Olmsted syndrome

Mutilating palmoplantar keratoderma with periorificial keratotic plaques

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In 1927 Olmsted1 reported the case of a young boy with mutilating palmoplantar keratoderma (PPK) and keratotic lesions of the lower lip, mouth corners, and anus. In subsequent years similar cases have appeared in the literature under the heading of Olmsted syndrome or PPK with periorificial keratoses.

We describe the clinical picture of a patient with this syndrome and report the results of our investigations into this peculiar keratinization disorder. We reviewed the literature and present a summary of all reported cases to date (Table I).1–30

CASE REPORT

A 2-year-old Arab girl from Gaza was admitted to our hospital because of painful, pruritic PPK and periorificial keratotic plaques, with limitation of hand function and difficulty in walking. She was healthy except for her skin condition and was born at term, after normal pregnancy and delivery. Her parents and brother were healthy and her mother had no history of spontaneous abortions. No other family member was known to have had any skin disease. Although the parents were allegedly non-consanguineous, it should be pointed out that according to a recent estimate, 32% of all marriages in the Israeli Arab population are consanguineous.31

The disease had started at the age of 6 months with hyperkeratosis around the nails. At the age of 18 months, erythema and thick horny areas developed on her palms and soles. Later, keratotic thickening of the skin progressively appeared around the orifices.

On examination we observed thick erythematous palms and soles, partially covered by a massive, uneven, fissured hyperkeratosis extending to the back of her fingers and toes, and back of distal feet. She had flexion deformity of the fingers, some of which were distally swollen. However, there were no constriction bands around the digits. The nails were dystrophic with subungual hyperkeratosis. Hyperkeratotic plaques were also present around the mouth, ear meatus, nostrils, and anus (Fig 1). Furthermore, hyperkeratotic areas were also noted in the inguinal folds extending to the upper inner aspect of her thighs and on her right elbow. Hair was sparse anteriorly and her teeth were normal. There was leukokeratosis on her tongue and buccal mucosa. The general physical examination was non-contributory and neurologic and developmental evaluation was normal. Ophthalmologic examination showed a punctate corneal opacity on her left eye. The following laboratory tests were normal: complete blood cell count, blood chemistries, zinc, amino acid, and biotinidase levels. Radiographs of hands and wrists, including bone age, were normal. Hearing test, otoacoustic emission, and brain stem—evoked response audiometry were all normal.

The child was initially treated with acitretin (1 mg/kg/d). Topical treatment included retinoic acid (tretinoin) cream and 5% salicylic acid ointment. After 1 year of oral acitretin the hyperkeratosis of the hands did not improve and there seemed to be some deterioration of hand function. At the same time there was sufficient regression of the hyperkeratosis on the soles to enable improved walking. We have no explanation for this paradoxical response to therapy.

