



Dystrophic calcifications point the way—Unusual and early diagnostic clue of Conradi-Hünemann-Happle syndrome

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INTRODUCTION

Conradi-Hünemann-Happle syndrome (chondrodysplasia punctata 2) is a rare X-linked dominant disorder of cholesterol metabolism that results in a spectrum of skeletal, cutaneous, and ocular abnormalities with an estimated prevalence of 1 in 100,000.^{1,2} The disorder results from a mutation in the emopamil-binding protein (*EBP*) gene encoding EBP, a 3β -hydroxysteroid- $\delta 8$, $\delta 7$ -isomerase.³ The mutation is lethal in boys, but in girls it results in a mosaic pattern of congenital ichthyosiform erythroderma within the first months of life, evolving into linear follicular atrophoderma and hypopigmented whorls distributed along Blaschko lines.³⁻⁵ Additional extracutaneous clinical findings include short stature, rhizomelic shortening of the limbs, craniofacial defects, and cataracts. Here we report a case of Conradi-Hünemann-Happle syndrome diagnosed in the first week of life, highlighting the characteristic histopathologic findings that were helpful in establishing the diagnosis.

CASE REPORT

A 1 day-old, 36-weeks-gestation premature female infant was transferred to the Brandon Neonatal Intensive Care Unit, C.S. Mott Children's Hospital at the University of Michigan for further management of a diffusely scaly rash present at birth. The mother had an uncomplicated pregnancy with an uneventful

Abbreviation used:

EBP: emopamil-binding protein

vaginal delivery. There was no history of consanguinity. The mother reported a remote maternal history of dwarfism. The baby was noted to be diffusely erythematous and scaly at birth, although there was no collodion membrane. The Apgar scores were 7 and 8 at 1 and 5 minutes, respectively, and she was in no acute distress. Laboratory studies were unremarkable.

On clinical examination, there was xerotic, featherlike, yellow-to-white hyperkeratotic scale diffusely involving her trunk and extremities (Fig 1). There were linear, shiny, smooth, erythematous thin streaks on both hands, lower leg, and dorsum of the foot (Fig 2). A punch biopsy was performed within a feathered-appearing scaly plaque on the left thigh, which found compact hyperkeratosis with intracorneal calcifications and conspicuous, dilated, keratin-filled follicular ostia with variable calcification (Fig 3). A von Kossa stain confirmed the intracorneal and infundibular follicular calcifications. These findings prompted further radiographic evaluation.

A chest radiograph found midthoracic vertebrae in a butterfly shape and hypoplastic lower thoracic

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Fig 1. Conradi-Hünemann-Happle syndrome with xerotic, featherlike, yellow-to-white hyperkeratotic scale distributed on the trunk and extremities.



Fig 2. Conradi-Hünemann-Happle syndrome shows linear, erythematous, smooth, streaks in association with feathered hyperkeratotic scaly plaques on the left lower leg and dorsal foot.

vertebrae. Stippling of the proximal humeral and femoral epiphyses was also noted. A skeletal survey found butterfly deformities of multiple thoracic vertebrae; deficient ossification in T10, T11, and L1 vertebrae; and scattered punctate opacities throughout the thoracic and upper lumbar spine.

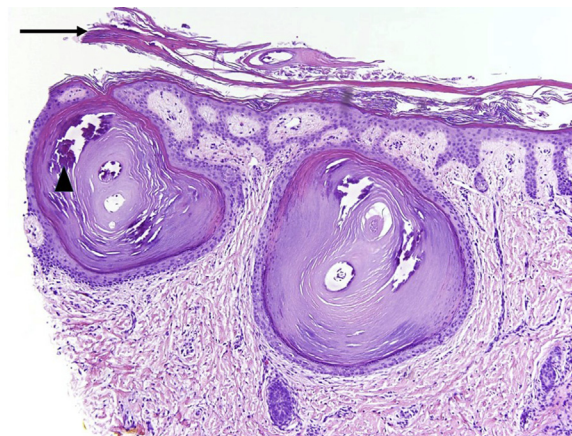


Fig 3. Conradi-Hünemann-Happle syndrome skin biopsy specimen shows hyperkeratosis with intracorneal calcifications (arrow) and dilated follicular ostia with keratotic plugging and calcification (arrowhead). (Hematoxylin-eosin stain; original magnification: $\times 100$.)

Stippled epiphyses were noted on the proximal humeri, proximal femurs, and distal femurs (Fig 4). The arms and legs were relatively normal in length, but the first metacarpals and great toe proximal phalanges were mildly hypoplastic.

