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CASE REPORT

Incontinentia Pigmenti in a newborn: Case report and review of the literature

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Abstract:
Incontinentia Pigmenti (IP) is a rare X-linked dominant genodermatosis resulting from mutations in IKBKG gene, affecting primary females. Most cases present with early dermatologic changes, but clinical features can be found in hair, teeth, nails, eyes, and central nervous system (CNS). A typical 4 stages skin chronologic evolution occurs from the first weeks of life and may persist into adulthood: vesicobullous, verrucous/inflammatory, hyperpigmentar and atrophic (some stages may overlap). A distribution pattern along Blaschko's Lines (BL) is typical. We describe a newborn report focusing on the aesthetic relevance and we enhance an early and correct diagnosis based on reviewed literature. A 6-day-old female neonate presented with a progressive vesicobullous eruption in the trunk, limbs and scalp, as well as infected skin lesions. No systemic involvement was found and she underwent intravenous antibiotherapy. Inflammatory markers, blood culture and polymerase chain reaction (PCR) studies to herpes simplex virus (HSV) and varicella-zoster virus (VZV) were negative. Skin biopsy was compatible with IP and IKBKG mutation was confirmed. There was spontaneous regression of most skin lesions. She had no extra-cutaneous complications and growth and psychomotor development were satisfactory until 18-months-old. This report alerts to a rare disease with potential morbidity and great aesthetic relevance, often misdiagnosed and mistaken for more common neonatal skin infections.

Keywords: *Genodermatosis; IKBKG mutations; Incontinentia Pigmenti; X-linked dominant disorder*
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Introduction

Incontinentia Pigmenti (IP, OMIM 308300) or Bloch-Sulzberger Syndrome is a rare X-linked dominant disorder usually lethal in utero in males. Postzygotic mutation/somatic mosaicism is the likely mechanism in most surviving males [3]. IP is caused by familial (10-25%) or sporadic de novo (>50%) mutations of IKBKG gene on chromosome Xq28 [11]. A common exon 4-10 deletion underlies around 65% of affected individuals [10] and was present in our case. IP has been considered a neurocutaneous syndrome as a result of neuroectodermal changes. International incidence of IP is 1 case per 40,000 population, with a male-to-female ratio of 19-37 [8] and predominantly affects whites [7]. To date about 1200 cases had been reported [10]. A particular skin involvement presents from birth and associated findings have been described (table 1). Landy and Donnai (1993) first describe the four stages of dermatologic changes: stage 1 (vesicobullous) with erythema, vesicles, and pustules; stage 2 (verrucous/inflammatory) with papules, verrucous and hyperkeratotic lesions; stage 3 (hyperpigmented) with hyperpigmented streaks and whorls; and stage 4 (atrophic) with hairless, atrophic and scarring linear streaks or patches. According to data stage 3 can persist until adulthood but is not present at birth. Also a distribution pattern along BL is typical and not all

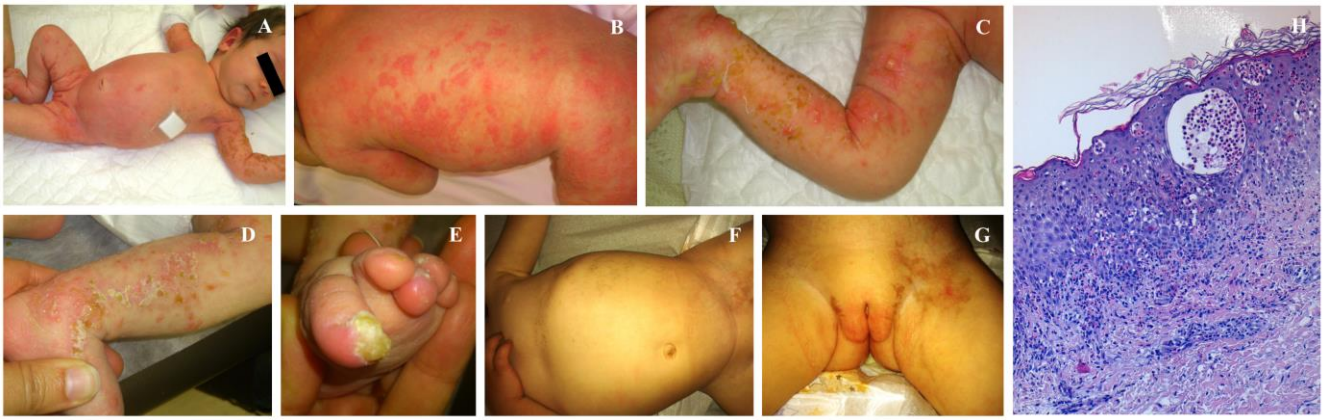

Figure 1. Incontinentia Pigmenti clinical stages: vesicobullous lesions - first stage (A,B,C); verrucous lesions and dystrophic nail- second stage (D,E); vortexed and hyperpigmented spots in trunk – third stage - (F,G). Skin biopsy (H): epidermis with spongiosis, exocytosis of numerous eosinophils and formation of intraepidermal vesicles. The superficial dermis contains a moderate perivascular inflammatory infiltrate consisting of eosinophils, macrophages and some lymphocytes. (HE 20x)

individuals experience all four stages which may overlap [10]. Minic et al. (2014) supported by Landy and Donnai (1993) presented clinical criteria for IP: major criteria are any of the 4 dermatological stages and minor criteria are dental, ocular, CNS, hair, nail, palate, breast, and nipple anomalies, as well as multiple male miscarriages and histopathologic skin features. Diagnosis is based on clinical criteria and supported by histological and genetic confirmation. Family history should also be taken into account.

Morbidity and mortality essentially result from extra-cutaneous ophthalmologic and neurologic complications, the last affecting approximately 30% of patients [9].

