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Lamellar ichthyosis in a female neonate without a collodion membrane

Kevin Chao[1] BS, Maria Aleshin[2] MD, Zachary Goldstein[2] MD, Scott Worswick[2] MD, Marcia Hogeling[2] MD

Affiliations: [1]David Geffen School of Medicine at UCLA, Los Angeles, California, [2]Department of Medicine, Division of Dermatology, David Geffen School of Medicine at UCLA, Los Angeles, California,

Corresponding Author: Marcia Hogeling 2001 Santa Monica Blvd Suite 1070, Santa Monica, CA, 90404, Tel: (310) 917-3376, Email: mhogeling@mednet.ucla.edu

Abstract

The term, autosomal recessive congenital ichthyosis (ARCI), describes a group of rare genetic skin diseases of cornification involving hyperkeratotic scaling at birth. The defective skin barrier function may lead to dehydration, body temperature instability, and high susceptibility to infections. In most cases of ARCI, neonates are born with a collodion membrane covering the body, often presenting with ectropion and eclabium. We report a premature female neonate presenting with hyperkeratotic scaling at birth without a collodion membrane. She was managed with placement in a humidified isolette, prophylactic antibiotics, dilute bleach baths, petrolatum ointment, and artificial eye drops. By the fourth week of life, there was marked improvement in her skin with the large, brown, plate-like scales on the trunk and extremities becoming lighter in color and finer in appearance. The ichthyosis genetic panel showed mutations in the *ABCA12* gene resulting in the lamellar ichthyosis phenotype of ARCI. Our literature review revealed at least 28 patients with ARCI who were not born as collodion babies. Although collodion babies are a hallmark of most ARCI cases, clinicians should be aware of neonates with ARCI born without a collodion membrane and expedite appropriate workup and treatment.

Keywords: ichthyosis, collodion, hyperkeratosis, genodermatosis, ABCA12

Introduction

Lamellar ichthyosis (LI) is a rare inherited disorder involving hyperkeratotic scaling at birth. It is one of 3 major phenotypes of autosomal recessive congential ichthyosis (ARCI), a rare disorder estimated to occur in approximately 1 in 200,000 births in the United States [1]. Neonates with ARCI most often present with a collodion membrane — a tight, clear parchment-like membrane that encases the bodies of affected infants at birth. The collodion membrane is shed a few days to weeks after birth, revealing the underlying phenotype. There are 3 major phenotypes of ARCI that are distinguished based on presentation and genes involved: LI, congenital ichthyosiform erythroderma (CIE), and harlequin ichthyosis (HI), [2-3]. In LI, the collodion membrane is replaced by a whitish and later thick, brown, plate-like adherent scale over the entire body. In CIE, scaling tends to be milder than in LI, with erythroderma and fine white scales. Harlequin ichthyosis is the most severe presentation and is often fatal [1-3]. Severely affected infants may show ectropion, eclabium, alopecia related to scarring, and palmoplantar keratoderma [1]. We present a female infant with LI who had no collodion membrane at birth.

Case Synopsis

The subject of this report is a female infant born at 32 weeks gestation to nonconsanguineous parents. The mother is a 20-year-old G1P1 with a history of asthma, anemia, and psoriasis. She denied drugs, alcohol, or tobacco use during pregnancy. Prenatal laboratory tests were unremarkable. Prior to delivery, the mother was treated for an *E. coli* urinary tract

infection with ampicillin, azithromycin, and cephalexin for 5 days from rupture of membranes to vaginal delivery. Labor was induced for suspected chorioamnionitis. At birth, the infant was noted to have thick, dry, grey-colored scales covering the majority of her body. She was not born with a collodion membrane. Her birthweight was 1710 grams.

The initial dermatologic exam showed diffuse, thickened, white moist scaling of the face, scalp, back, and buttocks, palmoplantar keratoderma with fissuring, single palmar creases, and contractures of the bilateral toes (**Figure 1**). She was also noted to have enlarged, low-set ears with dense accumulation of material within the ear canals and red conjunctiva. There was no evidence of ectropion, eclabium, perioral lesions, or gingival cyanosis.

