Case report

Verruciform xanthoma in recessive dystrophic epidermolysis bullosa Hallopeau-Siemens

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Introduction

Epidermolysis bullosa (EB) is a group of genetically determined disorders characterized by blister formation of the skin and mucosa, in response to minor mechanical trauma.[1] Blistering is caused by mutations of genes encoding structural proteins crucial for the mechanical stability of the epidermo–dermal junction.[1,2]

Epidermolysis bullosa is divided into three major types according to the level of cleavage: Epidermolitic EB simplex, junctional EB, and dystrophic dermolitic EB.[2–7] The most comprehensive classification scheme, based on the recommendation of the Subcommittee of the National EB Registry (USA) and an international consensus group, has attempted to incorporate molecular and clinical findings and combine certain phenotypes that cannot be distinguished by modern molecular analyses.[3,4]

Dystrophic EB (DEB) is characterized by dermolytic cleavage and is the result of gene mutations for anchoring fibril protein, type VII collagen. In most cases, COL^7A^1 gene mutations have been identified.[1,2] These can be inherited in an autosomal-recessive and autosomal-dominant way. Recessively inherited types are generally more severe. Recessive dystrophic EB of Hallopeau-Siemens (RDEB-HS) is considered to be the most severe form of dystrophic EB, and it is usually accompanied by numerous complications including skin and mucosal tumors.[1,8–15]

Verruciform xanthoma (VX) is a relatively rare and benign lesion most commonly occurring on the oral mucose.[16–18] Extra-oral lesions, such as vulva and penis, have been reported.[17,19–21] Verruciform xanthoma rarely arises on the skin and is mostly in the anogenital region.[16,17,21,22] According to Atherton, VX can occasionally be observed in severe dystrophic EB, but only one documented case was found in the literature.[23,24]

Here we present a case of VX arising on frequently traumatized skin in a patient with severe RDEB-HS.

Case Report

We present a 20-year-old Caucasian female patient with severe RDEB-HS who was frequently hospitalized and regularly checked and treated at our department. Many complications had been observed. In spite of adequate diet and nutritional supplements, the patient was seriously malnourished and had chronic anemia. The patient underwent several esophageal dilatations because of esophageal structures. Owing to limb contractures and digital fusion the patient had operations on her hands and left foot.

At 18 years of age, the patient developed a papillomatous lesion on the dorsal aspect of the left foot (Fig. 1). Following a complete surgical excision, the histopathologic analysis revealed changes consistent with a diagnosis of pseudo-carcinomatous hyperplasia.

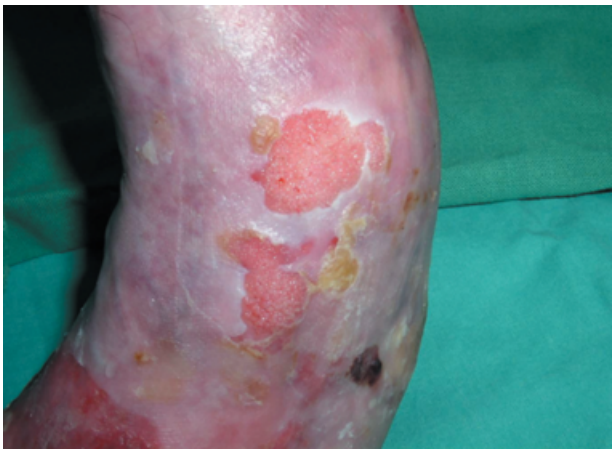

Figure 1 Two erythematous, well-demarcated, irregular plaque lesions with a papillomatous and verrucous surface on the dorsal aspect of the foot

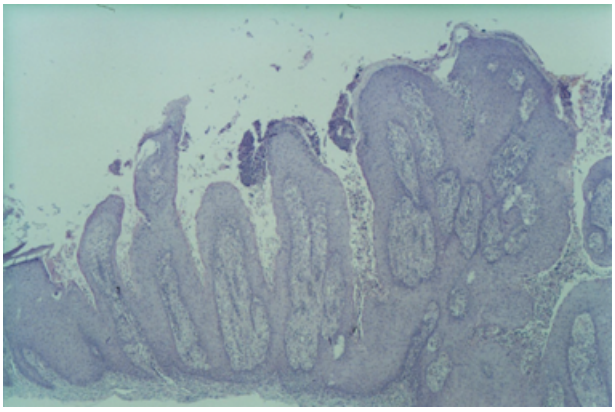

Figure 2 Thickening of the epidermis, hyperkeratosis and pronounced papillomatosis, with focal parakeratosis and an infiltrate of numerous neutrophils (hematoxylin-eosin stain, ×20)

