Bloch-Sulzberger syndrome: a case report

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Abstract

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is a very rare genodermatosis characterized by typical skin lesions accompanied by dental, central nervous system, bone and ocular abnormalities. Incontinentia pigmenti is usually observed among women, as this X-linked dominantly inherited disorder is lethal in males. The hallmark feature of IP is cutaneous eruption along the lines of Blaschko, usually accompanied by neurological disorders. Apart from clinical features of the disease, skin biopsy is the best diagnostic tool to confirm the diagnosis. We present a case of a newborn with typical vesicular and then verrucous lesions affecting the lower legs.

Key words: incontinentia pigmenti, Bloch-Sulzberger syndrome.

Introduction

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is a very rare X-linked dominantly inherited genodermatosis predominant among females as it is usually lethal in males [1-6]. There are however single reports of male patients with IP and XXY karyotype [7, 8]. Incontinentia pigmenti was first described by Garrod in 1906 [9], and further defined by Bardach [10], Bloch in 1926 [11], Sulzberger in 1928 [12] and Siemens in 1929 [13], however only the names of Bloch and Sulzberger feature in the eponym. Incontinentia pigmenti is a multisystem, ectodermal disorder characterized by skin lesions (100%) accompanied by dental (90%), central nervous system (CNS) (40%), bone (40%) and ocular (35%) abnormalities. In 1993, Landy and Donnai [4], after they had evaluated a group of over 100 patients with IP, proposed the diagnostic criteria for this neurodermatosis, as shown in Table 1.

Dermatologic manifestations are among the most important signs of IP as skin lesions observed in almost all individuals with IP are relatively easy to diagnose [1-4]. Fortunately, skin lesions are the least damaging aspect of the disease and actually do not require any treatment as spontaneous resolution of lesions is one of the features of the disease. The hallmark feature of IP is cutaneous eruption along the lines of Blaschko that evolves in four distinct stages:

- 1st stage: inflammatory, erythematous, vesiculobullous lesions, usually configured in a linear pattern (birth to 1-2 weeks),
- 2nd stage: papules, verrucous lesions with hyperkeratosis (2-6 weeks),
- 3rd stage: hyperpigmentation of the skin (3-6 months),
- 4th stage: hypopigmentation and atrophy of the skin (2-3 decade).

One of the late manifestations of IP are subungual tumors of IP (STIPs), which usually appear after puberty, between 15 and 40 years of life [14, 15]. Subungual tumors of IPs are usually observed on fingers rather than on toes, and clinically resemble plain warts, epidermoid cysts, fibromas, keratoacanthoma (KA) and squamous cell carcinoma (SCC) [16]. Subungual tumors of IPs tend to destroy the underlying bone of the distal phalanx, due to pressure necrosis. Subungual tumors of IPs may be associated with a very intense pain due to fast growth. Although the histological picture of STIPs may cause misdiagnosis as it resembles KA or SCC, radiographic appearance with bone destruction in the distal phalanx without accompanying sclerosis or periosteal reaction may help to make the right diagnosis [16].

Case report

We present a full-term infant with cutaneous manifestation of IP. The girl was born by uncomplicated delivery as the first child of unrelated parents in the 40th week of pregnancy (Hbd 40+6), Apgar 9 points and signs of intrauterine hypotrophy (body mass at birth 2360 g). On the third day of life, she developed linear rash on the skin

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Table 1. Diagnostic criteria for incontinentia pigmenti

Family history	Major criteria	Minor criteria
No evidence of IP in a first degree female relative*	• Typical neonatal rash: – Erythema – Vesicles – Typical hyperpigmentation – Linear, atrophic, hairless lesions • Mainly trunk following the Blaschko's lines • Fading in adolescence (hypopigmentation) • Eosinophilia	Dental anomalies, alopecia, abnormal nails, retinal disease
Evidence of IP in a first degree female relative**	• Suggestive history or evidence of typical rash • Skin manifestations of IP – Hyperpigmentation – Scarring • Hair abnormalities – Hairless streaks – Alopecia at vertex – Woolly hair • Dental anomalies • Retinal disease • Multiple male miscarriages	

**At least one major criterion is necessary for diagnosis in cases with no apparent family history; minor criteria support the diagnosis, **presence of any one or more of the major criteria strongly suggests a diagnosis of incontinentia pigmenti in cases with definitive family history*

of the medial and lateral side of the left lower limb. Examination revealed numerous papules and discrete vesicles on an erythematous background. Within few days, lesions spread on the skin of the right lower limb and the left arm. A significant asymmetry in the distribution of lesions was observed, since mainly the left side of the body was involved, with solitary lesions affecting the left forearm and numerous lesions on the left thigh and lower leg and the Achilles tendon (Figures 1, 2). On the skin of medial sites of both thighs, linear lesions were symmetric and arranged along the lines of Blaschko. The examination of hair and nails did not reveal any abnormalities.

