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Case Report

Beyond the usual suspects: a case of incontinentia pigmenti diagnosed after exhaustive exclusion

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ABSTRACT

Incontinentia pigmenti (IP) is a rare X-linked dominant disorder caused by IKBKG gene mutations. Due to its rarity, early diagnosis is often delayed despite characteristic clinical features. A 12-day-old female born to healthy parents presented with an asymptomatic vesiculobullous rash following the lines of Blaschko. Present since birth, the tense blisters and bullae spread to the flexural extremities and genitalia, largely sparing the trunk. Hair, nails, and mucosa were unaffected. Tests revealed mild eosinophilia (12.6%), while comprehensive infectious screens were negative. A skin biopsy yielded nonspecific results, notably lacking melanin incontinence. Driven by strong clinical suspicion, genetic testing was performed. PCR amplification confirmed a common deletion within the IKBKG gene, successfully establishing the diagnosis. Managed with topical steroids and antibiotics, the lesions largely subsided by four months of age. This case underscores the importance of recognizing Blaschko-linear vesiculobullous lesions in neonates and highlights the critical role of genetic screening in confirming IP when the histopathology is inconclusive.

Keywords: Incontinentia pigmenti, Bloch-Sulzberger syndrome, IKBKG gene, Lines of blaschko, Neonatal vesiculobullous rash, X-linked dominant

INTRODUCTION

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare, multisystem genetic disorder with a birth prevalence of approximately 1:140,000. It follows an X-linked dominant inheritance pattern and overwhelmingly affects females, with a female-to-male ratio of about 37:1.[1]

The disorder is caused by mutations in the IKBKG (formerly known as NEMO) gene, located on chromosome band Xq28. Because of the way X-linked dominant traits operate, the mutation is generally lethal in utero for males. Male survival is typically only seen in cases where the mutation is associated with somatic mosaicism or Klinefelter syndrome (where males possess an extra X chromosome, 47, XXY).

We describe a case of IP which despite presenting with typical clinical features was not recognised immediately as there is a lack of awareness about this rare disease.

CASE REPORT

A new born female born out of a non-consanguinous marriage, 12 days old affected by diffuse vesiculobullous rash over inner aspect of both upper limbs and thighs presented to us without any symptoms. She was born at 38 weeks of gestation and weighed around 2.8 kgs. She was delivered by Caesarean section. There was no significant respiratory distress. Entire pregnancy period was uneventful.

The patient's mother was otherwise a healthy woman of 37 years and this was her second child. First child did not

have any similar lesions nor any history of any other skin disease. There was no history of miscarriages. Mother was not on any regular medications nor suffering from any comorbid conditions. Her familial history was insignificant.

On clinical evaluation of mother, we did not observe any abnormalities of skin, nail or hair. Both maternal and paternal serology were negative for VDRL, HIV, HSV, HBV and HCV.

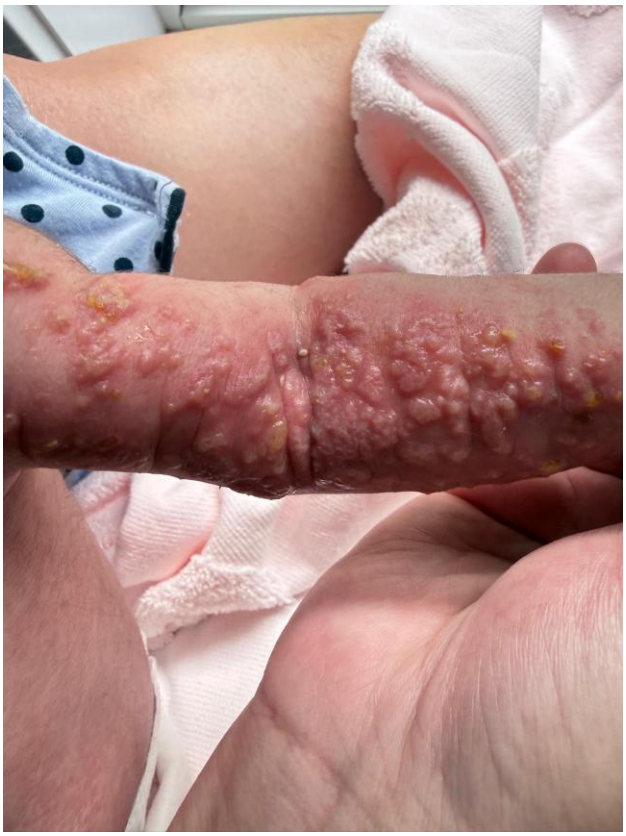


Figure 1: Vesicles and few nodules over cubital fossa of the baby at the time of initial presentation.

