas familiares y esporádicas). - Síndromes hemofagocíticos secundarios (a infección, a neoplasia, y a otras entidades). - Enfermedad de Rosai-Dorfman (Histiocitosis sinusal con linfadenopatía masiva). - Histiocitoma solitario con fenotipo macrofágico.
ENFERMEDADES MALIGNAS
Enfermedades de los monocitos
- Leucemias (según clasificación FAB revisada) - Leucemia aguda monocítica (FAB M5A y B) - Leucemia aguda mielomonocítica (FAB M4) - Leucemia crónica mielomonocítica - Tumor monocítico extramedular (Sarcoma granulocítico de tipo monocítico)
Enfermedades de células dendríticas
- Sarcoma histiocítico de células dendríticas (localizado o diseminado) - Según el fenotipo: Sarcoma de célula dendrítica folicular, de célula dendrítica interdigitante, etc. - Sarcoma histiocítico de células macrofágicas (localizado o diseminado)

Tabla II. Clasificación actual de las enfermedades histiocíticas (adaptado del grupo de trabajo de la OMS y de la Sociedad del Histiocito)

Table II. Current classification of histiocytic diseases (adapted from the working group of WHO and of the Histiocyte Society)

Las lesiones aparecen en el primer año de vida en 60 a 75% de los casos. Son congénitos entre el 5 y 20%. Los adultos se afectan en 10 a 15%. Las lesiones son múltiples en 20 a 30% de los casos. No se han observado casos familiares.

En cuanto a las manifestaciones clínicas no suelen comprometer el estado general, las lesiones cutáneas y viscerales tienden a la auto resolución, en el trascurso de 3-6 años, siguiendo un curso benigno y de buen pronóstico.

Las variantes clínicas principales son:

1. Micronodular o Papular (60%): pápula o nódulo amarillo, anaranjado o rosado, de 2 a 5 mm de diámetro frecuentemente localizada en la parte superior del cuerpo, y

2. Macronodular o Nodular (35%): tumores de 1 a 2 cm de diámetro, con telangiectasias en la superficie y con mayor frecuencia de afección mucosa y sistémica. Esta forma se ve más frecuentemente en adultos.

Las variantes poco usuales son: mixtas, gigante (término que se reserva para los nódulos que superan los 2 cm. de dinámetro [10], frecuentes en escápula y en nariz (Cyran), subcutáneas (lesión solitaria, congénita, profunda, > 2cm.) y otras (agrupadas, liquenoide, generalizada, máculo papular, reticulada, apareada).

En cuanto a la localización las lesiones cutáneas están irregularmente dispersas a lo largo de la piel sin una tendencia al agrupamiento, y se encuentran principalmente en la parte superior del cuerpo. Las membranas mucosas rara vez pueden estar afectadas. La manifestación extracutánea más común del XGJ (que se presenta principalmente en la forma papular, en niños <2 años, en formas múltiples y con formas subcutáneas) es la afectación ocular.

Las lesiones oculares pueden ocurrir en aproximadamente en el 1-10% de los niños y son casi siempre unilaterales pudiendo producir efecto masa, glaucoma, hifema e incluso ceguera. Las lesiones oculares pueden preceder o seguir a las manifestaciones cutáneas. En estos casos, podría estar indicada la revisión oftalmológica cada 6 meses hasta los 2 años de edad.

La variante nodular de XGJ de vez en cuando puede estar relacionada con manifestaciones sistémicas de los pulmones, los huesos, los riñones, pericardio, colon, ovarios, testículos y sistema nervioso central.

Se han descripto asociaciones de XGJ con enfermedades mieloproliferativas y también con la neurofibromatosis tipo I (NF1), entre otras [4]. La enfermedad mieloproliferativa más frecuentemente hallada es una variante de leucemia mielomonocítica o leucemia mieloide cronica tipo juvenil (LMC), con mala evolución y desenlace fatal en la mayoría de los pacientes [5]. La forma papular, que es la más frecuente y que se caracteriza por numerosas (hasta 100) lesiones firmes, son las que se pueden asociar en quizás un 20% de los pacientes con manchas café-au-lait de la neurofibromatosis y pueden estar relacionadas con leucemia mieloide crónica juvenil

Histopatológicamente se describen tres estadios evolutivos: Inicial (inicio de la proliferación histiocitaria, con prácticamente nula cantidad de células gigantes), Proliferativo (al observarse células espumosas o células de Touton), y Cicatrizal (cuando se evidencia fibrosis) [9].

La inmunomarcación de estos tumores demuestra positividad para CD45, CD68 y FXIII [11]. Casos S100+ no excluyen el diagnóstico de XGJ. El origen dendrocito dérmico de estos tumores se plantea en base a la positividad para FXIII (lo cual no explica la proliferación xantogranulomatosa en sitios extracutáneos). Casos CD4+ se han utilizado como evidencia de que los monocitos plasmáticos pueden ser el tipo celular constituyente principal de XGJ, en lugar del dendrocito dérmico [12]. Los hallazgos inmunohistoquímicos de las células histiocíticas se muestran en la Tabla III.

Progenitor hematopoyético CD34+				Precursores cutáneos mesenquimales (fibroblásticos)
IHQ	**Macrófago**	**Célula indeterminada**	**Célula de Langerhans**	**Dendrocito**
CD45	+	+	+	+
CD68	+	-	-	+
FXIII	-	-	-	+
S100	-	+	+	-/+
CD1a	-	+	+	-
Gránulo de Birbeck	-	-	+	-

Tabla III. Inmunomarcación de células histiocitarias

Table III. Immunostaining of histiocytic cells

En cuanto al tratamiento suele ser conservador ya que tienden a la auto resolución en 3 a 6 años dejando hipopigmentación, anetodermia o leve atrofia cutánea.

El estado de salud del niño no está afectado y su desarrollo físico y psicomotor es normal, salvo si hay complicaciones por su localización visceral o por asociación con otras enfermedades. Se describen algunos casos evolución fatal, pero éstos han tenido manifestaciones del SNC o hígado.

El cribado de una patología visceral o hematológica asociada debe estar guiado por la clínica y no debe realizarse indiscriminadamente en todos los pacientes con una forma aislada de XGJ. Se recomiendo sobre todo dentro de los 2 primeros años, hemogramas periódicos, ya que es la edad donde se observa el mayor pico de incidencia de la LMC juvenil.

El tratamiento es conservador, adoptando una actitud expectante, dado que el curso es benigno y autolimitado, sobre todo en las formas múltiples o en las gigantes (como en nuestro caso), evitando así las secuelas estéticas de la intervención.

La biopsia es necesaria ante duda diagnóstica, siendo en formas papulares y micronodulares (<2 cm), además, terapéutica.

Las acciones terapéuticas dependerán de los síntomas y complicaciones que ocasione. Cuando existe compromiso sistémico se debe realizar un seguimiento estrecho y sólo se tratan si modifican signos vitales. Los XGJ multisistémicos pueden requerir tratamiento con corticoides y/o quimioterapia. Se puede requerir cirugía. En cuanto al compromiso ocular exclusivo, pueden realizarse, según la gravedad del caso, tratamientos quirúrgicos, radioterapia, corticoides sistémicos o locales [6,7].

Conclusión

El XGJ es una enfermedad predominantemente de la edad pediátrica, benigna y autolimitada, con compromiso exclusivo de la piel en la mayoría de los casos, y que no requiere tratamiento alguno. Sin embargo deben realizarse todos los exámenes complementarios a los pacientes, con el fin de identificar compromiso extra cutáneo, asociaciones y evitar las posibles complicaciones.

El interés de comunicar este caso reside en que se trata de una variante clínica inusual (forma nodular gigante) de una condición común [8]. Esta patología por lo general es de aparición congénita o en los primeros meses de vida y en nuestro caso se ha iniciado en un niño mayor. Las lesiones cutáneas se localizan principalmente en cara, cuello, tronco superior y, con menos, frecuencia en raíz de las extremidades, encontrándose en nuestro caso afectación de la porción inferior del cuerpo, inclusive.

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AN ALLERGIC BULLOUS DRUG REACTION TRIGGERED BY LEVOFLOXACIN AND TRIMETHOPRIM / SULFAMETHOXAZOLE MIMICKING AN AUTOIMMUNE BLISTERING DISEASE

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Abstract
Introduction: Allergic drug reactions represent common clinical challenges. Selected allergic drug reactions present with blisters.
Case report: A 73 year old female was prescribed levofloxacin injection and trimethoprim/sulfamethoxazole for a urinary tract infection. Subsequently, the patient developed blisters on both of her hands and feet, associated with clinical pruritus. Clinically, bullae were observed on both of her palms and soles, associated with erythema.
Methods: Biopsies for hematoxylin and eosin (H&E) examination, as well as for direct immunofluorescence (DIF) were performed.
Results: Focal areas of the epidermis displayed diffuse, mild spongiosis. An acute inflammatory process extended into hair follicular units, with focal rupture of these structures. Focal subepidermal vesiculations were also noted in the areas of follicular unit rupture. DIF examination demonstrated faint linear deposits of anti-human fibrinogen at the basement membrane zone of the skin, as well as around several hair shafts. A similar fibrinogen deposition pattern also present around the upper dermal blood vessels.
Conclusions: In our practice experience, the most common cause of blistering diseases are allergic drug reactions, in contradistinction to primary autoimmune blistering disorders. Clinical physicians, pathologists and immunodermatologists should be aware that allergic drug reactions can mimic primary autoimmune blistering disorders, both clinically and in selected immunologic aspects.

Key words: cutaneous allergic drug reaction; direct immunofluorescence; biomarkers; hair follicle; trimethoprim/sulfamethoxazole; levofloxacin

Abbreviations and acronyms: Immunohistochemistry (IHC), hematoxylin and eosin (H&E), direct immunofluoresence (DIF), basement membrane zone (BMZ).

Cite this article:
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Introduction

Drug-induced allergic reactions are characterized by a spectrum of clinical and histologic patterns that include perivascular dermatitis, vesiculobullous lesions, pustular eruptions, sclerodermoid reactions, vasculitis, folliculitis/perifolliculitis and panniculitis [1-12]. While a single drug may elicit a range of reaction patterns, no reaction pattern is specific for a particular drug. Although the temporal link between initiation of drug therapy and the onset of the drug rash is critical to the diagnosis, drug reactions may also occur during the course of chronic drug administration [1,12].

Case report

A 73 year old female was prescribed levofloxacin injection and trimethoprim/sulfamethoxazole for a tract urinary infection. Subsequently, the patient consulted a dermatologist for development of blisters on both of her hands and feet with pruritus. Clinically, small blisters on erythematous base were seen on both of her palms and soles. Skin biopsies for hematoxylin and eosin (H&E) examination, and for direct immunofluorescence were taken in 10% formalin and in Michel's media, respectively. Following the biopsies, the patient's cutaneous lesions improved over a period of weeks following discontinuation of her trimethoprim/sulfamethoxazole and initiation of oral prednisone.

Methods

Direct immunofluorescence (DIF)

In brief, skin cryosections were prepared, and incubated with multiple fluorochromes as previously reported [3-8]. We utilized normal skin as a negative control, obtained from patients going under esthetic plastic surgery. To test the local immune response in lesional skin, we used antibodies to immunoglobulins A, G, M, and E, as well as Complement C3 and fibrinogen in DIF testing (all FITC conjugated, and all from Dako, Carpinteria, California). We also utilized monoclonal anti-collagen IV from Sigma (Saint Louis, Missouri, USA). We further utilized Texas red as a secondary DIF chromogen to further characterize the immune response within hair follicles.

Results

Examination of the H&E tissue sections demonstrated an acute inflammatory process. Focal areas of the epidermis displayed diffuse, mild spongiosis. The dermis displayed congested blood vessels. An acute inflammatory process extended into hair follicular units, with focal rupture of these structures. Focal subepidermal vesiculations were also noted in the areas of follicular unit rupture. A superficial, moderately florid, mixed perivascular inflammatory infiltrate was present within the dermis, featuring lymphocytes, histiocytes, neutrophils and eosinophils. No vasculitis was appreciated. Focally, necrotic epidermal keratinocytes were observed (Fig. 1). Direct immunofluorescence (DIF) studies were performed, and displayed the following results: IgG (-); IgA (-); IgM (-); IgD (-); IgE (-); complement/C1q (-); complement/C3 (+), accentuated around the upper dermal blood vessels; and collagen IV (++) around hair follicles, sweat glands and along the basement membrane zone (BMZ). Fibrinogen (++) was noted in a faint linear pattern at the BMZ and around dermal superficial blood vessels (Fig. 1).

Discussion

The diagnosis of an allergic drug reaction is based on a detailed clinical history, and a temporal correlation between initiation of medication therapy and onset of the rash [1-3]. Histopathology aids in the diagnosis, and immunofluorescence characterizes the nature of immune deposits. In a recent study, the most common manifestations of a cutaneous drug eruption were a maculopapular rash; other possible clinical manifestations included purpura, acneiform lesions, TEN/Stevens Johnson syndrome, erythema multiforme, exfoliative dermatitis and other blistering reactions [11]. Associated drugs included nonsteroidal antinflammatory drugs, antipsychotics, antibiotics, antileprotics/antitubercular drugs, steroids, antimitotics and cardiac and renal specialty drugs. Histopathological features were compatible with the clinical lesions in most of the cases. The most common immunoreactants in direct immunofluorescence were complement/C3 and fibrinogen, primarily noted around dermal blood vessels and at the BMZ [11].

Clues to the drug-induced nature of our cutaneous eruption include the presence of overlapping, incongruent histologic reaction patterns, the clinical features, and immunologic features observed in the DIF. While eosinophils represent an important histologic hallmark of an allergic drug reaction, they may also be conspicuous in skin rashes without a drug association. Furthermore, eosinophils may be histologically sparse or absent in some allergic drug reactions. Thus, increased awareness of the broad spectrum of cutaneous pathology and direct immunofluorescence patterns elicited by an increasing range of therapeutic agents is critical to the proper diagnosis of these disorders. Significantly, in our case, the DIF results do not represent a classic pattern observed in any primary autoimmune blistering disease.