We report a case of IP in a newborn female with skin manifestations from the sixth day of life and review the literature.

Case report

An 11-days-old neonate, first female child of nonconsanguineous parents, born after an uneventful pregnancy and delivery, was brought to the Emergency Department because of progressive infected skin lesions for the last five days. Her mother had Polycystic Kidney Disease (PKD) and no history of miscarriage. On physical examination the newborn presented vesicobullous lesions in scalp, trunk and upper limbs along BL lesions in the lower limbs (Figure 1: A,B,C). She had no systemic involvement and the investigation found no blood inflammatory markers, negative blood culture and PCR for HSV-1, HSV-2 and VZV (scrapings of skin lesions). Skin biopsy was performed by a dermatologist at the fourth day of hospitalization and histologic examination revealed characteristic features of IP (Figure 1-H). The patient was healed with intravenous antibiotherapy for seven days (flucloxacillin) and topic fusidic acid with global improvement of skin injuries at discharge. At 2-months-old follow up, dystrophic nails changes were found and one month later linear warty lesions were present along the left lower limb, suggesting IP stage 2 (Figure 1: D,E). The persistent skin lesions were treated with topic corticosteroids as recommended in literature [5]. Genetic testing was performed and confirmed the diagnosis of IP by a heterozygous state for the deletion exons 4 to 10 of IKBKG gene. The child remains in regular follow-up by dermatology, pediatrics and ophthalmology consultations. General growth, neuropsychomotor assessment and teeth, hair and ophthalmologic examination showed no changes. At 18-months-age she presented with vortexed hyperpigmented spots in trunk and a melanocytic nevus in the inferior-nasal iris quadrant, suggesting IP stage 3.

Discussion

IP probable first case was reported by Garrod in 1906 and in 1926 Bloch and Sulzberger firstly defined this identity as a clinical syndrome with unique features that includes typical cutaneous manifestations [8]. The name of the condition derives from melanin incontinence by melanocytes which is seen in the superficial layer of the dermis in IP, in contrast to the usual disposition in the basal epidermal layer.

Table 1 Incontinentia Pigmenti diagnostic criteria [4, 5, 6, 7, 8, 10]	
Major criteria	**Minor criteria**
(1) Typical neonatal vesicular rash with eosinophilia	(1) Delayed dentition, anodontia, cone shaped teeth, absent teeth
(2) Typical blaschkoid hyperpigmentation on the trunk, fading in adolescence	(2) Scarring alopecia, wooly hair
(3) Linear, atrophic hairless lesions	(3) Dystrophic nails changes
	(4) Ocular anomalies: cataract, uveitis, optic nerve atrophy, strabismus, retinal fibrovascular proliferation and detachment
	(5) Nipple and breast anomalies
	(6) Skull and palatal defects
	(7) Central nervous system anomalies: microcephaly, mental retardation, learning disabilities, seizures, spastic palsy and slow motor development, spastic paralysis,
	(8) History of maternal multiple male miscarriages
	(9) Histopathologic features on skin: spongiotic dermatitis with many eosinophils and large dyskeratotic cells during the vesicular stage

Diagnosis of IP should be early suspected in a well neonate with characteristic skin features. Certain infections and genetic disorders must be differentiated from this condition because a different approach may be needed. In our case vesicobollus lesions and infected pustules were supposed to be caused primary by an infection, and were treated accordingly.

In the early stages of disease, abundant eosinophils and other histologic findings (Table 1) differentiates it from similar skin lesions of the newborn, such as erythema toxicum neonatorum, zosteriform herpes simplex and diffuse cutaneous mastocytosis [1].

Other systemic manifestations, including ocular problems, CNS and dental abnormalities, may not be recognized until infancy or early childhood. They occur in nearly 80% of patients [8].

Besides clinical findings, IP diagnosis is based on molecular genetic testing of IKBKG whose mutations represent 85% of the affected patients [11]. A deletion that removes exons 4 through 10 of IKBKG is present in approximately 65% of affected individuals [10] and was reported in our case.

Revised diagnostic criteria of IP are present on Table-1 and the importance of IKBKG mutations and family history should be highlighted.

If IKBKG mutation status is unknown, and IP is not present in a first-degree female relative, at least 2 major criteria or 1 major and at least 1 minor criteria are required to make the diagnosis of IP. If IKBKG mutation status is unknown but IP is present in a first-degree female relative, then any single major criteria or 2 minor criteria are required to make the diagnosis. If IKBKG mutation has been confirmed, the presence of any major or minor criteria is required to make the diagnosis [8]. We did not find any relationship between renal cysts and IP.

Cutaneous lesions usually do not require treatment, although tacrolimus and topical corticosteroids are reported to hasten its resolution [4,5]. Emollients and topical antibiotics are useful when secondary bacterial infections are present.

General dentists could provide screening for dental complications and restorative dental care. Frequent ophthalmologic evaluations should be required (especially during the first year of life) and

techniques as xenon laser photocoagulation or cryosurgery could be used in retinal affections [2]. Seizures should be treated with anticonvulsants. It is supported that general pediatricians should perform regular neurodevelopmental assessments with referral to a neurologist or developmental pediatrician as warranted. If there is no evidence of CNS involvement, it is expected a normal neurodevelopment [7]. Finally, referral to geneticists is essential for genetic counseling.

This case demonstrates the importance of increasing awareness among neonatal skin lesions. According to previously literature, this disease is often misdiagnosed and mistaken for more common skin infections. An early and correct diagnosis of IP is crucial in reducing aesthetic impact by explaining it to family, as well as reassuming it´s probable improvement over time. The main goal in surveillance is to identify and control extra-cutaneous manifestations which are determinant for the prognosis.

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