At the time of birth, few vesicles were noted over volar aspect of right forearm. Her routine investigations were normal except for a decreased neutrophil count (53.1%) and subsequently an increased eosinophil (12.6%) count. Upon noticing these vesicles, she was evaluated for treponemal infection, cytomegalovirus infection, herpes simplex virus infection, rubella infection and toxoplasma infection via serological tests and all of these were found to be negative. Blood culture was found to show no growth after 5 days of incubation. Further, real time PCR was done to rule out presence of herpes simplex and varicella zoster DNA and these were found to be negative. Also, swabs taken from vesicles were shown to contain scanty growth of skin flora after culturing and *Staphylococcus aureus* was not isolated from the same. For past 12 days, baby was treated with saline compress and topical antibiotic therapy. Over time, lesions spread to involve inner aspect of entire upper limbs bilaterally. Also, vesicles started appearing over her thighs.

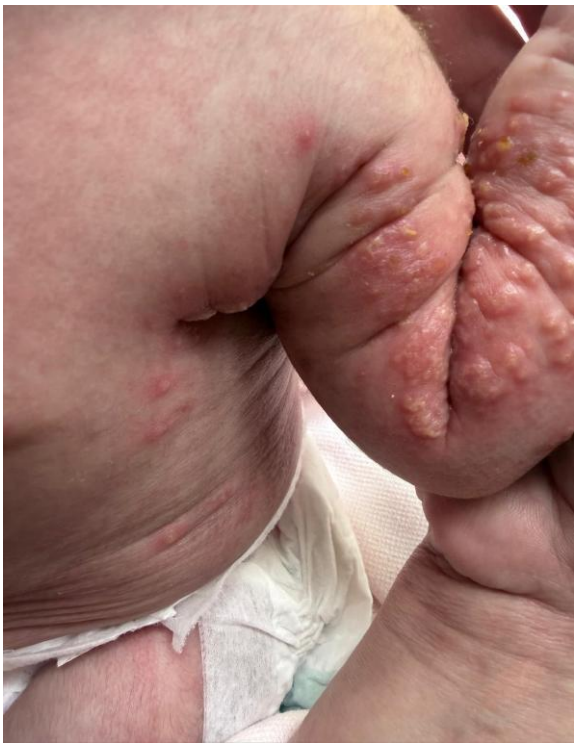


Figure 2: Vesicles and few nodules over trunk and cubital fossa of the baby at time of initial presentation.

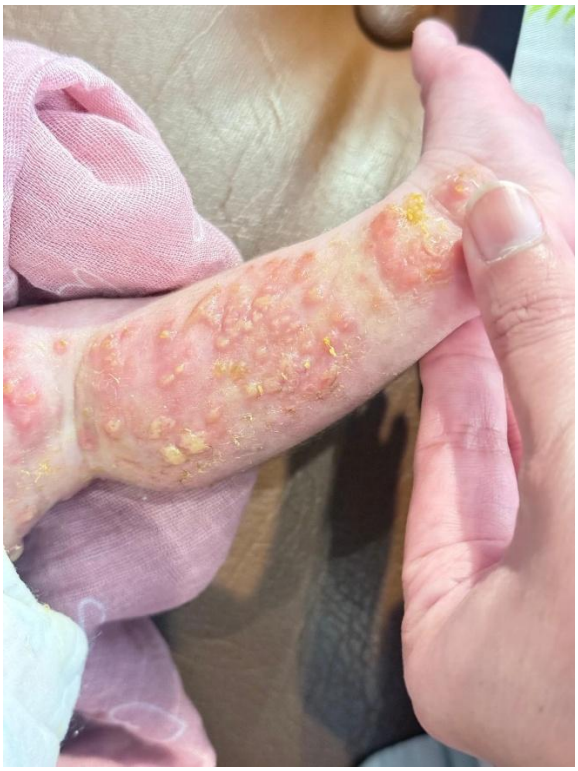


Figure 3: Vesicles over extensor aspect of lower limbs of the baby at the time of initial presentation.

