Transepidermal Elimination: Historical Evolution, Pathogenesis and Nosology

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Introduction
Dermoepidermal junction is the most complex structural and functional microscopic zone of the skin that enables both epidermal and dermal units to interact in many complex ways in order to perform various functions. Elimination of exogenous foreign substances or altered dermal constituents from dermis to the skin surface via epidermal channel is one of the functions of this zone which has been the mainstay in the pathogenesis of various perforating dermatoses.

Historical Aspects
The first case of perforating dermatosis was described by Josef Kyrle in 1916 who termed it as “hyperkeratosis follicularis et parafollicularis in cutem penetrans.” In 1927, Fisher described a patient with circinate papular eruption on neck containing perforating amorphous plugs but he did not elaborate further and considered it as an atypical presentation of what Kyrle had described before. The phenomenon of expulsion of such materials via epidermis was first observed in detail by Freudenthal in 1930 who identified it as amyloid in his own case. In the subsequent years, many such cases were reported and then in 1958, the term “elastosis perforans serpiginosa” was given for a particular variant of perforating disorder by Dammert and Putkonen. Mehregan also described a similar perforating disorder and coined them as “reactive perforating collagenosis.” In 1968, Mehregan described a series of 11 cases of “elastosis perforans serpiginosa” and based on such descriptions, he first proposed the concept of “transepidermal elimination” in 1970.

Definition
Transepidermal elimination is a purposeful, pathologic, dermoepidermal reactive phenomenon incited by exogenous substances or altered dermal constituents (of inflammatory, metabolic or neoplastic origin) and characterized by pseudoepitheliomatous hyperplasia of epidermis and/or follicular epithelium and formation of multiple transepithelial perforating channels, facilitating the extrusion of the altered dermal material or foreign substances to the exterior.

Concept of Transepidermal Elimination and Pathogenesis
During the conceptual formulation of transepidermal elimination, Mehregan described three types of epidermal reaction to foreign materials in the dermis. Those were:

- Type 1 reaction that includes the trapping and upward epidermal migration and desquamation of “inert particles” or “nonmotile cells” such as hemosiderin or

![Figure 1: Multiple umbilicated papules with central keratotic material in a case of acquired perforating dermatosis associated with diabetic mellitus](image)

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How to cite this article: Shah H, Tiwary AK, Kumar P. Transepidermal elimination: Historical evolution, pathogenesis and nosology. Indian J Dermatol Venereol Leprol 0;0:0.

Received: June, 2017. Accepted: October, 2017.
Shah, et al. Transepidermal elimination

Shallow, cup-shaped epidermal

Extensor of extremities and

Older lesions spontaneously

2

Dorsae of hands, forearms,

Down’s syndrome,

Small eroded papule of size up
to 6 mm, with hyperkeratotic
central plug.

Linear Koebnerization may be
evident

Acquired perforating collagennosis (ICD-10: L87.1) – Inherited form

Acquired adult form of reactive perforating collagenosis (secondary to
diabetes mellitus and chronic kidney disease/failure)

Perforating folliculitis

Table 1: Disorders of transepidermal elimination

| Classical classification of transepidermal elimination disorders | Other and unspecified conditions of transepidermal elimination |
|-----------------------------------------------------------------|---------------------------------------------------------------|
| Elastosis perforans serpiginosa (ICD-10: L87.2)                 | • Collagenome perforant verruciforme                           |
| A. Isolated form                                                | • Chondrodermatitis nodularis helicis chronica                 |
| B. Associated with –                                            | • Non-infective granulomatous disorders – granuloma annulare, |
| a. Penicillamine therapy                                        | necrobiosis lipoidica diabeticorum, rheumatoid nodule, sarcoidosis |
| b. Osteogenesis imperfecta                                      | • Dermatoses with calcification - Pseudoxanthoma elastica, calcified tumor of hair follicle origin (e.g. pilomatrixoma), calcinosis cutis, osteoma cutis |
| c. Marfan’s syndrome                                            | • Infectious diseases- Cutaneous tuberculosis, botryomycosis, |
| d. Ehlers-Danlos syndrome                                       | schistosomiasis, leishmaniasis, rhinosporidiosis, lobomycosis, |
| e. Acrogeria                                                    | chromoblastomycosis, histiod leprosy                           |
| f. Down’s syndrome                                              | • Others - Lichen nitidus, papular mucinosis, amyloidosis, melanoma, naevoid cellular nevus, vitiligo (melanocytorrhagy followed by transepidermal elimination of melanocytes) porokeratosis of Mibelli, hidradenitis suppurativa, eruptive vellus hair cyst, gout crystals, hair follicle stem cells, tattoo pigment |
| g. Cutaneous sclerosis                                           |                                                                 |