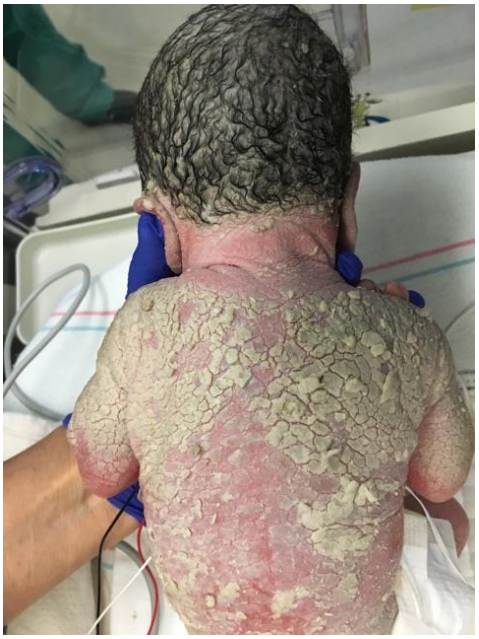

Figure 1. *Diffuse, thickened, white moist scaling of the face, scalp, back, and buttocks at 1 day of life.*

Ophthalmology, audiology, and otolaryngology consultations were also sought. An ophthalmologic exam showed no epithelial defects via fluorescein stain. Otolaryngology evaluation revealed mild conductive hearing loss related to scaling within ear canals.

Over the next 3 days, the scalp and lateral neck, back, posterior arms, and legs developed large, brown plate-like hyperkeratotic scales (**Figure 2**).

Figure 2. *Large, brown plate-like hyperkeratotic scales at 3 days of life.*

Hyperlinearity of the trunk and ventral extremities with finer scale was noted as well. White macerated plaques were present in the bilateral axilla. The soles became shiny and smooth.

Based on the patient's presentation, a workup for congenital ichthyosis was performed, in addition to standard neonatal labs. The karyotype was 46,XX with no apparent abnormalities on fluorescence in situ hybridization (FISH). Hematopathology microscopic exam was unremarkable with normochromic RBCs, normal platelets and monocytes and without prominent vacuolization of WBCs except for the presence of occasional vacuolated monocytes. An ichthyosis genetic panel was sent.

The patient was placed in a humidified isolette. She was started on IV ampicillin (50 mg/kg) and IV gentamicin (4.5 mg/kg) owing to concern for sepsis. The medications were discontinued after 48 hours of negative blood cultures. Petrolatum ointment (Aquaphor) was applied every 3 hours and dilute bleach baths were started daily to prevent infection and bacterial colonization. Artificial teardrops were applied for dry eyes. With these interventions, there was marked improvement in the skin such that the large, brown, plate-like scale on the trunk and extremities became lighter in color and finer in

appearance over the course of several weeks. Significant improvement in the keratotic scalp was noted as well. On discharge, the skin was pink, thick, and dry, moistened with petrolatum ointment.

After discharge, the ichthyosis genetic panel returned showing 2 mutations in the *ABCA12* gene, a missense mutation converting a codon for asparagine to serine in exon 28 and a frameshift mutation in exon 30, resulting in the LI phenotype of ARCI. Audiology revealed conductive hearing loss secondary to keratin buildup in the ear canals with normal inner ear function bilaterally and plans were made for otolaryngology to debride the accumulated skin every 6 months.

The infant was seen in follow up at 5 months of age and continues to have a milder phenotype of diffuse fine scaling, but no alopecia, nail abnormalities, ectropion, or eclabium (**Figure 3**).

