

Disorders of Transepidermal Elimination

Part 1

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Transepidermal elimination (TE) is a mechanism whereby foreign or altered constituents can be removed from the dermis. This process involves unique morphologic alterations of the epidermis, which forms a channel and thereby facilitates extrusion of the desired dermal components. The phenomenon of TE may occur as a primary process characterizing disorders, such as elastosis perforans serpiginosa and reactive perforating collagenosis. Occasionally, TE may occur as a secondary phenomenon. Well-known examples are perforating granuloma annulare and pseudoxanthoma elasticum.

Disorders of Transepidermal Elimination

The human skin is a complex organ in which the dermal and epidermal units function together in complex cellular interactions in response to various stimuli. Specifically, many foreign or altered biologic materials present in the dermis will incite such a series of events aimed at eventual dissolution, isolation, or removal of these objects via the epidermis. Dermal "foreign material" may be the consequence of inflammation, metabolic alterations, neoplastic cells, or external substances.

There are several mechanisms whereby dermal foreign material can be transported to the surface of the skin. Mehregan,¹ a pioneer in this field, differentiated three basic categories. In type 1, nonmotile cells such as erythrocytes or small inert particles (eg, hemosiderin) elicit minimal or no dermal reaction. These particles can be trapped between epithelial cells and carried upward to the surface during epidermal turnover. In type 2, larger cells, such as motile cells (eg, leukocytes) or organisms such as *Treponema pallidum* may actively migrate into the epidermal

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spaces and hence be carried upward. From the point of view of the dermis and epidermis, types 1 and 2 are relatively passive processes and have been termed "transmigration." This phenomenon is relatively common and is often an incidental finding. Once on the surface, the material is desquamated along with the adjacent corneocytes.

Type 3, however, involves active epithelial-dermal connective tissue interaction and is a purposeful, directional mechanism whereby dermal foreign components are actively eliminated through the epithelium. This process was observed by Freudenthal,² who observed small particles of amyloid being expelled through the epidermis in 1930. Mehregan formulated this phenomenon, termed it "transepidermal elimination" (TE), and supported the concept with an excellent series of observations of various pathologic entities.³ He succinctly defined this process as

characterized by varying degrees of pseudoepitheliomatous hyperplasia of the epidermis or follicular epithelium. Elongated tongues of newly formed epithelium extend into the corium surrounding the irritating material. Once the material is partially or completely taken into the proliferating epithelium, it is slowly moved upward by the force of maturing keratinocytes and eventually eliminated. A continuous flow and elimination of foreign material to the surface will result in formation of multiple transepithelial perforating canals.

The fact that a material was initially present in the dermis and subsequently arrives at the epidermal surface does not necessarily imply TE. For instance, foreign bodies or altered dermal components, which elicit a strong inflammatory reaction that ultimately leads to epithelial necrosis with purulent draining

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TABLE 1. Disorders of Transepidermal Elimination

Disorders in which TE is a constant feature
Elastosis perforans serpiginosa
Penicillamine
Osteogenesis imperfecta
Marfan's syndrome
Ehlers-Danlos syndrome
Acrogeria
Down's syndrome
Cutaneous sclerosis
Reactive perforating collagenosis
Collagenome perforant verruciforme
Chondrodermatitis nodularis helicis chronica
Disorders in which TE may occur as a secondary event
Granulomatous disorders
Granuloma annulare
Necrobiosis lipoidica (diabeticorum)
Rheumatoid nodule
Sarcoid
Dermatoses with calcification
Pseudoxanthoma elasticum
Calcified tumor of hair follicle origin
Calcinosis cutis
Osteoma cutis
Infectious agents
Botryomycosis
Schistosomiasis
Chromomycosis
Other
Lichen nitidus
Papular mucinosis
Melanoma
Nevocellular nevus
Porokeratosis of Mibelli

material through a sinus, does not represent TE. The sine qua non of this mechanism resides in the fact that the epithelium does not suffer major structural alterations and returns to normal when the process of elimination is terminated through depletion and exhaustion of the material being eliminated.

The signal that induces these reactive changes in epidermal architecture is unknown. Both infectious and noninfectious granulomas, exogenous foreign bodies, and altered dermal components have been implicated as the inciting event.⁴ Regardless of the type of material, close proximity to the epithelium is extremely important; for example, subcutaneous granulomas and deep foreign bodies usually do not induce epithelial hyperplasia.⁴ This has been demonstrated in experiments by Marks and Scheiander, who injected carageenan into different levels of the dermis.⁵ Material placed below the level of the hair papillae did not induce hyperplasia. In contrast, placement above this zone resulted in epidermal proliferation. Thus it appears that in TE elimination, the target substance must reside within a certain dermal-epidermal interaction zone.

Diseases that primarily exhibit the phenomenon of TE are distinct nosologic entities with characteristic clinical morphology, usually an umbilicated papule with a central core or plug and a unique histologic presentation. Within the framework of this and a subsequent article, the formulation of this eliminating mechanism is highlighted and its characteristic disorders emphasized. Most cogently, elastosis perforans serpiginosa (EPS) and reactive perforating collagenosis (RPC) are elaborated in detail, since these are primary disorders of TE. In addition, we elaborate on other entities that secondarily express the phenomenon of TE, including perforating granuloma annulare; pseudoxanthoma elasticum; melanoma; nevocellular nevus; calcinosis and osteoma cutis; nevus sebaceous; infectious agents, such as botryomycosis, chromomycosis, and schistosomiasis; necrobiosis lipoidica; chondrodermatitis nodularis helicis; papular mucinosis; cutaneous sclerosis; lichen nitidus; and rheumatoid nodule (Table 1).

Elastosis Perforans Serpiginosa

History

EPS was initially described by Fisher⁶ in 1927 in a patient with a circinate papular eruption on the neck. Histopathologic examination revealed a bluish-staining amorphous plug perforating through the epidermis. At that time, it was thought to be an atypical case of Kyrle's disease. Later, Lutz,⁷ in 1953, presented a 21-year-old man with irregularly shaped keratotic ridges composed of closely set nodules present on both sides of the neck. He assumed the lesions to be of hair follicle origin and termed them "keratosis follicularis serpiginosa."