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<th>Author</th>
<th>Sex, age onset, age examination</th>
<th>Description PPR</th>
<th>Periorificial hyperkeratosis</th>
<th>Nails, hair</th>
<th>Leukokeratosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted, 1927</td>
<td>M, after 6 mo, 2.5 y</td>
<td>Mutilating*, painful, CDB, SDA</td>
<td>Lower lip, mouth angles, anus</td>
<td>ND, dry hair</td>
<td>No</td>
</tr>
<tr>
<td>Costa, 1962</td>
<td>NM</td>
<td>Mutilating, PRG</td>
<td>Nose, mouth, anus</td>
<td>ND, NM</td>
<td>Tongue</td>
</tr>
<tr>
<td>Keir, 1967</td>
<td>F, 4 y, 11 y</td>
<td>Mutilating, CDB, SDA</td>
<td>No</td>
<td>ND, NM</td>
<td>NM</td>
</tr>
<tr>
<td>Atherton et al, Armstrong, et al, 1990</td>
<td>M, 1 y 4 mo, 3 y, son of case above</td>
<td>Mutilating, painful, CDB</td>
<td>Lower lip, mouth angles, nose</td>
<td>ND, NM</td>
<td>No</td>
</tr>
<tr>
<td>Ruiz-Maldonado et al, 1972</td>
<td>M, 13 y, 16 y</td>
<td>Mutilating, CDB, SDA</td>
<td>Anus</td>
<td>NM, lanugo hypotrichia</td>
<td>NM</td>
</tr>
<tr>
<td>Costa et al, 1984; Barnett et al, 1985; Hausser et al, 1993</td>
<td>M, birth, 2 y, 21 y, 36 y</td>
<td>Mutilating, severe pruritus, CDB, SDA</td>
<td>Nostrils, mouth angles, lower lip, ears</td>
<td>ND, congenital universal alopecia</td>
<td>Tongue</td>
</tr>
<tr>
<td>Harms et al, 1985</td>
<td>M, birth, 24 y</td>
<td>Nonmutilating, TRG</td>
<td>Nasolabia folds, nostrils, mouth angles, anus</td>
<td>ND, normal</td>
<td>No</td>
</tr>
<tr>
<td>Rivers et al, 1985</td>
<td>F (A), infant, 49 y</td>
<td>Mutilating, CDB, SDA</td>
<td>No</td>
<td>NM, NM</td>
<td>NM</td>
</tr>
<tr>
<td>Batti et al, 1989</td>
<td>M (B), infant, 31 y</td>
<td>Mutilating, severe pain, PRG</td>
<td>Mouth angles: persistent fissuring</td>
<td>NM</td>
<td>NM</td>
</tr>
<tr>
<td>Georgii et al, 1989</td>
<td>M (D), 2 y, 12 y</td>
<td>Mutilating, painful, CDB</td>
<td>Mouth, sacrum</td>
<td>No, normal</td>
<td>NM</td>
</tr>
<tr>
<td>Judge et al, 1991</td>
<td>M, birth, birth-2.5 y</td>
<td>Nonmutilating</td>
<td>Lower lip, mouth angles, chin, anus</td>
<td>ND, diffuse alopecia</td>
<td>No</td>
</tr>
<tr>
<td>Ueda et al, 1993; Yoshizaki et al, 2001</td>
<td>M, 2 wk, 11 y</td>
<td>Mutilating, painful</td>
<td>Lower lip, coccygeal area</td>
<td>ND, patch of alopecia</td>
<td>Tongue</td>
</tr>
<tr>
<td>Lucker et al, 1994</td>
<td>M, 3 mo, 33 y</td>
<td>Mutilating, severe pain</td>
<td>Lower lip, nasolabia fold, anus</td>
<td>ND, universal alopecia</td>
<td>NM</td>
</tr>
</tbody>
</table>
Table I. Cont’d

