Erosive Pustular Dermatitis: A Manifestation of Immunosenescence? A Report of 8 Cases

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Keywords

Cicatricial alopecia · Erosive pustular dermatosis · Barrier function · Immunosenescence · Hair immunology · Immune dysfunction

Abstract

Erosive pustular dermatosis (EPD) is a rare condition of the scalp and legs that is marked by crusted erosions or superficial ulcerations that may result in scarring alopecia and chronic wounds. The condition predominantly affects elderly female as compared to male patients. Its pathogenesis remains poorly understood. The majority of the cases in the literature are from the United Kingdom and continental Europe. In this series, we present 8 North American patients with EPD of the scalp, one of whom also had involvement of the legs and another with the involvement of the face. All our patients were advanced in age and had a predisposition to chronic actinic damage, which are common characteristics of EPD previously reported in the literature. We hypothesize that immunosenescence leads to an aberrant immune response to wound healing and, along with other factors such

as a loss of the normal epidermal barrier, ultraviolet damage, and hormonal factors, may contribute to the development of this condition.

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Introduction

Erosive pustular dermatosis (EPD) is a rare, but likely underreported condition with a predilection for the chronically sun-damaged scalp and, less commonly, the extremities, particularly the lower legs. There are also isolated reports of the condition presenting on the face [1] and mucosa [2].

EPD was first described by Burton in 1977 [3] and then by Pye et al. in 1979 [4]. The exact cause of the disease is still not fully understood. The characteristic finding of the disease is the development of sterile pustules and chronic crusted erosions. There is often seropurulent material underlying the crusted plaque. This condition has a slowly progressive and sometimes relapsing course. When eventual healing does occur, there is typically residual scarring

Table 1. Patient characteristics and potential trigger

Age, Sex years	Race	Potential trigger	Location of lesions	Microbiology	Treatment	
94	F	C	AK used imiquimod	Scalp	Heavy growth <i>Staphylococcus aureus</i>	Triamcinolone, mupirocin, cephalexin
89	F	C	SCC of scalp	Scalp, leg	Heavy growth <i>Staphylococcus</i> species	Clobetasol, doxycycline, mupirocin
86	M	C	Hypertrophic AK – had EDC	Scalp, face	Rare growth <i>Staphylococcus</i> species	Clobetasol
82	F	C	SCC and KA	Scalp	Heavy growth <i>Staphylococcus aureus</i>	Cephalexin, mupirocin, minocycline, dicloxacillin, fluocinonide
82	F	C	BCC	Scalp	Heavy growth <i>Staphylococcus aureus</i>	Tacrolimus, mupirocin, topical dapsone, clobetasol, intralesional kenalog, minocycline, cephalexin
79	M	C	AFX and SCC	Scalp	<i>Proteus mirabilis</i> , beta hemolytic streptococci, group G	Betamethasone dipropionate, ciprofloxacin, topical clindamycin, intralesional kenalog
70	F	C	SCC in situ and SCC	Scalp	Mixed flora	Topical clindamycin, clobetasol
87	F	C	Mohs for SCC	Scalp	No growth	Clobetasol

C, Caucasian; F, female; M, male; AK, actinic keratosis; SCC, squamous cell carcinoma; EDC, electrodesiccation and curettage; KA, keratoacantoma; BCC, basal cell carcinoma; AFX, atypical fibroxanthoma.

alopecia in affected areas of the scalp, or scarring with post-inflammatory hyperpigmentation on the legs [1, 5]. Triggering factors include various forms of damage to cutaneous integrity including physical and topical therapy, surgery, malignancy, and trauma [5–11]. Acute pustulosis of the scalp is a newer variant of the disease that has been recently described [12].

Patients

Our patient population consisted of 6 females and 2 males, all of Caucasian background. The mean age of the patients was 84 years, with the youngest patient being 70 years old and the oldest 94 years old. They were followed at a single hair disorders referral center at Kaiser Permanente Northern California. All of our EPD patients had a history of non-melanoma skin cancer or premalignant condition associated with chronic sun damage (Table 1). The skin of the scalp was almost uniformly atrophic. Suspected triggers varied amongst our patients. Our oldest patient of 94 developed crusted eroded lesions at the site of fluorouracil cream field treatment for a cluster of actinic keratosis of the scalp. Four of the patients were known for squamous cell carcinoma. One patient also had involvement of the anterior tibia region and another patient had involvement of the face. The clinical presentation was varied from scale crust to exudative ulcers with sterile pustules

(Fig. 1a–c). All patients had a bacterial and fungal culture as well as a punch biopsy performed. Fungal cultures were negative in all patients. A majority of patients had infection with *Staphylococcus* species.