In 1955, Miescher presented a classical description of EPS located on the neck of a 10-year-old boy.⁸ The eruption consisted of closely set keratotic papules each with a central plug arranged into hyperkeratotic ridges. Individual papules appeared to involute within 5 months, but the basic process continued unabated forming new lesions. Histologic evaluation revealed acanthosis, hyperkeratosis, and enlargement of the epidermal rete ridges, with interruption of the epidermis by a keratotic plug extending from the epidermis into the dermis. The plugs consisted of elastic fibers that were histologically well-preserved lower in the plug, but the higher ascending fibers appeared to lose their staining properties. A homogeneous mass of elastic fibers (elastoma) was present in adjacent dermal papillae; these papillae were surrounded by epidermal rete ridges that protruded downward, giving the appearance of the epidermis trying to envelope and eliminate the elastic fibers. Miescher

interpreted the process to be secondary to poor nutrition, resulting in "necrobiosis" and expulsion of the altered elastic tissue. He coined the term "elastoma intrapapillare perforans verruciforme" to describe this process.⁸

In the same year, Beening and Ruiters⁹ reported a similar case in a 13-year-old boy with Down's syndrome. They considered this to be identical to the condition described earlier by Lutz⁷ and termed it "hyperkeratosis follicularis serpiginosa." This was probably the first reported case of EPS appearing in conjunction with a genetic disorder. There are a number of entities with which EPS has been associated.

Dammert and Putkonen¹⁰ were the first to propose the name "elastosis perforans serpiginosa," in 1958. Their rationale was based on the histologic observation that the elastosis is not necessarily "intrapapillare" nor of follicular origin and that EPS described the salient histopathologic and clinical features of the disease in the least number of words.

Clinical Characteristics

In Mehregan's comprehensive review of 101 cases of EPS,³ 90% of patients were younger than 30 years old, with the range of 5–84 years. The male to female ratio was 4:1, with the majority of patients Caucasians. Ninety-four percent of the lesions were on the nape and sides of the neck; 26% on the upper extremities; 15% on the face; and occasional lesions on the lower extremities and trunk.

The primary lesion in EPS is an umbilicated dome- or conical-shaped papule that is greyish-yellow in color and attains 2–3 mm in height and diameter (Fig. 1). Each papule contains a central plug, which on forcible removal leaves a bleeding crater. The configuration of the papules may be discrete or irregularly arranged into serpiginous outlines, attaining open or closed rings or even S-shaped figures; however, centrifugal extension of EPS is not a feature of the disease. Depigmentation and even atrophy may exist in the center of these lesions. Eventually, when resolution occurs, the remaining skin usually appears normal but occasionally may have a slight pinkish hue. Nearby hair follicles may or may not be destroyed by scarring, and the overlying skin can appear similar to an area treated with diathermy.¹¹ Usually this condition is asymptomatic but may be quite pruritic at times.

Histology

EPS has a characteristic appearance when stained with hematoxylin and eosin or stains for elastic fibers

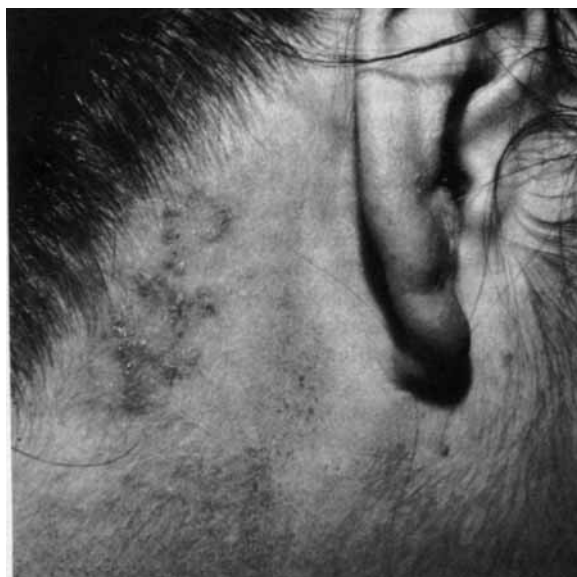


FIG. 1. Elastosis perforans serpiginosa (EPS) on the nape of the neck of a woman. The serpiginous configuration of umbilicated papules is well demonstrated.

(Verhoeff–van Gieson, acid orcein–Giemsa, or aldehyde fuchsin). The most significant histologic alterations include the presence of a canal filled with fibrous material extending from the dermis, through the entire epidermis, and communicating to the surface, where it is at its widest diameter (Fig. 2). The location of the channels may be peri- or trans-follicular.¹¹ Where the canal crosses a follicle, it tends to have multiple openings at the surface. Openings are usually occupied by a plug containing a mixture

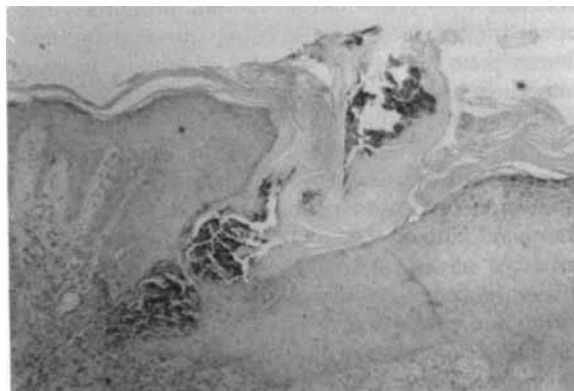


FIG. 2. Histopathology of EPS. The epidermal channel can be seen as a spiral in longitudinal section. Within the channel are altered eosinophilic elastic fibers. (H & E, $\times 100$)

of keratinous debris and bluish amorphous crust. The peripheral portion contains keratinous material, and a central portion of dense bluish-staining "necrobiotic" material consists in part of degenerated epithelial cells and pyknotic nuclei of inflammatory cells. Also present within the central area are many brightly staining eosinophilic fibers. The fibrous material occupies a tortuous channel and in cross section may occupy small, round, cystic spaces within the epidermis that appear to lie above one another, giving the appearance of a spiral seen in longitudinal section.¹² These spirals are not epidermal appendages: there are no connections with hair follicles or sweat ducts seen on serial section.