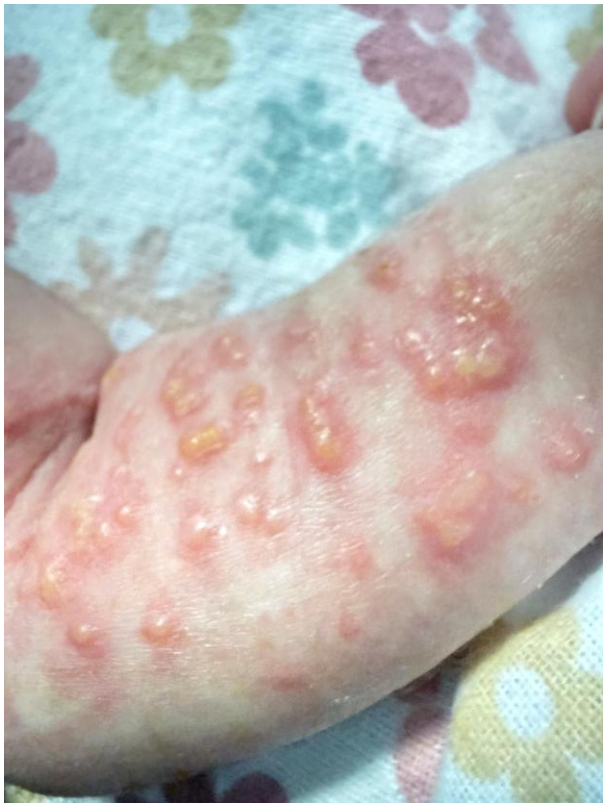


Figure 4: Close-up view of lesions of the baby at the time of initial presentation.

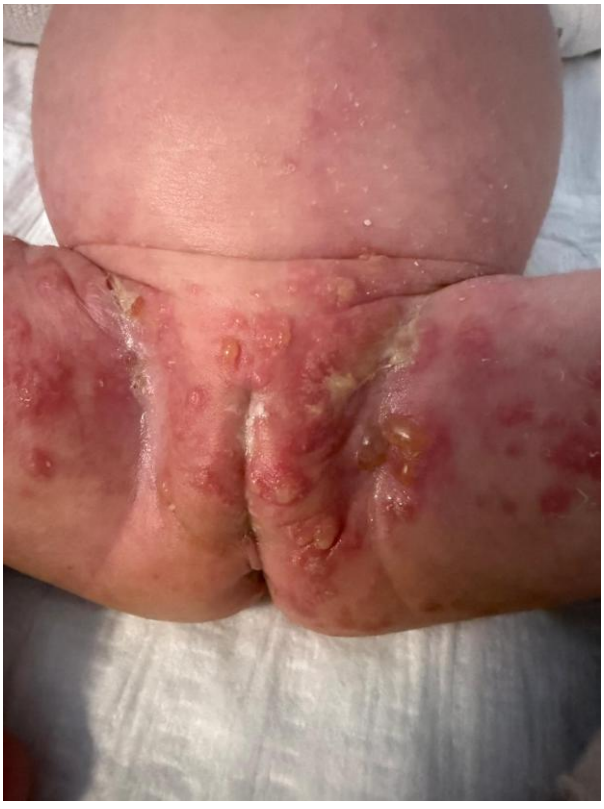


Figure 5: Involvement of genitalia of the baby at the time of initial presentation.

