Delineating the Perforating Dermatoses: Case Reports and a Review of the Literature

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Abstract

Perforating dermatoses (PD) are a rare group of papulonodular skin diseases with a distinct central keratotic core representing the transepidermal elimination of an altered dermal substance. Diagnosis is established via biopsy and histopathologic evaluation. The primary PD are best categorized into four groups: reactive perforating collagenosis (RPC), acquired perforating dermatosis (APD), elastosis perforans serpiginosa (EPS), and perforating calcific elastosis (PCE). The primary PD can be differentiated based on the perforating substance, the distribution of the lesions, and their unique associations. Diagnosis of a PD should prompt screening for underlying systemic disease. Treatment of the PD is often difficult, but numerous reports have shown success. Here we present our case reports and a thorough literature review incorporating all identified case reports and studies found on PubMed as of July 2015.

Introduction

Perforating dermatoses (PD) represent a rare group of papulonodular skin diseases with a distinct central keratotic core. The core represents the transepidermal elimination of an altered dermal substance.1 Diagnosis is established via biopsy and histopathologic evaluation. Whereas primary PD are diseases chiefly characterized by transepidermal elimination, secondary PD are a group of unrelated disorders in which transepidermal elimination is a minor phenomenon of another disorder.1 The primary PD are best categorized into four groups: reactive perforating collagenosis (RPC), acquired perforating dermatosis (APD), elastosis perforans serpiginosa (EPS), and perforating calcific elastosis (PCE). The primary PD can be differentiated based on the perforating substance, the distribution of the lesions, and their unique associations (Table 1).1 Diagnosis of a PD should prompt screening for underlying systemic disease. Treatment of the PD is often difficult, but numerous reports have shown success. Amongst the PD, a shared histopathologic sequence occurs, and findings depend on the stage of evolution.1 First, a hyperkeratotic plug or crust forms. The plug enlarges, inducing surrounding epidermal hyperplasia and occasional dyskeratosis. Inflammator cell aggregates may be seen in the plug and adjacent dermis. In well-developed lesions, the plug contains the perforating substances: collagen, elastic fibers, amorphous degenerated material, and/or altered follicular structures. Special stains may be used to help identify the perforating substance. The precise pathogenesis of the PD is unknown. It is postulated that the primary PD may be due to abnormal dermal substances, whether genetically altered or acquired. Other theories question whether the PD represent a unique pathologic process or are simply a result of mechanical exposure of dermal substances.1 Various classifications of the PD have been used in the literature, and various names have been reported for each entity. This has led to ambiguity and confusion. A useful classification scheme of all PD was proposed by Patterson in 1984:2

1. Perforation as an incidental histologic finding
2. Perforation associated with other cutaneous and systemic disorders (secondary PD)
3. Disorders chiefly characterized by perforation (primary PD)

Even more numerous are the variations of the primary PD in the literature. The authors feel the best classification is outlined in Table 1 and will be discussed in this review.

Case Reports

Case 1

A 17-year-old Hispanic male presented with a three-year history of spreading “warts.” He denied pain, pruritus, or manipulation of lesions and requested treatment for cosmetic concerns. Past medical history was significant for asthma, allergic rhinitis, and medulloblastoma. He had attempted numerous over-the-counter treatments, including topical salicylic acid and cryotherapy, with no improvement.

Physical exam revealed skin-toned, dome-shaped papules with a central keratotic core overlying the knuckles. (Figure 1). The lesions were most numerous over the dorsal hands (Figure 1), elbows (Figure 2), and knees. A punch biopsy of a representative lesion on the elbow was taken (Figure 3). There was a cup-shaped invagination of acanthotic epidermis with a plug of keratin, collagen, and inflammatory debris. High magnification revealed vertically oriented collagen fibers undergoing transepidermal elimination. Verhoeff-van...
A punch biopsy was taken from the lower leg, screening labs were ordered, and the patient was started on desoximetasone 0.25% ointment bid. The biopsy revealed a channel through an acanthotic epidermis filled with a plug of amorphous, degenerated material with overlying parakeratosis and underlying neutrophils (Figure 6). Verhoeff-van Gieson stain failed to demonstrate perforating elastic fibers. Labs revealed a low hemoglobin and elevated alkaline phosphatase, AST, and ALT.

RPC is histologically characterized by a cup-shaped invagination of acanthotic epidermis containing a plug of vertically oriented collagen fibers, keratin, and inflammatory debris. The connective tissue surrounding the plug is typically unremarkable. After the plug falls off, the epidermis atrophies. There is no gold standard of treatment for RPC. Treatment is not necessary since lesions may spontaneously resolve and are largely asymptomatic. Yasmeen et al. compared treatment between 10 patients with RPC and report the most successful responses were with oral isotretinoin and topical tretinoin combined with emollients. Other treatments reported with varying levels of success include: topical steroids under occlusion, photochemotherapy, UVB phototherapy, cryotherapy, allopurinol, methotrexate, and electrical nerve stimulation. Despite all treatment regimens, RPC often recurs.