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex, age onset, age examination</th>
<th>Description</th>
<th>Periorificial hyperkeratosis</th>
<th>Nails, hair</th>
<th>Leukokeratosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambiaghi et al, 1995; monozygotic twins</td>
<td>M, 4 mo, 15 mo, 3 y</td>
<td>Mutilating, painful, pruritus</td>
<td>Lower lip, nose, eyelids, ear meatus + concha</td>
<td>ND, thinning, coarse-dry, loss of eyelashes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>M, as above</td>
<td>Mutilating</td>
<td>Ear meatus + concha</td>
<td>ND, idem but normal eyelashes</td>
<td>No</td>
</tr>
<tr>
<td>Kress et al, 1996; Raskin et al, 1997</td>
<td>F, not at birth, 9 mo-11 y</td>
<td>Mutilating, painful, SDA</td>
<td>Periorbital, mouth, anus, vulva</td>
<td>ND, NM</td>
<td>NM</td>
</tr>
<tr>
<td>Santos et al, 1997</td>
<td>M, 6 mo, 35 y</td>
<td>Mutilating, TRG, CDB, SDA</td>
<td>Nose, mouth</td>
<td>Nails absent, universal alopecia</td>
<td></td>
</tr>
<tr>
<td>Frias-Iniesta et al, 1997</td>
<td>M, birth, 20 y</td>
<td>Mutilating, painful, PRG</td>
<td>No</td>
<td>Normal, normal</td>
<td>No</td>
</tr>
<tr>
<td>Larregue et al, 2000</td>
<td>M, 2 y, 7.5 y</td>
<td>Mutilating, painful, pruritus, TRG, CDB</td>
<td>Mouth, ears, anus</td>
<td>ND, normal</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>M, 6 mo, 9 y</td>
<td>Mutilating, PRG, CDB</td>
<td>Mouth, nose, anus</td>
<td>ND, NM</td>
<td>NM</td>
</tr>
<tr>
<td>Fonseca et al, 2001</td>
<td>F, 9 mo, 48 y</td>
<td>Mutilating: necessitating amputation hands/feet</td>
<td>Mouth, anus</td>
<td>NM, generalized hypotrichosis</td>
<td></td>
</tr>
<tr>
<td>Koch et al, 2001</td>
<td>F, 1 y, 17 y</td>
<td>Mutilating, painful</td>
<td>Chin, anus, vulva</td>
<td>ND, normal</td>
<td>No</td>
</tr>
<tr>
<td>Requena et al, 2001</td>
<td>M, early infancy, 19 y</td>
<td>Nonmutilating, TRG, PRG</td>
<td>Mouth, nose</td>
<td>ND, normal</td>
<td>NM</td>
</tr>
<tr>
<td>Bergonse et al, 2003</td>
<td>M, 2 y, 4 y</td>
<td>Mutilating, CDB</td>
<td>Mouth, nostrils</td>
<td>NM, universal alopecia</td>
<td>NM</td>
</tr>
<tr>
<td></td>
<td>M, 1.5 y, 16-48 y</td>
<td>Mutilating, painful, TRG, CDB, SDA, surgical amputation</td>
<td>Mouth, nostrils, anus</td>
<td>ND, diffuse alopecia</td>
<td>NM</td>
</tr>
<tr>
<td>Ogawa et al, 2003</td>
<td>F, lifelong, 7 y, 48 y</td>
<td>Mutilating</td>
<td>Mouth, nostrils, anus</td>
<td>ND, NM</td>
<td>NM</td>
</tr>
<tr>
<td>Batra et al, 2004</td>
<td>M, birth, 8 y</td>
<td>Mutilating, painful, TRG, CDB</td>
<td>Mouth angles</td>
<td>ND, hypotrichosis</td>
<td></td>
</tr>
<tr>
<td>Current case</td>
<td>F, 6 mo, 2 y</td>
<td>Mutilating, painful, pruritus, TRG, PRG</td>
<td>Mouth, ear meatus, nostrils, anus</td>
<td>ND, sparse anteriorly</td>
<td></td>
</tr>
</tbody>
</table>
| *Severe PPK with marked limitation of function.*
The histopathologic findings of palmar skin showed psoriasiform hyperplasia, hypogranulosis, and alternating parakeratosis and orthohyperkeratosis (Figs 2 and 3). An electron microscopic study of the involved palmar skin before treatment with acitretin demonstrated, in the malpighian layer, keratinocytes with well-developed desmosomes, increased intercellular spaces, finely distributed...
tonofilaments, and numerous glycogen granules (Fig 4). There was a reduced number of keratohyaline granules. A biopsy specimen from palmar skin, 4 months after the initiation of acitretin, demonstrated in the keratinocytes of the midmalpighian layer, large coarse densely packed bundles of tonofilaments, and in the granular layer, increased numbers of coarse keratohyaline granules (Fig 5). This may reflect the effect of acitretin on keratinization, increasing keratohyaline and keratin filament production and assembly (Fig 6). With light and scanning electron microscopy of scalp hair among 100 hairs from the sparse area, 7 showed pili torti and another 7 trichorrhexis nodosa type defects. No such defects were seen in 100 hairs from a normal area.

Genetic studies

In an attempt to investigate the molecular origin of Olmsted syndrome, we screened a number of genes previously implicated in the pathogenesis of mutilating PPKs. These included KRT1 (encoding keratin 1), GJB2 (encoding connexin 26), SLURP1 (encoding ARS component B), and LOR (encoding loricrin), which have been found to carry mutations in ichthyosis hystrix of Curth-Macklin, Vohwinkel’s syndrome, mal de Meleda, and Camisa syndrome, respectively. We sequenced all coding regions, including exon-intron boundaries, of each of these 4 genes and did not detect any pathogenic sequence alteration.

DISCUSSION

Olmsted syndrome is a severe keratinization disorder with diagnosis based on the clinical picture. There are as yet no known specific biologic markers nor has its genetic basis been elucidated.

The total number of published cases, including our own, to our knowledge, is 32. The main dermatologic findings are summarized in Tables I and II.

As in our patient, nonperiorificial keratotic lesions on different parts of the extremities (other than palms and soles) and in the intertriginous folds have frequently been mentioned. Such lesions appeared as linear, streaklike hyperkeratoses and follicular keratosis-like keratotic papules.

In the current case and in two monozygotic twins, scanning electron microscopy of hair revealed changes such as twisting of hair shafts, trichorrhexis nodosa, transverse fractures, and disturbance of the cuticle cell pattern.
Other manifestations

Eye lesions were observed in 22% of affected individuals with severe corneal involvement in two. 13,15 High-tone loss of hearing8,14 and congenital deaf-mutism27 were reported. Three patients showed joint laxity,13,15,23 one of whom had a family history of Ehlers-Danlos syndrome.9 Retarded physical development was present in 25% of patients whereas mental retardation was mentioned twice.1,4 Recurrent bacterial and/or candidal infections, mainly in keratotic areas, were common.14,15,19,23,25,26 Osteoporosis-osteolysis of hands and feet may occur.2,3,8,21,23,29 Ogawa et al29 have attributed this to either a genetic effect or to an inflammatory process.

