

NEONATAL INCONTINENTIA PIGMENTI – A CASE REPORT

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Abstract

Incontinentia pigmenti or Bloch-Sulzberger syndrome, is a rare multisystem, X-linked dominant disorder that most commonly occurs in female newborns. It is usually lethal, and most pregnancies with male fetuses result in miscarriage or stillbirth, while in female newborns, it can appear with different severity and multiorgan symptoms, including dermatological, neurological, ophthalmological, and dental abnormalities. Skin changes usually appear immediately after birth or in the first few weeks of life, following four stages: vesicular, verrucous, hyperpigmented, and hypopigmented. In the neonatal period, IP is clinically diagnosed based on the appearance of vesicles arranged in a linear pattern following Blaschko's lines, representing the first stage of skin involvement. The differential diagnosis of a vesicular eruption in a neonate is extensive and includes various infectious and non-infectious causes.

We report a case of a one-day-old female neonate who presented at birth with erythematous vesicles linearly distributed on the extremities, over the thorax and abdomen. Based on suspicious Blaschkoid skin lesions and eosinophilic skin infiltration in biopsy, incontinentia pigmenti was diagnosed.

Early recognition of IP is crucial for appropriate management and monitoring of potential complications, particularly those involving the central nervous system and eyes. Although there is no specific cure for IP, a multidisciplinary approach involving dermatologists, neurologists, ophthalmologists, and dentists can help optimize the quality of life of affected infants.

Keywords: incontinentia pigmenti, erythematous linear vesicles, Bloch-Sulzberger syndrome

Introduction

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare multisystem, X-linked dominant disorder that seriously affects skin, teeth, hair and the central nervous system. It is usually lethal, and most of the pregnancies with male fetuses result in miscarriage or stillbirth, while in female newborns it can appear with different severity and multiorgan symptoms ^[1,2]. In our case, the female predominance and the history of two male children born with skin lesions who died in the neonatal period suggest an X-linked dominant transmission.

Rarely affected surviving males are attributed to the presence of an extra X chromosome (Klinefelter's syndrome /XXY syndrome) or as a result of a mutation in some of

the body's cells (somatic mosaicism) with relatively mild effects^[3]. In the neonatal period, IP is clinically diagnosed based on the appearance of vesicles arranged in a linear pattern following Blaschko's lines, representing the first stage of skin involvement. These lesions are commonly seen at birth.

Case report

A female newborn was admitted to the neonatal department immediately after birth for vesicular skin lesions on the trunk and upper and lower limbs. She was born on term, after a regularly controlled, uncomplicated pregnancy, by vaginal delivery. The Apgar scores were 9 and 10 in the first and fifth minute. The birth weight was 3280 gr (at the 50th percentile), the length was 50 cm (at the 50th percentile). She was the first live child from a 28-year-old mother, who had a history of two male children born with skin lesions who died in neonatal age. The presenting signs in this newborn were multiple vesicular skin lesions on the trunk and upper and lower limbs with a linear distribution.

Physical examination showed multiple vesicles on the lower left limb, some with serous, surrounding erythema, and linear hyperpigmented lesions (Figure 1&2).



Fig. 1. The linear and whorled, Blaschkoid cutaneous appearance of the skin lesions



Fig. 2. Crops of erythematous vesicles were also noticed over the thorax, abdomen, and upper limbs .

No oral or mucous membrane lesions were identified. She had no fever, irritability or neurological symptoms.

The laboratory test showed no abnormalities in electrolyte levels and complete blood count, except for peripheral eosinophilia (>20%). C-reactive protein was normal. Serologic tests for toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (TORCH) were normal. Bacterial cultures of the blood and skin lesions were negative. A biopsy of a vesicle on the leg showed epidermal spongiosis with migration of numerous eosinophils within the

epidermis (eosinophilic spongiosis), intra-epidermal blisters filled with eosinophils and granulocytes.

Based on suspicious Blaschkoid skin lesions and eosinophilic skin infiltration in biopsy, incontinentia pigmenti was diagnosed. The treatment consisted of topical antiseptic therapy with 1 % Eosin once daily every other day and antibiotic ointment Mupirocin every second day. The patient was regularly followed until four months of age. A physical exam revealed only a linear crusty lesion on the lower left limb; other lesions resolved completely.

