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Verruciform Xanthoma: A Special Epidermal Nevus

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Congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome is a rare X-linked hereditary disorder. Presentation varies from ichthyosiform nevus to complete limb amelia. We present a 17-year-old adolescent girl who presented with a 16-cm exophytic mass of the right foot that had been growing for 7 years as well as knee contracture. Deformed nails with onychorrhexis were noted bilaterally. History of multiple nonlinear erythematous skin lesions covered by dry waxy scales involving multiple body folds with sharp midline demarcation was obtained. The patient's family history was negative for consanguinity and similar conditions. Radiography showed right leg hypoplasia and osteopenia. These findings fulfill the diagnosis of CHILD syndrome. Microscopically, psoriasiform epidermal hyperplasia with marked orthohyperkeratosis and neutrophilic exocytosis were noted. The papillary dermis was packed with foamy macrophages consistent with xanthomatous changes, namely verruciform xanthoma. Verruciform xanthoma, although rarely found in other conditions, is a characteristic finding.

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Case Report

A 17-year-old adolescent girl was referred to the plastic and reconstructive surgery department for evaluation of an exophytic mass on the right foot and right limb defects. The mass was located over the lateral aspect of the right foot (Figure 1A). It appeared at 10 years of age and had increased in size since then. On physical examination, the lesion was approximately 16 cm in greatest dimension. It had a fleshy, verrucous, mildly erythematous surface covered with purulent exudates. It also was malodorous and tender on palpation. On further evaluation, extensive hamstrings, chronic flexion contractures of the right knee, and disuse atrophy were noted. Radiographs showed hypoplasia and severe osteopenia of the right leg, severe knee contracture and dislocation, and extensive right foot rotation. Skeletal survey revealed skeletal asymmetry.

A detailed history revealed the patient to be the product of a full-term pregnancy and a normal vaginal delivery to a 25-year-old healthy mother. The mother had a smooth uneventful pregnancy and no prior miscarriages. At birth, the baby weighed 3200 g. The mother subsequently gave birth to 2 boys and 2 girls; none of these children were diagnosed with a similar condition. Family history was negative for consanguinity and similar conditions.

The patient had developed multiple skin lesions soon after birth (age, 15 days). These lesions involved the right side of the body including the inguinal fold, gluteal fold, and leg. They consisted of well-demarcated, diffuse, erythematous plaques covered with yellow waxlike scaling resulting in a distinctive ichthyosiform appearance (Figure 1B). The lesions were nonlinear, painful, and mildly itchy, more often in springtime. They had a waxing and waning clinical course but never completely disappeared. The contralateral side was minimally involved by linear erythematous plaques on the extremities. In addition to the skin lesions, the patient had nail lesions involving the fingers and toes bilaterally. The nails were replaced by grossly deformed hyperkeratotic material. The interdigital spaces were similarly affected. No

