Development of Segmental Superficial Actinic Porokeratosis during Immunosuppressive Therapy for Pemphigus Vulgaris

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Sir,

Porokeratosis (PK) is a heterogeneous group of hereditary or acquired disorders of keratinization with a broad clinical spectrum and various aetiologies. Common to all PK is the typical histological feature of a cornoid lamella, which corresponds to the hyperkeratotic rim of slowly centrifugal spreading lesions (1). Several subtypes of PK have been distinguished based on size, localization and number of lesions. However, porokeratosis of Mibelli (PKM) and disseminated superficial actinic porokeratosis (DSAP) are the most common clinically encountered subtypes.

CASE REPORT

A 68-year-old woman with pemphigus vulgaris since 2007 had received systemic glucocorticosteroids together with azathioprine and mycophenolate mofetil, without sufficient control of the autoimmune disorder. A cyclophosphamide/dexamethasone pulse therapy at 4-week-intervals was initiated instead. Unexpectedly, within 9 months after initiation of the pulse therapy the patient developed multiple asymptomatic erythematous plaques 3–8 mm in size on the right leg (Fig. 1a). The lesions were characterized by slightly elevated margins with either atrophic centres or overlying hyperkeratosis (Fig. 1b). Histopathological examination showed a cornoid lamella with underlying vacuolated keratinocytes and absent granular layer indicative of porokeratosis (Fig. 2). Typical predilection sites for DSAP, such as lower legs and forearms, were not involved. There was no family history of DSAP.

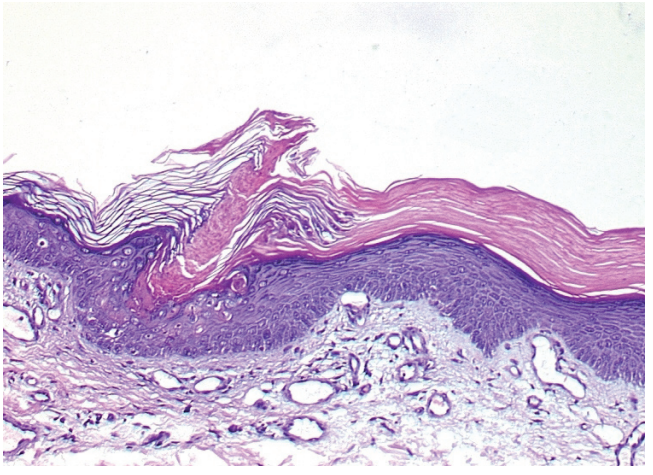

Fig. 2. Histology shows a cornoid lamella with underlying vacuolated keratinocytes and absent granular layer (haematoxylin and eosin ×40).

DISCUSSION

DSAP is an autosomal dominant disorder clinically characterized by symmetrical development of disseminated keratotic lesions predominantly on the lower extremities of middle-aged individuals. Ultraviolet (UV)-light exposure has been proposed as one of the triggering factors (1).

The presented case is unique because of the segmental development of DSAP in close temporal association to increase of immunosuppressive therapy. Immunosuppression has previously been considered as a triggering factor for the development of porokeratosis (2). Occurrence of porokeratosis has been described in transplant patients and in patients with primary or secondary im-

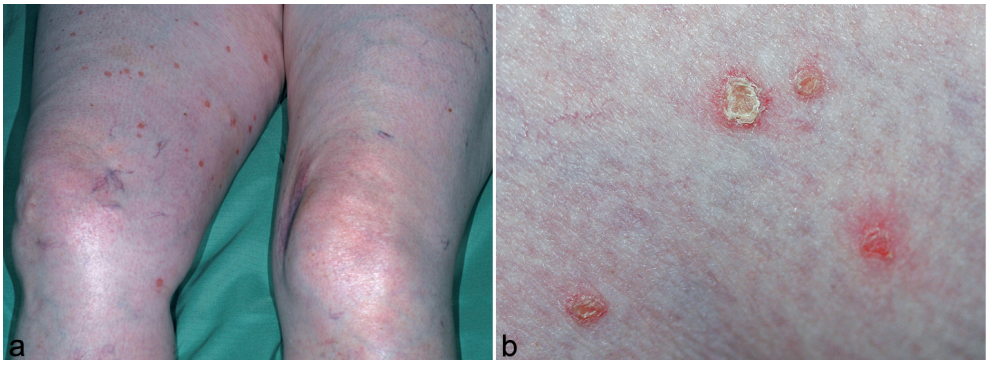

Fig. 1. (a) Disseminated superficial actinic porokeratosis in a segmental distribution reaching from the medial aspect of the right thigh to the calf. (b) Close-up view of asymptomatic, erythematous hyperkeratotic plaques, 3–8 mm in size.

mune deficiency syndromes, such as haematological malignancy and HIV infection, respectively (2). In the case of iatrogenic immunosuppression, the clinical course of PK may correlate with the dosage of immunosuppressive agents. Accordingly, two reports describe spontaneous complete resolution of PK after termination of immunosuppressive therapy (3, 4). Although a causal relationship between immunosuppressive therapy and the development of PK is conceivable, the underlying pathophysiological mechanisms remain unclear. One hypothesis is that local or systemic immune surveillance may be reduced by immunosuppressive therapy leading to insufficient detection and elimination of aberrant keratinocyte clones (1). Recently, gene expression analysis identified up-regulation of keratin genes involved in wound healing and genes essential for epidermal differentiation (e.g. S100 calcium-binding protein) as well as genes involved in the regulation of T-cell-mediated immune responses (5), the latter supporting the hypothesis that reduced immune-surveillance plays a role in the pathogenesis of DSAP.

Segmental lesions of DSAP are believed to be caused by genetic alterations of keratinocytes in early embryogenesis leading to altered activity of regulatory proteins (6). Two different forms of segmental manifestations of autosomal dominant dermatoses may be differentiated. First, type 1 segmental manifestation with an unaffected genetic background and heterozygosity in one specific segment. In this type of manifestation the typical clinical features of DSAP are limited to the affected segment. Secondly, type 2 mosaics are characterized by loss of heterozygosity of genes involved in the pathogenesis of superficial actinic porokeratosis (7). Clinically, this manifestation is characterized by disseminated porokeratotic lesions at the predilection sites accompanied by segments with a more severe phenotype commonly following the lines of Blaschko, increased disease activity and increased risk for malignant transformation (8–11). Based on the clinical appearance of disseminated lesions in a segmental appearance without a linear distribution, we propose in our case a type 1 mosaicism of DSAP. Development of lesions after intensification of immunosuppressive therapy suggests that a combination of post-zygotic mutated keratinocytes and immunosuppression contributed to the onset of DSAP.

Comparing mosaic keratinocytes derived from segmental lesions with wild-type keratinocytes of the same individual may therefore help to identify the gene of DSAP.

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The authors declare no conflict of interest.

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