The epidermis immediately surrounding the perforating canal is composed of flattened keratinocytes that appear to desquamate into the central plug. The nearby epidermis is acanthotic and produces small protruberances of epithelium into the upper dermis. These tongues of epidermis appear pseudoepitheliomatous and nonpallisading and are without a well-organized basement membrane.

The underlying dermis contains occasional foreign body granulomas of mononuclear phagocytes and multinucleated giant cells. When perilesional sections are stained for elastic fibers, there is a marked increase in the amount and thickness of fibers. Perilesional elastic fibers are seen extending vertically upward into dermal papillae and may lie adjacent to basal cells. In intervening areas between perforating canals, the superficial plexus of elastic fibers is relatively well-organized and appears normal. As one nears the perforating canals, a stream of connective tissue containing many altered elastic fibers is seen to enter the canals. The perforating elastic fibers extend to the surface of the lesion, where they can be seen adjacent to the parakeratotic stratum corneum. These fibers lose their characteristic staining properties and appear brightly eosinophilic using the acid orcein-Giemsa stain or yellow by the aldehyde fuchsin method. In contrast to elastic tissue, the amount of acid mucopolysaccharide in lesions of EPS is normal.

Ultrastructural abnormalities of the epidermis are restricted to the site where TE has occurred.¹³ Electron-microscopic examination of the dermis, on the other hand, shows elastic fibers organized into large strands or as an infiltrating substance interspersed between collagen bundles. Ill-defined structures are seen to run parallel to the axis of the elastic fiber, indicating a possible lack of homogenous organization. This is in conjunction with a filamentous material that appears to be newly assembled elastic fibers. The elastic fibers in turn are surrounded by tubular-appearing microfibrils. Amino acid analysis revealed

that the amount of elastic tissue in one patient was elevated to 3.5 times that of the control, whereas the amount of collagen was only minimally elevated in lesional skin.¹³

In some respects, the lesional skin of EPS resembles that of the newborn or embryonic cutaneous epithelium due to several observations. Overall, lesional elastic tissue appears similar to newly formed elastic fibers. The majority of collagen fibers in EPS are of small diameter and thereby resemble embryonic skin, while EPS lesions contain a similar amount of dermal hydroxylation to the newborn epidermis.¹³

Association with Other Disorders

EPS occurs in association with a number of connective tissue disorders and a wide variety of other diseases. In fact, as many as one quarter of all cases of EPS may occur in association with other anomalies.³

Penicillamine-induced EPS. There are at least nine reported cases¹⁴⁻²² of EPS following the administration of therapeutic doses of penicillamine, 1.5-2.0 g daily for up to 6 years.^{23,24} In 1972, Guilaîne et al.¹⁴ described the first case of EPS following penicillamine treatment for Wilson's disease (hepatolenticular degeneration). Subsequently, seven additional cases occurring in similar situations have been reported.¹⁵⁻¹⁹ The remaining patient developed EPS following penicillamine treatment for cystinuria (congenital defect of homocystine synthetase).²⁰

Clinically, penicillamine-induced EPS appears similar to primary idiopathic EPS with annular or circinate, keratotic, umbilicated papules on the lower face, sides of neck, axillae, and antecubital fossae; however, one patient had a discoid, firm-bordered penile lesion with a central depressed area within the inner margin of the hyperkeratotic ring.¹⁷

Penicillamine-induced EPS can be differentiated from the idiopathic type by electron-microscopic and, at times, light-microscopic examination. Three morphologically distinct forms of elastic fibers in penicillamine-induced EPS may be discerned. First, there are lateral ("lumpy-bumpy") perpendicular buddings from elastic fibers present in the deep dermis, having the same diameter as the elastic fiber.^{14,16,17} Second, Kirsch and Hukill¹⁷ found intense eosinophilia of the elastic fibers that were penetrating the epidermis, while those in the reticular dermis were less eosinophilic or appeared even basophilic. Third, elastic fibers lack the peripheral fibrils and the alternating bands of dense and light layers normally seen within the cortex.

Hashimoto and others have found the collagen fibers to be abnormal in several cases of penicillamine-

induced EPS.^{18,21-25} Fibrils were irregular in diameter and up to five times larger in diameter than normal fibrils, while transverse sections showed the outer limits of the fibrils to be rather ragged. These collagen abnormalities resemble those found in Ehlers-Danlos syndrome type I and disseminated connective tissue nevi. On this basis, it appears that there is sufficient difference in the composition and morphology of elastic and collagen fibers to allow differentiation between idiopathic or penicillamine-induced EPS.

Bardach et al.¹⁸ described a patient who had not only drug-induced EPS but also a large pulmonary air cyst. Identical light- and electron-microscopic changes in both cutaneous and adjacent pulmonary elastic tissue suggested to the authors that the penicillamine had induced a disseminated "cutaneo-visceral elastosis."

The pathogenesis of penicillamine-induced EPS in Wilson's disease is unknown, but it is tempting to suggest an etiologic role for penicillamine in producing relative local cutaneous deficits in copper and thereby interfering with normal copper metabolism in the skin.²⁰ More plausible is the theory of Siegal²⁶ that penicillamine inhibits lysine-derived polyfunctional, intramolecular, cross-linking formation during elastin synthesis. Higher doses may also inhibit lysyl oxidase. These changes could conceivably underlie faulty elastin formation with lumpy-bumpy fibers bulging in all directions beyond the confines of the elastic fiber.

Osteogenesis Imperfecta. Osteogenesis imperfecta (OI) involves connective tissue components with manifestations that include pathologic fractures and characteristic blue sclera. There are at least seven cases of EPS reported to occur in patients with OI. Lesions of EPS may occur in localized typical sites, appearing on the neck in five patients²⁷⁻³⁰ and the antecubital fossa in two.^{27,31} Disseminated lesions have been reported. Kingsley³² described the occurrence of "extensive and symmetrical" EPS in a 19-year-old man with osteogenesis imperfecta. On examination, histologic and clinical appearances are identical to those of the idiopathic variety.