Discussion

IP is caused by a mutation in the *NEMO/IKK- gamma* gene, an inhibitor of nuclear factor kappa B [NF-κB] kinase subunit gamma gene located on chromosome Xq28. NF-κB is central to many immune, inflammatory and apoptotic pathways^[4,5]. In our case, the female predominance and the history of two male children born with skin lesions who died in the neonatal period suggest an X-linked dominant transmission. Even without genetic studies, the combination of suspicious Blaschkoid skin lesions and eosinophilic skin infiltration on biopsy were sufficient to diagnose IP, according to the IP diagnostic criteria. However, genetic analysis should be performed for prenatal diagnosis and counseling for future pregnancies.

The most notable symptom during the neonatal period is skin lesions, usually present at birth and characterized by a linear pattern of erythema occurring along Blaschko lines. Vesicles and bullae appear on the extremities and trunk. These vesicles may vary in size from 1 mm to 1 cm or more, and pustules may also occur. Lesions like these usually evolve into a second stage, which is manifested with verrucous papules and plaques. This stage occurs in the first month and disappears within 6 months^[6].

Classically, skin lesions evolve through four stages: vesiculobullous eruption, verrucous lesions and hyperpigmented and hypopigmentation macules^[1,2,7].

The first stage, vesiculobullous, is presented at birth or within the first 2 weeks of life in 90% of patients and is characterized by a rash of erythematous blisters linearly distributed on the extremities, trunk, and scalp^[1,8,9]. The skin lesions follow Blaschko's lines, representing the routes of embryonic cell migration^[8]. Histologically, this phase is characterized by eosinophilia with dyskeratotic keratinocytes^[1,2,10].

The second stage, characterized by the eruption of hyperkeratotic verrucous papules and plaques, develops over the healing blisters and affects lower limbs^[1,2,8,9,11]. Histologically, it is characterized by acanthosis, papillomatosis, and dyskeratosis, which may last several weeks^[2,8,10,11].

The third stage, hyperpigmented linear skin lesion following Blaschko's lines, is the hallmark of IP. They usually appear between 3 and 6 months of age and manifest over a few months or years. However, their onset is highly variable, with some reports appearing even in the neonatal period^[12,13]. The presence of dermic melanin is a typical finding^[11].

The fourth phase of hypopigmentation can begin in childhood throughout adolescence. It is permanent and consists of hairless, anhidrotic patches and streaks, with or without atrophy, on the flexor surface of the lower limbs^[1,8].

The newborn may exhibit any of these stages because the early stages can occur in the uterus^[2,7,14].

Typical skin lesions and exclusion of an infectious etiology, as in our case, necessitated a skin biopsy for histopathological examination. The marked dermal eosinophilic infiltrates with epidermal spongiosis (eosinophilic spongiosis) and some apoptotic (dyskeratotic) cells were characteristic findings of the first vesicular stage IP^[5].

The differential diagnosis for the skin manifestations of IP varies by stage. Because a child with IP may have an infectious comorbidity, findings consistent with an infectious disease should be evaluated accordingly, regardless of the presence of IP.

A common differential diagnosis for the first stage of IP is congenital herpes simplex, where the skin changes have similar vesicular morphology (clusters or coalescing 2-4 mm vesicular lesions with surrounding erythema), but without linear distribution. It is usually transmitted during vaginal birth, presenting as a vesicular rash on the face or scalp in the first 7-10 days of life^[15].

Bullous impetigo, a bacterial skin infection caused by *Staphylococcus aureus*, should also be explored in differential diagnosis. It initially presents with vesicles that rapidly enlarge and form blisters more than 5 mm in size. After the blisters burst, a thin crust appears as an arch.

Erythema multiforme (EM) is another dermatologic condition frequently encountered in children. Its characteristic round target lesion usually has two rings surrounding the dusky-appearing central zone. Atypical lesions can be bullous or crusty, mimicking the appearance of stage I or II IP.