Acquired Perforating Dermatosis
APD is overwhelmingly the most common PD. This category includes all PD arising in adults that have been previously reported as acquired RPC, acquired EPS, Kyrle's disease, and perforating folliculitis, among others. The splitting of this group reflects the variable histologic morphologies found in lesions of APD depending on the stage of development. A biopsy may reveal perforating collagen, elastic fibers, amorphous degenerated material, and/or altered follicular structures.

The classification of APD has changed over time, and disagreement remains amongst authors. Kyrle's disease was first described by Kyrle in 1916 as "follicular et parafolliculairis in cutem penetrans" in a diabetic female with generalized hyperkeratotic nodules. Kyrle's disease is sometimes used synonymously with APD, and some describe it as the end stage of excoriated hyperplastic nodules of folliculitis. Patterson et al. propose that perforating folliculitis and acquired RPC are subsets of Kyrle's disease. Others suggest perforating folliculitis is not a specific disease, as perforation of follicles can occur in any folliculitis regardless of the etiology. The term "acquired perforating dermatosis" was first used by Rapini et al. in 1989. Kim et al. characterized the various APD lesions in a study of 30 cases as follows: KD-like hyperkeratotic papules, PF-like follicular infiltrating papules, EPS-like serpiginous hyperkeratotic papules, or RPC-like keratotic plugged umbilicated papules (most common: 66.7%).

APD occurs in middle-aged adults, with no gender or geographic predilection. In the largest study to date, Kim et al. report a mean age of onset of 55.5 years. APD generally presents as umbilicated papules and nodules with a central white keratotic core. The core is sometimes picked and physically removed by patients. Giant variants have been reported where lesions are 2 cm. Lesions can be found on any cutaneous surface, but the extensor lower legs are most common, and many cases are generalized and diffuse. Koebner's phenomenon is occasionally
CaCl₂ is used to treat dermatitis and pruritus. But there has been a report of conjunctival and mucous membranes, palms, and soles are generally spared, (hypothyroidism, hyperparathyroidism), amorphous, degenerated material and elimination of calcified collagen and elastic tissue. Histologically, APD shows cup-shaped peridermal and subepithelial contents, which may appear as perforation. Therefore, they advocate obtaining continuous imaging of the evolving lesions to guide understanding of the patho-histologic mechanism; however, that is not possible at this point. APD is proposed to originate from pruritus resulting in chronic scratching and epidermal hyperplasia. A similar process is seen in prurigo nodularis, a common concomitant condition seen with APD. This theory is supported by the presence of Koebnerization. Fujimoto et al. propose that scratching exposes keratinocytes to advanced glycation end product (AGE)-modified extracellular matrix proteins, specifically collagen types I and III. The interaction leads to terminal differentiation of keratinocytes via AGE receptor (CD 36) and results in keratinocytes along with glyced collagen moving upward through epidermis.

