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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Systemic retinoid therapy pachyonychia congenita with Etretinate

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The aromatic retinoid Etretinate (Tigason) modifies proliferation activity and the differentiation quality of keratinocytes. These pharmaco-dynamic effects explain its therapeutic application in cases of genodermatosis associated dys-, para-, or hyperkeratoses [3, 6, 7].

Pachyonychia congenita is a rare autosomal dominant hereditary genodermatosis. Major features are palmoplantar hyperkeratoses and pachyonychia [5, 8, 9]. In Type I pachyonychia congenita (Jadassohn-Lewandowsky syndrome), abnormalities of the mucosa (leukokeratoses) also appear in which malignant neoplasms can evolve.

The therapy with keratolytic measures, systemic administration of retinol (vitamin A) or local application of vitamin A acid (Tretinoin) is unsatisfactory [4]. Good results were reported about systemic administration of the aromatic retinoid Ro 10-9359, Etretinate (Tigason [1, 2]).

Case review

Patient 1

H.T. 60 years old, male.

Family history. The father had palmoplantar hyperkeratoses and thickened nails.
Own history. Since childhood, palmoplantar hyperkeratosis and thickened nails. 1944 and 1954, excision of anal leukokeratoses.

Findings at admission. Striated and plaque-shaped keratoses on palms and soles, thickened, extremely convexly curved nail plates, verrucous, jagged, dense tumors and leukokeratoses in the area of the lower lip, oral cavity, anal canal, and capillitium [9]. The visceral mucosa was not pathologic.

Course. Since 1975, local topical keratolytic treatments containing salicylic acid and urea, as well as mechanical removal of the hyperkeratoses have been used.

1980. Cryotherapy of a hyperkeratotic tumor on the capillitium and nail extraction of the most affected fingernails with sklerotization of the matrix.
Cryotherapy of verrucous leukokeratoses in the anal canal and the lower lip.

January 1981. After 3 months, reappearance of leukokeratosis on the lower lip.

June 1981. Cryotherapy of the tumor on the lower lip. Start of the systemic retinoid therapy with Etretinate. Administration of 75 mg/day orally over a period of several weeks and reduction to 30 mg/day resulting in complication-free healing of the lesions with the development of completely smooth mucosal surface.

October 1982. After 16 months, emergence of a new leukokeratosis on the lower lip at 25-30 mg retinoid observed.

June 1983 Flat leukokeratosis on the lower lip, cryotherapeutic treatment not required. Perianal epithelial transition zone and visceral mucosa not pathologic.
The nail abnormalities of the rest of the fingernails and toenails are unchanged.

October 1983. Start of a tuberculostatic three-way combination (INH, Rifampicin, Myambutol) for pulmonary tuberculosis. Four weeks later, increasing formation of massive palmoplantar hyperkeratoses and pronounced recurrence of the tumor on the lower lip despite continued retinoid therapy.
**Patient 2**

E.J. 42 years old, male.

*Family history.* Patient’s mother and two daughters had hypokeratoses on hands and feet.

*Personal history:* Hyperkeratoses and rhagades on palms, fingertips, and soles since early childhood. The nail plates are thickened and tend to have recurring purulent inflammation of the nail bed.

*Findings at admission:* Massive palmoplantar hyperkeratoses, some of which are painful when touched, arranged in a striated and plaque-shaped manner. Deep rhagades in the fingertips, interphalangeal joints, and heels. Thickening of all nail plates with yellow-brown dyschromia and pronounced subungual hyperkeratosis. Mucosa, hair, and dental condition normal.

*Course.* Years of local therapy with ointments containing salicylic acid, mechanical removal of the hyperkeratoses and repeated nail extraction without sklerotization of the matrix. Attempts at therapy with local tretinoin (vitamin A acid) application with and without the addition of urea were unsatisfactory.

*January 1982.* Start of oral treatment with Etretinate at 75 mg/day. After 4-week therapy regimen, recurrence of hyperkeratoses on hands and feet. After reducing the dosage to 35 mg/day, patient experiences for the first time ever a period during which both hands remain free of painful rhagades.