Histological examination in all cases showed a mixed dense dermal infiltrate consisting of lymphocytes, neutrophils, and plasma cells overlying an atrophic or eroded epidermis with hyperkeratosis and parakeratosis. Chronic sun damage of the patients' skin was clearly evident with the presence of solar elastosis (Fig. 1d).

Treatments included manual debridement of the crust as well as use of high-potency topical corticosteroids, intralesional corticosteroids, topical tacrolimus, topical dapsone, and topical and oral antibiotics. A summary of patient characteristics and treatments is listed in Table 1.

Discussion

Diagnosis of Exclusion

Diagnosis of EPD requires a high clinical suspicion in the appropriate clinical context and is a diagnosis of exclusion with the differential diagnoses including primary cutaneous bacterial and fungal infection and superinfection of a preexisting dermatological condition with causative agents such as *S. aureus*, *S. epidermidis*, *Pseudo-*

Fig. 1. Morphological and histological presentation of Erosive Pustular Dermatitis. **a** Draining pustules, dry crusting and erosion. **b** Hemorrhagic crust with surrounding erythema and hypopigmentation on right lower cheek. **c** Dry serous crusting with light erythema on areas of scarring alopecia. **d** Histological findings include epidermal atrophy, acantholysis, and focal erosion with dense mixed inflammatory infiltrate. **e** Well-demarcated erythematous plaque with superficial erosion on the right lower leg.

monas spp., human herpes virus, *Candida albicans*, and *Aspergillus ochraceus*. Noninfectious entities to consider in the differential include autoimmune blistering disorders (pemphigus vulgaris, pemphigus foliaceus, and cicatricial pemphigoid) and atrophic lichen planus, pyoderma gangrenosum, and malignancy such as squamous cell carcinoma. Pathology showing a mixed dense inflammatory infiltrate and coexisting actinic damage is supportive of the diagnosis of EPD.

Immune and Barrier Dysfunction

The immune system is thought to decline in fidelity and efficiency with age, resulting in an increased suscep-

tibility to infectious diseases and pathological conditions relating to inflammation or autoreactivity. This overall change in immunity is termed “immunosenescence.” The process in the elderly is thought to be the opposite of what happens after birth where the inborn or innate immune response is gradually complemented by the learned adaptive immunity. With immunosenescence, the immune system becomes less able to respond to foreign antigens and maintain tolerance to self [13–17]. The term “inflamm-aging” has been coined to describe the phenomenon of chronic low-level innate immune activation leading to increased oxidative stress. Reactive oxygen species are believed to be the driving force in the pathogenesis of

most if not all major diseases of non-resolving inflammation [18] and are also associated with immunosenescence [19].

The aging immune system is known to have less tolerance to self and an increased rate of autoreactivity. Hair follicles with their characteristic low-surface major histocompatibility complex (MHC) are classified as an immune privilege site, a title mainly attributed to several vital organs including the brain, testes, and cornea [20]. EPD may have an association with other autoimmune diseases [1, 21]. Recently, regulatory T cells (Treg), important for immune homeostasis, have been shown to preferentially localize to hair follicles [22, 23]. Interestingly, the Treg in association with hair follicles play an important role in establishing immune tolerance to commensal bacteria during the neonatal period [24]. Whether this critical function of Tregs and their ability to control unnecessary immune reactions is maintained later on in life is yet to be determined. Furthermore, complicating our understanding is the variation that exists in the microbiome population of elderly versus young individuals [25].

The barrier function of the skin decreases with age, as the result of age-related epidermal atrophy, elastolysis, and reduced collagen biosynthesis as well as increased collagen fibril fragmentation and degradation [26]. Alteration of skin architecture and epidermal barrier defects result in an increased susceptibility to cutaneous infections and deeper bacterial penetration of the epidermis [27, 28].

Given the clinical and pathologic features of EPD [29], signified by an aberrant inflammatory response to wound healing, chronic inflammation, and a predilection to infection in the elderly, it is intriguing to consider whether this condition is a manifestation of immunosenescence. Chemotherapeutic drugs known to lower the host immune function have also been shown to be associated with the development of EPD [30]. Interestingly, on the other end of the spectrum, EPD has been reported to occur in neonates who have incurred trauma to the scalp [31].

Other inflammatory cutaneous conditions that have been proposed to be manifestations of immunosenescence include pruritic papules of the elderly, prurigo nodularis, and Grover's disease [32]. The pro-inflammatory effects of innate immune cells have also been implicated in bullous pemphigoid, another condition seen almost exclusively in the elderly [33].

