Severely itchy skin lesions on extremities

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The aim of this presentation is to highlight the fact that recognizing unusual features of the disease and to enhance more understanding of its pathogenesis and management.
A 60-year-old female patient presented with 3 weeks history of coughing and itchy generalized skin rash mostly in lower limbs. She is a known diabetic and hypertensive on oral medications. The rash was not associated with fever, night sweat, diarrhea, joint pain or weight loss.
Physical examination revealed non-blanching petechial rash and vesiculobullous lesions containing clear or hemorrhagic fluid. Some lesions are crusted, ulcerated with central necrosis. The rash was mainly on lower limbs, also on back, abdomen, axillae and upper limbs.
Lab. investigations:

- CBC, LFT’s, renal function tests, electrolytes and coagulation profile were normal.
- ANA, ds-DNA, ENA, ANCA, C4, C3, IgA, RF and cryoglobulin were negative.
- HIV and hepatitis profile were negative.
- LDH, CK, CRP and blood glucose levels were high.
Investigation

CT Thorax with contrast                             Negative

CT Abdomen/Pelvis with contrast                     Negative

US LE Venous Doppler Bilateral  →  No evidence of DVT

Skin biopsy:
Skin punch taken from early erythematous lesion from chest
Histopathology

- Acanthosis, hyperkeratosis, parakeratosis and focal parakeratotic crust infiltrated with neutrophils
- Heavy perivascular chronic inflammatory cell infiltration predominantly lymphocytic infiltrate penetrating the dermal blood vessel walls with mild extravasation of erythrocytes

**DIAGNOSIS:**

LYMPHOCYTIC VASCULITIS
Based on the diagnosis of vasculitis, Oral Prednisolone tab. 100 mg daily was administered, patient showed good response but following the tapering of prednisolone tab. the rash relapsed.

On re-admission, skin biopsy was repeated. The specimen was taken from well developed lesion including the central adherent keratotic plug on right leg.
Histopathology

- Epidermal ulcerative lesion with dermal invagination. The ulcerative lesion shows full thickness epidermal necrosis with neutrophilic infiltrate.
- The underlying dermis demonstrates foci with altered collagen. Vertical collagen fibers are noted within necrotic epidermal lesion.
- Masson Trichrome special stain highlights the extruded epidermal collagen.
- Elastic stain fails to demonstrate elastic fibers.
- Gomori-Methamine silver stain is negative for fungal organisms.
- Dermal blood vessels demonstrate reactive changes associated with perivascular neutrophils.
- There is absence of vasculitis.
Hyperkeratosis overlying a cup shaped depression or invagination in the epidermis.

Prominent epidermal hyperplasia, which encompasses a central basophilic plug of keratin, collagen and inflammatory debris.
Central plug of basophilic debris and collagen with surrounding epidermal hyperplasia
The central crusted keratotic plug contains keratin, cellular debris and collagen fibres.

Perforating collagen bundles

**Elastica van Gieson stain**
Transepidermal elimination of red collagen fibers through the spinous layer and into the stratum corneum (Verhoeff–van Gieson stain)

**Verhoeff's stain**
- Elastic fibers and cell nuclei are stained black,
- collagen fibers are stained red
- other tissue elements including cytoplasm are stained yellow
Vertically oriented collagen fibers, perforating the epidermis from below (Masson-Trichrome stain, ×400)

**Masson Trichome**
- Collagen fibers stain green or blue
- Muscle and keratin will be red.
- Cytoplasm will be pink to red.
- Nuclei will be black.
Reactive Perforating Collagenosis
• Doxycycline capsule 100 mg daily started while oral steroids gradually tapered over 2 weeks till complete withdrawal of steroid
• Well controlled DM
• This resulted in almost complete clearance of skin lesions

Successful treatment of acquired reactive perforating collagenosis with doxycycline. Acta Derm. Venereol. 2002; 82 (5); 393-5
2 weeks after doxycycline therapy
2 weeks later
Perforating Dermatosis

- It is a group of disorders with trans-epidermal elimination of collagen, elastic tissue or necrotic connective tissue caused by unrelated pathologic abnormalities.
- These are papulo-squamous disorders characterized by keratotic plug or crust, in which dermal connective tissue is eliminated through epidermis.
Transepithelial Elimination (TEE)

- It is a phenomenon in which material from the dermis is extruded through the epidermis to the exterior with little or no disruption of the surrounding structures.
- The extruded material may include inflammatory cells, red cells, micro-organisms and extracellular substances, such as mucin or altered connective tissue components.
Molecular Mechanism

AGE: advanced glycation end product
KC : keratinocytes
TEE : transepidermal elimination

Journal of Investigative Dermatology (2010) 130,405-414
TEE in RPC
TEE in EPS
TEE in Perforating Folliculitis
TEE in Kyrle’s disease
collagen
elastic fibers
hair follicle
keratinocyte

Journal of Investigative Dermatology (2010) 130, 405-414
Papules typically are concentrated on hair-bearing portions of the extremities (arms, thighs) and buttocks.

