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[1] in 1916 who termed it as "hyperkeratosis follicularis et parafollicularis in cutem penetrans." In 1927, Fisher[2] 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[3] 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.[4] Mehregan[5] 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.[6,7]

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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.[7] 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

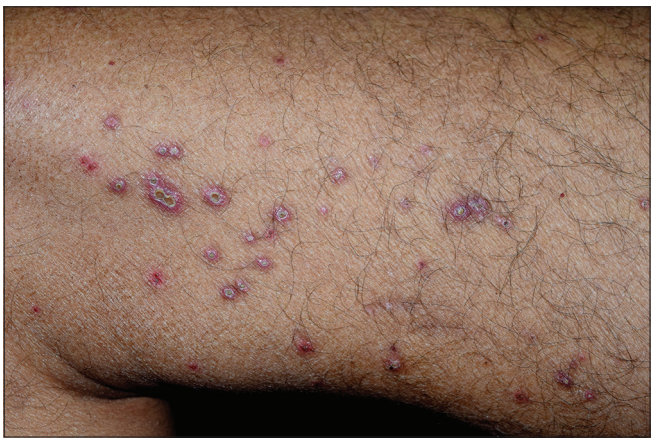

Figure 1: Multiple umbilicated papules with central keratotic material in a case of acquired perforating dermatosis associated with diabetic mellitus

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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) A. Isolated form B. Associated with – a. Penicillamine therapy b. Osteogenesis imperfecta c. Marfan's syndrome d. Ehlers-Danlos syndrome e. Acrogeria f. Down's syndrome g. Cutaneous sclerosis Reactive perforating collagenosis (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	• Collagenome perforant verruciforme • Chondrodermatitis nodularis helicis chronica • Non-infective granulomatous disorders – granuloma annulare, necrobiosis lipoidica diabeticorum, rheumatoid nodule, sarcoidosis • Dermatoses with calcification - Pseudoxanthoma elasticum, calcified tumor of hair follicle origin (e.g. pilomatricoma), calcinosis cutis, osteoma cutis • Infectious diseases- Cutaneous tuberculosis, botryomycosis, schistosomiasis, leishmaniasis, rhinosporidiosis, lobomycosis, chromoblastomycosis, histoid leprosy • Others - Lichen nitidus, papular mucinosis, amyloidosis, melanoma, naevocellular 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

Table 2: Differential diagnosis of classical peforating disorders

Clinicopathological Features	Inherited Reactive Perforating Collagenosis	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 elasticum, Marfan's syndrome, Acrogeria	Diabetes mellitus, chronic kidney disease, Renal failure and rarely hepatic dysfunction	Primary sclerosing cholangitis, renal failure, psoriasis, 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.

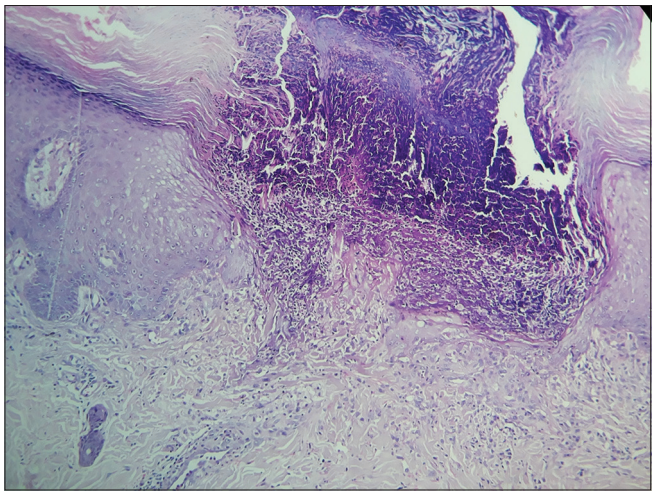

Figure 2: A cup-shaped channel containing degenerated collagen bundles and inflammatory debris [hematoxylin and eosin (H and E) ×100]