DISCUSSION

This infant presented with a generalized ichthyosiform erythroderma consistent with Conradi-Hünemann-Happle syndrome with highly characteristic histologic features. The presence of diffuse erythema with patchy featherlike hyperkeratotic scale and linear erythematous streaks alerted us clinically to the possibility of Conradi-Hünemann-Happle syndrome. Skin biopsy of the feathered scaly plaques found the characteristic keratotic infundibular plugging with intracorneal calcifications. These dystrophic calcifications within keratotic infundibular follicular plugs, especially when located in the stratum corneum, are a unique but underrecognized histopathologic feature of newborns with Conradi-Hünemann-Happle syndrome. They are not found in other ichthyoses, such as congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, bullous and nonbullous congenital ichthyosiform erythroderma, and autosomal recessive congenital ichthyosis.⁶ Recognition of this distinct histopathologic feature provided a key early diagnostic clue in our patient. Although the ichthyosiform skin findings and dystrophic calcifications typically resolve spontaneously after the first few months of life,⁶ the infant may later develop whorled Blaschko-linear follicular atrophoderma and hypopigmentation.⁷

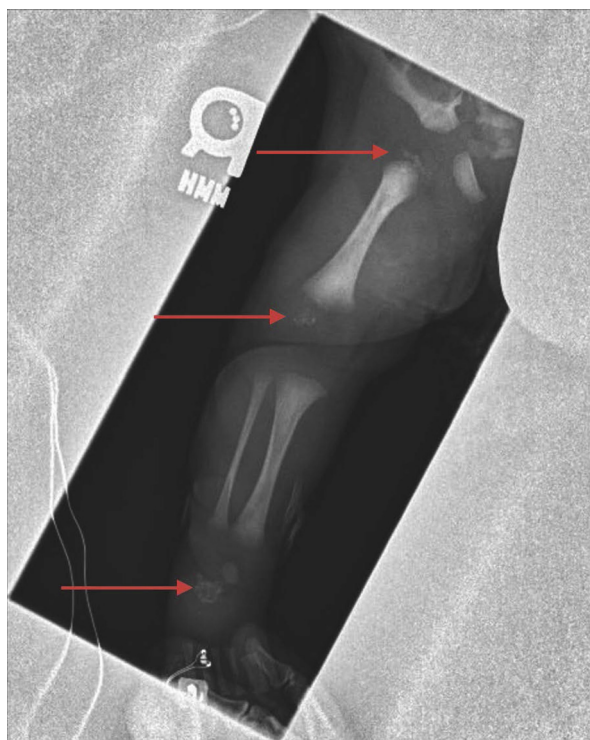


Fig 4. Conradi-Hünemann-Happle syndrome radiographic image shows stippled epiphyses on the proximal and distal right femur and at the ankle (arrows).

Radiographic evaluation prompted by the cutaneous findings provided further supportive evidence for Conradi-Hünemann-Happle syndrome. The metaphyseal stippling identified on radiographic examination of the long bones is characteristic of this syndrome and represents deposits of amorphous, calcified material that are present at birth but regress as the child ages.^{6,8} Although limb length discrepancy has also been described in Conradi-Hünemann-Happle syndrome, it was absent in our initial evaluation except for mild hypoplasia of the first metacarpals and great toe proximal phalanges.

In addition to the striking cutaneous and radiographic findings at birth, patients with Conradi-Hünemann-Happle syndrome may display additional features over time, including dysmorphic facies (flattening of the nasal bridge, hypertelorism, cranial asymmetry and frontal bossing, and a high arched palate), patchy scarring alopecia, and development of Blaschko-linear follicular atrophoderma with hypopigmentation. Skeletal findings may include hip dysplasia, joint contractures, asymmetric shortening of the humerus and femur, scoliosis, and talipes equinovarus deformities of the foot. Patients may also have

unilateral or bilateral sectorial cataracts.^{1,7} The lifespan of these patients is usually normal assuming the heart and lungs are not compromised by scoliosis and cognitive function is generally unaffected.¹

The mechanism underlying the clinical phenotype is thought to result from functional mosaicism of the *EBP* gene, which is involved in the cholesterol biosynthesis pathway.⁷ Mutations of the *EBP* gene result in the accumulation of 8-dehydrocholesterol along with other cholesterol precursors that alter the signaling of the sonic hedgehog pathway, which is responsible for the characteristic craniofacial abnormalities, limb asymmetry, and scoliosis.⁹ The mechanism responsible for the ichthyosis, however, is not definitively known, but evidence suggests that the lamellar granule contents of the keratinocytes in the stratum granulosum are abnormal.¹⁰

Conradi-Hünemann-Happle syndrome is a rare disorder that requires a multidisciplinary team approach for the proper diagnosis and management. Dermatologists play a central role in recognizing the distinctive feathery ichthyosis. Identifying the characteristic calcifications within the corneal layer and keratotic infundibular plugs on skin biopsy is critical to an accurate and timely diagnosis. Once the syndrome has been diagnosed, parents can be apprised of the natural history and long-term care needs. Because some of the characteristic cutaneous, skeletal, and ocular features may manifest only over time, longitudinal follow-up and multidisciplinary care in coordination with pediatric primary care, ophthalmology, and orthopedic surgery is required for proper management.

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