Marfan's Syndrome. There have been reports of EPS associated with two individuals having Marfan's syndrome,³³ and one with a high, arched palate who was otherwise normal.³⁴

Ehlers-Danlos Syndrome. In 1958, Meara³⁵ described a patient with Ehlers-Danlos syndrome with EPS in the antecubital fossa. Since the initial description, four similar cases have been described.³⁵⁻³⁸ London³⁶ presented a case of a 17-year-old man with EPS in conjunction with Ehlers-Danlos type IV (Sack-Barabas arterial ecchymotic type). Another case of EPS has been described by Christianson³⁹ in a

4-year-old boy who had a rupture of an anterior cerebral artery berry aneurysm but was otherwise normal. Eide⁴⁰ described EPS in association with fatal, widespread arterial rupture of the aorta, with dissection and elastosis of the endocardium and bronchiolar walls in a 30-year-old woman who was otherwise normal. Anning³³ described a similar case in an 18-year-old man with a dissecting aneurysm and EPS. It is conceivable that Christianson's case and the others occurred in individuals with an undiagnosed mild or incomplete form of Ehlers-Danlos type IV, since these individuals are prone to arterial rupture and hemorrhage.

Acrogeria. In 1980, Groot et al.⁴¹ reviewed the literature on acrogeria and found that 4 patients (all women) of a total of 19 (21%) also had EPS. These patients had typical lesions of EPS in both axillae, arms, neck, and thighs. Further, two patients had high, arched palates. Superficially, acrogeria may be similar to Ehlers-Danlos type IV, with conspicuous cutaneous blood vessels and easy bruising, but it is different in that there are neither gross ecchymoses nor intestinal hemorrhage in the former.

Down's Syndrome. Beening and Ruiter,⁹ in 1955, described the first cases of EPS in association with Down's syndrome. Thus far there have been at least 15 patients described in the literature.^{3,9,42-46} Lesions of EPS in most cases have a similar morphology and appear to occur in similar sites to the idiopathic variety; however, one of us (J.E.R.) has described the occurrence of atypical EPS in four Down's patients, three boys and one girl.⁴⁵ Lesions initially appeared as classical bilateral, hyperkeratotic papules on the neck and upper extremities. Several years later the circinate papules were replaced with linear and retiform hypopigmented scars, several of which contained a hyperkeratotic papule at one end. Isolated single papules were also seen. Biopsy of a lesion at one end of a scar was consistent with EPS.⁴⁵

Whyte and Winkelmann⁴⁷ found the incidence of EPS in Down's to be 0 among 287 institutionalized patients, although our study revealed an incidence of approximately 1%.⁴⁵ The chronicity of EPS in Down's can be exemplified by a 21-year follow-up of a patient who was refractory to innumerable treatments, including both topical and oral agents.⁴³ New lesions were still developing while old ones resolved, leaving hyperpigmented scars. This patient had an episode of scabies; interestingly, all mites recovered were within the skin lesions of EPS.

Crotty et al.⁴⁴ studied the biopsy specimens of EPS from the lesional skin on the thigh of a Down's patient compared with nonaffected buttock skin. Although there were no differences on light-micro-

scopic examination, electron-microscopic examination revealed the presence of abnormally fine fibrils (14.5 nm) in association with the collagen and elastin. They also saw globular formations (2,500 nm diameter) composed of fibrillar material (14.5 nm diameter) occurring in sites subjacent to the basal lamina. In contrast, nonaffected skin did not show these abnormalities. It therefore appears that EPS in Down's syndrome may differ in its natural evolution, duration, and ultrastructural appearance from the idiopathic type.

Cutaneous Sclerosis. Barr et al.⁴⁸ recently described the first report of EPS in association with morphea. A 16-year-old woman with morphea presented with arcuate keratotic papules in the antecubital fossae that were found on histologic examination to be typical of EPS. In 1981, a report was published of EPS in association with systemic scleroderma.⁴⁹ Both patients had never been treated with penicillamine. It has been postulated⁴⁸ that these represent examples of perforating morphea-scleroderma on the basis of the abnormal elastic fibers in the perforation in continuity with abnormal elastic fibers within the sclerotic foci. At this time it would seem prudent to consider this an epidemiologic association rather than a discrete entity of perforating dermatoses.

Disseminated EPS. Disseminated EPS has been reported in six patients with Down's syndrome,^{45,46} one individual with bilateral palmar simian creases who was otherwise normal,⁵⁰ and one patient with osteogenesis imperfecta.³²

Miscellaneous Conditions. There are numerous other defects, both cutaneous and systemic, that are tenuously associated with EPS,³⁹ including case reports of Rothmund-Thompson syndrome,⁴⁷ bone defects, keratosis pilaris, ichthyosis, keratoderma of the palms and soles, hyperpigmentation, ecchymoses, alopecia, congenital cataract, small stature,³⁹ and folliculitis ulerythematosus reticulata.⁵¹ In Christianson's review of 30 cases³⁹ he found that keloids occurred following biopsy in 8. Catterall⁵² later confirmed this. There have been two interesting cases of EPS involving the ear, one in an 11-year-old boy with the ear as the sole site of involvement and the other in a 12-year-old boy with lesions on the ear in conjunction with other lesions elsewhere.⁵³

Genetics of EPS

The association of EPS with certain genodermatoses is striking, and figures have ranged from 26%³ to 37%.⁵⁴ MacCaulay presented a patient with EPS lesions that appeared on one arm to be followed by a strikingly symmetric lesion of EPS on the other arm.

It was theorized that symmetry of lesions of EPS would possibly indicate a genetic or acquired defect *in utero*, with the expression of pathology being prior to the 18th day of gestation.⁵⁵ Woerdeman⁵⁶ reported the first familial occurrence of EPS in a girl and her two brothers. A leukocyte chromosomal evaluation performed on the girl had normal results. Her parents and two other brothers were normal.

Recently, Ayala and Donofrio⁵⁷ reported two brothers with classic idiopathic EPS on clinical and histologic examination. There was no family history of any heritable disorders of connective tissue disease. Seventeen of 36 total family members were examined, and no associated diseases nor other cases of EPS were found. They postulated that since there have been no examples of vertical transmission of EPS reported and since there are now two families in whom EPS has occurred in the siblings, the mode of inheritance may be autosomal recessive.