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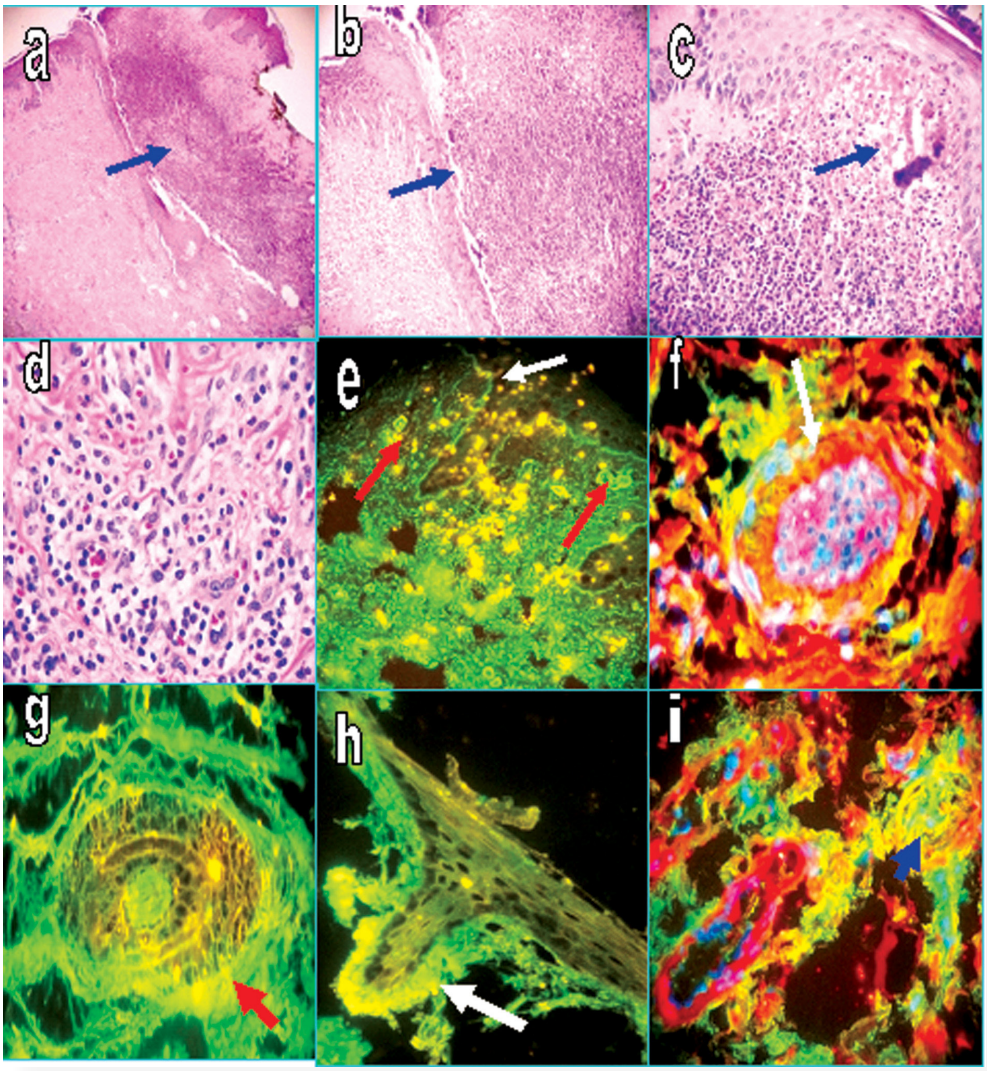

Figure 1. a through d, H & E staining. In **a and b,** note a blister cleft at the periphery of a hair follicle, and an early subepidermal blister cleft (blue arrows) (100x). The subjacent dermis features significant edema, as well as a superficial, perivascular mixed inflammatory infiltrate featuring plasma cells and eosinophils. **c.** Note the focal subepidermal blister, and a strong subjacent inflammatory infiltrate featuring lymphocytes, histiocytes, eosinophils and neutrophilic debris (200x). In **d,** we highlight dermal edema, focal lymphocytic exocytosis and dermal extravasation of red blood cells within the infiltrate of **1c** (400x). **e** Through **i**, DIF. **e.** DIF showing faint basement membrane zone linear staining (green staining; white arrow) and also positive staining around the superficial dermal blood vessels (red arrows) using FITC conjugated anti-human fibrinogen. **f.** Shows a multicolor DIF. The white arrow highlights faint BMZ staining around a hair follicle shaft with FITC conjugated anti human fibrinogen (green-yellow staining). Background dermal collagen is stained with Texas red conjugated anti-collagen IV antibody (red staining). **g.** Similar to **f,** but utilizing single color DIF and only the fibrinogen antibody (red arrow). **h.** DIF showing a pathologic separation of the epidermis of the specimen, and focal subepidermal FITC conjugated fibrinogen reactivity (yellow staining; white arrow). **i.** Multicolor DIF showing two hair follicles, each separate from the adjacent dermis. Close to the follicles, please note that an adjacent nerve is positive for FITC conjugated anti-human fibrinogen (yellow staining, blue arrow). Background dermal collagen is stained with Texas red conjugated anti-collagen IV (red staining).

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GOUT - INDUCED BY INFLIXIMAB?- CASE REPORT

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Abstract
Gout is a metabolic disease caused by a disturbance in purine metabolism; crystals of monosodium urate are deposited in tissues, such as joints, kidneys, and soft tissues, producing an inflammatory response. A 52-year-old woman presented in our department with 1 month history of firm, white papules, nodules and plaques over digits. She has been suffered from Rheumatoid Arthritis for many years, she has been under Infliximab therapy for more than 2 years, with good evolution of the disease. She had marked joint deformities of the proximal interphalangeal joints and slight ulnar deviation at the metacarpophalangeal joints bilaterally.

Key words: Gout; infliximab; rheumatoid arthritis

Cite this article:
Anca Chiriac, Alice Chirana, Anca E Chiriac, Ancuta Codrina: GOUT - induced by Infliximab?- case report. Our Dermatol Online. 2012; 3(4): 344-345

Introduction

Gout is a metabolic disease caused by a disturbance in purine metabolism; crystals of monosodium urate are deposited in tissues, such as joints, kidneys, and soft tissues, producing an inflammatory response [1].

Case Report

A 52-year-old woman presented in our department with 1 month history of firm, white papules, nodules and plaques over digits. She has been suffered from Rheumatoid Arthritis for many years, she has been under Infliximab therapy for more than 2 years, with good evolution of the disease. She had marked joint deformities of the proximal interphalangeal joints and slight ulnar deviation at the metacarpophalangeal joints bilaterally (Fig. 1).

Laboratory investigations, including full blood count, coagulation screen, serum chemistry and liver function tests, were all within normal limits. She had positive rheumatoid factor and hiperuricemia (her uric acid level was 19.2 mg/dL -normal up to 6.1).

The histopathology established the diagnosis : the presence of an amorphous material in the dermis, formed by aggregates of urate crystals, surrounded by an inflammatory reaction consisting of macrophages, lymphocytes, and giant cells (Fig. 2, 3).

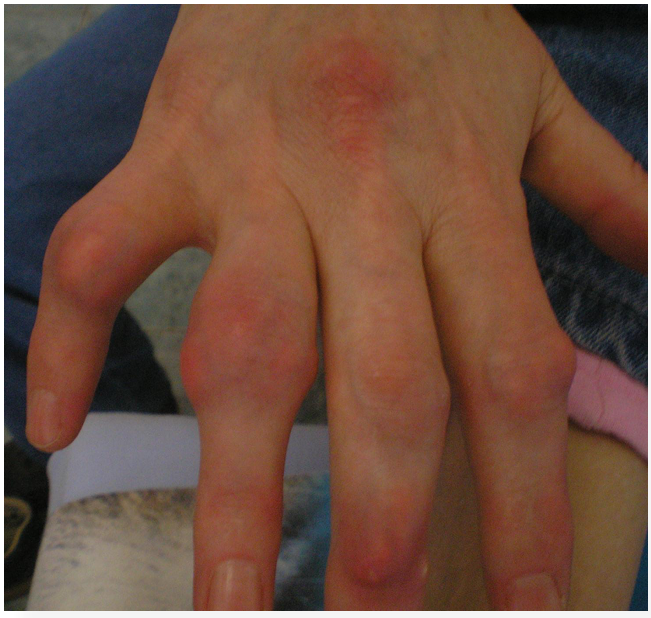

Figure 1. 52-year-old woman with nodules and plaques

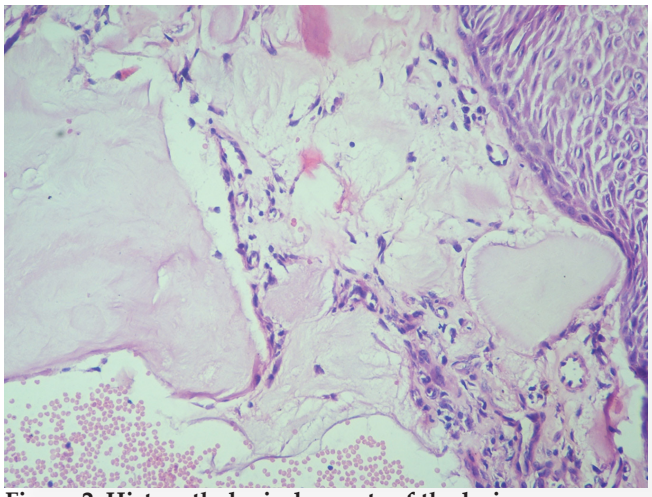

Figure 2. Histopathological aspects of the lesion

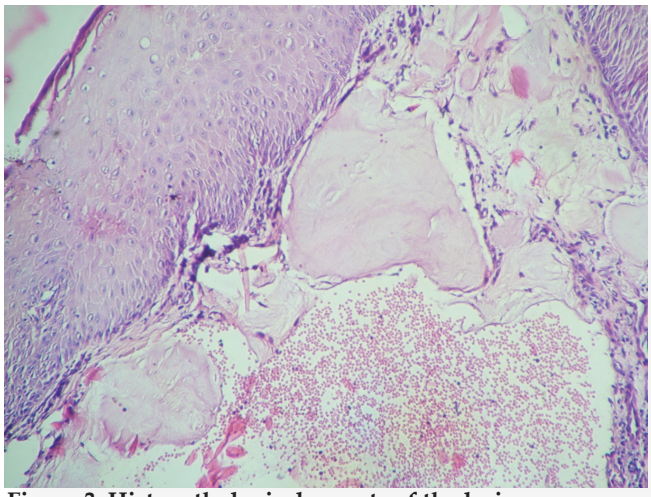

Figure 3. Histopathological aspects of the lesion

Discussion

In this case tophi were presented as nodules at the distal interphalangeal joints, dorsal aspect of the proximal interphalangeal and metacarpophalangeal joints and toes. They arised in a postmenopausal woman (as they usually do, because of the absence of the protective effect of estrogen on acid uric level), with no previous signs of gout. Tophi had a progressive evolution over a few months, with a spontaneous drainage and a subsequent ulceration on the toe.

Among the risk factors for gout, in this case, we could not include: alcohol intake, use of thiazide diuretics, renal dysfunction or hypertension; but we thought of Infliximab as a risk factor [2].

The differential diagnosis included calcium pyrophosphate deposition disease (pseudogout), calcinosis cutis, and rheumatoid or cholesterol nodules [3,4], but the diagnosis of gout was strongly considered on the clinical, histopathological grounds corelared with the hiperuricemia. The risk of gout increases with increasing hyperuricemia, although serum uric acid levels may be elevated without clinical evidence of gout [3].

Although many medications also favor this condition, such as low-dose aspirin, cyclosporine, ethambutol, pyrazinamide, ritonavir, levodopa, and nicotinic acid [4], we consider that it is the first case reported in the literature as gout induced by Infliximab in a patient with Rheumatoid Arthritis, taking into considerations that Infliximab is a therapy of choise in chronic tophaceous gout [5].

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HOW TO DIFFERENTIATE MUCINOUS ECCRINE CARCINOMA FROM CUTANEOUS METASTASIS OF BREAST CARCINOMA?

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Abstract
Eccrine skin tumors are rare and represent only 0,05% of all cutaneaous neoplasms. They represent a pitfall especially with cutaneous metastases of carcinoma which are more frequent. We report the case of a 60-year-old woman presented with a frontal scalp mass whose histologic and immunohistochemical features concluded initially to a cutaneous metastasis of breast carcinoma. The diagnosis was reviewed because of the absence of a breast lesion. The final diagnosis was primary sweet gland carcinoma.
Histologic distinction between cutaneous metastatic breast carcinoma and primary cutaneous adnexal neoplasms can be very challenging or even impossible. This case illustrates this difficulty and puts emphasis on the necessity of keeping in mind the distinctive features between these two entities.

Key words: metastatic breast carcinoma; eccrine mucinous carcinoma; pitfall

Cite this article:
Mona Mlika, Emna Boudabbous, Aida Ayadi-Kaddour, Lamia Kassar, Faouzi El Mezni: How to differentiate mucinous eccrine carcinoma from cutaneous metastasis of breast carcinoma? Our Dermatol Online. 2012; 3(4): 346-348

Introduction

Approximately 25% of the patients with breast cancer develop cutaneous metastases. The major differential diagnosis of cutaneous metastatic breast cancer is represented by sweat gland carcinoma which accounts for about 0,05% of all cutaneous neoplasms [1,2]. Treatment and prognoses of these two entities differ radically making accurate histologic diagnosis mandatory. Indeed, the presentation of these two entities is often distinct. Cutaneous metastasis of breast carcinoma presents as multiple lesions in patients with a previous diagnosis of primary breast carcinoma, whereas, sweat gland carcinoma presents as a single cutaneous lesion in patients with unknown history of breast cancer. However, cutaneous metastases of breast carcinoma can be difficult to distinguish from sweat gland carcinoma when the diagnosis is based mainly on histologic features and the clinical circumstances are unknown by the pathologist.
We describe a new case of sweat gland carcinoma which presented a real diagnostic dilemma.

Case Report

A 60-year-old woman presented with a frontal scalp mass which appeared 6 months ago. The patient was asymptomatic and had no history of trauma. Physical examination revealed a painless mass measuring 0.5 cm. Incision biopsy was performed and microscopic findings consisted in a dermal malignant tumor proliferation arranged in clumps and lobules surrounded by an abundant mucoid stroma and separated by thin fibrous septa. Tumor cells were monomorphic, rounded with cytoplasmic vacuoles of mucus secretion and atypical nucleolated nuclei (Fig. 1a, 1b). Immunohistochemical findings showed a nuclear expression of estrogenic and progesteronic antigens (Fig. 1c). Tumor cells didn't express HER2-Neu antigen (Fig. 1d). These microscopic findings were suggestive of a cutaneous metastasis of an eventual mucinous breast carcinoma. A mammography and a chest MRI were performed targeting the primary breast lesion and showed no breast lesion.
Facing these radiologic findings, we concluded to a cutaneous mucinous eccrine carcinoma. So that, the lesion was totally resected and the patient presented no complications after one year of follow up.

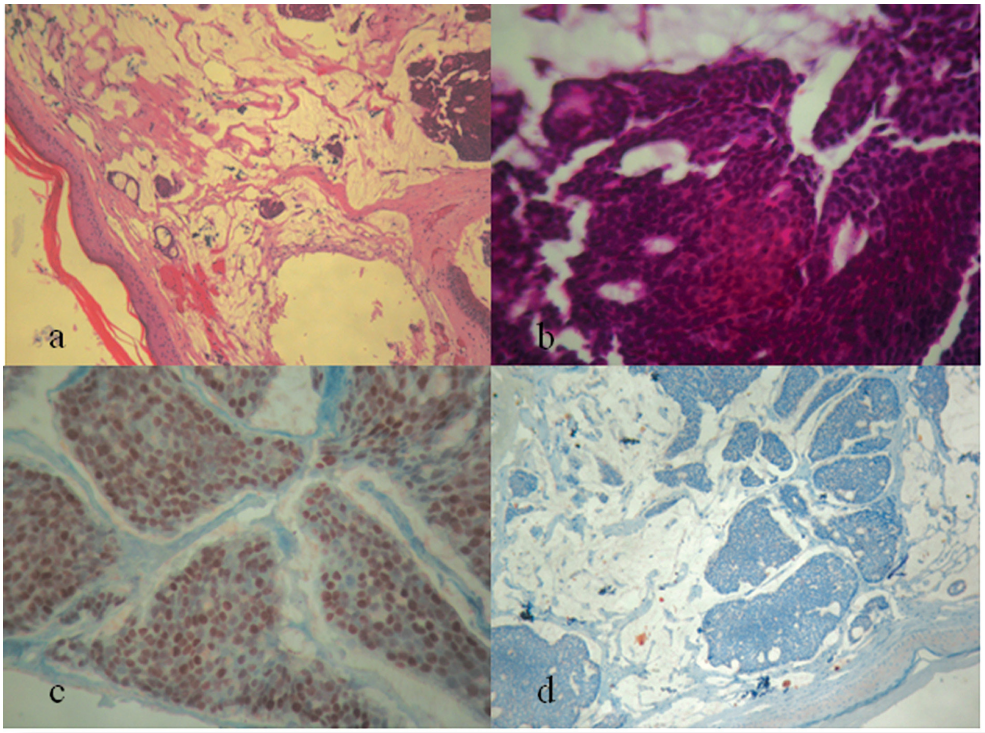

Figure 1. a) Dermal malignant tumor arranged in lobules (HE x 250), b) Tumor cells are monomorphic, rounded with cytoplasmic vacuoles of mucus secretion and atypical nucleolated nuclei. They are surrounded by an abundant mucoid stroma (HE x 400), c) Nuclear expression of estrogenic antigen (HE x 400), d) Absence of expression of Her2-neu by tumor cells (HE x 400).

