Atypical Skin Blistering in Ichthyosis Prematurity Syndrome: A Case Report of a Novel Homozygous Variant in the *SLC27A4* Gene

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Abstract

Skin blistering in infants can be alarming, as it may result from various conditions, including infections, autoimmune disorders, congenital disorders, and other underlying diseases. Here, we report a 16-month-old child who has experienced skin blistering since the age of 9 months. Clinical suspicion prompted genetic testing, which revealed a previously undescribed homozygous missense variant, *(c.1523C>T)*, in the *SLC27A4* gene. This finding confirms the diagnosis of Ichthyosis Prematurity Syndrome (IPS). Skin blistering, a rare and atypical manifestation of IPS, remains undocumented.

Keywords: Ichthyosis, Blistering, Eosinophilia, Syndrome

Introduction

The presence of blisters and erosions in an infant presents a significant diagnostic challenge, necessitating a thorough evaluation to distinguish between a broad range of differential diagnoses, including inherited disorders, infectious etiologies, immunobullous diseases, and traumatic injuries.[1]

Here we are reporting a case of a 16-month-old child who began exhibiting generalized pruritus and skin blistering at 9 months. The complex clinical picture, marked by premature birth and neonatal complications, suggested a potential diagnosis of Ichthyosis prematurity syndrome. Extensive evaluation, however, revealed a novel homozygous missense variant *c.1523C>T* in the *SLC27A4* gene, emphasizing the critical role of genetic analysis in diagnosing unusual dermatological conditions and expanding our understanding of skin pathophysiology. This case illustrates the diverse diagnostic considerations—from inherited disorders to acquired diseases—necessary when addressing pediatric skin anomalies.

IPS is typically characterized by premature birth, respiratory distress, and a thick layer of vernix caseosa-like hyperkeratosis at birth, followed by persistent ichthyosis, pruritus, and eosinophilia. Despite initial resolution, patients often experience chronic skin dryness, follicular hyperkeratosis, and scaling, with variable severity.

Case Report

A 16-month-old boy, previously healthy, was brought in by his parents due to persistent generalized itching and skin blistering that began at 9 months of age. His perinatal history included premature birth at 34 weeks, neonatal respiratory distress, and a thick covering of vernix caseosa-like scales [Figure 1]. He was born to healthy consanguineous parents and had one healthy sibling. The parents provided photos, which displayed scattered tense

blisters and erythema at various sites on his body on multiple occasions [Figure 2]. Upon clinical examination, there were no distinctive facial features. His skin examination revealed generalized xerosis and healed blisters on various parts of his body. A white dermatographism was elicited, while mucosal and nail examinations were unremarkable, and systemic assessments were normal.

Figure 1: shows generalized verrucous hyperkeratosis and vernix caseosa-like desquamation at birth.

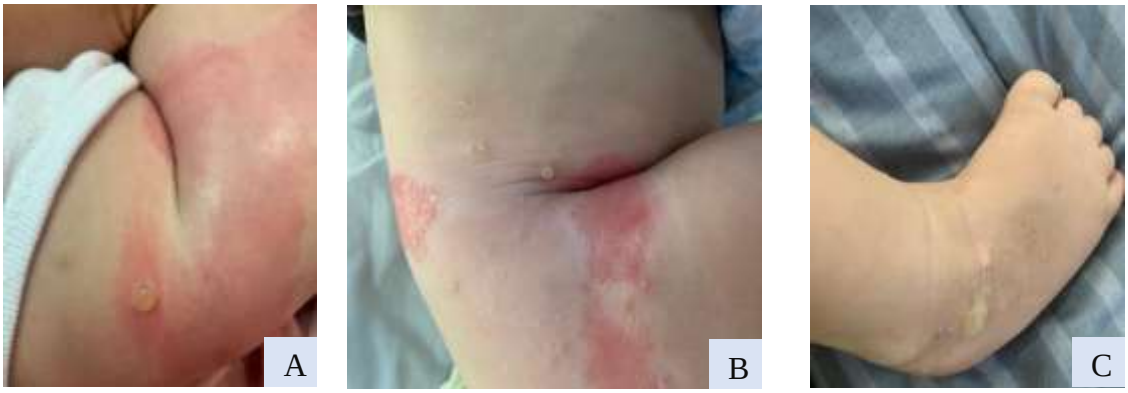

Figure 2: shows scattered tense blisters with an erythematous background over the thigh (A), groin (B), and dorsum of the foot (C).

Laboratory results indicated significant eosinophilia (5.7 x 10^9/L, reference range 0.1-0.5 x 10^9/L). A skin biopsy and skin swab were not performed at the time due to the absence of active blisters.

Given the patient's history of prematurity, neonatal respiratory distress, and eosinophilia, Ichthyosis Prematurity Syndrome was suspected. Genetic testing using whole-exome sequencing identified a previously undescribed homozygous missense variant (*c.1523C>T, p.Thr508Met*) in the *SLC27A4 gene*, confirming the diagnosis of Ichthyosis Prematurity Syndrome (IPS). The patient was started on antihistamine syrup and emollients. On subsequent follow-up visits, the patient demonstrated marked improvement in pruritus, with a significant decrease in the frequency of blister formation.