Other studies suggest that the interaction of keratinocytes with altered structural proteins plays a role. Fibronectin is increased in both the serum and lesional skin of diabetic and renal failure patients with APD. Fibronectin is an extracellular matrix protein involved in epithelial cell signaling, movement, and differentiation. It plays a role. Fibronectin is increased in both the serum and lesional skin of diabetic and renal failure patients with APD. Fibronectin is an extracellular matrix protein involved in epithelial cell signaling, movement, and differentiation. It binds collagen IV and keratinocytes and may induce epithelial proliferation and transsepidermal elimination. One study identified type IV collagen from the basement membrane as the specific type of collagen eliminated. Other proteins overexpressed in APD include: transforming growth factor beta-3 (TGF-β3), matrix metalloproteinase-1 (MMP-1), and tissue inhibitor of metalloproteinase-1 (TIMP-1); however, this may simply reflect normal wound healing in these sites. An abundance of neutrophil remnants has been found in early lesions of APD, leading some to believe that proteolytic enzymes, such as collagenase and elastase, play a role. The enzymes may transgress the epidermis and digest extracellular matrix components, leading to destruction of anchoring fibrils and collagen IV, ultimately resulting in their elimination. Another theory pinpoints diabetic microvasculopathy as the culprit. Microvasculopathy leads to dermal necrosis by hypoxia. This would incite the elimination of the necrotic dermal material. This mechanism is supported by positive periodic acid-Schiff staining of thickened blood vessel walls in the upper dermis in diabetic patients with APD. Other proposed hypotheses involve deposition of substances such as calcium salts, uric acid, hydroxyapatite, or silicon, and metabolic disturbances leading to alteration of fibers, prompting their elimination. Another theory proposes a role of abnormal vitamin A or D. Anecdotal success of antibiotics for treatment has led to the idea of a possible infectious etiology. There are also familial reports of APD. One family in India has 22 members afflicted with so-called Kyrle's disease over five generations. Unique features are also noted within the affected family members, including eye changes and palmoplantar lesions. There are no clinical studies conducted regarding treatment for APD, and therefore there is no gold standard. Conventional treatments have been derived from case reports. Kim et al. report 93.3% of patients responding to topical steroids and 80% responding to antihistamines to decrease pruritus. Control of pruritus and treating any underlying disease is the key to treatment. Other commonly reported treatments include intralesional steroids and topical retinoids. Other reported treatments include: UVB, PUVA, oral retinoids, and mexitetrate. Some dialysis patients have been cured of disease after transplant. Allopurinol has recently emerged as a useful treatment of APD. Hoque et al. successfully treated four patients with a giant variant with allopurinol. The theory behind the use of a xanthine oxidase inhibitor is that it reduces oxygen free radicals, which cause collagen damage and skin necrosis. Allopurinol is also reported to inhibit neutrophil activity. Antibiotics have been used to treat culture-negative APD. Clindamycin is reported to have cleared a case after Kasiakou et al. noted the inflammatory histologic findings and suspected an infectious cause, thought to be anaerobic bacteria. Doxycycline has also been used successfully in cases of APD. Metronidazole was successfully used in another case in which biopsy showed inflammatory infiltration in the lesion. As opposed to clindamycin, metronidazole does not have any anti-inflammatory properties, which supports an infectious etiology. A vitamin D₃ synthetic analogue, tacalcitol, used in the treatment of psoriasis has also been used to treat APD. Tacalcitol inhibits the proliferation of keratinocytes and simultaneously modifies inflammatory mediators. Since APD lesions contain significant inflammation and epidermal hyperplasia-like psoriatic lesions, Escribano-Stable et al. decided to use this treatment on a case refractory to topical steroids and antihistamines. They report achieving complete remission after two months.

**Elastosis Perforans Serpiginosa**

Lutz first described EPS in 1953 and termed the disease “keratosis follicularis serpiginosa” based on the unique configuration. In 1955, Miescher characterized the specific pathologic finding of perforating elastic fibers and termed the disease “elastoma intrapapillare perforans verruciform.” Dammert and Putkonen coined the current name in 1958. EPS can either be idiopathic (most
It is reported that 40% of EPS patients have an underlying genetic disorder involving fibrous tissue including: Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan syndrome, pseudoxanthoma elasticum (PXE), scleroderma, Rothmund-Thomson syndrome, acrogeria, and Moyamoya disease. An extensive history and physical exam should be performed when establishing the diagnosis. However, pediatric dermatologists collectively do not routinely perform genetic testing on the sole basis of EPS in an otherwise healthy child.

EPS has a predilection for males in a 4:1 ratio and most commonly occurs in the second decade of life. EPS is characterized by 2 mm to 5 mm, keratotic papules in a serpiginous or annular configuration. Rings of papules may be up to several centimeters in diameter. Lesions are most commonly located on the lateral neck but can also appear on the face and flexural extremities. There are isolated case reports of EPS on the axilla and glans penis. EPS is typically asymptomatic.

Diagnosis is established through biopsy. EPS lesions show eosinophilic elastic fibers and other basophilic debris filling tortuous channels that span from the papillary dermis to the epidermis. In adjacent dermal tissue there are many inflammatory cells including lymphocytes, macrophages, and multinucleated giant cells and also altered elastic tissue. Elastic fibers are best highlighted by special stains like Verhoeff-van Gieson, which stains elastin black. Additionally, altered elastic tissue is then eliminated through macrophages, and multinucleated giant cells and also altered elastic tissue. Elastic fibers are best highlighted by special stains like Verhoeff-van Gieson, which stains elastin black. Furthermore, elastic tissue is then eliminated through macrophages, and multinucleated giant cells and also altered elastic tissue. Elastic fibers are best highlighted by special stains like Verhoeff-van Gieson, which stains elastin black.

Pass et al. documented the first drug-induced EPS in a patient with Wilson's disease on long-term treatment with penicillamine. EPS has also been documented in patients taking penicillamine for cystinuria. Thirty-three percent of patients on high-dose therapy will develop EPS. EPS has also been recognized in patients on low-dose treatment for rheumatoid arthritis, primary biliary cirrhosis, and scleroderma. Still, penicillamine-induced EPS accounts for only 1% of all EPS cases. The elastic fibers seen in these cases have a distinct lumpy appearance with lateral buds. Penicillamine is hypothesized to disrupt desmosine crosslinks within elastin by inhibiting the enzyme lysyl oxidase. The damaged elastic tissue is then eliminated through the epidermis. Theories regarding the role of copper metabolism in EPS are debunked by the presence of EPS in patients taking penicillamine for diseases other than Wilson's. Penicillamine has also been shown to cause other cutaneous changes like pseudo-PXE and acquired cutis laxa by damaging elastic tissue. Furthermore, penicillamine has been found in the skin of an EPS patient 25 years after discontinuation of the drug. This may explain why discontinuing penicillamine does not prevent more EPS lesions from developing.

