

Exacerbation of Porokeratosis during Etretinate Therapy

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Four patients with disseminated superficial porokeratosis (DSP) were treated with the oral aromatic retinoid etretinate. Using the standard dosage of 1 mg/kg/day, 3 patients showed exacerbation of cutaneous lesions 4–6 weeks after initiation of treatment. Because of additional severe generalized itching and discomfort in all patients, treatment had to be discontinued. The clinical exacerbation correlated with a significant increase in the lymphohistiocytic dermal infiltrate beneath the cornoid lamella. In our experience the use of etretinate triggered the exacerbation of porokeratotic lesions with associated side effects showing that their use is not necessarily of benefit as previously reported. Key words: Retinoids; Side-effects; Disseminated superficial porokeratosis (DSP).

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The classical form of porokeratosis, first described in 1893 by Mibelli (1), is characterized by annular plaques with a hyperkeratotic, sharply elevated rim and central atrophy. The lesions occur anywhere on the integument in relatively small numbers. In 1937, Andrews described a more disseminated superficial variant of the original form (2); subsequently further variants have been defined (3–5). The histological hallmark of all of these forms is the cornoid lamella, a column of parakeratotic cells, elevating at the periphery of lesions. The most common clinical symptom described by patients, particularly during exacerbation, is pruritus. Induction and/or exacerbation of superficial disseminated porokeratosis has been associated with exposure to UV-light (3, 6) and immunosuppression (7, 8).

Since most porokeratoses appear to be genetically predetermined (9, 10), treatment and management is difficult and controversial. Because retinoids have been reported to be of variable benefit in patients with porokeratosis (11–15), we wanted to evaluate the effect of the oral aromatic retinoid etretinate on 4 consecutive patients suffering from porokeratosis.

METHODS

Patients (Table I)

Four consecutive patients (2 females, 2 males), age range 63 to 67 years (mean 64 years), were evaluated for treatment.

Patient no. 1. A 65-year-old male patient who developed disseminated superficial actinic porokeratosis (DSAP) 5 years prior to first examination at our Department. He reported exacerbation and increased itching of skin lesions subsequent to sun exposure. Family history for porokeratosis was negative. Numerous typical lesions were found on legs and arms and solitary lesions on the trunk. Previous treatments, including local steroids and salicylic acid containing creams, had proved ineffective.

Patient no. 2. A 66-year-old male patient who first noticed the development of brownish maculae on his trunk and lower extremities approximately three decades ago. Two years after initial presentation, plantar and palmar involvement was also noticed, after which the diagnosis porokeratosis plantaris, palmaris, and disseminata (PPPD) was established. Family history revealed similar lesions in the patient's father and son. Besides local application of steroids and urea, no other treatment had been performed.

Patient no. 3. A 67-year-old female presented with DSAP of 7 years' duration. She had no family history and developed her first lesions upon exposure to natural sunlight. Lesions were found concentrated on the distal portions of her arms and legs, to a lesser degree on the proximal parts, and on the trunk. Besides unsuccessful local application of urea, no other treatment modalities had been tried. Accompanying pruritus was hard to control.

Patient no. 4. A 63-year-old female who showed exacerbation of her previous discrete disseminated superficial porokeratotic lesions of 15 years' duration following chemotherapy for breast cancer. Her sister also presented with discrete porokeratotic lesions. No previous treatment had been performed.

Treatment

Before initiation of treatment, patients underwent a complete clinical and laboratory examination including analysis for erythrocyte sedimentation rate, complete blood cell counts, clotting time, fasting blood glucose, liver enzymes, serum electrolytes, serum iron, cholesterol and triglycerides, uric acid, blood urea nitrogen, and serum creatinine. All values were within the normal range.

Table I. Patients characteristics and response to etretinate therapy

E: exacerbation; I: induction of new lesions

Pat. no.	Diagnosis	Sex/Age	Triggering mech.		Response to etretinate
			UV light	Immuno-supp.	
1	DSAP	M/65	+	-	E/I
2	PPPD	M/66	+	-	E/I
3	DSAP	F/67	+	-	E
4	DSP	F/63	-	+	No change

After obtaining informed consent from all patients, treatment was initiated with the retinoid Tigason® (etretinate) at a dosage of 1 mg/kg day. Patients were carefully monitored for side effects and examined once weekly.

RESULTS (Table I)

Three patients (nos. 1, 2, 3) showed exacerbation of porokeratosis after 3–6 weeks of treatment (Fig. 1). Lesions increased in diameter, became more erythematous, and the hyperkeratotic ridge became more prominent. In patients 1 and 2 a few new lesions were induced. Lesions in patient 4 remained unchanged after 6 weeks of therapy and no new lesions appeared.

At the same time, all 4 patients developed severe generalized itching. Persistent increase in intensity of pruritus forced us to discontinue treatment after 5 to 6 weeks. Even though retinoids were discontinued, pruritus persisted. Systemic antihistamines and

local steroid creams provided only minor relief from itching, which finally cleared 4–7 weeks after retinoids were discontinued. The porokeratotic lesions needed 6–12 weeks after stopping of treatment to return to their pre-treatment appearance. Of the possible side effects associated with retinoids, mild cheilitis and xerosis were observed in all patients.

Before and after treatment, 4 mm punch biopsy specimens from representative lesions were obtained from all patients. Histology before treatment revealed a column of parakeratotic cells (cornoid lamella) at the periphery of the lesion and a central atrophy of the epidermis. In the dermis an inflammatory infiltrate, consisting mainly of lymphocytes and histiocytes could be identified (Fig. 2a).

After treatment the cornoid lamellae showed an increase in total size. The most impressive change however, was the significant increase in the inflammatory dermal infiltrate (Fig. 2b).