Discussion

The clinical presentation of recurrent blistering in infancy warrants a comprehensive differential diagnosis, including hereditary epidermolytic disorders, infectious etiologies, autoimmune bullous diseases, and other less common dermatological conditions. Based on the history of recurrent blistering starting at 9 months of age, inherited causes of blistering were initially considered. Epidermolysis bullosa (EB), particularly the simplex subtype, was suspected; however, the absence of mucosal involvement, nail changes, and a negative family history made EB less likely. Congenital ichthyoses were also part of the differential. For instance, epidermolytic ichthyosis typically presents in the neonatal period with generalized erythroderma, fragile superficial blisters, and subsequent hyperkeratosis. In contrast, our patient exhibited tense, localized bullae without preceding erythroderma or later development of scaling, making this diagnosis unlikely. Similarly, milder keratinopathic ichthyoses, such as ichthyosis bullosa of Siemens (associated with KRT2 mutations), may produce transient blistering but usually occur in the setting of diffuse scaling and a positive family history. Infectious causes, including bullous impetigo and herpes simplex virus (HSV), were also considered; however, the chronicity of the lesions, their tense, non-clustered nature, and absence of fever or systemic signs made these less likely. Autoimmune blistering disorders, such as infantile bullous pemphigoid, were briefly considered, but there were no urticarial lesions, mucosal involvement, or widespread blistering. Overall, the presence of recurrent, tense, non-traumatic bullae in the absence of mucosal involvement, erythroderma, or other syndromic and systemic features did not align with any of the above differentials. After excluding more common inherited, infectious, and autoimmune causes of blistering, the clinical presentation and genetic findings were most consistent with Ichthyosis Prematurity Syndrome, despite its atypical manifestation with blistering.

Ichthyosis prematurity syndrome (IPS) is a rare form of congenital ichthyosis with characteristic prenatal and postnatal clinical features. It is inherited via an autosomal recessive mode.[2,3] The true incidence of IPS is underestimated. While the majority of reported cases have originated from the Scandinavian population[4,5] only one case has been documented from Oman to date.[6]

IPS results from a mutation in the *SLC27A4* gene that codes for the fatty acid transport protein 4 (FATP4). While the *c.1523C>T* variant in the *SLC27A4* gene found in our patient has not been previously described in the literature, it is listed in public genetic databases with the reference number rs765311079. The FATPs are transmembrane proteins responsible for transporting exogenous fatty acids into cells and activating them. Additionally, they play a unique role as acyl-CoA synthetases for very long-chain fatty acids (VLCFAs), a function that lowers the activity of VLCFA-CoA synthetase and incorporates VLCFAs into polar and neutral lipids.[2]

Deficiency of FATP4 contributes to the clinical features of IPS through different mechanisms. Impairing skin barrier function by reducing activation and incorporation of ultra-long-chain fatty acids (ULCFA) into epidermal lipids. Impaired activation of ULCFA leads to the accumulation of free ULCFA in cells, which in turn triggers proinflammatory signals and oxidative stress in the epidermis.[7,8]

It has been shown through animal studies that multiple FATPs, particularly FATP4, have an important role in skin barrier function during embryonic and neonatal periods, but not during the postnatal period, as other FATPs can compensate. This could potentially explain the spontaneous resolution of skin manifestations shortly after birth.[9]

Keratin debris accumulation links the condition prenatally to polyhydramnios, separation of fetal membranes, and echogenic amniotic fluid. Post-delivery medical evaluations often reveal that the inhalation of keratin fragments causes respiratory distress in infants born prematurely with IPS. Newborn IPS infants have erythrodermic skin at birth, covered by thick, greasy scales resembling vernix caseosa, which typically resolve quickly, but patients are often left with chronic findings such as pruritic ichthyosis, scaling, and follicular hyperkeratosis. Eosinophilia is among the characteristics observed in IPS.[10]

Eosinophilia is often observed in the neonatal period and can persist into adulthood. The exact mechanism leading to eosinophilia in IPS is not fully understood, but it is believed to be related to the chronic inflammatory state induced by abnormal skin barrier function caused by mutations in the *SLC27A4* gene. The persistent

eosinophilia may also be linked to the atopic conditions frequently seen in these patients, such as atopic dermatitis, asthma, and allergic rhinitis.

The immunological profile of IPS patients often shows elevated levels of IgE, which is consistent with the atopic nature of the syndrome. The chronic skin inflammation and barrier dysfunction in IPS may lead to increased antigen exposure and subsequent eosinophil activation and recruitment. Histological examinations often reveal perivascular inflammation with eosinophils in the skin.[11]

Our patient exhibited both the classic features of IPS and skin blistering, which raises doubts about the clinical diagnosis. Previous reports did not include skin blistering as a feature of IPS. In our case, intense eosinophilia leading to separation at the dermo-epidermal junction could be the underlying mechanism.

Previous studies have shown no obvious correlation between the type of FATP4 mutation and IPS phenotype.[12]

The most critical period for infants with IPS is the neonatal stage. The aspiration of amniotic fluid debris causes respiratory distress, which can potentially lead to transient respiratory failure. Immediate and effective neonatal care, including ventilatory support, is paramount for survival during this period. Managing the critical neonatal period generally improves the long-term prognosis for individuals with IPS. The skin abnormalities, such as ichthyosis, follicular hyperkeratosis, xerosis, and white dermatographism, tend to persist but are less severe compared to the neonatal stage. Appropriate dermatological care can manage these skin conditions, and they typically do not pose life-threatening risks.[13]

Conclusion

Our case underscores the complexity of diagnosing and managing rare dermatological conditions, particularly in pediatric patients. The identification of a previously unreported homozygous missense variant in the *SLC27A4* gene expands our understanding of the genetic basis of IPS and highlights the importance of genetic testing in elucidating the underlying mechanisms of such disorders. The atypical manifestation of skin blistering in our patient emphasizes the need for thorough clinical evaluation and consideration of genetic etiologies in similar cases. Moving forward, further research is warranted to explore the relationship between specific gene mutations and clinical phenotypes, paving the way for more targeted diagnostic and therapeutic interventions in the management of IPS and related disorders.

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