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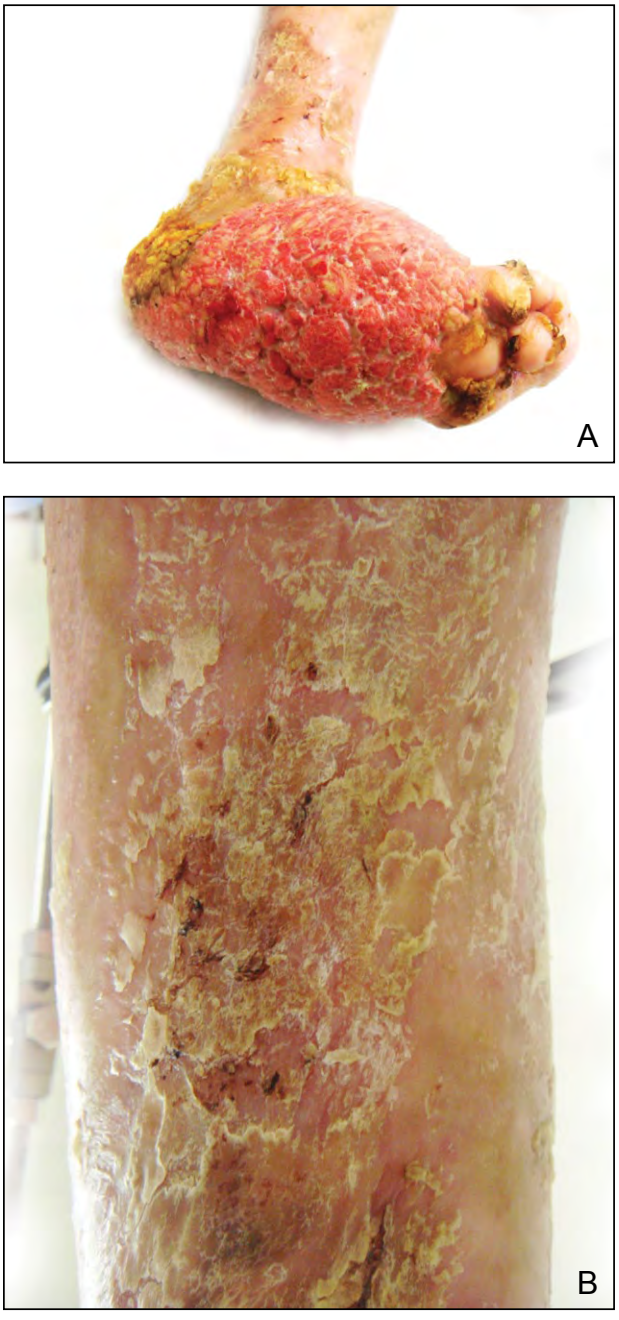

Figure 1. A mass on the lateral aspect of the right foot showing a verrucous erythematous surface (A). Diffuse erythematous plaques covered with yellow waxlike scaling resulting in a distinctive ichthyosiform appearance also were present (B).

mucous membrane or facial involvement or alopecia were noted. Development and intelligence were appropriate for age with good school performance. Moreover, a complete systemic workup showed no associated visceral involvement.

Based on these findings, the patient was diagnosed with congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome. Molecular analysis detected a missense mutation (p.A105V) in the coding region of the NAD(P) dependent steroid dehydrogenaselike gene, *NSDHL*, confirming the diagnosis.

The patient underwent debridement and excision of the right foot lesion with release of the contractures and split-thickness skin grafting, followed by closed reduction of the dislocated right knee, supramalleolar osteotomy of the right ankle, and application of an Ilizarov external fixator.

The right foot lesion was submitted to the pathology department at our institution. Grossly, the lesion (16×9×5 cm) was exophytic and composed of fingerlike projections (Figure 2A). Histologic examination revealed an excision biopsy extending to the subcutaneous fat. Sections exhibited papillomatosis and psoriasiform epidermal hyperplasia (Figure 2B) with marked orthohyperkeratosis intermingled with zones of parakeratosis. The epidermis showed marked acanthosis with expansion of the granular layer underneath the hyperkeratotic areas. Exocytosis of neutrophils forming microabscesses reminiscent of Munro microabscesses were noted throughout the entire lesion (Figure 2C). The core of the fingerlike projections was expanded and packed by lipid-laden macrophages (xanthomatous changes)(Figure 2D). Perivascular lymphohistiocytic superficial and deep infiltrates were noted with numerous plasma cells. The superficial and deep vascular networks showed thickening and dilatation. The subcutaneous fat was unremarkable.

Comment

The acronym CHILD syndrome was proposed for congenital hemidysplasia with ichthyosiform erythroderma and limb defects.[1] Today, however, it stands for congenital hemidysplasia with ichthyosiform nevus and limb defects.[2] It is a rare condition[3] that is an X-linked dominant, male-lethal, multisystem birth defect. The severity of the limb defects may vary from hypoplasia of some metacarpals or phalanges to complete absence of an extremity. Axial bones, including the vertebrae, clavicle, scapula, and ribs, also may be involved.[1] Patients with CHILD syndrome may have unilateral hypoplasia of the brain, cranial nerves, or spinal cord; some may show mild intellectual impairment. However, bilateral involvement has been described, with contralateral anomalies of the skin, bone, and viscera being minimal. Other characteristic findings may include destroyed nails replaced by keratotic clawlike material with or without onychorrhexis. It also is associated with ipsilateral alopecia.[1]