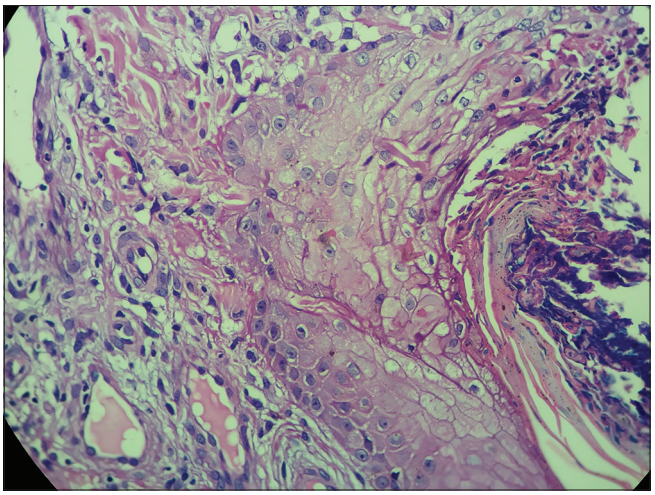

Figure 3a: Epidermal slits containing vertically oriented bundles of collagen. Surrounding epidermis is acanthotic and exhibits lymphocytic infiltration (H and E ×400)

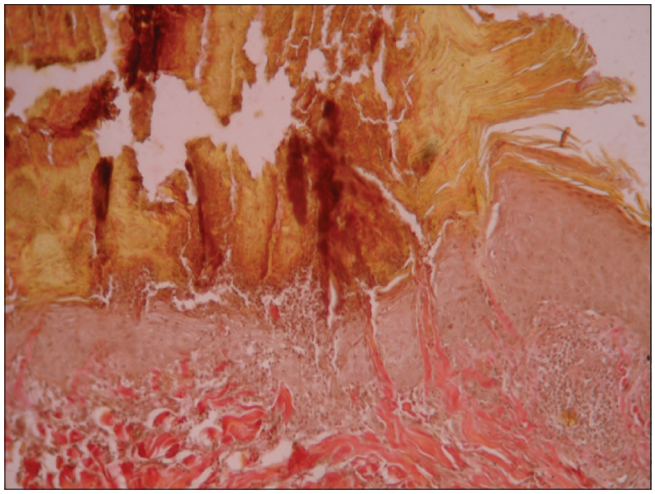

Figure 3b: Multiple epidermal channels showing vertically oriented collagen fibers (Verhoeff-Van Gieson stain ×400)

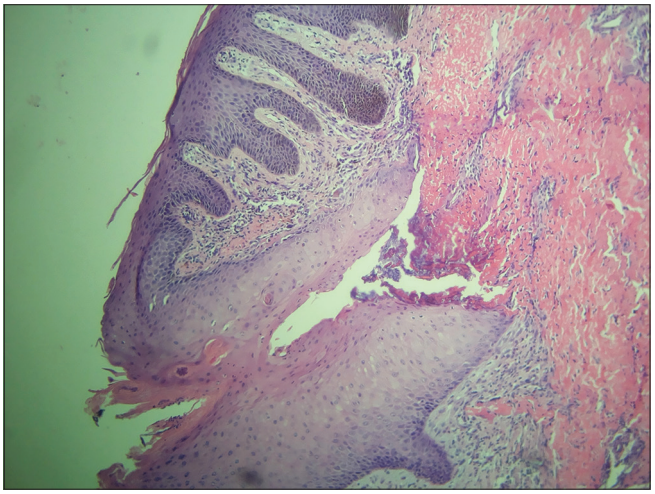

Figure 4a: Brightly eosinophilic fibers are seen within the extruded material, mixed with keratinous debris and a mixed inflammatory cell infiltrate (H and E ×100)

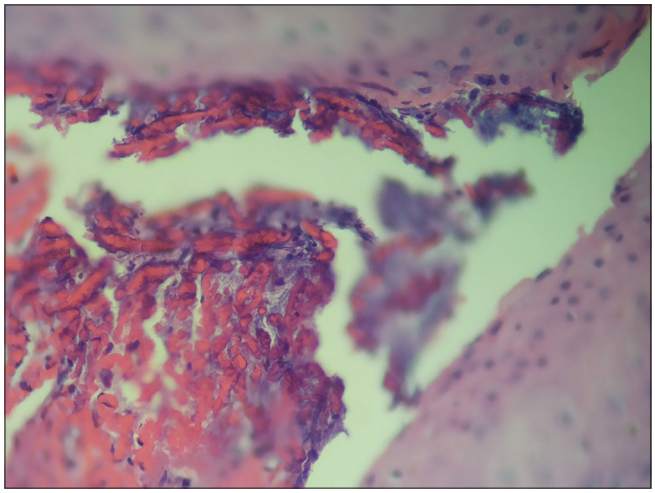

Figure 4b: Brightly eosinophilic fibers with lateral budding are seen within the extruded material (H and E ×400)