Diagnosis

Identification is based on the characteristic clinical appearance with verrucous papules containing a central plug and histologic presentation of perforating elastic fibers through an epidermal channel as described earlier. Main⁵⁸ described a quick diagnostic procedure whereby lesions of EPS are scraped superficially with a scalpel and a smear made on a slide that is then stained with Giemsa stain. This Romanofsky stain induces the elastic fibers to appear bright red with a basophilic periphery. Although this diagnostic test may be specific for EPS and possibly other disorders of elimination, further studies to indicate specificity of this diagnostic technique are required.

Treatment

In most cases EPS is largely refractory to treatment and does not appear to be affected by any associated disorders. It usually resists destructive therapies. Rosenblum⁵⁹ used a liquid nitrogen spray technique with a wide-field spray and treated the lesions of EPS for 8 seconds with complete thawing in 20 seconds. Two treatments 7 days apart resulted in complete resolution of all lesions without scar formation. These lesions had been refractory to intralesional and topical steroids. Favorable therapies in other reports have included cellophane tape stripping,^{3,47} Dichlorotetrafluoroethane cryotherapy,⁴⁷ and application of solid carbon dioxide.¹⁹ More therapeutic failures than successes have been reported, however, and include topical and intralesional steroids,^{19,53} keratolytics,⁵³ and vitamin E (300 mg daily).⁵⁰ In considering treatment modalities for EPS, one must be cognizant of a high incidence of keloid formation (27%) when these

individuals have biopsy specimens taken.³⁹ Unfortunately, the incidence of keloids following treatment attempts is unknown. On the whole, most individuals must learn to live a peaceful coexistence with their lesions until the lesions resolve spontaneously due to some unknown stimulus.

Reactive Perforating Collagenosis

History

Reactive perforating collagenosis was first described in an excellent succinct report in 1967 by Mehregan.⁵⁹ His patient was a 6-year-old girl with an unusual epithelial response to superficial trauma. At 9 months of age, she experienced numerous discrete papules located over the extremities, many in a linear distribution, suggesting Koebnerization of the lesions. Histologic observations led Mehregan⁵⁹ to suggest the name "reactive perforating collagenosis" (RPC).

Clinical Characteristics

Clinically, RPC starts as a 1-mm papule that evolves over 3–4 weeks to 6 mm in size and occurs often in sites exposed to trauma (Fig. 3). The papules become umbilicated and contain a central plug of horny material that can be removed with a curette only with some difficulty, often leaving a bleeding crater. With time the central umbilication becomes shallower and the plug is eliminated. By 2 months, the lesions disappear completely, leaving a scar or area of hypopigmentation. Although each individual lesion has a finite life span, a person may have recurrent lesions that erupt over time, persisting for as long as 37 years.⁶⁰

A total of 47 patients with RPC have been described (Table 2). Approximately 56% were male patients and 44% were female patients. Onset (when indicated) was prior to 1 year of age in 18% and during childhood in 58%. Only 10 patients were reported with an onset during adulthood (older than 18 years of age), and they appear to constitute a separate group. The extremities are involved in 100% of reported cases, predominantly on the extensor aspects. Specific sites include the extensors of the hand in 58% of patients, the trunk in 40%, and the face in 27%. The vast majority (66%) of patients related onset of the lesions to trauma, usually insect bites and scratches, although precipitation from acne lesions⁶¹ or even corporal punishment⁶² have been reported. Only two patients specifically denied relationship to trauma.^{62,63}

Lesions of RPC can be induced experimentally and may be site-dependent (extensor aspect preferred). Bovenmeyer⁶⁴ first reported successfully inducing lesions in a 4-year-old girl. Using the extensor surface

of the left forearm, he was able to produce lesions by scratching the skin with a 25-gauge needle. Neither a tongue blade nor a needle prick was effective in inducing lesions in a similar site. Since then, several authors^{61,65–67} have been able to induce lesions in the presacral area, upper back, and extensors of the wrist, forearm, and fingers using a variety of methods, including pinprick, scratch, and superficial abrasion with a 4-mm punch. Sites where lesions could not be produced in experiments are the upper thigh,⁶⁴ scapula,⁶⁵ and flexor forearm.⁶³ Cold has been reported to exacerbate the total number of lesions in four patients,^{64,65,68} and four patients reported "intolerance" to cold.⁶⁵ One patient,⁶⁹ however, reported worsening of the eruption in spring.

Histology

The histopathology of RPC varies with the age of the lesions, and step sections must be performed on all specimens to document the presence of TE of collagen.⁵⁹ Sections of early nonumbilicated lesions show perilesional epidermis to be acanthotic. In the center there is a widened dermal papillae containing bluish connective tissue confined to the upper dermis. There is no underlying inflammatory infiltrate, while the overlying epidermis is thinned and the stratum corneum has a thin layer of parakeratosis.

On examination of older umbilicated lesions, a cup-shaped crater containing a plug, which is parakeratotic, with degenerated collagen and numerous exocytic inflammatory cells is visible. Masson's trichrome and phosphotungstic acid-hematoxylin stains for collagen reveal that the central plug consists of refractile hyalinized and altered collagen that is eliminated in a transepidermal fashion. Since the direction of elimination is perpendicular to the epidermis, the collagen fibers can be easily seen within the plug and in numerous small perforations within the underlying epidermis. The epidermis of the lateral wall of the crater is slightly acanthotic with hypergranulosis and hyperkeratosis. The upper dermis shows a minimal phagocytic and lymphocytic infiltrate with a slight increase in vascularity,⁵⁹ and some authors have reported the additional presence of reactive granulation tissue.⁶¹

On examination of resolving lesions of RPC,⁵⁹ a much smaller, shallower crater containing predominantly parakeratotic keratin with only small foci of degenerated collagen is visible. At the base of the plug, the epidermis is almost regenerated. Here the malpighian cells appear to contain abundant cytoplasm with a large amount of glycogen in larger cells; however, the granular layer is absent and the basal