Two years after the surgical excision, a slowly enlarging and asymptomatic lesion was observed on the dorsal aspect of the patient's left foot. The lesion did not respond to treatment with either topical antibiotics or corticosteroids under occlusion. The clinical picture consisted of two erythematous, fairly well-demarcated, irregular plaques with a papillomatous and verrucous surface. Excision and histologic examinations of the lesions were performed.

The histology was consistent with the diagnosis of VX and included the thickening of the epidermis, hyperkeratosis and pronounced papillomatosis (Fig 2). Focal parakeratosis with the infiltrate of numerous neutrophils was found on the epidermal surface. Infiltration with foamy histiocytes and prominent vessels was observed in the very elongated dermal papillae (Fig 3).

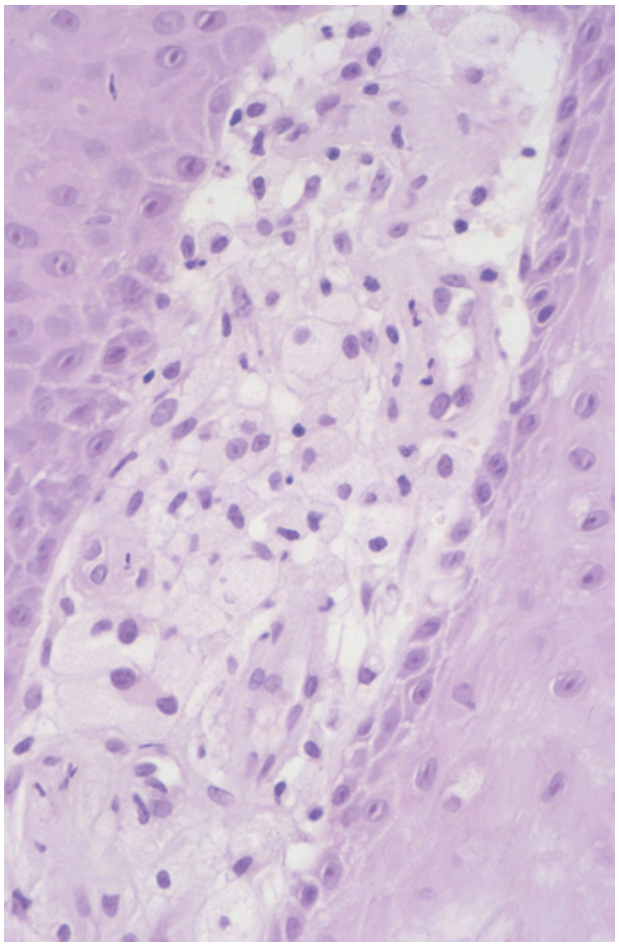

Figure 3 Infiltration with foamy histiocytes and prominent vessels in the very elongated dermal papillae (hematoxylin-eosin stain, ×100)

Discussion

Verruciform xanthoma is a relatively rare, benign lesion.[16–18] It was first described by Shafer, and clinically appears as an erythematous or yellow-tan hyperkeratotic plaque, pedunculated lesion or papillomatous tumor with verrucous or granular surface.[25-27]

The lesion is usually solitary.[22,26] The predilection site is the oral mucosa.[18,22,25] The most common location of VX on the oral mucosa is the gingival margin and other areas of the masticatory mucosa.[18,27] Extra-oral lesions, such as vulva and penis, have been reported.[19–21,28] Only rarely does VX arise on the skin; mostly in the anogenital region.[19,22,29]

The etiology of VX is not known, but it is considered to be a reactive condition.[18,19,24,26,27] Physical agents seem to play a preponderant role, although viral agents may occasionally be involved.[30] A case report was recently published regarding VX on the scrotum in association with human papillomavirus,

which was detected by electron microscopy, immunohistochemistry, and polymerase chain reaction.[30] Other authors did not detect human papillomavirus infection in their cases of cutaneous VX.[22,28]