Dilated follicular infundibulum filled with mixture of keratin, basophilic debris, inflammatory cells and degenerated collagen fibers.
large keratotic papules distributed widely throughout the body. The papules contain a central keratotic plug, which histologically correlates with keratin and necrotic debris.
small papules erupt and grouped in a confined area, eventually becoming serpiginous. The central core of each papule contains a compressed aggregate of fibrous material and cellular debris
Reactive Perforating Collagenosis

- The major abnormality in RPC is focal damage to collagen and the elimination of the disrupted collagen through the epidermis.

- The underlying cause of reactive perforating collagenosis is unknown.
  - Abnormal response to superficial trauma: A frequent association with pruritus, the tendency to the Koebner phenomenon and the distribution of lesions on trauma-prone areas provides evidence that superficial trauma (e.g. scratching) may play a part in its etiology.
Reactive perforating collagenosis

2 forms
- Inherited
- Acquired
The inherited form

- Starts in early childhood as small papules on the extensor surface of the hands, the elbows and the knees following superficial trauma.
- Each skin colored papule increases to a size of about 6 mm over 3–5 weeks and then becomes umbilicated, with a keratinous plug.
- The lesions regress spontaneously in 6–8 weeks to leave a hypopigmented area or slight scar, but new lesions may appear.

Reactive Perforating Collagenosis

**Acquired form**

- The bulk of the coarse granular basophilic material that is extruded by TEE appears to derive from the nuclei of PMNL.

- Lysosomal enzymes derived from leukocytes might be responsible for the altered staining of collagen fibres and the impairment of keratinocyte adhesion, which allows TEE of dermal components.
The diagnostic criteria for the adult (acquired) form of RPC, as follows:

- Onset of lesions after age 18 years
- Umbilicated papules or nodules with a central, adherent keratotic plug
- Elimination of necrotic basophilic collagen bundles into a cup-shaped epidermal depression as seen in biopsy specimens

Associations

- Chronic renal failure, often with underlying diabetes*
- Other nephropathies without diabetes
- Hypothyroidism, hyperparathyroidism
- Liver dysfunction**
- Malignancies
- Indinavir***

* Brenner and Rector's the Kidney, Ninth Edition 2012
** Br. J. Dermatol. 142 (2): 390-1
Specific investigations

- Skin biopsy with Masson trichrome stains and Verhoeff–van Gieson stains
- Serum blood urea nitrogen, creatinine
- ALT, AST, alkaline phosphatase, bilirubin and uric acid
- Serum glucose, oral glucose tolerance test or hemoglobin A1C
- Hepatitis C virus antibodies
- Thyroid function tests
Management

- When the underlying cause is not apparent, serum chemistry for renal and liver function tests and oral glucose tolerance test or hemoglobin A1C may be helpful.
- Most often, conditions such as diabetes mellitus and renal failure will be known to the patient who presents with perforating skin lesions.
- The lesion can disappear with stabilization of renal failure and/or correction of hyperglycaemia.
Management

Minimizing pruritus is important because many of the perforating disorders typically exhibit a Koebner phenomenon, meaning that lesions develop in traumatized or scratched skin.

So it is important to instruct the patient to avoid scratching the lesions.
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*Treatment of Skin Disease: Comprehensive therapeutic strategies.*

Consider Perforating disorders when ulcer with keratotic plugs is found

A good interdisciplinary cooperation is crucial for the early recognition by histopathology

Definitive diagnosis of the perforating disorders depends on the demonstration of trans-epidermal elimination on skin biopsy

Differentiation between the different forms of perforating disorders can be accomplished by Masson trichrome stains for collagen (RPC), Verhoeff–van Gieson stains for elastic tissue (EPS)
Conclusions

- Management of the perforating diseases involves determination of underlying etiologies.

- Once the diagnosis of underlying diseases is ascertained, treatment is directed at associated symptoms.
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THANK YOU