Discussion

The distinction between adnexal tumors and cutaneous metastases of breast cancer may be difficult. Based on clinical characteristics, adnexal tumors are mainly observed as unique lesion in opposition to cutaneous metastasis of breast carcinoma which consists generally in multiple lesions that are observed in women with a past medical history of breast carcinoma. Otherwise, in some cases, when the breast cancer is indolent or when the pathologist hasn't sufficient clinical informations, the microscopic differentiation between these two entities may be very challenging. The histologic similarities between these lesions have been attributed to their common embryologic derivation in particular their origin as ectodermal downgrowths from the epidermis. Microscopically, eccrine mucinous carcinoma is characterized by large pools of basophilic mucin which are compartmentalized by delicate fibrous septa, thereby creating a honeycomb pattern. Within the lakes of mucin are small "floating" islands and bizarre clusters of neoplastic epithelial cells, sometimes exhibiting a cribriform arrangement. The epithelial component is denser at the periphery of the tumor. Small glandular or tubular structures containing mucin or showing signs of apocrine secretion occur rarely. The small neoplastic cells are cuboidal, round, or oval with abundant cytoplasm that may be vacuolated. Nuclei are small with mild atypia. Mitoses are rare. The mucin is PAS positive, hyaluronidase and sialinase labile, and consists in non-sulphated acid mucopolysaccharides with sialic acid [3]. Otherwise, cutaneous metastatic mucinous carcinoma of the breast is characterized by proliferation of clusters of generally uniform, round cells with minimal amounts of eosinophilic cytoplasm, floating in lakes of mucus. Delicate fibrous septa divide the mucous lake into compartments. The cell clusters are variable in size and shape; sometimes with a tubular arrangement; rarely, they assume a papillary configuration. Atypia, mitotic figures and microcalcifications are not common [3]. Facing these histologic similarities, some authors searched for discriminating antibodies, so that, previous studies using antibodies to evaluate the expression of various proteins, including estrogen and progesteron receptors, anti-gross cystic disease fluid protein (BRST-2), carcino-embryonic antigen, S-100 protein and epidermal growth factor have shown trends in staining patterns that may be helpful. There has been no report to date of a single marker that reliably makes the distinction between these neoplasms. The diagnostic value of c-erb-B2 antibody have been explored showing an overexpression of this antigen in 33% of the eccrine mucinous carcinoma and in 20% of the breast carcinoma. This result made this antibody unreliable in differentiating both entities. A large study carried by Busam and coworkers evaluated the staining pattern of primary cutaneous sweat gland carcinoma and primary or metastatic breast carcinoma [4]. They found promising results with the epidermal growth factor receptor (EGF-R) which is a protein that has significant homology with HER-2. They showed that 81% of the sweat gland carcinomas were EGF-R positive, with a predominantly strong, diffuse membraneous pattern. On the other hand, only 17% of the metastatic breast carcinomas were EGF-R positive with a focal expression. Hiatt KM and colleagues tried to determine if EGF-R antibody could be applied for the histologic differentiation of metastatic breast carcinoma from primary cutaneous adnexal neoplasms.

They compared cutaneous metastasis of breast carcinoma with the primary lesions which were known as over expressing HER-2 antigen. They found that 77 to 100% of HER-2 positive primary tumors maintained HER-2 expression in secondary localizations. While, among the 10% to 34% of breast carcinomas which over-expressed the HER-2 protein, only 3% cutaneous apocrine and eccrine neoplasms in this study had any HER-2 expression [5]. According to these results, in our case the tumor cells didn't express HER2- Neu antigen. These results put emphasis on the fact that despite their similar morphology and embryologic derivations, the expression of EGF-R antigen in association with the differential staining pattern based on HER-2 expression suggests that cutaneous adnexal tumors and mammary glands carcinomas are nosologically different from each other.

In another study conducted by Rollins-Raval and colleagues, a large panel of antibody was used to differentiate these neoplasms. This panel consisted in mammoglobin, p63 and three basal cytokeratins (CK5 , CK17 , CK14). The authors recommended the use of this panel to differentiate most cases of sweat gland carcinoma and ductal cutaneous metastases of breast carcinoma which were generally positive for mammoglobin and negative for p63, CK5, CK17 and CK14 [2].

Conclusion

The distinction between cutaneous metastatic breast carcinoma and primary cutaneous adnexal neoplasms is very difficult or even impossible. Microscopic appearance is quite similar and the distinctive antibodies are non consensual. Pathologists should keep in mind that these two entities may express hormone receptors and that the distinction might be enabled using some antibodies such as Her2-Neu, EGF-R or P63 antibodies.

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A RARE CASE OF HERPES ZOSTER OTICUS IN AN IMMUNOCOMPETENT PATIENT

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Abstract
Herpes zoster oticus in healthy persons is uncommon, though it has been described in immunocompromised patients. We describe a case of disseminated herpes zoster oticus in an elderly man with no apparent immunosuppressive condition. The patient was treated successfully with oral Acyclovir. We suggest that disseminated zoster can occur in an immunocompetent host and should be promptly recognized and treated to prevent serious complications.

Key words: herpes zoster oticus; immunocompetent host; geniculate ganglion; otalgia

Cite this article:
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Introduction

Ramsay Hunt syndrome (RHS) is first described by James Ramsay Hunt in 1907 [1]. It is caused by the reactivation of latent varicella-zoster virus (VZV) that has remained dormant within sensory root ganglia (commonly the geniculate ganglion) of the sensory branch of the facial nerve. Involvement of sensory branch of the geniculate ganglion of facial nerve leads Herpes zoster (HZ) oticus which is also known as RHS. Individuals with decreased cell-mediated immunity resulting from carcinoma, radiation therapy, chemotherapy or human immunodeficiency virus (HIV) infection are at greater risk for reactivation of latent VZV. Physical stress and emotional stress often are cited as precipitating factors. Incidence and clinical severity increases when host immunity is compromised. However it is uncommon to see Herpes zoster oticus in healthy individuals. In this report, we describe the clinical course of a patient who presented with Herpes zoster oticus in the absence of a known immunosuppressive condition. A brief review of literature on this topic is also presented.

Case Report

A previously healthy 65-year old man presented with a 3-days history of vesicular lesions with erythematous base on neck. It was followed by the spread of vesicular eruption to involve external external auditory meatus of right side, and pinna over next 2-days. These are fluid filled vesicular eruptions which bust and break down on 2nd-3rd day with subsequent scab formation. There is no facial weakness. On examination, there was no lower motor neuron facial palsy. A neurologic examination revealed no weakness in the marginal mandibular branch of the left facial nerve. There is no any sign of loss of ipsilateral nasolabial fold or weakness in the temporal branch of the facial nerve. There were painful adherent crusts and scabs in left conchae and external auditory meatus (Fig. 1), associated with unclear hearing of left ear. The oral cavity and oropharynx were normal. Ocular examination demonstrated no nystagmus and normal conjunctiva. He has given history of stressful life events (sudden 3 deaths in family) in past 4 months. Review of systems was negative. The patient is not able to tell history of chickenpox during childhood or any recent exposure to it. There was no past history of diabetes, cardiac or pulmonary disease or lymphoma. The patient has not been on immunosuppressive or other medications. There is history of Psoriasis 2 years back showing on and off symptoms but on regular treatment. Patient is alcoholic, habit of tobacco chewing and occasional Pan chewing. On examination, the patient was afebrile (37.4°C). He had vesicles but not pustules, with crusting and swelling, in the distribution of the cervical division of VII (facial) cranial nerve. The left pinna is swollen, tender and red. There was no tympanic membrane involvement. Vesicles and scabs in various stages were also present lateral side of neck, in front of sternum and external ear (Fig. 1) and behind Right pinna (Fig. 2) and there was no lymphadenopathy.

Pulmonary, cardiovascular and abdominal examinations were normal. Complete blood count Hb- 13 gm%, BSL® - 81.5 mg% peripheral smear, routine biochemistry, liver function tests, and chest x-ray were normal. CD4 and CD8 lymphocyte counts were 1.34 × 109/L and 0.61 × 109/L respectively (CD4:CD8 ratio = 2.2). Serology for Human Immunodeficiency Virus (HIV), Hepatitis A, Hepatitis B, and Hepatitis C were negative and RPR was non-reactive. Skin biopsy from fresh vesicle on the cheeck and external ear showed ulceration with acute inflammation, necrosis and intranuclear inclusions within epithelial cells. The direct fluorescence antigen staining from skin lesions was positive for VZV. The patient was started on oral Acyclovir 800 mg every 8 hours. In the next 5 days, the eruption of new vesicles ceased, the rash started to resolve and his clinical status improved.

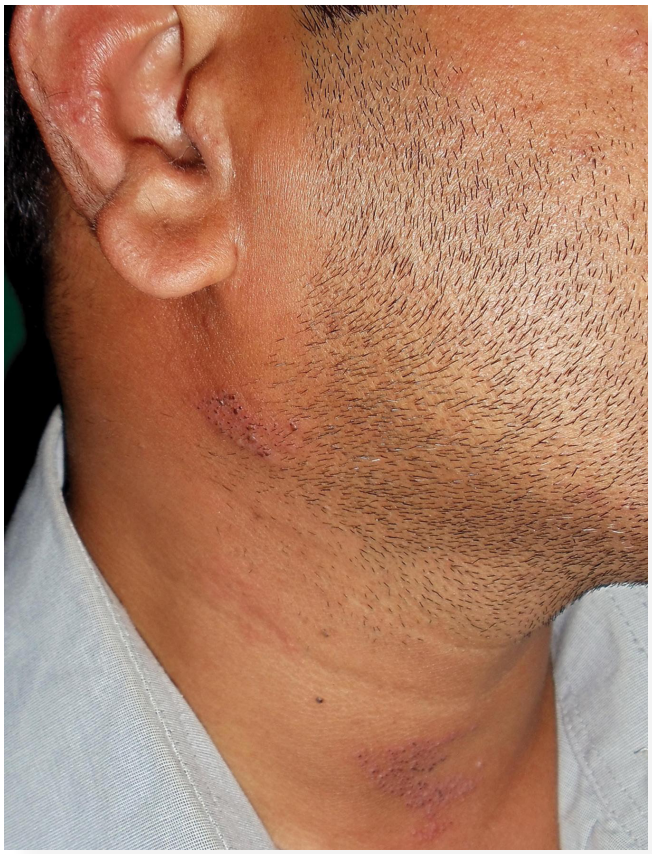

Figure 1. Vesicles below right pinna and in front of sternum

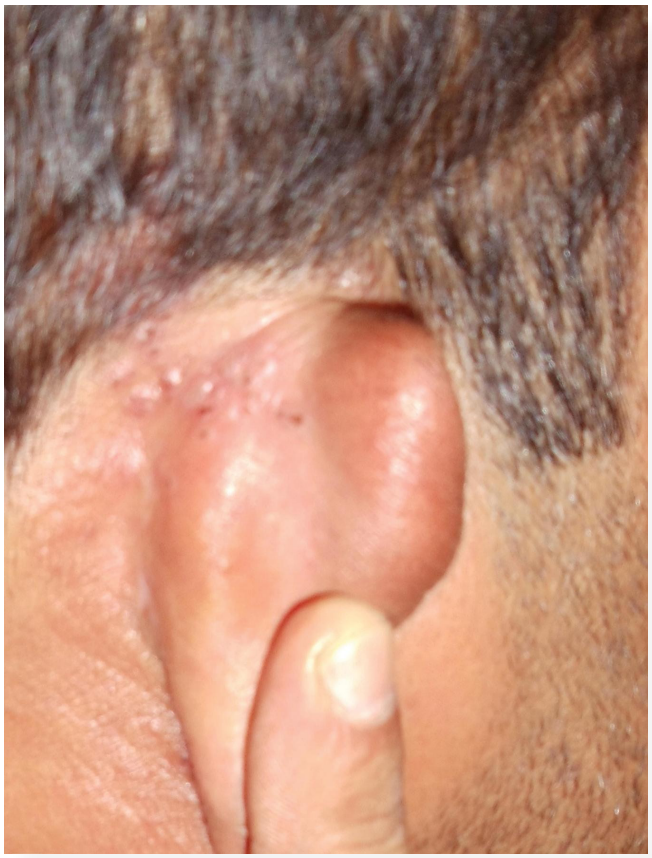

Figure 2. Vesicles behind right pinna

Discussion

Herpes zoster, also called shingles is the consequence of reactivation of latent VZV from the dorsal root ganglia. It is characterized by unilateral vesicular eruptions within a dermatome. Ramsay Hunt syndrome is a painful rash around the ear that occurs when the varicella zoster virus infects a nerve in the head. In Ramsay Hunt syndrome, the virus is believed to infect the facial nerve near the inner ear. This leads to irritation and swelling of the nerve. Herpes Zoster is seen a disease of older people (> 60 years old). The severity and incidence of the disease is depend on the cellular immunity of the patient [2]. This RHS type 2 is shingles of the geniculate ganglion, means the herpes zoster virus lies dormant in various nerve cells in the body and in check by the patient's immune system. During an illness that suppresses the immune system, the virus is reactivated and travels to the end of the nerve cell, where it causes the symptoms described above [1]. This complication of zoster has been described in immunocompromised persons (HIV, cancer, patients on immunosuppressive therapy) and reported to be as common as 10%-40% [3,4]. However, Herpes zoster oticus in otherwise healthy persons who are not on immunosuppressive therapy and have no underlying cancer is rare. In our search we could identify less than ten cases with disseminated zoster in otherwise healthy persons [5,6]. Our patient presented with characteristic skin findings of herpes zoster oticus. The skin biopsy findings supported the clinical diagnosis of VZV. In our patient, significant age related depression in cellular immunity with history of psoriasis, alcoholic could have contributed to the dissemination of herpes zoster. Elderly patients should be recognized as a group in whom the risk of HZ oticus is higher than the average immunocompetent host. Patient of VZV without any immunosupression are at risk of infection of visceral organs, particularly lungs, liver and brain. Other complications include corneal ulceration and post herpetic neuralgia [3]. Therefore, identification and aggressive treatment of disseminated herpes zoster infection in elderly immunocompetent hosts is important. The treatment of choice is intravenous Acyclovir 10 mg/kg every 8 hours for 5–7 days. As patient reported earlier without complications, we preferred oral acyclovir for 5 days along with adjuvant drugs.

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A RARE CASE OF HERPES ZOSTER OTICUS IN AN IMMUNOCOMPETENT PATIENT

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Varicella zoster virus (VZV) is an ancient virus. Herpes viruses have existed since the Devonian period, 400 milion years ago [1], when living creatures were represented by sharks, fish, amphibians. The origins of the ancestral VZV date from about 70-100 milion years ago (Cretaceous period) [2], the living creatures were dinosaurs, reptiles, snakes, amphibians, birds and mammals. Between 50-70 milion years ago VZV evolved in ancestral primates (derived from small mammals). In Africa 6 milion years ago VZV existed in hominids, then Homo erectus and finally Homo sapiens carried for a long period of time VZV.

Homo sapiens migrated from Africa to China, India, subsequently to Europe. In North America Homo sapiens brought VZV from Asia (via Bering land bridge) 10.000-15.000 years ago [2].

VZV causes two different disease: chickenpox (typically occurs in children) and herpes zoster (shingles) most often in adults and elderly persons (by the reactivation of latent VZV).

Herpes zoster is a neurocutaneous disease characterised by cutaneous lesionsin a the areas of a cranial or spinal nerve.