Reactive perforating collagennosis (ICD-10: L87.1) – Inherited form

Acquired perforating dermatosis –Kyrle’s disease (ICD-10: L87.0) and acquired adult form of reactive perforating collagenosis (secondary to diabetes mellitus and chronic kidney disease/failure)

Perforating folliculitis

Table 2: Differential diagnosis of classical perforating disorders

| Clinicalopathological Features | Inherited Reactive Perforating Collagennosis | Elastosis Perforans Serpiginosa | Kyrle’s Disease | Perforating Folliculitis |
|--------------------------------|---------------------------------------------|--------------------------------|----------------|-------------------------|
| Morphology                     | Small eroded papule of size up to 6 mm, with hyperkeratotic central plug. Linear Koebnerization may be evident | Non-follicular papules of 2-5 mm size arranged in linear, arcuate or serpiginous pattern | Predominantly non-follicular dome shaped papules of size 2-8 mm (may coalesce) with a central cone shaped keratotic plug. Linear Koebnerization may be present | Erythematous discrete follicular papules (2-8 mm) with central keratotic plugs |
| Age of onset                   | 1st decade                                  | 2nd decade                    | 4th decade     | 2nd to 4th decade       |
| Distribution                   | Dorsae of hands, forearms, elbows, knee, lower legs | Nape and sides of the neck, face and upper limb | Extensor of extremities | Extensor of extremities and buttocks |
| Course                         | Older lesions spontaneously regress leaving hypopigmentation or superficial scar and new lesions continue to develop till adult life | May involute spontaneously in years leaving reticulate atrophic scars | Lesions clear with control of underlying disease | Persists for years with periods of remission |
| Known Inciting factors         | Scratching, insect bite, folliculitis and cold exposure | Unknown | Unknown | Chemical irritation, chronic rubbing |
| Underlying diseases            | Unknown                                     | Down’s syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, Pseudoxanthoma elastica, Marfan’s syndrome, Acrogeria | Diabetes mellitus, chronic kidney disease, Renal failure and rarely hepatic dysfunction | Primary sclerosing cholangitis, renal failure, pruritus, HIV infection, juvenile acanthosis nigricans |
| Histopathologic features       | Shallow, cup-shaped epidermal invagination (lined by acanthotic epidermis) contain degenerated collagen bundles and basophilic debris. Thin epidermis at the base of invagination with fine slits through which vertically oriented collagen fibres are extruded out | Narrow oblique/wavy transepidermal channel coursing through an acanthotic epidermis, containing eosinophilic fragmented elastic fibers and basophilic granular debris. Increased numbers and size of elastic fibres in papillary dermis admixed with mixed inflammatory cells adjacent to the channel | Follicular or parafollicular keratotic plug with focal parakeratosis, small basophilic debris with no demonstrable collagen or elastin, embedded in an epidermal invagination. Irregular epithelial hyperplasia. Granulomatous suppurative cellular infiltrate | Dilated follicular infundibulum filled with compact ortho and parakeratotic plug and degenerated basophilic nuclear debris. Altered collagen and elastin (not increased) near perforating channel. Perifollicular mixed inflammatory cell infiltrate and occasionally remnants of hair shaft |

- Amyloid and erythrocytes, respectively, which are not capable of eliciting sufficient dermal reaction.
- Type 2 reaction that involves migration of microorganisms and motile cells such as Treponema pallidum and leukocytes into the epidermal spaces to be carried upward with physiological desquamation process.