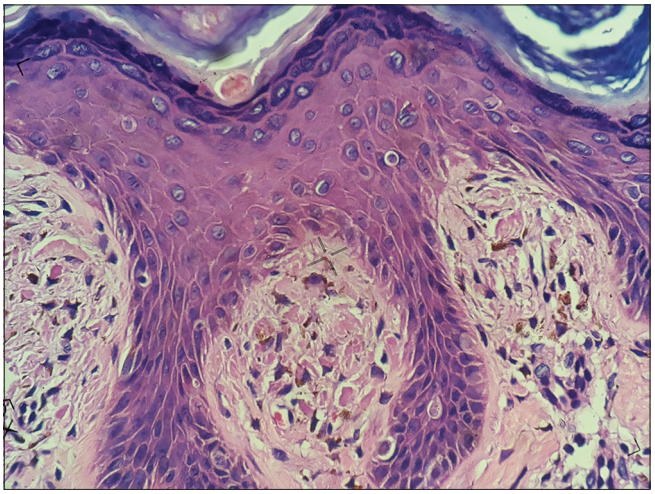

Figure 5: Uniformly stained pink globules occupying the dermal papilla. Overlying epidermis is acanthotic. Similar eosinophilic globule seen at the junction of granular layer n corneal layer (H and E ×400)

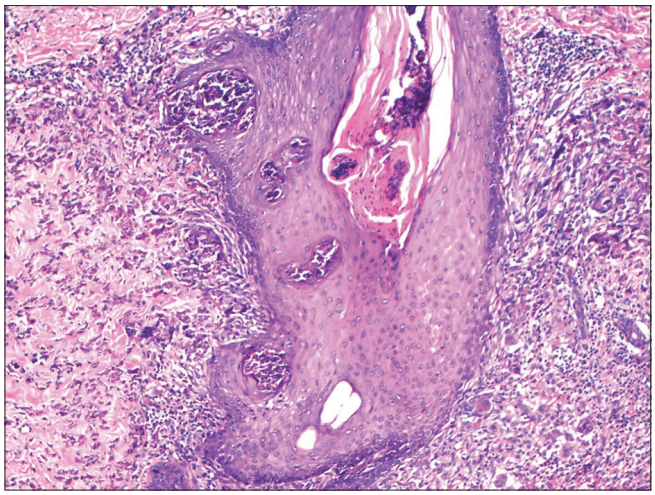

Figure 6: Short fragmented basophilic fibers mixed with inflammatory cells seen extruding epidermis (H and E ×400)

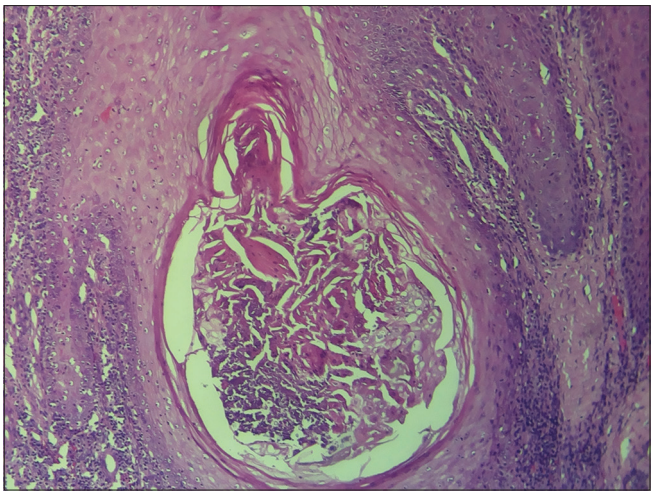

Figure 7: Granulomatous infiltration engulfed by follicular unit in tuberculosis verrucosa cutis (H and E ×400)

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.[8] Recently, the receptor for advanced glycation endproducts has been suggested to play a role in the pathogenesis of acquired reactive perforating collagenosis by modulating the collagen–keratinocyte interaction and keratinocyte migration.[9]

Some authors have described yet another type of transepidermal elimination where necrotic and altered dermal material gets incorporated in the follicular lumen, followed by slow elimination to the surface. This process is the hallmark of perforating folliculitis, but may also be seen in infective and noninfective granulomatous conditions such as lupus vulgaris and Jorge Lobo's disease (through infundibular epithelium), respectively.[10,11]

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.[12]

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.[13]

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.[14] 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:[14] 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]

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Conflicts of interest
There are no conflicts of interest.

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