Significantly, squamous cell carcinoma developed in the area of PPK in two cases.9,10,24 Yoshizaki et al24 cite one report in the Japanese literature on plantar verruca carcinoma in Olmsted syndrome.36 The patient of Ogawa et al29 had squamous cell carcinomas on her left leg and right ankle and, although a nonsmoker, she developed adenocarcinoma of the lung. Dessureault et al37 reported the occurrence of malignant melanoma in the area of the plantar keratoderma. A number of other cornification disorders have been associated with an increased prevalence of squamous cell carcinoma, including KID syndrome,38 Howel–Evans syndrome,39 Huniez syndrome,40 and, recently, Netherton’s syndrome.41

Of note is the description of partial cutaneous expression of Olmsted syndrome in two families. In one of them the mother3 of a boy4 with full-blown Olmsted syndrome presented the typical mutilating PPK but had no periorificial hyperkeratoses. In the family described by Rivers et al,12 mutilating PPK without periorificial involvement appeared in two generations. However, in the third generation a boy had the full-blown syndrome.

A minority of the published cases showed some atypical features. In one patient14 the disease started as “ichthyosis” on the trunk and keratodermas appeared only at the age of 30 years. In another one,7 the dermatosis started at 13 years of age and the nonmutilating palmar lesions appeared as tiny hyperkeratotic foci. The patient of Harms et al11 showed nonmutilating palmarplant lesions resembling striate PPK.42 In two other cases15,27 PPK was not mutilating. Whether such atypical cases really belong to Olmsted syndrome will be determined when the molecular genetics of the syndrome are discovered.

Except for several isolated abnormalities, laboratory investigations have been noncontributory including blood zinc levels and karyotype. Biopsy specimens of PPK usually showed acanthosis with orthokeratotic or parakeratotic hyperkeratosis and poor or absent granular layer. In 3 cases the epidermis showed an increase in mitoses. In one case8 there were “many mast cells” in the dermis, the significance of which was not clear. The few scalp biopsy specimens revealed follicular ostial hyperkeratosis, absent or hypotrophic pilosebaceous follicles with dystrophic hairs, and calcified pilar structures.

Previous electron microscopic studies produced variable results. The corneocytes contained lipid droplets and remnants of cytoplasmic organelles whereas keratohyaline granules were decreased or absent,10 or large, polygonal, or star-shaped, and occasionally absent.25 In another report corneocytes contained nuclei, keratohyaline granules, or cytoplasmic organelles.29 Keratinosomes were present.25,10 Keratinocytes had large nuclei with visible nucleoli, some of them containing centrioles, even at the level of the stratum malpighii.23

The mode of inheritance has not been clearly established. An autosomal dominant or X-linked dominant trait10 and an X-linked recessive transmission23 have been suggested. In one report12 the disease was present in 3 generations and an affected father transmitted it to his son. This rules out X-linked recessive inheritance and strongly indicates autosomal dominant transmission in this family. Finally, there may be more than one mode of inheritance in Olmsted syndrome just as in other genodermatoses such as erythrokeratodermia variabilis.15 Larregue et al23 have suggested that although keratitis, alopecia, and keratosis follicularis are probably part of Olmsted syndrome, the occasional joint laxity could be attributed to a contiguous gene syndrome.

In the differential diagnosis of Olmsted syndrome, consideration of several genodermatoses with PPK have been suggested in addition to psoriasis inversa, chronic mucocutaneous candidiasis, and acrodermatitis enteropathica.23 The latter was suggested not infrequently, but blood zinc levels were found to be normal in more than 10 reports. Acrodermatitis enteropathica “is a pustular, exudative, crusted dermatosis and not a keratoderma.”44 Actually the full-blown Olmsted syndrome, with its typical mutilating PPK and periorificial keratoses, is usually distinctive enough to lead to the correct diagnosis.

Treatment is often disappointing. Surgical removal of the keratotic palmoplantar masses with subsequent autografting was followed by recurrence of the hyperkeratosis except in one case.16 The donor site of the graft may heal with hyperkeratosis (Koebner’s phenomenon).25 Oral synthetic retinoids may be effective but often are only partially so or not helpful at all.
REFERENCES


