Disseminated Porokeratosis Palmaris and Plantaris Treated with Imiquimod Cream to Prevent Malignancy

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Sir,

Disseminated porokeratosis palmaris and plantaris (DPPP), a subtype of porokeratosis Mibelli, is a rare autosomal dominant genodermatosis first described by Guss et al. in 1971 (1). An early review of the literature showed that 7% of 250 patients with porokeratosis subsequently developed skin tumours (2). Squamous cell carcinomas (SCC), Bowen's disease (BD), and rarely, basal cell carcinomas (BCC) have all been observed on underlying forms of porokeratosis (3). In the past 30 years, only five case reports of metastases derived from SCC on underlying porokeratoses have appeared. BCC have been described only three times in association with porokeratosis (4–6). We report here a 63-year-old man with DPPP, who subsequently developed malignancies. DPPP is present in six members of the patient's family over four generations, beginning with the patient's grandmother, and further affecting the patient's father, brother, daughter and niece (7). The widespread and multifocal nature of BD and SCC in this case, prompted us to examine additional treatment strategies, including topical imiquimod (Aldara®, 3M-Medica, Borken, Germany). To date, standard therapy for porokeratotic diseases comprises symptomatic treatment by application of keratolytics or other topical agents, while skin carcinomas are normally treated by excision. Imiquimod is a topical immune response modifier primarily approved for the management of anogenital warts. Imiquimod was recently approved as a supplementary new drug for the treatment of BCC in parts of Europe and actinic keratosis in the USA. Because porokeratotic lesions have a tendency towards malignancy, we decided to treat our patient with imiquimod.

CASE REPORT

A 63-year-old patient presented with DPPP on his palms, soles, arms and legs, and subsequently developed multiple skin tumours identified as BD and SCC. Pinhead-sized hyperkeratotic papules had appeared on the patient's distal arms and legs since the age of 20, which subsequently developed into itchy, red-brown porokeratotic lesions with central atrophy and marginate scaling (Fig. 1A). In the histological examination, a cornoid lamella, a thin column of closely stacked, parakeratotic cells extending through the stratum corneum, and an atrophic centre were present. An inflammatory infiltrate was found consisting of lymphocytes and histocytes in the upper dermis and missing granular layer underneath the cornoid lamella (Fig. 2). The number of lesions increased slowly with the patient's progressing age, accompanied by subungual hyperkeratotic changes in the fingernails and toenails. Tumour growth, accompanied by itching, began on the arms and more predominantly on the legs approximately 6 months prior to treatment in our department. The tumours reached a diameter of about 3 cm and developed bloody-crusted and hyperkeratotic surfaces. A previous excision and histological examination of a tumour on the leg revealed a SCC.

After excision of a further 11 SCC and BD lesions, the porokeratotic lesions were treated with 5% imiquimod cream, and standard biochemical parameters were monitored during treatment. After initial treatment with imiquimod under an occlusive foil every other day for 3 weeks, imiquimod cream was applied three times a week without occlusion for another 6 months. Within the first 2 days of treatment, moderate redness occurred around the lesions. After 3 weeks of treatment, the inflammatory reaction around the lesions became more pronounced, prompting us to continue treatment without occlusion. After 6 months of treatment, the porokeratotic

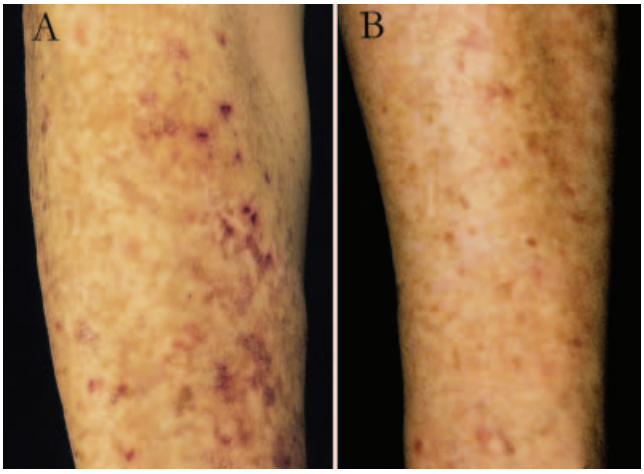

Fig. 1. (A) Untreated disseminated porokeratosis palmaris and plantaris lesions on the leg. (B) Lesion sites after treatment with imiquimod for 6 months.

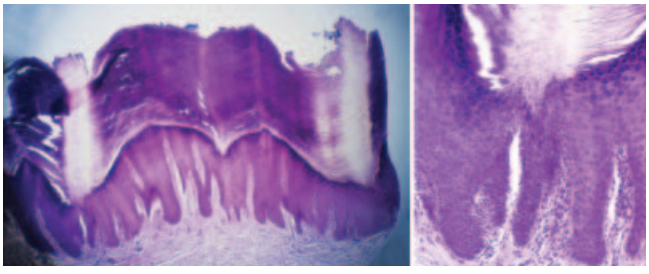

Fig. 2. Typical histology of a disseminated porokeratosis palmaris and plantaris lesion with cornoid lamella (closely stacked parakeratotic cells extending through the stratum corneum).

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lesions were less visible and the surrounding inflammation had decreased. Clinical examination by two independent observers showed that the roughness, itching, scaliness and red-brown colouring of the porokeratotic plaques were significantly reduced (Fig. 1B).

DISCUSSION

DPPP and the other variants of porokeratosis are disorders of keratinization which are characterized by typical histological features, predominantly represented by porokeratotic lesions on palms, soles and the extremities. Cellular changes in porokeratotic plaques may include insidious asymptomatic cellular atypia followed by in situ cancer growth and BD. Imiquimod's mechanisms of action are only partly known. To date, the target lesions for imiquimod treatment have been virus-associated (HPV) tumours and superficial epithelial skin tumours such as actinic keratosis and BCC (8). Imiquimod acts via the induction of cytokines such as interferon-γ, interferon-α, tumour necrosis factor, and interleukin-1, -6, -8, -10, and -12, which induce T-helper cell-dependent immune responses. Normally T-helper cells are responsible for immune surveillance. Part of this surveillance is related to the activation of tumour suppressor genes, in particular the p53 gene. There is evidence to suggest that p53 tumour suppressor protein is involved in the carcinogenesis of porokeratosis. In various studies, overexpressed or mutant p53 was found below the cornoid lamella of porokeratotic lesions and was always present in bowenoid lesions (8–11). As it has been reported that imiquimod modulates p53 tumour suppressor protein, this may explain the effectiveness of the drug in the treatment of porokeratotic lesions.

Imiquimod cream treatment of porokeratosis Mibelli without any sign of malignancy is described in only two case reports; one of which reports a porokeratotic lesion with inflammation and induration within weeks of treatment with imiquimod. After 5 weeks of treatment, total clearance of the lesion occurred and no recurrence was observed at 1-year follow-up (12, 13). Our findings, in combination with this report, suggest that imiquimod is more effective in treating porokeratosis than classical methods like keratolytic agents (e.g. salicylic acid), topical 5-fluorouracil, isotretinoin, CO_2 laser treatment, or cryotherapy. Regardless of the clinical type of tumour, treatment objectives during the precursor stage must concentrate on preventing the development of invasive malignancies. Imiquimod's influence on the p53 tumour suppressor protein may have an effect in preventing malignancies in patients with porokeratosis, but clinical studies remain necessary to evaluate imiquimod in a preventive setting.

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