As a distinct cutaneous entity, this condition is characterized by an inflammatory ichthyosiform

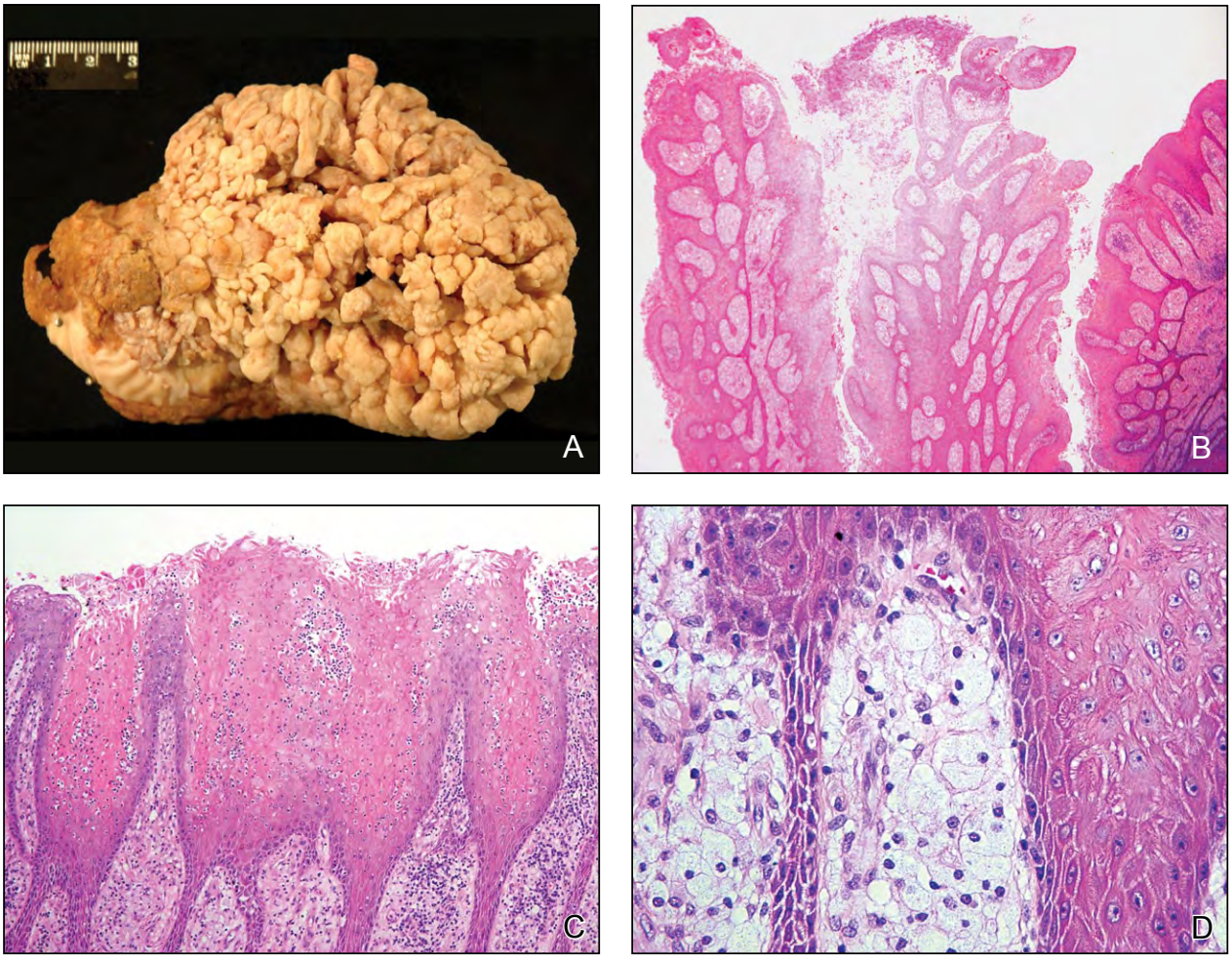

Figure 2. Gross photography of the lesion showed an exophytic mass with fingerlike projections (A). Papillomatosis and psoriasiform epidermal hyperplasia were present (B)(H&E, original magnification ×20). Neutrophilic exocytosis forming microabscesses reminiscent of Munro microabscesses were noted (C)(H&E, original magnification ×100). The papillary dermis was packed with foamy macrophages showing xanthomatous changes (D)(H&E, original magnification ×400).

nevus showing a unique lateralization and strict midline demarcation.[2] Unilateral erythema and scaling usually are present at birth but also may develop during the first weeks of life.[1] Spontaneous partial regression is not uncommon,[4] but involvement of new skin areas may occur.[1] Skin lesions typically spare the face.

Histologically, the skin lesions show psoriasiform epidermal hyperplasia with marked hyperkeratosis and parakeratosis with sparse superficial and deep perivascular lymphocytic infiltrates.[5] Exocytosis of neutrophils forming accumulations reminiscent of Munro microabscesses also is present.[2] The presence of verrucous structures filled with xanthomalike cells containing lipid droplets (verruciform xanthoma) is uncommon but characteristic.

Verruciform xanthoma is a histopathologic pattern characterized by foam cell aggregates packing the papillary dermis.[6] Initial damage to keratinocytes by an inciting agent followed by degeneration and foam cell response was proposed as a possible pathogenetic mechanism.[7] This phenomenon is reported to be associated with various neoplastic or inflammatory conditions, such as fibroepithelial polyp, warty dyskeratoma, actinic keratosis, seborrheic keratosis, squamous cell carcinoma, lichen planus, discoid lupus erythematosus, lymphedema, and epidermal nevus.[8] Sporadic cases of verruciform xanthoma presenting as an asymptomatic solitary lesion affecting anogenital or perioral areas have been reported. However, almost all case reports describing this phenomenon in an inflammatory linear verrucous epidermal nevus were reclassified as examples of CHILD nevus after further examination, either by detailed history and physical examination or by genetic testing.[9]