A few short remarks:

- usually a prodrome of dermatomal pain precedes the appearance of the rash and subsequent of typical lesions;
- the duration and intensity of zoster pain vary greatly even in immnucompetent persons, sometimes postherpetic neuralgia (PHN) may persist months-years and requires neurological consult;
- there are patients who experience acute segmental neuralgia without cutaneous eruption (zoster sine herpete); in these cases the rise of VZV antibodies represents a proof of diagnosis;
- zoster oticus is rare, even in immnuocompromised persons; facial paresis is reported in zoster oticus in immunocompetent patients;
- viral culture is the golden diagnostic standard; PCR detects VZV-DNA in fluids and tissues in some difficult cases;
- direct immunfluorescence assay with labeled VZV-specific monoclonal antibodies is rare recommended in practice, where we prefer Tzanck-test; Tzanck test is simple, not expensive, easy to perform, but unable to distinguish between VZV and HSV (herpes simplex virus) infection;
- extremely rare we perform skin biopsy to confirm diagnosis, even in zoster oticus;
- regarding the treatment we prescribe also Brivudin 125mg/day 7 days to limit acute symptoms, to prevent PHN and complications of herpes.

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- sharks - fish - amphibians	- dinosaurs - reptiles - snakes - amphibians - birds - mammals	Ancestral primates	Hominids	Homo erectus	Homo sapiens
400 milion years ago	100-70 milion years ago	70-50 milion years ago	6 milion years ago		

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LOCALIZED TUBERCULAR SWELLING IN THE HAND MASQUERADING AS A GANGLION-A RARE CASE REPORT

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Abstract
Musculoskeletal system involvement in tuberculosis is rare. Especially rare is the involvement of hand. The affected hand can present in different modes ranging from dactylitis to multiple tubercular lesions. Here we present a localized lesion which was initially diagnosed as a ganglion.

Key words: hand tuberculosis; ganglion; dactylitis

Cite this article:
Nithya Raghunath, Sreekar Harinatha, Kiran Petkar, Sreeharsha Harinatha: Localized tubercular swelling in the hand masquerading as a ganglion - A rare case report . Our Dermatol Online. 2012; 3(4): 353-354

Introduction

Musculoskeletal system is one of the commonly involved in non-pulmonary tuberculosis. It is a chronic and progressive disease that mostly affects weight bearing joints [1]. Tuberculosis (TB) of hand is a rarely described entity. Though it has been reported in the literature occasionally, its presentation as a localized swelling is rare [2-5]. The most striking and often worrisome feature of these cases is the delay between onset of symptoms and correct diagnosis. TB is a major public health problem in India.

India accounts for one-fifth of the global TB incident cases. Each year nearly 2 million people in India develop TB, of which around 0.87 million are infectious cases. With such endemicity, tuberculosis should always be a differential diagnosis for any atypical swellings.

Case Report

A 34 year old gentleman presented with complaints of swelling over his right hand (Fig. 1). Though it did not hinder his daily activities, he complained of occasional pain in the swelling. On examination there was a 2x3cms smooth surfaced firm swelling over the dorsum of right hand. There was neither restriction in the wrist movements nor any neurovascular deficits. He had undergone hand and chest radiography which were normal. A clinical diagnosis of ganglion was made. The lesion was excised in toto and sent for histopathologic examination (Fig. 2). The diagnosis of tuberculosis was made on the basis of characteristic histopathology (Fig. 3), a positive culture for *Mycobacterium tuberculosis* and a positive smear for acid-fast bacilli. The hand was splinted and anti-tubercular treatment was started. At 6 months follow-up the patient was doing well.

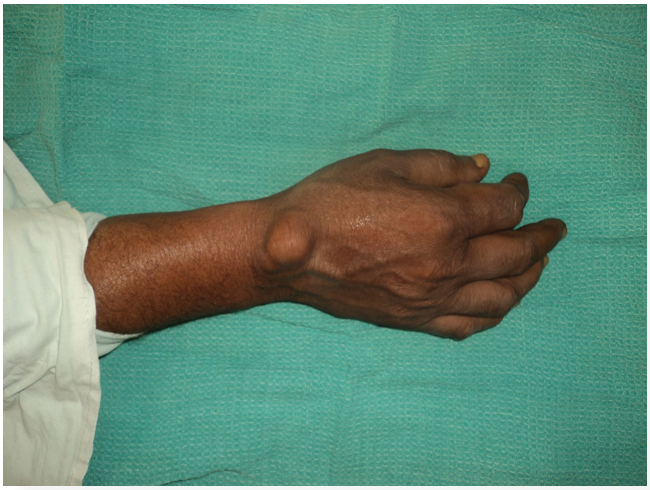

Figure 1. Swelling over the dorsum of right hand

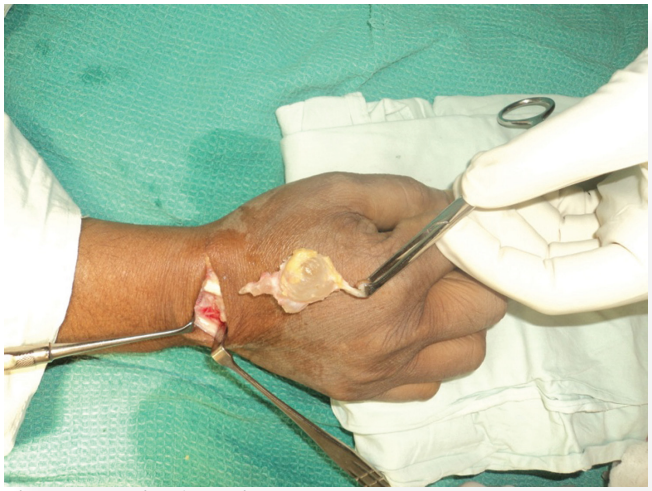

Figure 2. Excised specimen

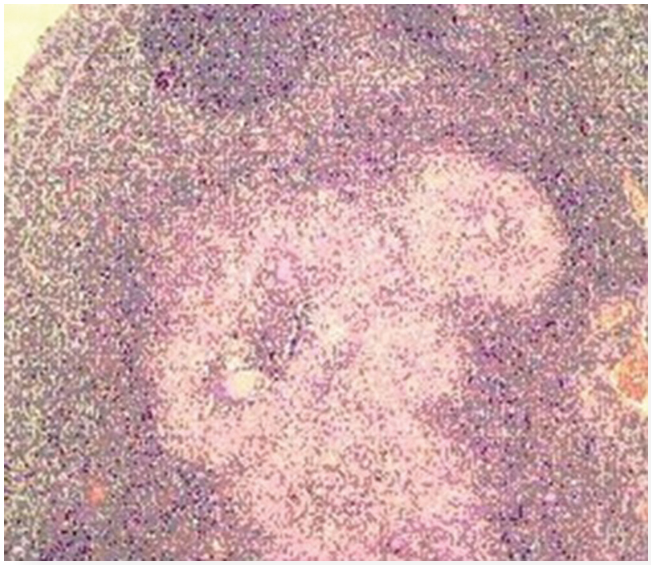

Figure 3. Histopathology picture showing characteristic granuloma and giant cells

Discussion

Tuberculosis of hand is a rare clinical manifestation. Pain and swelling are the most common presenting features, and discharging sinuses can occasionally be seen [6]. The manifestation is usually resembles tenosynovitis, sometimes even involving the carpal tunnel. Occasionally there can be tubercular synovitis of the wrist or flexor tenosynovitis. Nerve conduction in such cases show delayed conduction at the carpal tunnel. Tuberculosis of the fingers is also known as spina ventosa, but it is suggested that all tubercular lesions of the hand should be referred to as 'tuberculosis of the hand' [7]. Tuberculosis of the fingers is seen typically in the phalanges and interphalangeal joints and is said to be uncommon after five years of age. During childhood these short tubular bones have a lavish blood supply via a nutrient vessel entering the middle of the phalanx in which the first inoculum becomes lodged [8]. Bony tuberculosis of the phalanges and metacarpals can mimic bone tumours and a histopathological examination is necessary for diagnosis. This is especially true for asymptomatic lesions which mimic ganglion. With the successful management of pulmonary tuberculosis and worldwide resurgence of musculoskeletal tuberculosis there is an increase in cases affecting atypical sites, including the hand. Further studies with longer follow-up are required to develop early diagnostic tools and treatment protocols to expedite treatment and hand function.

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PHTHIRIASIS PALPEBRARUM

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Abstract
Phthiriasis palpebrarum of the eyelashes is not an uncommon condition when hygienic condition are inadequate. The lice occupy, chiefly, the roots of the eyelashes, to which they cling tenaciously, while the shafts of the cilia are covered with their brown nits. The patients with the symptom of pruritus of the eyelids and with clinical findings resembling exfoliation on the surface of lid skin and seborrhea accumulation on eyelashes must carefully be examined by slit lamp in order to avoid misdiagnosis. In the cases diagnosed as having lid eczema and seborrheic blepharitis, lice and nits might easily be overlooked and treatment might remain ineffective. Various treatment options are available from medical; mechanical removal of nits and lice, cryotherapy. In this short review we are describing in details about the organism, clinical features, mode of transmission, treatment about Phthiriasis palpebrarum.

Key words: eye lashes; crab louse, nits; phthiriasis palpebrarum

Cite this article:
Sujatha Vijayalekshmi: Phthiriasis palpebrarum. Our Dermatol Online. 2012; 3(4): 355-357

Introduction

Lice are wingless insects, which can produce three types of pediculosis in human beings when hygienic conditions are inadequate. They are Pediculus pubis (crab lice), Pediculus capitis (head lice), Pediculus corporis (body lice). Among them Pediculus pubis infest mainly the hairs of genital region; however infestation of axilla, beard, eyebrows and eyelashes (Phthiriasis palpeberum) may occur.

Character of Pediculi

Pediculi belong to the P*hylum Arthropoda*. Class insecta and order *Hemiptera*. The body of these organisms is divided into head, thorax and abdomen. Three pairs of legs are present on thorax. They are wingless insects and they have piercing and sucking mouthparts. The insect is about 1/12 inch long and is oval in shape. The hominoxious, haematophagic parasite resembles the head and body louse except its second and third pairs of legs and claws are stouter. The abdomen is more or less telescopic so that the first three abdominal spiracles (segments 3, 4 and 5) are almost in one transverse line. The abdomen is broader than its length, resembling a crab [1]. The adult female is greyish white, 3-4 mm long, the male is slightly smaller. The legs are adopted for grasping hairs. The most anterior pair of legs is slender, with fine claws and a serrated surface, allowing for traction (and mobility) on even glabrous skin [2]. Posterior sets of legs are increasingly thick for improved grasp of hair shafts during sleep and attachment of eggs [2]. While firmly grasping host hair shafts, females may lay up to 3 eggs each day. With an incubation period of 7-10 days, eggs may be visible to the naked eye as 0.5 mm, brown-opalescent ovals. Cemented to the hair shaft, chitin egg cases contain areopyles that allow air to directly contact the developing, internal egg. Multiple tactile septae protrude from the head, legs, and dorsum, allowing Pediculosis pubis to sense its environment. Although the average life span of Pediculosis pubis may be as long as 1 month, death occurs within 48 hours following removal from the host [3].

Ophthalmologists are concerned with only Pediculus Pubis, as this is the variety that is found between the eyelashes. Strangely, Pediculus capitis (hair-louse) and Pediculus corporis (body-louse), though they breed nearer the eyes do not infest the eyelashes. Each variety keeps to its own region, and the parasites, live upon the blood which they suck from the skin. They grasp the skin, with their jaws and bring their sucking organs into use, at the same time exuding a poisonous salivary secretion. Which sets up pruritus. Occasionally, isolated palpebral involvement has been described [4-6].

Mode of transmission

Three types of flattened wingless lice, which require host hair, attack human beings and causes pediculosis. They are Pediculus capitus (head louse) in scalp area, Pediculus corporis (body louse) and Phthirus pubis in the inguinal area and pubic area.

There is an increase incidence of Pediculosis in developing countries because of the poor sanitary conditions and increase in sexual activity among adolescent people and not infrequently by bedding [7]. In children pediculosis of eye lashes is the most common site, as terminal hair is absent in most part till puberty [8]. Eyelashes also provide moist environment and temperature is apt for the hatching of the eggs. Importantly, although pre-pubertal children with phthiriasis palpebrarum are usually infested by direct contact with a parent or shared fomites, sexual abuse must be thoroughly ruled out.

Clinical Features

The symptoms range from bilateral itching, irritation, visible lice or nites. On examimnation there could be blepharitis, conjunctival inflammation, lymphadenopathy, infection at the site of lice bite [6]. Blood tinged debris is common in lid margins and eye lashes. Bluish spots of infected lid margins -maculae caruleae may be seen [6]. A case of marginal keratitis is also reported [9]. The translucent oval nits which locate into the bases of the eyelashes and on the cilia are often confused with the crusty excretions of seborrheic blepharitis [6]. Diagnosis can be made by close examination of lashes and lid margins with slit lamp in order to identify the lice and nites.

Treatment

Manual removal of visible lice and eggs with a forceps is standard therapy. Alternatively, eyelashes may be extracted in their entirety [10]. Full removal of eyelashes is followed by complete regrowth in 3-4 weeks. However, such mechanical efforts are quite tedious and may be hindered by low patient tolerance and the firm adherence of eggs to eyelash structures.

Alternative management strategies are legion, but all may have prohibitive adverse effects or present technical difficulties. A time-honored therapy, application of 1 percent yellow mercuric oxide, at a dose frequency of 4 times daily for 14 days, often requires impressive patient compliance for effective treatment [11]. In addition, this treatment may be accompanied by chemical blepharitis, conjunctivitis, lens discoloration, tearing, and photophobia [12]. The agent is also difficult to obtain. Cryotherapy or argon laser phototherapy may allow destruction of ectoparasites but are both associated with discomfort and risk of ocular injury [13,14]. Both safety and efficiacy are highly operator dependent. Topical application of gamma-benzene hexachloride may be employed; however previous reports link use to ocular irritation and potential neurotoxic effect [15,16]. „Smothering" lice by twice daily application of plain white petrolatum may be efficacious, but is not ovicidal and thereby risks incomplete therapy [17]. Topical malathion solution 0.5 percent or 1 percent shampoo may be effective after just a few applications, but it is neither approved nor entirely proven safe for ocular use [18,19]. Although oral ivermectin (250mcg/kg; two doses given at one week interval) appears to be an attractive option, there is only scant published evidence of its efficacy, and it is not approved for this indication [20]. Because many cases of ocular phthiriasis occur in children, the relative contraindication for administration to pediatric patients under 15kg body mass adds an additional complication to the use of this agent.

Although the exact mechanism of pilocarpine 4 percent gel remains unclear, previous studies report effective Pediculosis pubis clearance without adverse events following such application [21,22]. Speculation on the mechanism of action includes an anticholinergic induction of louse paralysis via neuronal depolarization or a direct pediculocidal action [21,22]. From a pragmatic standpoint, pilocarpine gel is inexpensive, readily available, and approved for direct ocular use. There was a recent report suggesting the mechanical removal with the help of a white petrolatum ointment (Vaseline) the eyelashes were cleaned with 50% tea tree oil. Nits and lice were successfully eradicated without recurrence 10 days after daily treatment with petrolatum ointment and 10% tea tree oil eyelash cleansing [23]. Patients must launder all bedding, clothing, towels and washcloths, all of which may harbor adult lice and their eggs. Temperatures exceeding 131°F for more than 5 minutes will eradicate all viable eggs, nymphs, and adult lice. Because Pediculosis pubis eggs may incubate for up to 10 days, careful sealing of all potentially contaminated fabric materials in air-tight plastic bags for 2 weeks must coincide with medical attempts at eradication.

Conclusion

As soon as the diagnosis is made in the cases of PP, to prevent extension of disease, prompt treatment and patient isolation should be considered. The patients with the symptom of pruritus of the eyelids and with clinical findings resembling exfoliation on the surface of lid skin and seborrhea accumulation on eyelashes must carefully be examined by slit lamp in order to avoid misdiagnosis. In the cases diagnosed as having lid eczema and seborrheic blepharitis, lice and nits might easily be overlooked and treatment might remain ineffective.