The pathogeneses of VX is also unknown.[18,24,26,27] It has been postulated that epithelial damage and degeneration are the primary events initiating the development of the lesion.[24,26,31] The entrapped, degenerated epithelium might lead to the eventual formation of lipid droplets which are taken up by the dermal cells.[22,24,26,31] The factor initiating the entrapment and subsequent degeneration of the epithelium is not determined.[22,26] A local infection, irritation, and a trauma could be contributing factors.[26]

Alternatively, the xanthoma cells could be the result of a leakage of lipoproteins from small blood vessels with phagocytosis by dermal cells.[24] A histologic hallmark of VX foam cells might be derived from dermal dendritic cells.[22] According to some immunohistochemical and ultrastructure findings, xanthoma cells have been shown to be cells of the monocyte/macrophage lineage as well as fibroblasts and endothelial cells.[18,24,32]

Lipid metabolism is usually normal although multifocal verruciform xanthoma has been reported in the upper aerodigestive tract, bone marrow, and liver of a child with a systemic lipid storage disease.[31,33,34] Verruciform xanthoma can be sporadic or associated with inflammatory, autoimmune, immunodeficient, metabolic, neoplastic, or congenital diseases.[35] Only rarely does it occur as a secondary reaction in lesions with marked epidermal hyperplasia, such as epidermal nevus and inflammatory linear verrucous epidermal nevus.[26,28,36,37] It is a histologic finding very characteristic of (CHILD) naevi, it can also be observed in pemphigus vulgaris and it has been reported in a patient with lymphedema of the leg.[23,26,38]

There have been cases of VX occurring in patients following bone marrow transplantation and graft versus host disease (GVHD) developing after bone marrow transplantation.[29,39] Therefore, immunologically mediated damage to the epithelium was speculated to be related to the pathogenesis.[29,39] Meyers *et al.* reported VX in association with discoid lupus erythematosus.[40]

Histopathologic features are hyperkeratosis, acanthosis, and uniform elongation of rete ridges of the epidermis.[41] Proliferation of squamous epithelium covering the lesion have a verrucous, papillary or flat pattern.[18,27] Foam or xanthoma cells containing abundant cytoplasm are typically confined to the papillary dermis.[22,26,27] Periodic acid-Schiff (PAS) staining shows numerous foam cells that contain PAS-positive granules in cytoplasm.

Although epidermal atypia is not a characteristic finding, there have been cases of squamous cell carcinoma (SCC) and carcinoma *in situ* arising within VX.[19,29] Careful microscopic examination to detect irregular architectural and cytological atypia is therefore necessary.[19] Several biopsies should either be taken from larger lesions or lesions should be resected in order to reduce the risk of SCC development.[19]

Risk of cutaneous carcinomas in EB patients is well known and they usually arise in areas subject to repeated trauma, blistering and scaring.[9,11,12,42,43] The risk for development of cutaneous carcinoma is highest in DEB, most commonly in RDEB, but their appearance has also been described in junctional-EB.[44–46] Most of these tumors are SCC, but basal cell carcinoma, Bowen disease, Kaposi sarcoma, giant keratoacanthoma, and malignant melanoma may also occur.[8,9,11–14,42,44,47]

The mechanism of an early onset of SCC in patients with EB is unclear. Repeated trauma of the epidermis certainly plays a major role for cancer development and progression as well as reduced immune functions that have been confirmed in patients with EB.[48] Alterations in tumor suppressor genes have been demonstrated in SCC occurring in RDEB patients.[49]

Although the predilection site of SCC is traumatized skin, it can occur at other locations as well as on the oral mucosa and esophagus.[9,11,12,42] Squamous cell carcinoma in EB patients grows rapidly and metastasizes more frequently leading to high mortality rates in these patients.[8,9,11–13,42]

We would like to point out that patients with dystrophic forms of EB should be monitored regularly for the increased risk for skin and mucosal carcinoma. Verruciform xanthoma is a rare condition with a usually benign clinical course but malignant transformation has been described. As EB patients have an increased risk of development of SCC, VX should be excised in patients suffering from EB.

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