The CHILD nevus is the cutaneous hallmark of CHILD syndrome and is distinctly different from all

other types of epidermal nevi.[9] In contrast to inflammatory linear verrucous epidermal nevus, the presence of yellow waxlike scales giving the ichthyosiform appearance, the mildness or even absence of itching, the nonlinear arrangement even though the lesions may follow the lines of Blaschko, the pronounced affinity for body folds (ptychotropism), and the histopathologic features of verruciform xanthoma can make the distinction.[4] Sebaceous nevus syndrome can be distinguished both clinically and histologically from CHILD nevus by the linear distribution and the absence of erythema and scaling.[5] Unilateral ichthyosis hystrix (keratinocytic epidermal nevus) can be excluded because granular degeneration is not found in CHILD nevus. In Proteus syndrome, the clinical features are characterized by overgrowth of multiple tissues. The disease has a progressive course and mosaic distribution of lesions, which have not been described in CHILD syndrome.[5]

Mutations in *NSDHL* at Xq28 were identified to be the cause of CHILD syndrome. Nonfunctional *NSDHL* might cause the CHILD phenotype through a lack of cholesterol or other sterols downstream of the block in biosynthesis, or by the accumulation of intermediates upstream of the product generated by *NSDHL*.[10] In contrast to all other epidermal nevus syndromes, which can be explained by genomic mosaicism,[5] the skin lesions in CHILD syndrome usually are confined to one side with strict demarcation in the midline of the trunk. The striking lateralization may be because the origin of a clone of organizer cells coincides and interferes with X-inactivation.[11]

Conclusion

In summary, CHILD nevus represents a distinct cutaneous entity. Recognition of this particular skin entity is important for genetic counseling because a woman with an isolated CHILD nevus has an increased risk for giving birth to a daughter with a severe multisystem defect, the CHILD syndrome.

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