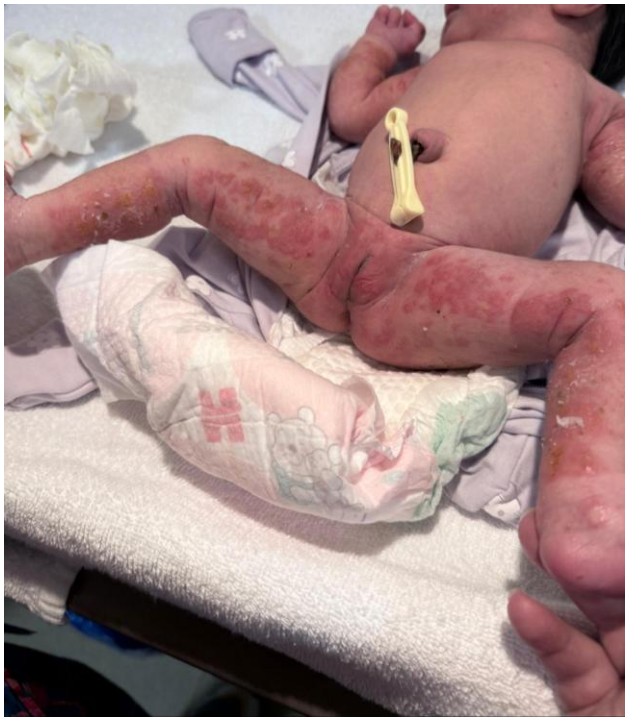
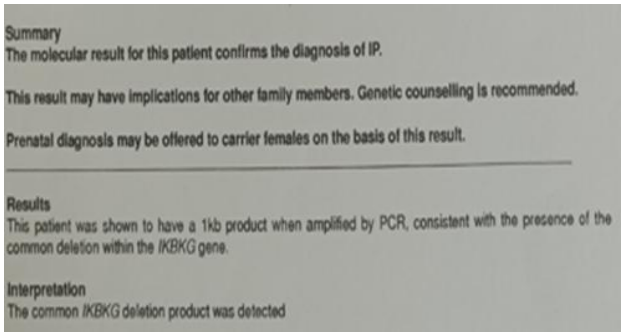


Figure 6: Involvement of lower limbs of the baby at the time of initial presentation.

At the time of presentation, we noted clear tense blisters and bullae upon inflammatory base over flexural aspect of both upper and lower extremities and involving genitalia. Few nodules were felt on palpation. Trunk was relatively spared except for few blisters. Few of them were discrete, but majority of them coalesced to form larger bullae.

Oozing, crusting and scaling were also noted over cubital and popliteal folds. Lesions were noted to be in a linear arrangement which followed lines of Blaschko and seemed to be asymptomatic. Hair, nail and mucous membranes were within normal limits. Nikolsky test was found to be negative (Figure 1-6).


Summary
The molecular result for this patient confirms the diagnosis of IP.

This result may have implications for other family members. Genetic counselling is recommended.

Prenatal diagnosis may be offered to carrier females on the basis of this result.

Results
This patient was shown to have a 1kb product when amplified by PCR, consistent with the presence of the common deletion within the *IKBKG* gene.

Interpretation
The common *IKBKG* deletion product was detected

Figure 7: Genetic study report assessed by PCR.

She was asked to get a biopsy done. Biopsy findings were: Epidermis showed orthokeratosis with occasional dyskeratotic cells, without any intraepidermal blisters or inflammation or spongiosis. No melanin incontinence /

melanophages could be seen. Hence, biopsy report was labelled as nonspecific and was told to correlate clinically.

Figure 8: Cubital fossa of the baby 4 months later.

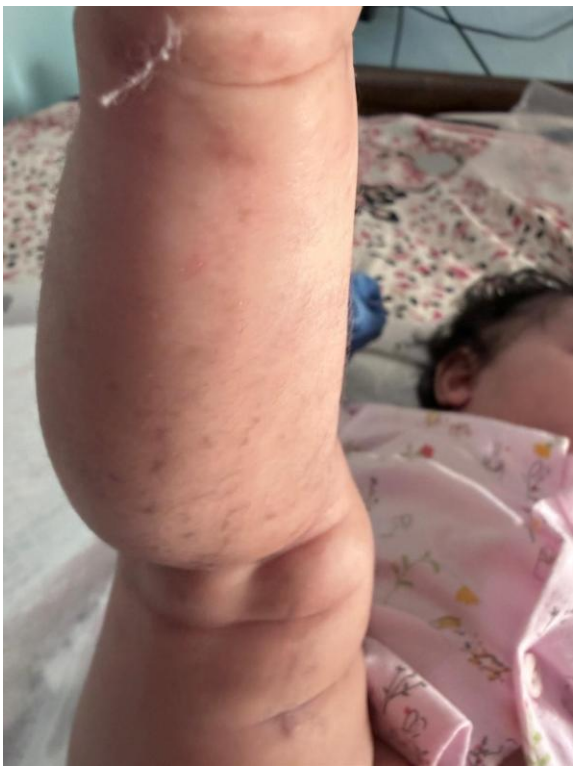


Figure 9: Linear hyperpigmention over lower limb 4 months later.