*November 1982.* After 10-month maintenance regimen, occurrence of a slow re-emergence of hyperkeratoses on the heels that could be controlled with local keratolytic measures. The nail abnormalities were unchanged in comparison to January. No occurrence of acute paronychias.

The retinoid therapy had to be discontinued in January 1983 due to increasing alcohol abuse.

*July 1983.* After 6 months, massive recurrence of hyperkeratoses on hands and feet. Paronychias on the majority of the fingernails.

**Discussion**
Systemic retinoid therapy with Etretinate (Tigason) is an essential enhancement of therapeutic options in the treatment of pachyonychia congenita. The recurrence of the palmoplantar hyperkeratoses at an initial dose of 1 mg/kg body weight/day is especially impressive. The occurrence of recurring hyperkeratoses and leukokeratoses can be delayed at a maintenance dosage of 0.5 mg/kg body weight if these abnormalities are first carefully removed by surgery. Discontinuing or reducing the dosage too sharply leads to recurrence.

In our patients, the administration of Etretinate did not sufficiently remedy nail abnormalities. This coincides with reports by other authors [2]. We consider systemic therapy with the aromatic retinoid Etretinate to be a suitable basic therapy for pachyonychia congenita, however, it requires a maintenance dosage of 0.5mg/kg body weight/day of a combination with other measures (Table 1). Whether retinoid therapy can prevent the malignant transformation of the mucosal abnormalities of Jadassohn-Lewandowsky syndrome remains to be tested through additional long-term investigations.

Side effects such as effluvium, hypertriglyceridemia, or heptatotoxicity were not observed in our patients.

An interaction of Etretinate with Phenytoin is known. Whether the massive exacerbation of the symptomatology that occurred during administration of tuberculostatic medication is due to an accelerated inactivation of Etretinate (for example, through enzyme induction) can only be assumed. However, it is known that rifampicin in particular can induce a drug-metabolizing enzyme system (Cytochrom P450), so that hormonal contraceptives are metabolized in an accelerated manner and contraceptive protection can no longer be guaranteed. The ortho methyl group at the phenol ring of Etretinate is also metabolized via this enzyme system and the substance inactivated through it. Thus it is plausible that a reduction in the effectiveness of retinoid therapy could be caused by increased metabolization of Etretinate after a rifampicin-induced increase in Cytochrom P450 activity. Experimental data or further clinical observations on this hypothesis are pending (G. Goerz, personal communication).
Figure 1: Patient H.T., 60 years, male. Pachyonychia congenita. Verrucous hypokeratotic tumor of the lower lip before onset of therapy.

Figure 2. Patient H.T., 60 years, male. Pachyonychia congenita. Recurrence of tumor 3 months after cryotherapy.

Figure 3. Patient H.T., 60 years, male. Pachyonychia congenita. No recurrence 3 months after further cryotherapy and simultaneous retinoid therapy with Etretinate, 75 mg/day.

Figure 4. Patient H.T., 60 years, male. Pachyonychia congenita. Recurring leukokeratosis 16 months after start of retinoid therapy at a maintenance dosage with 30 mg/day Etretinate.

Table 1. Therapy in the treatment of pachyonychia congenita

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<thead>
<tr>
<th>I. Systemic therapy</th>
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<tr>
<td>- Etretinate (Tigason)</td>
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<td>initial: 1.0 mg/kg body weight/day</td>
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<td>Maintenance: 0.25-0.5 mg/kg body weight/day</td>
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<th>II. Local therapy</th>
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<tr>
<td>- Keratolytics</td>
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<td>- Tretinoine (VAS)</td>
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<th>III. Surgical therapy</th>
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<td>- Excision</td>
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<td>- Nail extraction including sklerotization of the nail matrix, skin graft</td>
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<td>- Cryosurgery</td>
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<td>- Dermabrasion</td>
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<th>IV. Prevention</th>
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<tbody>
<tr>
<td>- Permanent etretinate therapy</td>
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<td>- Orthopedic shoes</td>
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<td>- Job counseling</td>
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<td>- Genetic counseling</td>
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