754

Indian Journal of Dermatology, Venereology and Leprology | Volume 84 | Issue 6 | November-December 2018
Figure 2: A cup-shaped channel containing degenerated collagen bundles and inflammatory debris [hematoxylin and eosin (H and E) ×100]

Figure 3a: Epidermal slits containing vertically oriented bundles of collagen. Surrounding epidermis is acanthotic and exhibits lymphocytic infiltration (H and E ×400)

Figure 3b: Multiple epidermal channels showing vertically oriented collagen fibers (Verhoeff-Van Gieson stain ×400)

Figure 4a: Brightly eosinophilic fibers are seen within the extruded material, mixed with keratinous debris and a mixed inflammatory cell infiltrate (H and E ×100)

Figure 4b: Brightly eosinophilic fibers with lateral budding are seen within the extruded material (H and E ×400)

Figure 5: Uniformly stained pink globules occupying the dermal papilla. Overlying epidermis is acanthotic. Similar eosinophilic globule seen at the junction of granular layer n corneal layer (H and E ×400)
The above two, being relatively passive processes with the absence of specific dermoepidermal reaction, have collectively been termed as “transmigration.” Of note, by definition transepidermal elimination is an active process of elimination of dermal foreign materials, hence these two are not included under the nosology of transepidermal elimination.

- There is a third type of dermoepidermal interaction which is an active and unidirectional elimination process whereby dermal altered material and foreign components (e.g. calcium, collagen, elastin) are actively extruded out through the epidermis. This is called “transepidermal elimination”.

Without going into the detail of each example of transepidermal elimination, the sequence of pathological events can be generalized and summarized. It starts with the binding of foreign or altered dermal constituents to a receptor which is still unidentified. It incites a dermal reaction releasing some chemical mediators leading to epidermal hyperplasia and formation of multiple transepidermal perforating channels. The foreign substances get surrounded and phagocytosed by the epidermal cells of these perforating channels and are subsequently moved upward to the surface. Of note, the process of transepidermal elimination has also been reported to occur through eccrine duct opening in one case of cutaneous leishmaniasis in human immunodeficiency virus (HIV) positive patient wherein amastigotes were found within the epithelial cells of secretory eccrine glands and ducts indicating the feasibility of elimination through eccrine duct opening.

**Prerequisites**

There are two chief prerequisites for transepidermal elimination. These are:

- **Nature of the inciting dermal stimulus**
  
  Stimulus should not be very irritant, otherwise epidermal necrosis would occur. Neither should it be inert, or else there would be no dermal reaction. Hence, stimulus should be irritant enough to induce inflammation and reactive hyperplasia of epidermis without any major structural alteration or necrosis.

- **Location of the dermal stimulus**
  
  According to the previous literature experiences, the foreign dermal stimulus cannot lead to transepidermal elimination unless that stimulus is located within a specific dermal–epidermal interaction zone that is “above the level of the hair papillae” in the dermis. More superficial or deeper location of the stimulus will not result in transepidermal elimination.

**Nosology**

All perforating dermatoses exhibiting transepidermal elimination characteristically present with a common clinical morphology: umbilicated papules with central hyperkeratotic plug [Figure 1] and unique histopathologic findings. Depending on the presence or absence of preexisting dermatosis, disorders of transepidermal elimination are broadly classified into two categories: primary perforating dermatoses including elastosis perforans serpiginosa and reactive perforating collagenosis (inherited form), and...
secondary forms appearing in preexisting disorders. This extended classification has now been condensed to four classical entities based on the primary defect and nature of extruding dermal foreign substances (identified by proper staining and histopathologic examination): Reactive perforating collagenosis, Kyrle’s disease, elastosis perforans serpiginosa and perforating folliculitis [Figures 2-7 and Table 1].

Clinical and histopathologic features of these four perforating conditions have been summarized in Table 2.15

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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