Other neonatal skin conditions, such as erythema toxicum neonatorum and eosinophilic pustular folliculitis can result in eosinophilic skin infiltration. Still, they can be readily differentiated clinically by their transient, non-evolving nature, predominant pustular appearance and non-blaschkoid distribution. Eosinophilic skin infiltration may be seen in several conditions, including allergic contact dermatitis, bullous pemphigoid and insect bite reactions^[16].

This eosinophilic infiltration is due to an eosinophil-selective, NF-κB-activated chemokine, eotaxin, which is released in the inflammatory cytokines^[17].

In our case, the eosinophil count in peripheral blood was significantly increased by >20% (normal range 0-10%), which is usually associated with dermal infiltration. The peripheral eosinophilia seen in the early stages of IP may result from the production of eotaxin, an eosinophil-selective cytokine, during the inflammatory cascade that results from a loss of NEMO/IKK—gamma activity. Activation of eosinophils with subsequent release of cellular proteases may trigger the development of the vesicular stage of IP^[17].

Other organs may also be affected in various ways in patients with IP. These manifestations may not be seen or recognized until infancy or early childhood.

The most affected system other than the skin is the central nervous system in 10-40% of patients. Seizures are the most common neurological complication that usually develop within the first few weeks of life and are associated with poorer prognosis. Other CNS manifestations include slow motor development, microcephaly, ataxia, mental retardation, spastic paralysis, cerebral atrophy, cerebral microangiopathy and hemorrhagic strokes^[2,7,8].

Ocular disease may occur in about 35% of patients with IP, manifested by strabismus, microphthalmia, pigmentary retinal changes, retinal vessel anomalies with areas of ischemia, and cataracts. It typically appears before 5 years of age^[2,9].

Other additional disorders include hair abnormalities in up to 50% of patients, such as alopecia, sparse hair, hypoplasia of eyebrows and eyelashes. Dental abnormalities occur in more than 80% of patients, manifested by delayed tooth eruption, hypodontia, dentition defects and peg-shaped teeth. Nails may be involved in up to 40% of patients, with dystrophy resembling onychomycosis and subungual fibromas associated with underlying bone deformities of the phalanges^[9,11].

In our case, other organs and systems were not affected. Neurological and ophthalmological examinations were performed with no abnormalities.

Diagnostic criteria for IP are divided into two groups: major criteria (typical neonatal vesicular rash with eosinophilia, typical Blaschkoid hyperpigmentation on the trunk, linear, atrophic hairless lesions) and minor criteria (dental anomalies, alopecia, woolly hair, abnormal nails).

In the absence of a family history, the presence of at least one major criterion is necessary. The presence of minor criteria supports the diagnosis of IP. With a positive family history, the presence of any major criterion strongly supports the diagnosis of IP^[7].

Skin lesions do not require specific treatment, although measures to prevent bacterial superinfection are necessary^[1,8]. In our patient, the therapy consisted of topical antiseptic treatment with 1% Eosin once daily every other day and antibiotic ointment Mupirocin every second day. The patient was regularly followed until four months of age. A physical exam revealed only a linear crusty lesion on the lower left limb; other lesions resolved completely.

When IP manifests by multisystem involvement, long-term, individualized, multidisciplinary follow-up is necessary, with evaluation and follow-up by dermatologists, neurologists, ophthalmologists, and dentists.

Generally, most patients with IP who did not suffer serious complications in the newborn period or through infancy can have normal life expectancy and lead a healthy life. The skin pigmentation usually fades and sometimes disappears completely.

In conclusion, IP must be considered as a diagnosis in any female newborn with vesicular skin lesions distributed linearly on the trunk and lower limbs at birth or during the first few weeks of life. Family history of similar skin lesions and male-gender abortion also supports this diagnosis.

Early recognition of IP is crucial for appropriate management and monitoring of potential complications, particularly those involving the central nervous system and eyes. Although there is no specific cure for IP, a multidisciplinary approach involving dermatologists, neurologists, ophthalmologists, and dentists can help optimize the quality of life of affected infants.

Conflict of interest statement. None declared.

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