TABLE 2. *Reactive Perforating Collagenosis: Reported Cases*

Case No.	Author	Sex	Age at Presentation	Age at Onset (Years)	Type of Trauma	Parental Affected Sites	Unaffected Areas	Consanguinity
1	Kanan ⁶⁵	M	Early chldhd	26	Scratches and abrasions	Face, hands (dorsa), feet	Trunk, palms, soles	Positive
2	Kanan ⁶⁵	F	Early chldhd	28	Scratches and abrasions	Face, hands, feet (dorsa)	Trunk, palms, soles	Positive
3	Kanan ⁶⁵	M	Early chldhd	20	Scratches and abrasions	Hands & feet	Trunk, palms, soles	Positive
4	Kanan ⁶⁵	M	Early chldhd	40	Scratches and abrasions	Hands & feet	Trunk, palms, soles	Positive
5	Kanan ⁶⁵	M	Early chldhd	32	Scratches and abrasions	Hands & feet	Trunk, palms, soles	Positive
6	Kanan ⁶⁵	M	Early chldhd	32	Scratches and abrasions	Hands & feet	Trunk, palms, soles	Positive
7	Kanan ⁶⁵	F	Early chldhd	24	Scratches, abrasions, & mosquito bites	Hands & legs	Trunk, palms, soles	Positive
8	Mehregan ⁷⁹	F	9 months	6	Superficial scratches elbows, knees	Dorsa of hands, forearms	Trunk, palms, soles	NS
9	J. Weiner ⁷⁹	F	Early infancy	11	Superficial scratches arms and legs	Scalp, hands (dorsa)	Trunk, palms, soles	NS
10	J. Weiner ⁷⁹	M	Early infancy	6	Superficial scratches arms, legs, and face	Scalp, hands (dorsa)	Trunk, palms, soles	NS
11	Mehregan ¹	NS	Chldhd	Adult	Superficial scratches legs, scalp, trunk	Hands (dorsa), arms	Palms, soles	NS
12	Mehregan ¹	NS	Chldhd	Chldhd	Superficial scratches scalp, trunk	Hands (dorsa), arms, legs	Palms, soles	NS
13	Mehregan ¹	NS	Adult	Adult	Superficial scratches scalp, trunk	Hands (dorsa), arms, legs	Palms, soles	NS
14	Mehregan ¹ (siblings)	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms, legs bites	Trunk, palms, soles	NS
15	Mehregan ¹	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms, and legs	Trunk, palms, soles	Negative
16	Mehregan ¹ (siblings)	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms & legs bites	Palms, soles, upper thighs	NS
17	Mehregan ¹	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms & legs	Palms, soles	NS
18	Mehregan ¹	NS	Chldhd	Adult		Scalp, hands (dorsa), arms, legs, trunk	Palms, soles	NS
19	Mehregan ¹ (siblings)	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms, legs bites	Trunk, palms, soles	NS
20	Mehregan ¹	NS	Chldhd	Chldhd	Scratches and mosquito bites	Hands (dorsa), arms, legs	Trunk, palms, soles	NS
21	Bovenmyer ⁶⁴	F	4 years	6	Cat scratches, insect bites	Face, extensor legs, forearms, buttocks	Palms, soles, upper thighs	Negative
22	A. Weiner ⁶²	M	1 year	6 on one occasion	Sites of corporal punishment	Face, extremities, trunk	Palms, soles	NS
23	A. Weiner ⁶²	F	18 mnths	8	Not constantly obtained	Face, extremities, trunk	Palms, soles	NS
24	Mohri ⁶³	M	20	20	None	Elbows, not linear	Rest of body	NS
25	Shitara ⁷³	NS	NS	Adult	NS	NS	NS	NS
26	Miwa ⁷⁴	NS	NS	Adult	NS	Hands, elbows, buttocks	Palms, soles	NS
27	Nair ⁶⁰	M	10	51	NS	Extensor extremities with Koebner	Trunk, palms, soles	Negative
28	Nair ⁶⁰ (father)	M	3	40	NS	Dorsa hands, extensor extremities face, scalp, palms, soles (all over)	Mucosal	NS
29	Nair ⁶⁰ (children)	F	3	12	NS	Extensor extremities and trunk	NS	Positive
30	Nair ⁶⁰ (children)	F	5	10	NS	NS	NS	Positive
31	Nair ⁶⁰ (children)	M	NS	1½	NS	Extremities	NS	Positive
32	Fretzin ⁶¹	F	5	24	Insect bites, acne papules	Arms, legs	NS	NS
33	Jillson ⁶⁹ (siblings)	M	1	1	NS	Back of hands, arms, elbows, knees	Trunk, palms, soles	NS

TABLE 2. Continued

Case No.	Author	Sex	Age at Presentation	Age at Onset (Years)	Type of Trauma	Parental Affected Sites	Unaffected Areas	Consanguinity
34	Jillson ⁶⁹	M	1	4	NS	Back of hands, arms, elbows, knees	Trunk, palms, soles	NS
35	Poliak ⁶⁶	F	Black adult	41	NS (on dialysis)	Extensor extremities	Trunk, palms, soles	NS
36	Poliak ⁶⁶	F	Black adult	51	NS	Extensor extremities, trunk, face	Palms, soles	NS
37	Poliak ⁶⁶	M	Black adult	80	Scratch (on dialysis)	Extensor extremities, trunk, face	Palms, soles	NS
38	Poliak ⁶⁶	F	Hispanic adult	57	Scratch (on dialysis)	Extensor extremities, trunk, face	Palms, soles	NS
39	Poliak ⁶⁶	M	Hispanic adult	77	NS	Extensor extremities, trunk, face	Palms, soles	NS
40	Poliak ⁶⁶	M	Black adult	65	Scratch (on dialysis)	Extensor extremities	Trunk, palms, soles	NS
41	Cochran ⁷⁶	F	Black adult	41	NS (on dialysis)	Trunk, arms, central back	Palms, soles	NS
42	Cochran ⁷⁶	F	Black adult	36	NS (on dialysis)	Extensor arms, upper back	Palms, soles	NS
43	Cullen ⁶⁷	F	Black chldhd	19	Insect bite, scratch	Dorsa hands, extensor forearms, trunk, thighs	Palms, soles	NS
44	Pasricha ⁶⁸	M	3	23	NS	Extensor extremities	Trunk, palms, soles	NS
45	Bingul ⁷¹	F	3	11	Cat scratch	Dorsa hands, extremities, extensors, flexors	Trunk, palms, soles	NS
46	Nyfors ⁷² (Siblings)	M	1 month	3	Tree scratches	Begin on trunk, then face, extremities, dorsa hands	Palms, soles	NS
47	Nyfors ⁷²	M	5	7	NS	Extremities, face, dorsa hands	Trunk, palms, soles	NS

NS, not significant.

cell layer appears to be incompletely developed with a partially organized basement membrane. The remaining altered dermal collagen is eliminated through a narrow tunnel within the epidermis in the center of the lesion, the lining epithelium of the tunnel being well-organized. The underlying dermis shows slight vascularity and minimal inflammatory infiltrate.