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NASZA DERMATOLOGIA Online
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PIEZOGENIC PEDAL PAPULES IN A YOUNG FEMALE

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We hereby report a case of a 28 year old female who presented to us in the outpatient Department of Dermatology, STD and Leprosy SMHS hospital (associated teaching hospital of Govt. Medical College Srinagar) with complaints of appearance of multiple painful skin coloured swellings over the heels and lateral borders of both feet since the last 8 years (Fig. 1). They became progressively more painful on walking or standing for long periods. These swellings used to disappear on lying down, and lifting feet of the ground. There was no other significant medical or surgical history. On examination the patient was obese with a body weight of 83 kgs,with normal systemic and cutaneous examination. Tender skin coloured papules and nodules (0.5×2cm) were appreciated over the heels and lateral borders of both feet in standing position, which disappeared as the patient was made to lie down.

Piezogenic pedal papules is a condition that occurs in individuals after prolonged standing or running and is presumed to result from herniation of fat through connective tissue defects. Patients are usually males. Lesions commonly occur as bilateral flesh-coloured, asymptomatic papules over the medial and lateral aspects of the heels. They become apparent only when the body weight is borne by the heels. Lesions are also reported to occur on the wrists. Sometimes they may be painful. Biopsies show fragmentation of dermal elastic tissue and herniation of subcutaneous fat into the dermis. Treatment consists of weight reduction, use of foam rubber footpads or foam-fitting plastic heel cups, avoidance of both long periods of standing and excessive trauma, and surgery.

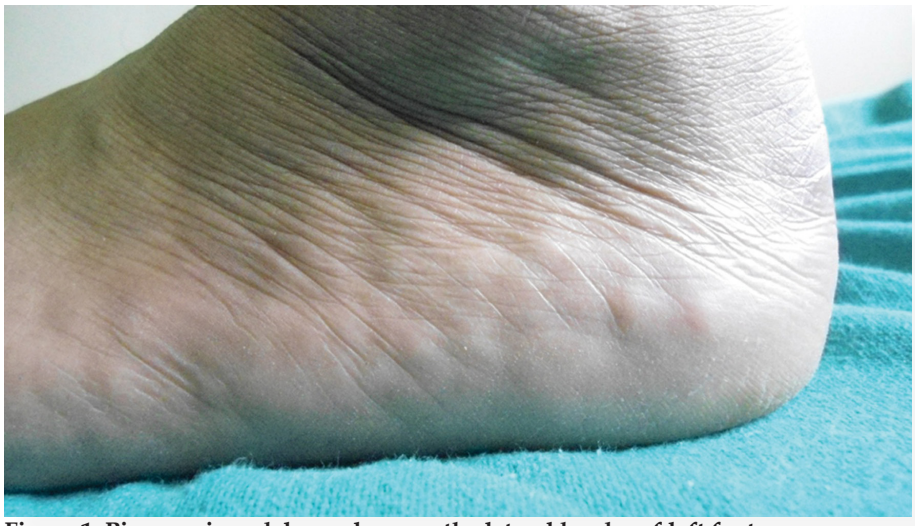

Figure 1. Piezogenic pedal papules over the lateral border of left foot

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NASZA DERMATOLOGIA Online
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MNEMONICS IN DERMATOPATHOLOGY

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A mnemonic is any learning technique that aids information retention [1,2]. This technique of learning has been used in all the sciences including medicine. In dermatology, in particular, many mnemonics were made and used by many residents during their training periods and afterward [1]. As an evidence of its effectiveness dermatology textbooks, like Requisites in Dermatology: Dermatopathology incorporated these mnemonics.

However many mnemonics are, not popular, not very inclusive, not important, complicated, long, not easy to remember or not user friendly; and hence such mnemonics are not used frequently.

In Table I, I listed few mnemonics in dermatopathology, which I thought may be useful.

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The mnemonics	Remarks
HAAPPIED (for conditions with eosinophilic spongiosis)	**H**erpes getationis **A**rthropod bite **A**llergic contact dermatitis **P**emphigus **P**emphigoid **I**ncontinentia pigmenti **E**rythema toxicum (spongiosis adjacent to follicle) **D**rug
LEMONS (for the differential diagnoses of small round blue cell tumors) [3]	**L**ymphoma **E**wing sarcoma **M**elanoma, **O**lfactory / **O**ther (esthesioneuroblastomas, rhabdomyosarcoma or Markel cell carcinoma) **N**euroblastoma **S**mall cell carcinoma **„MR. LEMONS"**, might refer to a similar thing; **M**elanoma **R**habdomyosarcoma **L**ymphoma **E**wing's sarcoma **M**eduloblastoma **O**lfactory **N**euroblastoma **S**mall cell (oat cell)

Table I. Selected mnemonics in dermatopathology

The mnemonics	Remarks
Life **C**an **G**et **C**omplicated (for the types of necrosis)	**L**iquifactive **C**oagulation **G**angrene **C**aseous 'Life' used since necrosis is 'death'
3 **M** (cytological changes of herpes infection)	**M**ultinucleation **M**olding, nuclear **M**argination of nuclear chromatin
PLAID (for conditions with subepidermal split, and neutrophils stuffed in dermal papillae)	**P**emphigoid (bullous) **L**upus (bullous SLE) **A**cquista (Epidermolysis Bullosa Acquista) **I**gA, linear **D**ermatitis herpetiformis
PTICS (for conditions with neutrophils in the stratum corneum)	**P**soriasis **T**inea **I**mpetigo **C**andida **S**yphilis

Table I. Selected mnemonics in dermatopathology (continued)

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LINEAR LICHEN PLANUS PIGMENTOSUS AND COINCIDENTAL IPSILATERAL FACIAL NERVE PALSY: AN UNUSUAL OBSERVATION

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Iffat Hassan, Parvaiz Anwar Rather, Peerzada Sajad: Linear lichen planus pigmentosus and coincidental ipsilateral facial nerve palsy: An unusual observation. Our Dermatol Online. 2012; 3(4): 361-362

Sir,

A 30 year old male from West Bengal, presented to our outpatient department on 28th June 2012, with 5 months duration of asymptomatic pigmentation in a linear fashion on left side of face and forehead, which started as a small pigmented spot on left side of glabella and gradually increased in size. There was no history of trauma, photosensitivity, preceding skin eruptions, significant drug or family history. In 2009, patient had suffered from left side idiopathic facial palsy (Bells palsy) which has improved considerably now. General physical and systemic examination was normal. Cutaneous examination showed unilaterally distributed, non scaly, non atrophic, linear streak of bluish-black pigmentation, continuous and interrupted, extending from left side of vertex of scalp, through forehead to side of nose and upper lip (Fig. 1a, b). There was slight facial asymmetry with left side flatter than that of right side along with other features of a mild left sided facial palsy (Fig. 2a, b). Hair, nail and mucus membrane examination was normal. With a differential diagnosis of lichen planus pigmentosus (LPP), ashy dermatosis, linear epidermal nevus, linear LP, a punch skin biopsy was taken and sent for histopathologic examination, which under haematoxylin and eosin staining showed pigment incontinence, colloid bodies, basal vacuolation and lymphocytic exocytosis without eosinophils, suggesting the diagnosis of LPP (Fig. 3a, b). Absence of prior papular eruption helped us to rule out lichen planus and classical histopathologic findings pointed to the diagnosis of lichen planus pigmentosus (LPP). Nothing abnormal was found in complete blood count, liver function test, kidney function tests and hepatitis B & C serology. Thus we report the rare case of linear LPP in a patient with same side facial nerve palsy as a coincidental finding.

Lichen planus, a papulosquamous disease, is classically characterized by pruritic, violaceous papules with many clinical variants. Linear lichen planus is a well defined entity with many case reports [1,2]. Similarly, lichen planus pigmentosus (LPP), first described by Bhutani et al. [3], is a rare variant of lichen planus, and appears as mottled or reticulated hyperpigmented, dark brown macules or papules most common on sun exposed areas such as the face, neck and flexural folds [4,5]. Less common presentations include zosteriform pattern on the trunk [6], linear unilateral lesion on the extremity [7] and involvement of non sun-exposed areas such as thigh [8]. The cause of LPP is unknown, but an immunologic mechanism mediates its development, as well as that of lichen planus [9]. Clinically, LPP differs from classical lichen planus by exhibiting dark brown macules and a longer clinical course without pruritus or scalp, nail, or mucosal involvement [3]. LPP is a close differential diagnosis of erythema dyschromicum perstans (ashy dermatosis) [10]. The relation of EDP to lichen planus (LP) is uncertain, both have several clinical, histological and immunohistochemical similarities and often coexist, making some authors consider EDP a variant of LP [11].

Linear LPP is considered as a combined type of linear lichen planus and LPP and there have been only a few reports on this in the dermatologic literature [12-15], especially from India [16]. The linearity of the lesion is probably related to Blaschko's lines, which suggests that the predisposition to develop LPP might be determined during embryogenesis [2]. The clinical coexistence of same side facial nerve palsy preceding the linear lesions of LPP found in our case seems to be just a coincidence.

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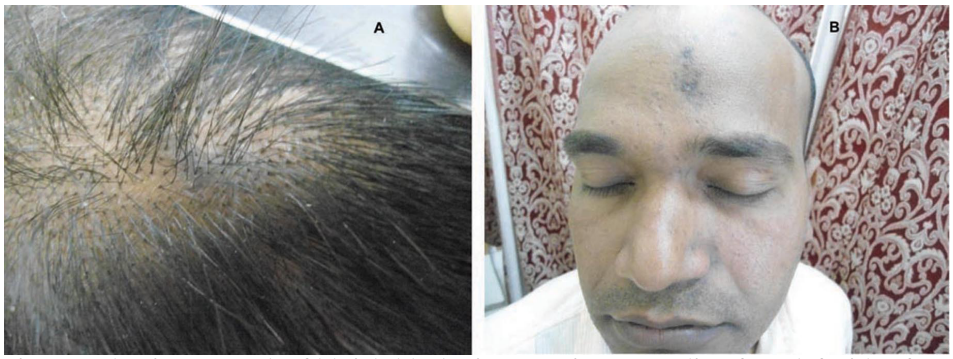

Figure 1a,b. Linear streak of bluish-black pigmentation, extending from left side of vertex of scalp (a), through forehead to side of nose and upper lip (b).

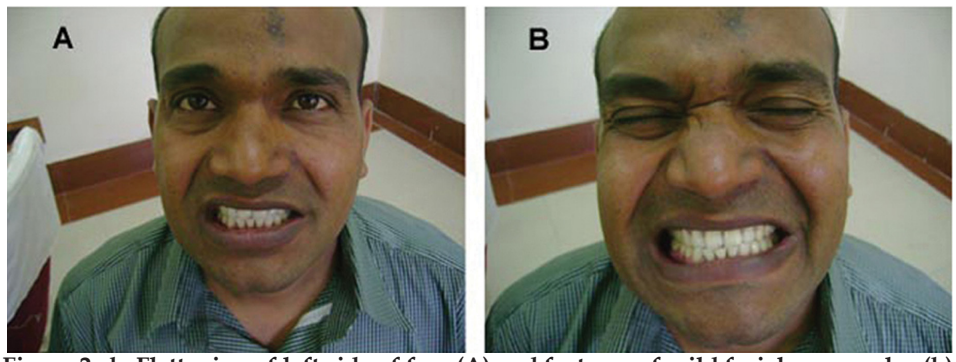

Figure 2a,b. Flattening of left side of face (A) and features of mild facial nerve palsy (b).

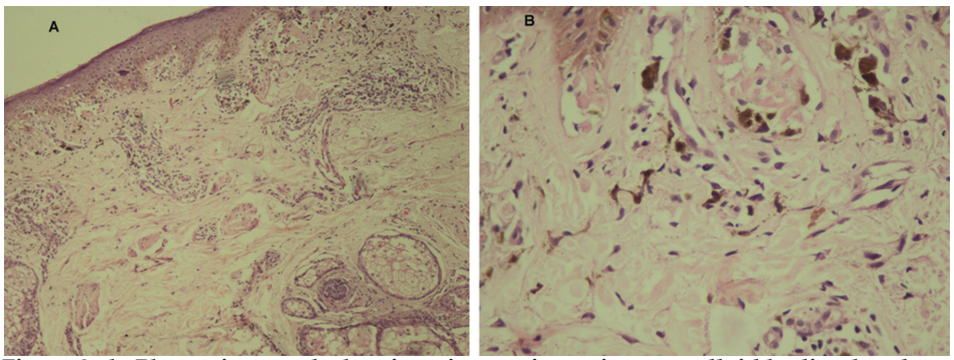

Figure 3a,b. Photomicrograph showing pigment incontinence, colloid bodies, basal vacuolation and lymphocytic exocytosis without eosinophils. H&E; 10X (Fig. a), 40X (Fig. b).

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HURLEY DISEASE - SHORT COMMENT

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Short comment to a previous article:
Chiriac A, Foia L, Pinteala T, Chiriac AE: Acne inversa (Hurley clinical stage ii): case report. Our Dermatol Online. 2011; 2(4): 215-216.

Sir,

The patient refused the surgery and we recommended him resorcinol 30% in vaseline, vitamin C high doses orally (2g/day) and a two-month treatment with Sultametoxazol 4cp/day (Biseptol, Cotrimoxazol) plus Rifampicine 300 mg/day, with very good results (as seen in the picture).
Unfortunatly we were obliged to stop the systemic medication due to the gastro-intestinal side effects, although the laboratory investigations were all within normal limits.

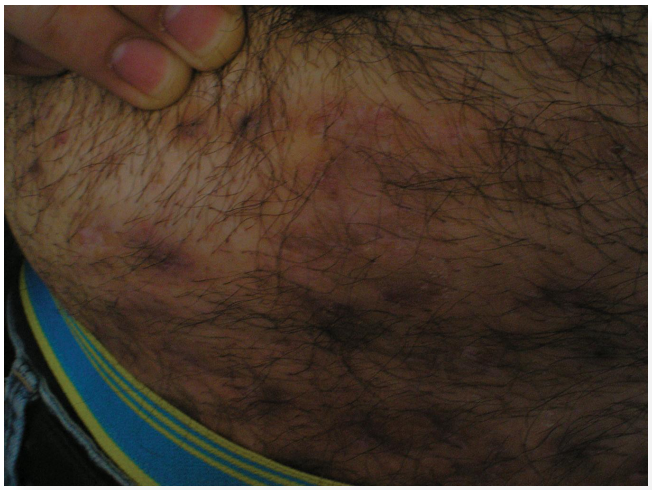

Figure 1.

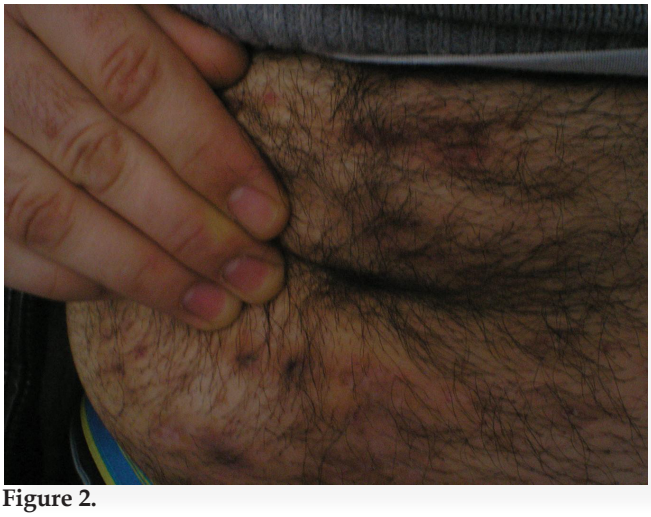

Figure 2.

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NASZA DERMATOLOGIA Online
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THE PROBLEM OF SYNONYMS

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Daifullah Al Aboud: The problem of synonyms. Our Dermatol Online. 2012; 3(4): 364-365

I read with great interest the recent paper by Al Aboud [1], about the problem of synonyms in medical literature.

I concur with the author that this problem needs to be addressed by the concerned people, now before later.

Dr Al Aboud elaborated on the synonyms of multiple symmetric lipomatosis. However, in medicine, one can find multiple synonyms for dozen, if not hundreds of diseases.