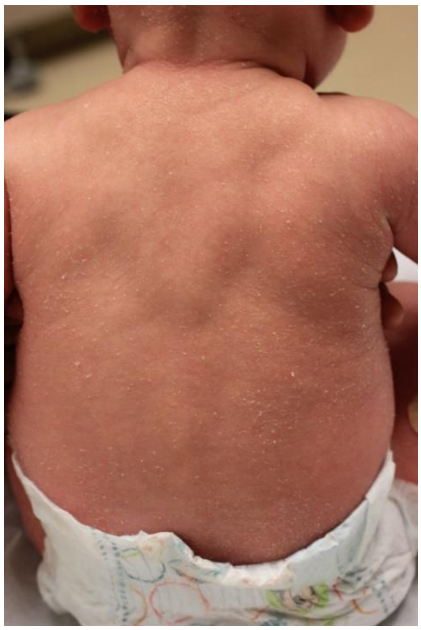

Figure 3. *Diffuse fine scaling at 5 months of age.*

Case Discussion

The presence of the thick, white vernix-like scale on the scalp and no collodion membrane at birth initially led to the inclusion of keratitis-ichthyosis-deafness (KID) syndrome and ichthyosis prematurity syndrome (IPS) in the differential diagnosis [4]. Keratitis-ichthyosis-deafness syndrome is an autosomal dominant disorder caused by mutations in the *GJB2* gene encoding connexin 26 and presents with congenital deafness, nail dystrophy, hypotrichosis, natal teeth, and progressive keratitis later in life. Icthyosis prematurity syndrome is an autosomal recessive disorder caused by mutations in *FATP4* encoding a fatty acid transport protein. Patients are typically premature at 30-34 weeks gestation, similar to our patient, and present with significant skin improvement over time to a mild folliculocentric ichthyosis. However, the thick, white scaling lesions in our patient later gave way to large, brown plate-like hyperkeratotic scale characteristic of LI.

The ichthyosis genetic panel of our patient showed mutations in *ABCA12* gene resulting in the LI phenotype of ARCI. *ABCA12* encodes an ATP-binding cassette (ABC) transporter, which plays an important role in lamellar granule formation and secretion of essential lipids in the epidermis necessary for the proper development of the lipid bilayer of the skin barrier [7, 8]. Pathogenic variants of the gene adversely affect this process, resulting in hyperkeratosis and improper barrier formation [5-7]. Overall, pathogenic variants in *ABCA12* account for approximately 5% of ARCI cases [7], whereas pathogenic variants in *TGM1* are the most common, accounting for 34%-55% of ARCI and 90% or more of severe LI cases [1]. In addition to *ABCA12* and *TGM1*, LI has also been reported to be caused by pathogenic mutations in *ALOXE3*, *ALOX12B*, *CERS3*, *CYP4F22*, *NIPAL4/ICHTHYIN*, and *PNPLA1*[2, 3].

Most reported cases of ARCI present at birth with a collodion membrane, although it was notably absent in our patient. We conducted a literature search using PubMed regarding patients with ARCI born without a collodion membrane. To our knowledge, there were 4 genetic studies of ARCI that presented certain clinical data for such patients [9-12]. The results are summarized in Table 1 except for reference [11], which did not specify the number of patients born without a collodion membrane. Lefèvre et al. analyzed 21 patients with ARCI from Mediterranean countries in the study of the mutations of *NIPAL4/ICHTHYIN* associated with LI [11]. Most of these patients were not born as collodion babies but presented with erythroderma

at birth. Afterwards they presented with features of LI including whitish, grayish scaling, which was most exaggerated in the periumbilical region, on the lower part of the body, and on the buttocks. Hyperlinearity of palms and soles was also noted. The 4 studies coupled with this case show that neonates with LI or CIE subtypes of ARCI can present without a collodion membrane. Including 11 patients at a conservative estimate in the study of Lefèvre et al. who were not born as collodion babies [11], the literature review revealed at least 28 patients with ARCI born without a collodion membrane – thus our case serves to supplement the relatively few number of reported cases.

Because of the defective skin barrier, neonates with ARCI are at increased vulnerability to infections, excessive insensible water loss, and poor temperature regulation. Although there is no cure for this inherited disorder, application of creams and ointments with a high lipid content, infection prevention, hydration, maintenance of body temperature, and proper nutrition together with care for the eyes and ears are major elements in the management of infants with ARCI [4, 13].

Conclusion

We describe an ichthyotic neonate born without a collodion membrane, subsequently diagnosed with LI related to ABCA12 mutations. This case highlights the importance of recognizing the presentation of the congenital ichthyoses early and providing affected neonates with prompt and adequate treatment. Although collodion babies are a hallmark of most ARCI cases, clinicians should be aware of patients with ARCI born without this signature finding. Genetic testing is important to support the diagnosis and plays a decisive role in determining an accurate diagnosis.

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