Stains for calcium, elastic tissue, and acid mucopolysaccharide are negative in the plug and exhibit no increase in the dermal papillae at any stage. Similar light-microscopic features are seen in both naturally occurring lesions of RPC and experimentally induced lesions.⁶¹

Electron-microscopic examination of the epidermis in early lesions shows complete disappearance of the basal lamina. Desmosomes are intact, but bundles of normal-appearing collagen fibers appear interspersed within widened intercellular spaces.⁷⁰ Mohri⁶³ studied the dermis of a regressing lesion and found that the collagen was disrupted by large masses of fine filamentous material, accumulations of small vesicular bodies, and phagocytes.

As to the pathogenesis of this disorder, RPC lesions are almost always invoked by some sort of superficial trauma, although interestingly deeper wounds, such as surgical incisions, do not induce lesions.⁶¹ The

pathogenetic effects can be constructed as follows. In response to trauma, injury to dermal connective tissue occurs, resulting in alteration of papillary collagen. Reactive epithelial hyperplasia in the adjacent epidermis occurs, while the directly overlying epidermis becomes thin and shows multiple foci of disruption through which altered collagen and sparse inflammatory cells are eliminated. As underlying dermal material is transferred from the dermis to the surface, the epidermis sinks into this area, which was formerly occupied. The process of TE continues unabated until the entire supply of altered collagen



FIG. 3. Linear Koebner phenomenon in lesion of reactive perforating collagenosis (RPC). Individual morphology of RPC consists of umbilicated papules in a linear arrangement on the dorsa of the extremities. (Courtesy of Scott W. Bronstein, M.D.)

TABLE 3. Cases of RPC with Adult Onset

Author	Onset	Sex	Diabetes	Nephropathy	Dialysis	Retinopathy	Pruritus	Other
Mehregan ¹	Adult	—	—	Yes	Yes	—	—	
Mohri ⁶³	20 yrs.	—	—	—	—	—	—	Wegener's granulomatosis
Poliak ⁶⁶	Adult	F	Yes	Yes	Yes	Yes	Yes	
	Adult	F	Yes	Yes	No	Yes	Yes	
	Adult	M	Yes	Yes	Yes	Yes	Yes	
	Adult	F	Yes	Yes	No	Yes	Yes	
	Adult	M	Yes	—	No	Yes	Yes	
Cochran ⁷⁶	Adult	M	Yes	—	Yes	Yes	Yes	
	41 yrs.	F	Yes	Yes	Yes	Yes	Yes	RPC cleared with UVB
	36 yrs.	F	Yes	Yes	Yes	—	Yes	RPC treated with UVB

is exhausted. At this point, a repair phenomenon occurs in which epidermal reconstitution closes off the eliminating channels. The keratotic plug at the surface gradually sloughs off via normal epidermal turnover, leaving minimal or no scarring.

Association with Other Disorders

Conditions associated with RPC include: ricketts,⁷¹ ricketts-like bone changes,⁵⁹ bilateral coxa vera,⁷² Wegener's granulomatosis,⁶³ lichen amyloidosus,⁷³ rheumatoid arthritis,⁷⁴ and Henoch-Schonlein purpura.⁷⁵

There appears to be a specialized subset of RPC, defined by adult onset and the presence of diabetes mellitus. These cases are summarized in Table 3. Ten cases of RPC with onset in adulthood (older than 18 years of age) were recorded in the literature.^{1,63,66,76,77} Of these 10 patients, 8 had diabetes mellitus (7 of the 8 had diabetic nephropathy), 1 had chronic renal disease and was on dialysis (it was not stated whether diabetes was present),¹ and 1 had Wegener's granulomatosis.⁶³ Of all the patients with diabetes and RPC (a total of nine),^{60,66,76} eight fall into the group defined above (with onset of RPC in adulthood), while the sole diabetic with onset at 10 years of age had only "mild" diabetes. Thus using the criteria of onset of RPC in adult years, the physician must be alert to the concomitant presence of diabetes mellitus, which, if present, may be severe with diabetic nephropathy. Patients with diabetes and RPC had lesions resembling classical RPC in all aspects, except for age of onset and a tendency to be pruritic although dialysis-induced pruritus may be responsible in some cases. Cullen⁶⁸ was able to treat the pruritus successfully with UVB light. Poliak⁶⁷ was able to induce skin lesions experimentally in two of his patients with diabetic adult onset RPC. Lesions of RPC differ from

so-called Kyrle's disease on the basis of many criteria (discussed below), such as the presence of linear Koebnerization, the tendency to remain discrete, and the presence of TE of collagen.

Genetics of RPC

There were 25 patients (52%) with RPC who had affected family members (mostly siblings). Of these 25 patients, 10 had a history of parental consanguinity. Considering this genetic background, the evidence leads us to postulate an autosomal recessive mode of inheritance, although further genetic studies are necessary to delineate more clearly the mechanism of transmission.