Ultraviolet Exposure

One of the hallmarks of EPD is chronic actinic damage. Oxidative stress on the epidermal keratinocytes and

fibroblasts cells may have a contributory role in the development of EPD.

A possible explanation for the development of EPD is that chronic ultraviolet exposure leads to the modification of intracellular components. These modified factors are kept hidden internally until cell damage in the form of malignancy, trauma, etc. occurs. In genetically susceptible individuals, these factors, once released into their environment, activate the innate and adaptive immune systems. The age-related over-activation of the innate immune system described above, combined with the inability to properly heal wounds, may contribute to the chronic presentation of EPD. That the driving force of the disease is the exaggerated immune response is evidenced by a recent report of concomitant elevation of serum matrix metalloproteinase-3 in patients with EPD [34] and multiple cases that have been successfully treated with immunosuppressive therapies [2, 35–37]. Amplification of the immune reaction can also be triggered by topical treatments used in dermatology including imiquimod, 5-fluorouracil, and ingenol mebutate, which have been reported to cause EPD in chronically sun-damaged patients [8, 38, 39].

Hormonal Influence

As the majority of the affected patient population consists of postmenopausal women, the hormonal state of the patient may play a role in the pathogenesis of the disease. It is well known that, following menopause, the skin becomes thinner and exogenous estrogen therapy can reverse the process by increasing dermal collagen content [40–43]. The need for optimal gonadal steroid hormones for proper wound healing has been described in both human and mouse models [44–47]. Zhou et al. [48] have recently shown that female mice without ovaries had delayed cutaneous wound healing, with a thinner epidermis and fewer proliferating keratinocytes in the wound bed. Ashcroft and colleagues [49, 50] demonstrated that intrinsic aging is associated with excessive inflammation and protease activity [49] and topical estrogen can accelerate wound healing by reestablishing a proper immune response in elderly patients [50]. Ample evidence exists regarding the role of estrogen in protecting against oxidative stress [51–52].

EPD of the Leg and Venous Stasis

EPD of the leg is an under-recognized condition with nonspecific clinical and histological features. Most of the cases in the literature are associated with chronic venous insufficiency. Whether the venous insufficiency contrib-

utes to its development or is a coincidental finding is still not known. Stasis dermatitis secondary to chronic venous insufficiency is a common condition while EPD of the leg is rare even amongst these patients. Brouard et al. [53] reported that less than 0.5% of patients presenting to their leg ulcer clinics developed EPD of the leg. There are also reports of EPD of the leg presenting in the absence of stasis dermatitis [54]. We believe that, although the poor circulatory status in patients with venous stasis may impair the proper healing of EPD of the leg, the two entities have a divergent pathophysiology. These patients share an elderly age and long history of sun exposure as well as previous trauma in the site of EPD development, which are most likely the primary contributing factors in development of EPD of the leg.

Treatment

Treatments described in the literature and used in our patients address the underlying pathophysiology of immune dysregulation associated with poor wound healing in EPD. The mainstay of treatment is immunosuppression with topical superpotent corticosteroids or systemic prednisone. Other topical regimens that have been successfully used include topical calcineurin inhibitors [36, 55, 56]. Topical [57] and systemic dapsone [2] have also been used to address the abnormally exaggerated immune reaction in these patients. Retinoids, which suppress the immune system by normalizing the Toll-like receptor 2-mediated immune response, have also been effective in some cases [58, 59]. Retinoids also have the added benefit of reestablishing the collagen content in the dermis and thus promoting proper wound healing [60, 61]. EPD patients may also benefit from topical and sys-

temic estrogen therapy. As discussed above, estrogen has the benefit of increasing skin collagen content, thickness, elasticity, and hydration, which improves the rate of wound healing in postmenopausal women [50, 62]. Photodynamic therapy (PDT) has both been shown to trigger and treat EPD [63, 64]. A case series using aminolevulinic acid PDT was successful in treating 8 patients [65]. The authors of the study concluded that PDT with methyl aminolevulinate should be avoided because its increased lipophilic property and longer incubation period may have contributed to toxicity in their patients, thus triggering EPD.

Conclusion

As described in our series and in others, EPD may be a manifestation of immunosenescence in concert with other contributing factors such as loss of normal epidermal barrier, ultraviolet damage, and hormonal factors. A better understanding of the pathophysiology of EPD will help address this complex condition in the elderly and enable strategies for prevention, early recognition, and improved treatment.

Statement of Ethics

All subjects have given their informed consent and the study protocol was approved by the Kaiser Permanente Vallejo medical ethics committee.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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