Most theories for EPS pathogenesis focus on altered elastic fibers. A hypothesis presented by Fujimoto et al. through in vitro studies demonstrated that elastic fibers interact with and influence the differentiation of keratinocytes. They propose that altered elastic fibers accumulate in the dermis and induce upward movement and differentiation of keratinocytes via elastin-receptor protein, 67 kDa. Expression of 67 kDa elastin-binding protein has not been reported in normal epidermal keratinocytes but is overexpressed in elastin-rich connective tissue. Other reports have implicated immunologic dysfunction like that seen in Down syndrome. Reports of EPS implicating dysfunctional epidermal barrier from mechanical trauma, chemicals like calcium chloride salt water, and scabies are best classified as APD.

As with other perforating disorders, there are no clinical trials or gold standards for treatment. Several treatments are described with mixed efficacy and poor long-term success. Destructive modalities attempted include cryotherapy, curettage, electrocautery, dermabrasion, excision, tape stripping, topical salicylic acid, and CO2 laser. Caution is advised, as there is risk of scarring with these modalities. Furthermore, treatment is not necessary, as EPS remains localized and asymptomatic. Mixed results are also reported using topical and intralesional steroids, UVB, erbium-doped yttrium aluminum (Er-YAG) laser, and pulsed dye laser. Successful case reports are described using topical imiquimod, topical calcipotriene ointment, and systemic isotretinoin. Topical tazarotene was used with remission of lesions that recur when medication was discontinued. Phenotin was tried in one case with no success. There are also reports of successful treatment of resistant cases with photodynamic therapy and topical allium cepa-allantoin-pentaglycan gel.

Perforating Calcific Elastosis

PXE is an exceedingly rare disease and is both histologically and clinically similar to PXE. Some authors argue PCE is a localized form of PXE, while others say it is a separate entity. PCE is acquired and localized, whereas PXE is an autosomal-recessively inherited, multi-organ systemic disease. PCE has also been reported as "peribulbarial perforating PXE." The first case of PCE was diagnosed as EPS with PXE by Schutt in 1965. Lund and Gilbert reported PCE as a separate entity in 1976, terming it "perforating PXE," and Lever and Schaumburg-Lever coined the term "PCE" in 1989.

PCE occurs most commonly in middle-aged, obese, multiparous African-American females. Woo and Rasmussen reviewed 22 cases of PCE and reported an 82% female preponderance with a mean age of onset of 43 years. PCE presents as yellowish verrucous plaques with keratotic papules scattered at the periphery. Lesions are usually exclusively distributed on the abdomen, especially periumbilically; however, there is a report of lesions on periareolar skin in one patient and on the axilla of another. Histologically, PCE shows short, thick, basophilic, calcified elastic fibers residing in the lower dermis. EPS, in contrast, reveals non-calcified elastic fibers in the upper reticular and papillary dermis. The pathogenesis of PCE is unknown. Prazan et al. propose lesions originate from repeated stretching of the skin from multiparity, obesity, ascites, or surgery.

No successful treatments have been identified for PCE. Failed treatments include topical tretinoin and topical steroids.

Secondary Perforating Dermatoses

Secondary perforating dermatoses are a group of unrelated disorders in which a substance is transspidermerally eliminated as a minor phenomenon of another disorder. As with the primary PD, the epidermis becomes hyperplastic, surrounds the substance being eliminated, and causes the upward extrusion via keratinocyte maturation. Secondary PD include substances that are endogenous (chondrodermatitis nodularis helicis, hematomas, calcinosis cutis, lichen nitidus, papular mucinosis, amyloidosis), exogenous foreign materials (silica, wood, suture), infectious organisms (chromoblastomycosis, leprosy, schistosomiasis, tuberculosis, leishmaniasis), granulomas (granuloma annulare, necrobiosis lipoidica, sarcoidosis, rheumatoid nodules, tophaceous gout), and neoplastic cells (melanoma, Paget's disease, mycosis fungoides, pilomatricoma, nevus sebaceous).

Perforation in these dermatoses is best considered an incidental finding.

Conclusion

The PD have been classified and named in numerous ways in the literature, which has led to confusion. This thorough literature review attempts to compile all available case reports and studies of the PD from PubMed. The primary PD are best organized into four groups. Diagnosis of a PD should prompt the evaluation for underlying disease. Further studies are needed to elucidate effective treatment options.

References


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