Treatment

Treatment of this disorder is often frustrating and unrewarding. Recently Cullen⁶⁷ treated a 25-year-old woman with tretinoin 0.1% cream, which decreased the total number from 12–21 to 0–2 lesions. Oral forms of treatment have included: antibiotics,^{60,64,78} such as erythromycin and tetracycline; oval vitamin A 100,000 Units daily^{67,79}; oral prednisone 20–50 mg/day⁶⁷; methotrexate, with some response⁶⁴; and oral proteolytic enzyme AnanaseTM, 200 mg tid.⁶⁷ Other agents have included topical keratolytics^{72,79}; topical steroids with or without occlusion⁶⁹; intralesional steroids⁷⁹; and ultraviolet light B in diabetic patients on renal dialysis.⁷⁶ Isotretinoin undoubtedly would be of some benefit, especially since it affects keratinization and prior responses to topical tretinoin have been encouraging.

Collagenome Perforant Verruciforme

Collagenome perforant verruciforme (CPV) was first described by Woringer and Laugier in 1963.^{80,81}

A 19-year-old man had numerous cuts and lacerations after falling through a glass roof. Three weeks later, flesh-colored hyperkeratotic papules developed in the sites of lacerations consisting of 2–5 mm erythematous papules arranged in linear or grouped configurations. Remission was evident without treatment within 3 months, with almost complete disappearance of the lesions. Histologic examination showed papillomatosis and hyperkeratosis with a channel disrupting the epidermis. Within this space were basophilic nonelastic collagen bundles extruding from the dermis to the surface of the skin. Later, Delacretaz and Gattlen⁸¹ described another case of CPV in a 6-year-old boy who sustained trauma to his right thigh. Three weeks later, a 2 × 4.5-cm plaque appeared at the site of injury, consisting of 30–40 papules, each with a central keratinous plug. The plaque resolved within 3 months. They presented two other atypical cases—a 12-year-old boy following injection of a corticosteroid and a 30-year-old woman following removal of a mole—calling these examples of TE of traumatically altered collagen.

Although CPV and RPC are similar in many aspects, they differ in several ways.⁸² CPV evolves in a single episode, without reported familial background (although the number of reported cases is extremely small). RPC does not always have a history of specific immediate trauma, appears mostly on the dorsa of the fingers, and has onset in childhood or in adult diabetics and can continue up to 37 years (although individual lesions resolve in 1–2 months).⁶⁰ Until the number of reported cases of CPV has increased, one cannot generalize about the true nature of this entity and probably best regard it as a separate but very closely related entity to RPC.

Chondrodermatitis Nodularis Helicis Chronica

Chondrodermatitis nodularis helicis chronica (CNHC) probably represents a distinct separate entity with TE as the primary pathologic event. In 1980, Goette⁸³ and Cruz⁸⁴ independently proposed that the pathogenesis of CNHC was due to this form of elimination. CNHC almost exclusively affects Caucasian males in their middle years. Typical appearance is a well-defined ½-cm nodule that appears pink to pearly-grey. The lesions appear most often on the helix and rarely on the anthelix (Fig. 4). There is an adherent central crust that, on removal, will reveal a small erosion or cup-shaped depression with a pinpoint channel. These lesions may be bilateral and can be quite tender, especially with pressure.

Bard⁸⁵ reviewed 24 cases in which the adjacent

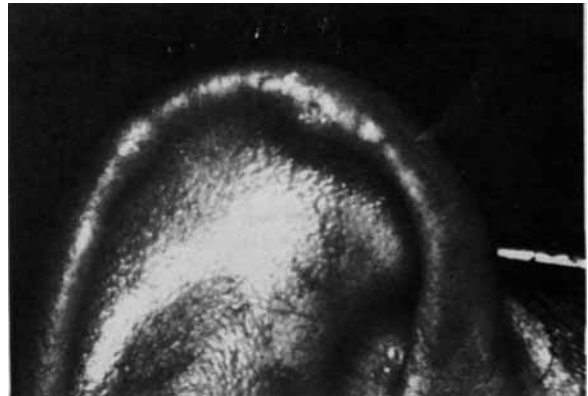


FIG. 4. A painful nodule with a central plug is present on the helix of the ear, consistent with chondrodermatitis nodularis helicis chronica (CNHC). (Courtesy of Detlef K. Goette, M.D.)

epidermis was acanthotic or exhibited pseudoepitheliomatous hyperplasia with a central crater-like depression and channel (Fig. 5). The underlying dermis contained a homogeneous fibrinoid material in a milieu of altered dermal collagen. The collagen bundles were swollen and intensely eosinophilic. Elastic fibers often showed degeneration where dermal changes were most prominent. Granulation tissue, a chronic granulomatous and inflammatory infiltrate, telangiectasias, and solar elastosis could be seen in the majority of specimens. There was evidence of underlying perichondritis. Changes in the cartilage were found by Bard⁸⁵ to be inconsistent, whereas Goette⁸³ found 10 of 17 biopsy specimens to contain “degenerated” cartilage. Abnormal collagen may be the inciting factor in the pathogenesis. It has been



FIG. 5. Histopathology of CNHC demonstrating transepidermal elimination TE of altered dermal collagen. (×100) (Courtesy of Detlef K. Goette, M.D.)

proposed that CNHC is a primary disorder of TE, representing a perforating actinic granuloma.⁸³ Anatomy, vascular deficiency, trauma, and actinic damage may also be important in the pathogenesis.

Drug Names

isotretinoin: Accutane
penicillamine: Cuprimine, Depen
tretinoin: Retin-A

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Phototherapy

Phototherapy has lately resumed a respectability lacking since the turn of the century and the days of Finsen. In medicine, phototherapy and photochemotherapy are routinely used in certain skin diseases and neonatal jaundice, and there is much interest in the use of lasers with porphyrin for the phototherapy of internal neoplasia. In the cosmetic sector, solaria are in vogue for skin tanning (the UK Health and Safety Executive has issued a guidance note for operators); and white-skinned people continue to expose their bodies to natural sunlight despite the correlation between solar exposure and skin cancer. Holiday resorts in Britain have examined the potential of large solaria—airhouses accommodating 20 or more persons in which the concave inner surface provides a diffuse reflecting surface—to compensate for sunless summers. Most tanning facilities, however, are made for individual use. The lamps may emit much more spectral power than the equivalent wavebands of the solar spectrum; consequently, the risk of burning and photosensitisation is higher than with sunlight, especially as satisfactory radiometry is difficult with multitube arrays.—*Skin photobiology. Lancet.* 1983;1:566.