In this letter, I am giving another example with Menkes disease, for which there are eight names in medical literature.

Menkes disease is a very rare X-chromosome disorder affecting copper metabolism [2,3]. Menkes et al. in 1962 [4], first described the disease in a family of English-Irish descent living in New York, who presented by early retardation in growth, peculiar hair, and focal cerebral and cerebellar degeneration [4].

The disease leads to psychomotor retardation, pili torti, pallor, seizures and death in infancy or early childhood. There is marked skin pallor and laxity resembling cutis laxa. The responsible gene has been identified as a copper-transporting ATPase. Disruption of copper-dependent oxidation of tyrosine to dihydroxyphenylalanine (DOPA) results in diminished tyrosinase activity which manifests clinically as diffuse cutaneous hypopigmentation [3].

The initial diagnosis of Menkes disease is suggested by clinical features. Serum copper and ceruloplasmin levels are low, but interpretation may be difficult in the first Months of life. Definitive diagnosis can be made by demonstration of abnormal intracellular accumulation of copper in cultured fibroblasts. Examination for hair shaft Abnormalities can usually be accomplished with light microscopy using phase contrast optics. Unfortunately, the prognosis for MKHS is still grim, with most patients dying by the age of 3-4 years. Administrations of oral and parenteral copper have not proven successful [2].

The disease is named after John Hans Menkes [5-7] (1928-2008) (Fig. 1). Menkes, was born in Vienna. In 1939, following the German annexation of Austria, the family fled Austria and immigrated to the USA via Ireland. Menkes was then eleven years old. Menkes, son and grandson of physicians, followed the family tradition and studied medicine, despite his wish to become a journalist [6].

Menkes became head of pediatric neurology at the Johns Hopkins Hospital and later at the University of California, Los Angele (UCLA) [6].

In 1974 he entered private practice but returned to academic medicine in 1984 as professor of neurology and pediatrics at UCLA [6].

In 1997 he was named director of pediatric neurology at the Los Angeles' Cedars-Sinai Medical Center.

He identified Menkes disease, maple syrup urine disease and other congenital disorders of the neural system and established the pediatric neurology program at UCLA5. Menkes has published numerous papers and a textbook of child neurology. He has also written several novels. He has received some literary prizes [6].

He was named one of the „Best Doctors in America" in 1992, 1994 and 1996 and was among the „American Men and Women of Science" in 1996 [6].

He died Nov. 22 at Cedars-Sinai Medical Center in Los Angeles of complications of chemotherapy for colonic carcinoma. He was 79 [5].

Over the years, there was a debate about the best name for Menkes disease. Some authors think that, "Kinky hair disease" proved a designation useful in detection of new cases, since the hair change is an easily remembered feature by which physicians can be alerted to the condition. While others, pointed out that the hair may not be abnormal, and that serum copper determination is a simple and reliable diagnostic test, therefore they suggested "congenital hypocupraemia", as a preferred designation [8].

Table I, illustrate the discrepancy in the number of citations obtained using the synonyms for this disease. Although , this medical condition fits well into a „syndrome", „Menkes disease", seems to be the most currently and frequently, used for this condition.

Finally, I agree with Dr Al Aboud, about the importance of having a uniform and standard terminology in medical field, although this goal is difficult to achieve [1].

The names	Number of citations in PubMed using the term as a search words
Copper transport disease	1675
Kinky-hair syndrome	912
Menkes disease	1301
Menkes' disease	927
Menkes syndrome	1030
Menkes' kinky-hair syndrome (MKHS)	890
Steely-hair syndrome	903
Trichopoliodystrophy	895

Table I. The different numbers of citations obtained from searching the PubMed with synonyms of Menkes disease, as of 1 July 2012

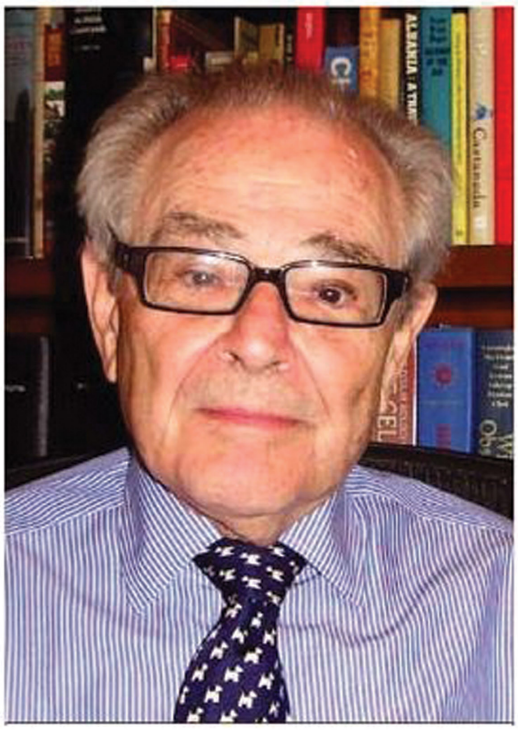

Figure 1. John Hans Menkes (1928-2008). Reprinted with permission from Neurology Today, an official publication of the American Academy of Neurology

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SIMILAR NAMES AND TERMS IN DERMATOLOGY; AN APPRAISAL

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In medicine, one can find easily an abbreviation which stand for few different things as well as many similar words.

The similarities in the words in medical field include the names of the drugs and the names of the diseases.

The names might be similar in „written communications'' which is known as ''look alike'' or in „verbal communications'' which is known as „sound alike''.

In a busy health care work environment, drug products are often mistaken for other products because of similar names.

Hundreds of articles have been published about „Look alike and sound alike'' drugs. These papers listed the drugs with a similar names in each specialty and discussed the possible confusion which may result among them. The different strategies to tackle this confusion have been elaborated [1-5].

The similarities in the names, specially, of drugs in medical field, are a cause of confusion to the health care providers and hence a great source of risk to the patients.

Medication errors contribute substantially to patient injury and death, with 25% of these errors attributed to drug names that look or sound alike [5].

Errors involving look-alike names are common when the names are handwritten and errors with sound-alike names are common when the names are spoken. The problem involves both brand names and generic drug names. However, brand (proprietary) names are the most common to be confused.

Examples of the numerous drug names that have been confused because they look and/or sound similar include Celebrex (celecoxib), Cerebyx (fosphenytoin), and Celexa (citalopram) [3]. In another example, the antihistamine Zyrtec syrup (cetirizine) has been confused with the histamine H2-receptor antagonist Zantac syrup (ranitidine) for pediatric patients.

Factors such as poor handwriting and clinical similarity may exacerbate the problem. Several Measures to decrease medication errors due to confusing drug nomenclature are suggested, in order to maximize patient safety [1-4].

For instance, in medication orders that are communicated orally, whether in person or by telephone or other auditory device. It is recommended that drug names be confirmed by spelling the name, providing both the brand name and the generic name, or providing the indication for use. It is also recommended that the person receiving the order repeat it to the person transmitting the order. Storing similarly named drugs separately and using auxiliary labels to differentiate the products in medication storage areas, was also suggested [1-4].

Overall, this problem can be alleviated through actions by regulatory agencies, pharmaceutical manufacturers, healthcare professionals, and patients [1-4].

In dermatology, in particular, confusing dermatologic drug names do, also, exist [5].

Moreover, the problem of „look- or sound-alike'' names is not limited to the drugs but also involve the names of the diseases and other terms in dermatology literature.

As a matter of fact, one can find a single term, for two different things.

Hutchinson's sign is a clinical sign which may refer to two different things [6,7]. The first is the pigmentation of the nail fold in association with melanonychia as a sign of melanoma. The second thing, is skin lesion on the tip of the nose as a sign of ophthalmic herpes zoster. This occurs because the nasociliary branch of the trigeminal nerve innervates both the cornea and the tip of the nose. This sign is named after Sir Jonathan Hutchinson (1828 –1913), who was an English surgeon, ophthalmologist, dermatologist, venereologist and pathologist [7].

The most common type of names which may cause confusion with other names is the eponyms. An eponym is a name that comes from a person's name [8,9].

Possibly for non-dermatologist, one may think that „Sweet'' in „Sweet's syndrome'', is „a taste of sugar''. But, this syndrome was named for Dr Robert Douglas Sweet, who first described it 1964 [10].

Similarly, „Mali'' in the term acroangiodermatitis of Mali [11,12], does not refer to Republic of Mali but for Dr Mali, who described it 1965, in 18 patients having mauve colored macules and papules predominantly over the extensor surface

of feet with underlying chronic venous insufficiency [11].
Similar name might be thought for and confused with another person, for example verrucous carcinoma of Ackerman is named after Lauren Vedder Ackerman (1905-1993) and not, A. Bernard Ackerman (1936-2008).
One may see also identical names for 2 different eponyms. For examples „Sjögren'' in „Sjögren's syndrome'' (Sicca syndrome), is named after Henrik Samuel Conrad Sjögren (1899-1986), Swedish ophthalmologist. Whereas, „Sjögren'', in „Sjögren-Larsson syndrome'', is named after, Karl Gustaf Torsten Sjögren (1896-1974), Swedish physician, psychiatrist and inheritance researcher [13].
Similarly, „Stewart'' in „Stewart-Treves syndrome" [14], (a malignancy that arises within chronic lymphedema), is different from the one in'' Stewart-Bluefarb syndrome''. The latter is a type of acroangiodermatitis which was described independently by Stewart as well as by Bluefarb and Adams on the legs of patients with arterio-venous malformations [11]. The term, pseudo-Kaposi sarcoma, is generally used synonymously with acroangiodermatitis of Mali, but is a broader term and includes both acroangiodermatitis of Mali and Stewart-Bluefarb syndrome [11].
We have also published that, there are 2 „Bart's'' in the eponyms of dermatology. Dr Bruce J Bart, who is behind „Bart syndrome'', and Dr Robert Bart, who was one of the men behind „Bart-Pumphrey synrome'' [15].
„Look-alike or sound-alike'' eponyms are not rare. This is because there is extensive list of eponyms bearing the name of the same scientist [16,17]. In Table I, we listed examples of scientists whose names are eponymously linked to more than one condition in dermatology literature.
It goes without saying that consolidation of the nomenclature is needed in medicine. The concept of „re-naming'' the similar names of drugs or diseases, to prevent possible confusion, has been debated over the years and there is a still controversy over this topic. Neverthless, healthcare providers need to be, at least, vigilant about the similarities in the names, in particular those which may potentially cause a patient harm.

Scientist	Examples of diseases linked his name	Remarks
Abraham Buschke (1868-1943), German dermatologist	Buschke-Löwenstein tumour	Verrucous carcinoma of genital skin
	Buschke-Ollendorff syndrome	Dermatofibrosis lenticularis disseminate
Henri Gougerot (1881-1955), French dermatologist	Gougerot-Blum disease	Lichenoid type of pigmented purpura
	Gougerot-Carteaud papillomatosis	Confluent and reticulate papillomatosis
François Henri Hallopeau (1842-1919), French dermatologist	Acrodermatitis continua of Hallopeau	Pustular eruption of the fingers and toes
	Hallopeau-Siemens syndrome	Recessive dystrophic epidermolysis bullosa
Josef Jadassohn (1863-1936), German dermatologist	Jadassohn-Lewandowsky syndrome	Pachonychia congenita
	Nevus sebaceous of Jadassohn	Yellowish to orange or tan hairless plaquelike lesions, usually present at birth

Table I. Examples of scientists whose names are eponymously linked to more than one condition in dermatology literature

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EPONYMS IN DERMATOLOGY LITERATURE LINKED TO NORWAY

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An eponym is a word derived from the name of a person. The use of eponyms has long been contentious, but many remain in common use.

Medical literature in general, has many eponyms, coined after scientists from all over the world.

In this communication, we shall highlight on selected eponyms linked to Norway in dermatology literature.

Norway has a population of about 5 million and it is the second least densely populated country in Europe. Yet, it was, and still the birthplace for great scientists. The strive for scientific advance and humanitarianism are among the characteristics of this small country. It has few examples of medical scientists that has discovered and cultivated unknown territory [1].

Most dermatologists are aware of the term „Norwegian scabies", which is currently best known as „crusted scabies", a condition where the patient may harbor up to many millions of mites. This type of scabies was called Norwegian scabies on account of its first recognition in Norway in 1848 among patients with leprosy [2].

The well-known whonamedit website, (www.whonamedit.com), listed till now more than 30 medical eponyms linked to Norway.

But some of these medical eponyms are no longer in common use in medicine.

For example, Følling's disease or Følling's syndrome is the eponymous name for the autosomal recessive metabolic genetic disorder; Phenylketonuria (PKU) [1] .

Asbjørn Følling (1888-1973), was a Norwegian physiologist. He discovered „his disease" (phenylketonuria = PKU) in 1934. He discovered the first link between metabolic disease and brain development [1].

Another example of medical eponym linked to Norway, which is not popular at present time is Harbitz-Müller syndrome, which is best known, as familial hypercholesterolemia [3].

Francis Gottfred Harbitz (1867-1950), and Carl Arnoldus Müller (1886-1983), were both Norwegian physicians. From 1925 to 1938, the pathologist, Francis Harbitz, published several reports on sudden death and xanthomatosis. Harbitz called attention to certain peculiarities of the xanthomatosis. Microscopically he found that the so-called foam cells are more marked and more characteristic than in senile arteriosclerosis [3].

However, some medical eponyms linked to Norway are still in common use.

In Table I [4-10], we listed selected eponyms in dermatology literature, which are linked to Norway.

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Eponyms in dermatology literature linked to Norway	Remarks
Boeck's sarcoidosis	This eponym (also, called Boeck's sarcoid and sarcoidosis Boeck), is now largely replaced by the term "sarcoidosis".In 1899, Cæsar Peter Møller Boeck (1845-1917), (Fig. 1), Professor of Dermatology in Kristiania (now Oslo), published his pioneer article called "Multiple benign sarkoid of skin". Boeck coined the name sarcoidosis which stems from the Greek words "sark" (meaning flesh) and "oid"(meaning like). His uncle was Karl Wilhelm Boeck (1808-1875), known for his work on syphilis [4]. Together with Boeck, the English physician, Jonathan Hutchinson (1828-1913), and the French physicians, Ernest Besnier (1831-1909), and Henri Tenneson (1836-1913) were all pioneers in sarcoidosis work, even though the connections between them were made clear many years later [4]. Boeck coined an instantly acceptable term, sarkoid, and perhaps most important, he accurately and lucidly depicted the classic histologic features of this characteristic granuloma. 'So, history justifies the term Boeck's sarcoidosis" [4,5]. Boeck's compatriot, Ansgar Kveim (1892-1966), presented, in 1941, the Kveim reaction for diagnostic use. The swede, Jörgen Schaumann (1879-1953), demonstrated early the generalized character of the disease. His compatriot, Sven Löfgren (1901-1978), described the combination of erythema nodosum, polyarthritis, fever, and bilateral hilar lymphadenopathy, called Lofgren's syndrome, the most usual form of acute sarcoidosis [4].  **Figure 1. Cæsar Peter Møller Boeck (1845-1917). Courtesy, National Library of Medicine**
Hansen's disease	This term is used as a synonym for leprosy. Descending from a Danish family, Gerhard Henrik Armauer Hansen (1845-1917) (Fig. 2), Graduated in medicine in 1866 from the University at Christiana (the former name of Oslo). He began his work on a disease known as leprosy at the age of 26 and as an assistant of Daniel Cornelius Danielssen(1815-1894),attheLungegaardenHospital[5].WhileDanielssenleanedtoward heredity as a dominant factor in leprosy, Hansen's conviction was that the disease must have an infectious causal agent [5]. In about 1871, Hansen began to observe tiny little rods in tissue specimens and considered they could be the etiologic agent of leprosy, the more he found these rods in all the infiltrated nodular lesions in his patients. Finally, he proposed on February 28, 1873, that the rods were bacilli, responsible of leprosy [5]. He edited the journal <<Lepra>>. Hansen was also an eminent zoologist engaged in studies involving mollusks and worms; since 1874, he was president of the Bergen Museum of Natural History. Armauer Hansen died on February 12, 1912, and the funeral ceremonies took place in the Museum of Bergen where his ashes are still kept [5].