Because of strong clinical suspicion, patient was asked to get genetic screening done wherein patient was shown to have a 1 kb product which when amplified by PCR was consistent with the presence of the common deletion within IKBKG gene. Hence diagnosis of IP was confirmed (Figure 7).

Patient later presented at 4 months of age and now lesions have almost subsided with linear hyperpigmentation persisting over affected areas (Figure 8 and 9). Patient gives history of exacerbations and remissions during the past 3 months and were managed with mild topical steroids and topical antibiotics.

DISCUSSION

IP is a rare, multisystem ectodermal dysplasia inherited in an X-linked dominant pattern. The condition is driven by mutations in the IKBKG gene located at the Xq28 locus, which encodes a critical component of the nuclear factor kappa B (NF-κB) signaling cascade.[1]

Diagnosis is heavily guided by a distinct temporal evolution of skin lesions, which are often accompanied by systemic complications involving the teeth, eyes, and central nervous system (CNS), including mental retardation, microcephaly, spastic paralysis, and seizures.[1,2]

The dermatological progression of IP is its diagnostic hallmark, presenting in four distinct but overlapping phases:[2]

Stage 1

Vesiculobullous

Emerging during the first few months of life, this phase features recurrent, sterile, eosinophil-rich blisters. These present in a linear distribution along the lines of Blaschko, primarily on the inner limbs. Necrotic keratinocytes are a prominent histological feature.

Stage 2

Verrucous

Developing roughly 2 to 6 weeks post-delivery, this stage is characterized by linear, wart-like (verrucous) growths on the distal extremities. Similar to the first stage, necrotic keratinocytes remain prominent.

Stage 3

Hyperpigmented

Typically appearing between 12 and 26 weeks as the initial inflammatory stages subside (though it can occasionally be present from birth), this phase brings

hyperpigmentation to the trunk and skin folds. These changes generally persist through adolescence.

Stage 4

Hypopigmented/atrophic

Presenting anytime from early adolescence into adulthood, this final stage leaves pale, hairless, and atrophic streaks or patches, most commonly on the calves.

Extracutaneous manifestations include as following.[1-6]

Dental

Affecting 50% to 75% of individuals, dental anomalies are common and include delayed eruption, missing teeth (hypodontia), and peg-shaped or conical teeth. Prompt dental intervention is recommended to improve outcomes.

Ophthalmologic

Eye abnormalities occur in roughly 20% to 77% of cases, predominantly manifesting as retinopathy. Key issues involve retinal vascular defects (such as avascular zones, abnormal looping, anastomosis, and reduced macular blood density).

Other reported issues include cataracts, strabismus, optic nerve atrophy, microphthalmia, and the retinal detachment.

CNS

About 33% of patients experience neurological complications like developmental delays, spastic paresis, and seizures. Routine neurodevelopmental monitoring and pediatric neurology consultations are vital.

Hair and nails

Occurring in 28% to 38% of cases, appendage anomalies include sparse hair growth, hypoplastic eyebrows and eyelashes, and scarring alopecia (most often on the scalp's vertex). Nail dystrophy and fibromas may also develop.

In contrast to the extensive systemic complications often associated with IP, our newborn patient currently demonstrates an isolated cutaneous presentation.

Skin

The patient exhibits the classic progression of early-stage IP, starting with neonatal erythematous blisters containing eosinophils, which have subsequently healed, leaving linear pigmentation across the extremities.

Ocular and CNS

At present, the infant displays normal ophthalmologic and clinical neurological functions. Furthermore, there is no family history of neurological disease.

Appendages

Because the patient is a newborn, no hair or nail abnormalities have been observed yet. Additionally, neither parent exhibits any history of hair or nail involvement.

CONCLUSION

Although presenting with isolated cutaneous IP and no current systemic complications, this patient requires long-term multidisciplinary monitoring (pediatric neurology, ophthalmology, and dentistry) due to the disease's progressive nature.

This case highlights the need to suspect IP in neonates with vesiculobullous lesions following Blaschko's lines, and emphasizes genetic screening as the definitive diagnostic tool when histopathology is nonspecific.

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