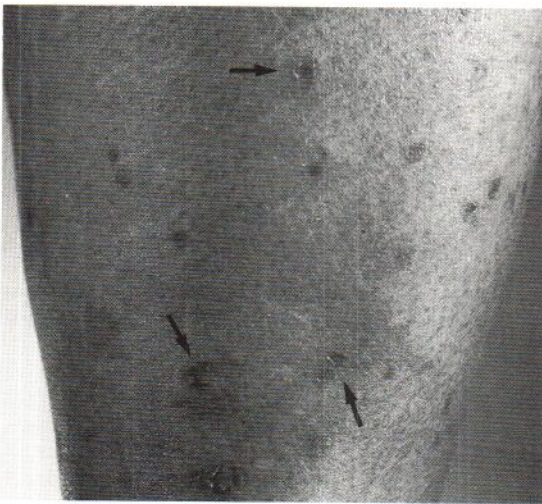


Fig. 1. Disseminated superficial porokeratotic lesions on the right calf of patient no. 3 (a) before treatment, (b) 6 weeks after etretinate therapy. Previous lesions appear more erythematous and more pronounced. Arrows indicate identical lesions.



Fig. 2. (a) Histology of porokeratotic lesion (right lower arm) before etretinate therapy, showing cornoid lamella rising from an epidermal invagination. Note the atrophy of epidermis within the cornoid lamella (right half) and a mild dermal cellular infiltrate. (b) Histology of exacerbated porokeratotic lesion (right lower arm) after etretinate therapy, presenting with marked cornoid lamella and a much more dense dermal cellular infiltrate (H&E, $\times 100$).

DISCUSSION

A wide range of therapeutic approaches have been tried for the treatment of the different variants of porokeratosis; in general, most treatments have proven to be of some practical value, but lesions tend to recur. In our own experience the systemic use of etretinate induced exacerbation of skin lesions with prolonged severe itching. These findings are not in accordance with the majority of previous reports on this subject (Table II).

The first report on the use of retinoids in porokeratosis was published by Pehamberger & Konrad: a case of linear porokeratosis showed good response. The authors also mentioned two cases of DSAP in which treatment with retinoids "did not show a good

therapeutic effect" (11). On the other hand, Kariniemi et al. were able to control the skin symptoms and pruritus in one patient with DSAP by administration of 50–100 mg etretinate for 40 days (12). Even though lesions improved clinically, control-histology after treatment showed persistence of cornoid lamella (12). In another study, two patients, suffering from disseminated porokeratosis Mibelli, were treated orally with etretinate which improved their condition. However, the ultrastructural alterations were still evident and after suspension of treatment the skin lesions recurred (13). Hacham-Zadeh & Holubar observed an improvement of porokeratotic lesions in a 30-year-old man following long-term treatment (21 weeks) with oral etretinate in a dose-range between 75 and 50 mg/day (14).

Table II. Studies on the use of retinoids

E: etretinate; I: isotretinoin, in the treatment of porokeratotic lesions (++ very good, + good, +/- moderate, - no response)

Reference	No. of pats	Diagnosis	Drug	Dosage Duration	Response
Pehamberger (11)	1	Linear porokeratosis	E	1 mg/kg/day 7 weeks	+
Pehamberger (11)	2	DSAP	E	1 mg/kg/day not mentioned	+/-
Kariniemi (12)	1	DSAP	E	100–50 mg/day 8 weeks	++
Bundino (13)	2	Porokeratosis Mibelli	E	75–50 mg/day 5 weeks	+
Hacham-Zadeh (14)	1	Porokeratosis Mibelli	E	75–50 mg/day 21 weeks	+
Schwarz (15)	1	DSAP	E	75 mg/day 3 weeks	-
McCallister (16)	1	PPPD	I	1 mg/kg/day 20 weeks	+
Marschalko (17)	1	PPPD	I	50 mg/day 3 weeks	+

Schwarz et al. (15) used etretinate in a dosage of 75 mg/day for 3 weeks in a patient with DSAP. Because of lack of response, additional treatment with PUVA was performed. Marschalko & Somlai observed marked improvement in one patient with porokeratosis plantaris, palmaris, et disseminata (PPPD) after 3 weeks of etretinate, 50 mg/day (16). In a more recent report, McCallister et al. (17) used isotretinoin for treatment of PPPD, with limited success: lesions recurred after discontinuation of this treatment.

All these studies, which do not present significant data regarding long-term follow-up, show that possible positive effects were short-lived and lesions invariably reappeared upon discontinuation of treatment.

The rationale for the use of retinoids in our patients was based on the known effects of this drug on cellular turnover, especially in disorders of disturbed keratinization, e.g. psoriasis, Darier's disease, pityriasis rubra pilaris, ichthyosis vulgaris, etc. (18, 19).

There is no clear explanation for the exacerbation and induction of lesions associated with the massive cellular dermal infiltrate observed in our patients. Different therapeutic effects may point to the fact that the appearance of porokeratotic lesions may depend on a number of genetic and other unidentified factors.

Clearly the observed side effects could be attributed to the well known initial transient worsening effect of retinoids. However, since this transient and sustaining effect has not been described in any of the available reports (11–17) we consider it unlikely. Recent studies on the pharmacokinetics of the late phase elimination of etretinate (persistence of serum levels from a minimum of 5 weeks to up to 2 years in cases of long-term treatment) might help explain the persistence of lesions and particularly its sustained side effects (20).

The exacerbation and induction of porokeratotic lesions as well as marked generalized pruritus observed in our patients point to the fact that the use of the oral aromatic retinoid etretinate can have a deleterious influence on the course of this skin disorder.

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