Table I. Selected Eponyms in dermatology literature linked to Norway

Figure 2. Gerhard Henrik Armauer Hansen (1841-1912). Courtesy, National Library of Medicine

Eponyms in dermatology literature linked to Norway	Remarks
Refsum's disease	Refsum disease is an autosomal recessive inborn error of lipid metabolism classically characterized by a tetrad of clinical abnormalities: retinitis pigmentosa peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid (CSF) without an increase in the number of cells. The disease presented in the skin as ichthyotic changes [7-10]. Sigvald Bernhard Refsum (1907-1991) (Fig. 3), was an outstanding Norwegian neurologist, highly respected and recognized both nationally and internationally. He first described this disorder and noted the hereditary aspect. In his monograph from 1946 he named the disease "heredopathia atactica polyneuritiformis"; however, it was rapidly known as Refsum's disease. Twenty years later, two German scientists, Klenk and Kahlke, detected large amounts of a peculiar branched-chain fatty acid, phytanic acid, in a Refsum patient. This started an amazing revelation of the biochemical background of the disease, and also led to a logical and effective treatment. Although Refsum's disease is extremely rare, it has become well-known due to this elucidation of both the normal metabolism of phytanic acid and the pathophysiology of the disease [7-10].  **Figure 3. Sigvald Bernhard Refsum (1907-1991). This figure is reproduced with permission from the great Norwegian encyclopedia (Store norske leksikon), Available Online at; http://snl.no/Sigvald_Bernhard_Refsum**

Table I. Selected Eponyms in dermatology literature linked to Norway (continued)

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EPONYMS IN MEDICAL LITERATURE LINKED TO NURSES

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Nursing is one of the oldest professions in the human life. It is a profession within the healthcare sector focused on the care of individuals.

An eponym is a word derived from the name of a person. Most of the eponyms in medicine are after physicians and rarely to other healthcare providers like nurses.

In Table I [1-8], I highlighted on two famous medical eponyms that are linked to nurses. The association with the name of a nurse represents beyond doubt a special feature and reflects the great contributions, these nurses made.

There is no wonder that both eponyms are for females, as it is around the world, nurses have been traditionally female. And despite equal opportunity legislation, nursing has continued to be a female-dominated profession.

Eponyms in medical literature linked to nurses	Remarks
Nightingale Pledge [1-6]	The Nightingale Pledge is a traditional pledge that was taken by new nurses. It is a modified Hippocratic Oath designed specifically for nurses. Named after Florence Nightingale (Fig. 1), it was composed by a committee chaired by Lystra Gretter, an instructor of nursing at the old Harper Hospital in Detroit, Michigan, and was first used by its graduating class in the spring of 1893. In modern times, a number of institutions have modified or dropped the pledge altogether. The pledge is often used in ceremonies and programs during National Nurses Week (May 6-12) during which Nightingale's birthday (May 12) and Nurses Day (May 6) both take place. It celebrates Nightingale, her contributions, and nurses everywhere. Florence Nightingale (1820-1910) was a celebrated English nurse, writer and statistician. She came to prominence for her pioneering work in nursing during the Crimean War, where she tended to wounded soldiers. She was dubbed „The Lady with the Lamp" after her habit of making rounds at night. An Anglican, Nightingale believed that God had called her to be a nurse. Nightingale laid the foundation of professional nursing with the establishment, in 1860, of her nursing school at St Thomas' Hospital in London, the first secular nursing school in the world, now part of King's College London.

Figure 1. Florence Nightingale (1820 –1910). Courtesy, National Library of Medicine

Table I. Selected eponyms in medical literature linked to Nurses

Eponyms in medical literature linked to nurses	Remarks
Sister Mary Joseph's nodule [7,8]	It is a metastatic lesion of the umbilicus originating from intra-abdominal or pelvic malignant disease. The English surgeon Hamilton Bailey, in his famous textbook "Physical Signs in Clinical Surgery" in 1949, coined the term "Sister Joseph's nodule" after Sister Mary Joseph (1856-1939) (Fig. 2) a superintendent nurse at St. Mary's Hospital in Rochester, Minnesota, USA, who was the first to observe the association between the umbilical nodule and intra-abdominal malignancy. The expression has become widely accepted and used. Although Baluff in 1854 and Nelaton in 1860 had already described umbilical metastases, the best known description of the metastasis of carcinomas to this site as "trouser button navel" was published in 1928 by William James Mayo (1861-1939), son of William Worrall Mayo (1815-1911), the founder of the Mayo Clinic in Rochester, Minnesota. This phenomenon is supposed to have been pointed out to Mayo by his long-serving head surgical nurse Sister Mary Joseph. Sister Mary Joseph, daughter of Irish immigrants, belonged to the 3rd order of the Holy Francis, was distinguished for her skills, intelligence and devotion to nursing which was also her calling. She worked for many decades at the world-famous Mayo Clinic and taught generations of young nurses. In recent years, the original surgical building at Saint Mary's Hospital has been named "Joseph Building" in her memory.

Figure 2. Sister Mary Joseph (1856-1939). Courtesy, National Library of Medicine

Table I. Selected eponyms in medical literature linked to Nurses (continues)

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EPONYMS LINKED TO MELANOCYTIC NEVI

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There are many types of terms used in the nomenclature of skin conditions [1]. One of these types is naming these conditions after the scientists who first described or made a great contribution to those conditions [2]. These type of terms, otherwise known as eponyms are commonly used in dermatology literature [1].

In a tabulation view, I listed in Table I [3-25], selected eponyms who are linked to melanocytic nevi. Some of these eponyms are still in use and some are being replaced by other terms. One reason for the changing trend in the naming of moles is the emerging new concepts in the understanding of these skin lesions. For example a new classification based on the histological pattern („silhouette") of melanocytic nevi was suggested to be used preferably over the old classification of nevi of „junctional," „compound," and „dermal" nevi [4-5].

There is still no uniform nomenclature in some types of melanocytic nevi and it is clear that some consolidation of the nomenclature is needed in this area [3].

However, the continuous improvement in our understanding of nevi and new insights into the molecular heterogeneity of nevi, e.g., BRAF- and NRAS-mutational status, will allow more precise molecular-morphological correlations in the near future [5].

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Eponymous melanocytic nevi	Remarks
Clark's nevus	It is an atypical nevomelanocytic lesion. Dysplastic (atypical, Clark's) nevi are clinically distinctive nevi with characteristic histology and an increased risk of melanoma change [3-5]. Clark's nevus shows the architectural atypia. The atypical architectural features include asymmetry, irregular peripheral border of the lesion, shoulder phenomenon (extension of the junctional component of a compound nevus beyond its dermal component), lentiginous growth of solitary melanocytes along and focally in between elongated rete ridges, and bridging of junctional melanocytic nests. The term dysplastic (atypical) nevus syndrome, (OMIM155600) refers to the familial or sporadic occurrence of multiple dysplastic (atypical) nevi in an individual. Familial cases of this syndrome were originally called the B-K mole syndrome (based on the surnames of two of the probands) and the FAMMM syndrome (familial atypical mole/malignant melanoma syndrome) [3]. Contraversy surrounding the use of the term 'dysplastic' in the title has led to the suggestion that the term 'atypical mole syndrome' is more appropriate. The use of the term 'Clark's nevus' as a synonymous term ignores its origin; the term was used by Ackerman for a nevus with architectural atypia in the form of a junctional shoulder extending beyond the dermal one [3]. A small minority of dermatologist and dermatopathologists in the USA use the term Clark's nevus. It is probably even smaller in other countries. Clinically these are usually larger than ordinary nevi (more than 5mm in diameter), and often show a mixture of tan, dark brown, and pink areas [3]. While Clark nevus overlaps with dysplastic nevus, the terms are not interchangeable. The diagnosis of dysplastic nevus indicates both architectural and cytologic atypia. Clark nevus, while showing architectural atypia, is composed of cytologically unremarkable melanocytes. Clark nevi have been eponymically named after Wallace H. Clark, Jr., who, in 1978, first drew attention to this particular type of nevus by studying numerous melanocytic nevi in patients with concomitant melanomas.
Jadassohn-Tieche nevus	This term was once used for a blue nevus. Blue nevus is a dermal melanocytic lesion which present as a blue-black macule or papule found most commonly on the extremities. It is almost invariably acquired after infancy [3,6]. It is named after Max Tièche (1878-1938), a Swiss physician and Joseph (Josef) Jadassohn (1863-1936), a German dermatologist [7]. It has been suggested that, the epithelioid combined nevi (ECN) fell into three phenotypes with morphologies that most closely paralleled those pictured by Carney and Ferreiro in the Carney complex: the classic or Carney complex pattern (ECN-CC), those that showed overlap with deep penetrating nevus (ECN-DPN), and those that have many dermal Spitz's nevus features, (Blue + Spitz's nevus; (ECN-BLITZ). The latter (blitz nevus is simply a combination of epithelioid blue and Spitz features in the one lesion [8].
Masson neuronevus	It is more commonly, known as neural nevus, or neurotized melanocytic nevus. In this nevus, the nevus cells may assume a neuroid appearance with spindle shaped cells and structures resembling Meissner's tactile body [9,10]. It is named after, Claude L. Pierre Masson (1880-1959), a French--born Canadian pathologist [10].
Meyerson's nevus	It is a junctional, compound, or intradermal nevus surrounded by an eczematous halo which may be pruritic [11,12]. Halo dermatitis around a melanocytic nevus was first described in 1971: by Meyerson [12]. Meyerson's nevus is also referred to as halo dermatitis, halo eczema and Meyerson's phenomenon. Halo-like changes around pigmented melanocytic lesions can take a number of forms. Halo nevus or Sutton's nevus, is an example of a regressing benign nevus with a depigmented zone around the nevus [13]. A ring of deeperpigmentation around benign nevi with an intervening narrow non-pigmented zone giving a target-like appearance has been termed the Cockarde (also spelled as Cocarde and Cockade) nevus [3]. There are also other types of nevi which are characterized by variation in the color. Eclipse nevus is a lesion characterized by a tan center and an irregular darker brown peripheral rim that is occasionally discontinuous [3]. Melanocytic nevi with eccentric foci of hyperpigmentation ("Bolognia sign") can be considered as a melanoma-simulating type of acquired melanocytic nevus [14].
Miescher's nevus	It is a subtype of ordinary, or common, melanocytic nevus [3-5,15]. They are benign melanocytic proliferations which most commonly occur on the face and present as firm, tan to brown dome-shaped papules. In this "endophytic" nevus, nevus cells extend to the deep reticular dermis; the terms "endophytic" describe the histological arrangement of the melanocytic cell aggregates rather than the clinical appearance. This nevus is named after Alfred Guido Miescher (1887-1961), an Italian-born Swiss dermatologist.

Table I. Selected eponyms linked to melanocytic nevi

Eponymous melanocytic nevi	Remarks
Nevus of Ito	A dermal melanocytic condition affecting the shoulder area [3]. Initially described by Minor Ito in 1954 [16].
Nevus of Nanta	A nevus of Nanta is characterized by the presence of cutaneous ossification (osteoma cutis) in an existing melanocytic nevus [3]. It is named after a french dermatologist, André Nanta (1883-1963) [17].
Nevus of Ota	It is a dermal melanocytic lesion. It is a diffuse, although sometimes slightly speckled, macular area of blue to dark-brown pigmentation of skin in the region of ophthalmic and maxillary divisions of the trigeminal nerve. There is often conjunctival involvement as well [3]. Two a acquired dermal melanocytoses that appear in adult life, often in the distribution of the nevus of Ota have been described. Hori's nevus refers to bilateral nevus of Ota-like macules, usually on the malar regions, while sun's nevus is acquired unilateral nevus of Ota [3]. Ota (also spelled Ohta) was a Japanese author, dramaturge, poet, art historian, and literary critic, as well as a licensed doctor specializing in dermatology during the Taisho and early Showa periods in Japan [17]. Ota's pen name was Mokutaro¯ Kinoshita or Kinoshita Mokutaro¯. Ota served at several universities in Japan as professor of dermatology and a noted leprosy researcher [17].
Pointillist nevus	This term has been used for rare nevi with multiple, tiny, dark, brown to black dots on a skin-colored background [18]. These nevi with the varie- gated pigment, were called the pointillist nevi, in reference to the pointillist style of painting.
Reed's nevus	Reed's nevus, also known as, pigmented spindle cell nevus of Reed. It is now regarded as a distinct entity and not as a variant of the spindle-cell type of Spitz nevus, although the distinction between a Reed nevus and a pigmented Spitz nevus is not always easy [3,19,20]. It present as a well-circumscribed deeply pigmented papule, usually of recent onset, frequently located on the thighs of young adult females. It is named after, Richard J. Reed.
Spitz's nevus	Spitz nevus, also known as benign spindle and epithelioid cell nevus, is a variant of nevocellular nevus. This title recognizes the important contribution of Sophie Spitz (1910-1956), an American pathologist, who for the 1st time in 1948, published criteria for the diagnosis of specific lesion of childhood which despite some histological resemblance to malignant melanoma, was known to behave in a benign fashion [3,4,21]. Kamino bodies named after contemporary American dermatopathologist, Hideko Kamino, are dull pink areas of trapped basement membrane material within the epidermis seen in these nevi [22].
Sutton's nevus	Sutton's or halo nevus is characterized by presence of a depigmented halo up to several millimeters in width around a melanocytic nevus [3]. It is named after Richard Lightburn Sutton (1878-1952), an American dermatologist [13]. However, Happle [23] had reported that an accurate depiction of the halo nevus has been left by Matthias Grünewald in his painting "The Temptation of St. Anthony", which is part of the Isenheim altar piece (1512-1516), which is now exhibited in Colmar, Alsace. He added that, Sutton in 1916 only described a "leucoderma acquisitum centrifugum", leaving the nature of the central lesion in the dark. He concluded that, the term Sutton nevus appears less appropriate than the alternative eponymic designation "Grünewald naevus". The term is "Grünewald-Sutton nevus" also suggested for this nevus [24].
Unna's nevus	Unna's nevus is a subtype of ordinary, or common, melanocytic nevus [3-5]. They are benign melanocytic proliferations which most commonly present as soft papillomatous lesions of the trunk, neck and extremities. In these" exophytic nevi", the melanocytic cell aggregates are arranged in the papillary dermis. The term "exophytic" describe the histological arrangement of the melanocytic cell aggregates rather than the clinical appearance. It is named after Paul Gerson Unna (1850-1929), a German dermatologist [25].

Table I. Selected eponyms linked to melanocytic nevi (continued)

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MEDICAL EPONYMS LINKED TO HAIR

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An eponym is a word derived from the name of a person, whether real or fictional. A medical eponym is thus any word related to medicine, whose name is derived from a person.

Nevertheless, some ancient medical scientists who made researches and their names were linked to medical conditions, hence become „eponyms'' are now „anonyms", in the sense that little is known about them.

In Table I [1-12], I listed some commonly used medical eponyms which are primarily linked to hair.

As it is seen from the table, the „hair eponyms'' are not limited to the hair disorders but also, the anatomical structures, inside the hair follicle.

Tracing the historical origins of medical eponyms can be fraught with dilemmas, particularly when the evidence for the naming comes from portraiture, as in Queen Anne's sign [12].

There is a rise and fall in the usage of eponyms in medical literature as there is ongoing dispute whether to use or not to use them. However, it is obvious that those eponyms coined for any old and common medical conditions, are likely to be continually used.

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Medical eponyms linked to hair	Remarks
Adamson's fringe	In growing hairs, the margin between the mitotically active hair bulb and the inactive hair shaft is known as Adamson's fringe [1]. It is named after, Horatio George Adamson (1866–1955).
Björnstad syndrome	It is an autosomal recessive disorder associated with sensorineural hearing loss and pili torti [2]. It was first characterized in 1965, in Oslo, by Prof. Roar Theodor Bjørnstad (1908–2002).
Carvajal syndrome	Carvajal syndrome (CS) (also known as "Striate palmoplantar keratoderma with woolly hair and cardiomyopathy" and "Striate palmoplantar keratoderma with woolly hair and left ventricular dilated cardiomyopathy,". Carvajal-Huerta (1998) described 18 patients with a confirmation of epidermolytic palmoplantar keratoderma, woolly hair, and dilated cardiomyopathy, examined clinically and histologically in Ecuador between 1970 and 1997 [3]. CS might be a variant of Naxos disease (ND), which was first described by Protonotarios et al., in families originating from the Greek island of Naxos [4]. ND is a rare autosomal recessive inherited association of right ventricular dysplasia/dilated cardiomyopathy with woolly hair and palmoplantar keratoderma.
Henle's Layer of the Internal Root Sheath	It is named after, Jacob Henle (1809-1885) [5].
Huxley Huxley's Layer of the Inner Root Sheath	It is named after, Thomas Henry Huxley (1825–1895) [6].
Graham-Little-Piccardi-Lasseur syndrome	Also, called as Lassueur-Graham-Little-Piccardi syndrome or Piccardi-Graham Little-Lasseur syndrome. It is a rare lichenoid dermatosis defined by the triad of multifocal cicatricial alopecia of the scalp; noncicatricial alopecia of the axilla and groin; and a follicular lichen planus eruption on the body, scalp, or both. It was initially described by Piccardi in 1913. In 1915, Sir Ernest Graham-Little (1867-1950) published a similar case observed by Lassueur. Since then several case reports of this syndrome have been published [7].
Menkes disease (MD)	Also, known as, Menkes' kinky hair syndrome is a multisystemic lethal disorder due to impaired copper transport and metabolism with pili torti [8]. Menkes and collaborators defined the syndrome in 1962 on the basis of five boys in the same family. John Hans Menkes, was Austrian-American paediatrician and writer, born 1928.
Netherton syndrome (NS)	NS is characterized by the triad of trichorrhexis invaginata, ichthyosis linearis circumflexa, and an atopic diathesis [10]. It is named after E.W. Netherton. Who described a 4-year old girl with scaly red and different hair, which he called bamboo hair, because of how it looked in the microscope. Nine years earlier, the Italian dermatologist Come described a condition in a young woman with a ring shape change in her skin, which he called itcthyosis Linearis circumflex. These two descriptions were considered to be related.
Queen Anne’s sign	It is also known as, the sign of Hertoghe. It is a laterally truncated eyebrow, and is a sign of hypothyroidism. The sign is named for Eugene Hertoghe of Antwerp, a pioneer in thyroid function research. The eponym is disputed by some and the association with Anne of Denmark is based on portraiture, and history does not suggest that she suffered hypothyroidism [11,12].

Table I. Selected medical eponyms linked to hair

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MEDICAL EPONYMS LINKED TO NAILS

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The nails are affected by several dermatological and systemic diseases, and it is uncommon to find an isolated nail abnormalities.

However, there are some diseases, in which the nails are affected primarily and similarly there are syndromes in which the nails affection is one of its major components.

Some medical conditions in which there is a link to the nails are known eponymously (Tabl. I).

However not all „nails eponyms'' are used commonly. For example, there are eponymous synonyms for nail–patella syndrome (NPS) [1]. NPS is defined by three major features: nail anomalies, skeletal anomalies and renal disease. It is also known as, Fong disease, Österreicher-Turner syndrome, or Turner-Kieser syndrome, nevertheless this syndrome is best known as nail-patella syndrome [22].

Fong disease is the eponym given after Edward Everett Fong, an American radiologist, born 1912, and who discovered the disease in 1946.

John W. Alden Turner was an American physician. His name was associated with NP, because of his description of two extensively affected families [23]. (The designation Turner syndrome, however, leads to confusion with the XO syndrome).Willibald Kieser, was, a German physician, whereas, Walther Österreicher, was an Austrian physician, born 1901.

In „nails eponyms'', there are eponyms which refer to the same condition like Plummer-Vinson or Paterson-Kelly syndrome.

Lastly there are „nails eponyms'', which may not survive more because of the improvement in our genetic understanding for the conditions they were named for.

For instance, pachyonychia congenital types are currently best known by the genetic defects rather than its earlier eponymous types Jadassohn-Lewandowsky syndrome and Jackson-Lawler syndrome.

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Medical eponyms linked to nail	Remarks
Bart-Pumphrey syndrome	This syndrome is characterized by knuckle pads,leukonychia, palmoplanter keratoderma and Sensorineural deafness. This syndrome is first described by Dr Schwann, from Poland and appeared later in English literature by Robert S. Bart (Dermatologist) and Robert E. Pumphrey (Otolaryngologist); both from USA [1].
Beau's lines	Beau's lines are deep grooved lines in the nail plates [2]. The duration of the insult may be estimated by the longitudinal width of the damage. This condition of the nail was named by a French physician, oseph Honoré Simon Beau (1806–1865), who first described it in 1846.
Bywaters' lesions	Bywaters' lesions are cutaneous infarctions that occur in nail fold and around the nailbeds in patients with rheumatoid arthritis.They are small, brown to purpuric, painless lesions on the nail fold, nail edge, or digital pulp that are transient and often go unnoticed [3-6]. Bywaters first described them in 1957.
Hutchinson's sign	It is pigmentation of periungual tissue as a sign of melanoma [7,8]. It is named after, Sir Jonathan Hutchinson (1828–1913). Periungual pigmentation is, also, present in a variety of benign disorders, for which the term "Pseudo-Hutchinson's sign" is suggested [7].
Jackson-Lawler syndrome	It is a type of pachyonychia congenital (PC) - a disease that is characterized by severe thickening of the nail due to massive nail hyperkeratosis. It is first described by Jackson and Lawler in1951 [9].
Jadassohn-Lewandowsky syndrome	Another type of PC. It is named after two famous German dermatologists, Josef Jadassohn (1863-1936) and his assistant, Felix Lewandowsky (1879-1921) [10].
Iso-Kikuchi syndrome	It is a rare condition characterized by various forms of nail dysplasia commonly involving the index fingers [11]. The first case report of this condition was by Kamei, in 1966. Ryosuke Iso (1937–2009), a Japanese plastic surgeon collected a series of patients and defined the clinical syndrome. Reported later, by Ichiro Kikuchi, a contemporary Japanese dermatologist, who coined the term 'congenital onychodysplasia of the index fingers' (COIF) [11,12].
Mees' lines	Mees' lines or Aldrich-Mees' lines or Reynolds' lines are transverse white bands on the nail plate laid down during periods of stress, or appear after an episode of poisoning with arsenic, thallium or other heavy metals, and can also appear if the subject is suffering from renal failure or other systemic insults [13-15]. Although the phenomenon is named after Dutch physician R.A. Mees, who described the abnormality in 1919, earlier descriptions of the same abnormality w ere made by Englishman E.S. Reynolds in 1901 and by American C.J. Aldrich in 1904. Mees' lines need to be distinguished from Muehrcke's lines, which represent an abnormality of the vascular nail bed and disappear when the nail is compressed.
Muehrcke's nails	Muehrcke's nails, or Muehrcke's lines, or leukonychia striata, are changes in the fingernail [16] that may be a sign of an underlying medical disorder, most commonly hypoalbuminemia. White lines (leukonychia) extend all the way across the nail and lie parallel to the lunula (half-moon). In contrast to Beau's lines, they are not grooved. Muehrcke's lines were first described by Robert C. Muehrcke (1921-2003), an American physician in 1956.
Paterson-Kelly syndrome	Paterson-Kelly syndrome or Plummer-Vinson presents as a classical triad of dysphagia, iron deficiencyAnemia and esophageal webs [17]. The syndrome eponym has been frequently discussed. The most used name is Plummer-Vinson syndrome,named after Henry Stanley Plummer (1874–1936) and Porter Paisley Vinson (1890–1959) who were physicianson the staff of the Mayo Clinic. Another term is Paterson-Kelly syndrome, named after, Donald Ross Paterson (1863–1939) and Adam Brown-Kelly (1865–1941), both British laryngologists, who published their findings independently in 1919. They were the first to describe the characteristic clinical features of the syndrome [17].

Table I. Selected medical eponyms linked to nails

Medical eponyms linked to nail	Remarks
Plummer's nail	Onycholysis as a sign of hyperthyroidism. It is named after, Henry Stanley Plummer, who was an American internist and endocrinologist [18].
Plummer-Vinson syndrome	See Paterson-Kelly syndrome, above.
Quincke's pulse	Alternate blanching and flushing of the nail bed due to pulsation of subpapillary arteriolar and venous plexuses; seen in aortic insufficiency and other conditions and occasionally in normal persons [19]. It is named after, Heinrich Irenaeus Quincke (1842-1922), who was a German internist and surgeon.
Terry’s (white) nails	Terry’s (white) nails, is seen in association with systemic diseases like, hepatic failure, cirrhosis, diabetes mellitus, congestive heart failure, hyperthyroidism, and malnutrition. Terry's nails were first described by the British physician Richard Terry, who investigated this nail-bed abnormality in 82 of 100 consecutive patients with hepatic cirrhosis [20,21].

Table I. Selected medical eponyms linked to nails (continued)

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THE MEN BEHIND INCONTINENTIA PIGMENTI

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Incontinentia pigmenti (IP), listed in the Online Inheritance of Man (OMIM), under the number (#308300), is an x-linked dominant condition that affects skin, teeth, eyes and may also have neurological problems. The IP name describes the histological characteristics, the incontinence of melanin into the melanocytes cells in the epidermal basal layer and its presence in superficial dermis [1,2].

Garrod reported the first probable case of incontinentia pigmenti in 1906 and described it as a peculiar pigmentation of the skin in an infant with mental deficiency and tetraplegia. Subsequently, Bloch and Sulzberger further defined the condition in 1926 and 1928, respectively, as a clinical syndrome. Hermann Werner Siemens (1891-1969), is a German dermatologist, who also, contributed to the description of this disease and his name is also linked to the eponyms of this disease.

IP is caused by mutations in the NEMO (NF-κB essential modulator) gene, the protein product of which protects against tumor necrosis factor-α-induced apoptosis.

Between 900 and 1,200 affected individuals have been reported in the scientific literature. Most of these individuals are female.

Cutaneous findings are the most common manifestation of IP and usually represent the presenting signs. They are divided into four overlapping stages: (1) vesiculobullous, which favors the extremities during the first few months of life (but occasionally recurs during childhood in association with a febrile illness); (2) verrucous, which favors the distal extremities in patients one to six months of age (and sometimes adolescents); (3) hyperpigmented, which favors the trunk and intertriginous sites from three months of age through adolescence; and (4) hypopigmented/atrophic, which affects the calves in adolescents and adults [1,2].

The extracutaneous manifestations of IP, which are less frequent than are the skin findings, are more likely to cause morbidity. These include dental abnormalities (such as small teeth or few teeth), eye abnormalities that can lead to vision loss, and central nervous system (CNS) abnormalities also occur in one-third of IP patients and can include seizures, developmental delay, and spastic paresis. However, most people with incontinentia pigmenti have normal intelligence. Infants with IP should be referred to a pediatric ophthalmologist for evaluation and close follow-up. In addition, neurodevelopmental status should be monitored, and a pediatric neurologist consulted if problems arise [1,2]. Early dental intervention is also recommended.

Incontinentia Pigmenti International foundation (IPIF) is a voluntary nonprofit organization founded in 1995. Its mission is to encourage and support research on IP, and to provide family support and education. Further details about this organization can be seen at its official website, http://www.ipif.org/

There are several synonyms for IP. These includes Bloch–Siemens syndrome, Bloch–Sulzberger disease, Bloch–Sulzberger syndrome, Bloch-Siemens-Sulzberger Syndrome, melanoblastosis cutis, melanoblastosis cutis linearis, nevus pigmentosus systematicus, and pigmented dermatosis, Siemens-Bloch type.

However, Bloch–Sulzberger syndrome, is the most common eponym for this disorder, I am going to highlight on the dermatologists behind this eponym.

Bruno Bloch (1878- 1933)

Bruno Bloch is, a Swiss dermatologist [3-5] (Fig. 1). He graduated from the University of Basel in 1900 and obtained his doctorate in 1902. He received further education at the medical and dermatological clinic in Basel, as well as in Vienna under Gustav Riehl (1855-1943), Berlin, Paris, and in Bern under Josef Jadassohn. In 1908 he was appointed as head of dermatology at the University of Basel, where he was habilitated for dermatology and syphilology in 1909. In 1916 he was called to the newly established chair of dermatology at the University of Zurich, where he remained until his death in 1933 [3].

Bloch founded the collection of moulages at the Department of Dermatology, Zürich University Hospital. This collection is still well preserved and offers the possibility of following Bloch's scientific interests [4].

To mark the occasion of the 75th anniversary of Bruno Bloch's appointment to the Chair of Dermatology in Zurich, a commemorative lecture was established. The speaker paid tribute to his professional achievements and to the careers of some of his followers (Wilhelm Lutz, Basel; Marion B. Sulzberger, New York; Edwin Ramel, Lausanne; Hubert Jäger, Lausanne; Werner Jadassohn, Geneva; Guido Miescher, Zurich) [5].

Marion Baldur Sulzberger (1895-1983)

Marion Baldur Sulzberger, was one of the most famous American dermatologists [6,7] (Fig. 2). He had received his training in dermatology in Zurich (Switzerland) from 1926 to 1929. The collection of moulages in Zurich still preserves outstanding wax models of Sulzberger's scientific work. They are impressive examples of the purpose and value of moulages at the beginning of the 20th century being used as teaching aids but also as documents and illustrations in scientific articles and textbooks [6].

He began his medical studies in Geneva, Switzerland, in 1920, but later changed to the University of Zurich. During this period he came into contact with Josef Jadassohn (1863-1936), professor of dermatology in Bern, and Bruno Bloch (1878-1933), who had been appointed to the chair of dermatology at Zurich in 1916 [7].

When he returned to America. He entered private practice with Fred Wise (1881-1950) [7].

In 1949 Sulzberger became professor of dermatology and syphilology of the New York University-Bellevue Medical Center. He retired from the chair of dermatology in 1961, but three years later he accepted an appointment as professor of clinical dermatology at the University of California in San Francisco. He retired from his tenure in 1970 [7].

Figure 1. Bruno Bloch (1878- 1933). Courtesy, Dermatologisches Zentrum Berlin

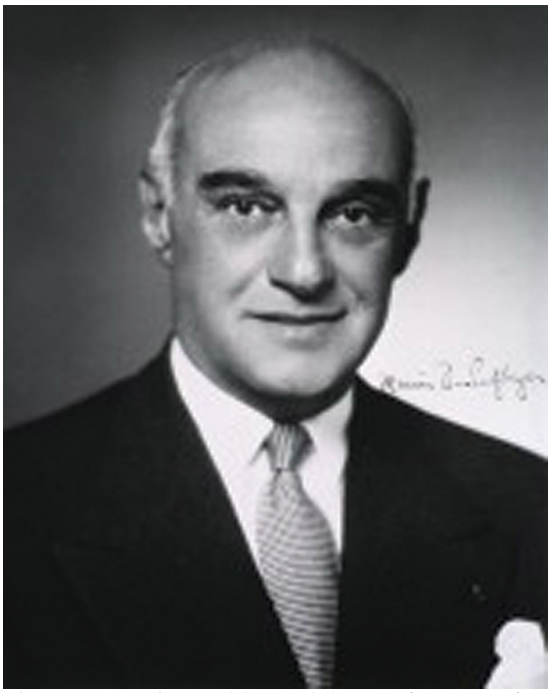

Figure 2. Marion Baldur Sulzberger (1895-1983). Courtesy, National Library of Medicine

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