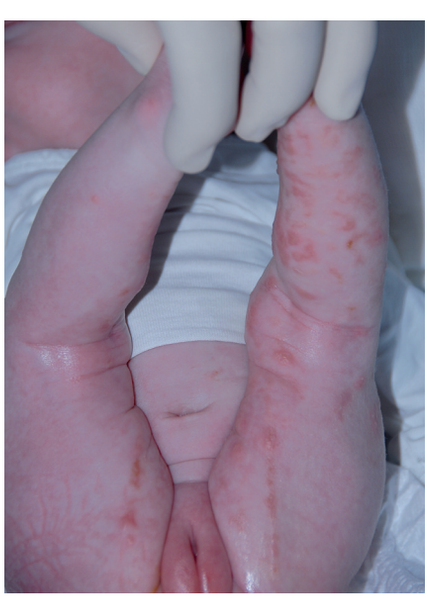

Figure 1. Erythematous lesions and papules on erythematous background arranged along the lines of Blaschko on the skin of the lower limbs

Diagnostic approach

A standard diagnostic approach in IP includes a skin biopsy with assessment of the nervous system and the organ of vision [1-4, 7, 8, 17, 18]. Neurologic examination revealed slightly increased muscle tone with no other anomalies. A cranial ultrasound did not reveal any abnormalities of the brain structures. On ophthalmological examination, the anterior chamber of the eye was normal, while scarce extravasations were observed on the fundus. The X-ray of the skeletal system did not reveal any abnormalities. C-reactive protein (20.47 mg/l) and leukocytes in the peripheral blood were elevated

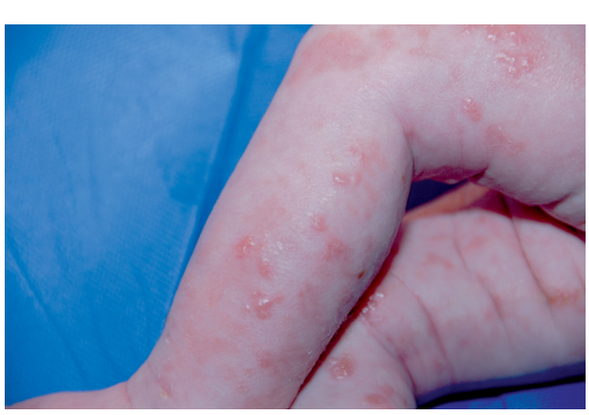

Figure 2. Erythematous lesions, papules and vesicles arranged along the lines of Blaschko on the skin of the lower limbs

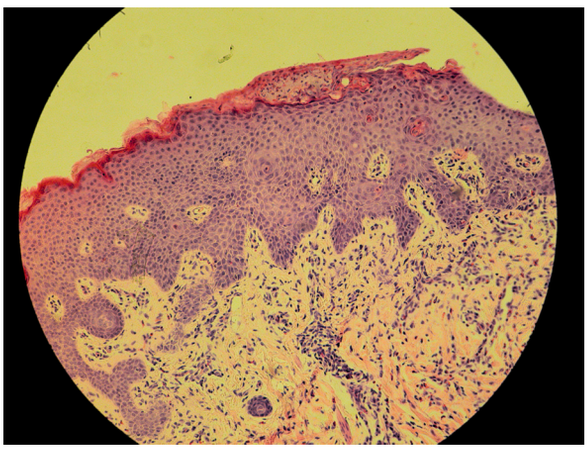

Figure 3. Vesicular stage of IP: subcorneal vesicle, epidermis with spongiosis, orthokeratosis, hypergranulosis and inflammatory infiltration of epidermis with leukocytes, histiocytes and eosinophils

(14.9-29.6 K/μl) as signs of pneumonia were observed in the first days of life. Additionally, glucose blood levels showed hypoglycemia (25-60 mg/dl). Intrauterine blood smear did not reveal eosinophilia, which is a significant sign in IP.

Histological examination of the skin biopsy

The skin biopsy was performed by a dermatologist on the 20th day of life. Histological examination revealed characteristic features of the first, vesicular stage of IP which are as follows: epidermis with spongiosis, orthokeratosis, hypergranulosis and inflammatory infiltration with leukocytes, histiocytes and eosinophils (Figure 3).

The skin biopsy in the vesiculobullous stage usually demonstrates inflammatory dermatitis, with subcorneal vesicles filled with numerous eosinophils, while the warty stage merely reveals hyperkeratosis and chronic inflammation of the dermis. Finally, the pigmentary stage demonstrates melanin, which is found in the dermis or engulfed by dermal macrophages. The study of Fraitag *et al*. [19] revealed that most of the 26 biopsies in the late stage (IV) of IP showed a slight atrophy and some scattered apoptotic cells in the epidermis, epidermal hypopigmentation and a reduced melanocyte number, while the dermis appeared thickened and homogeneous and revealed a complete absence of hair follicles (23/26) and sweat glands (22/26). Furthermore, in the investigated biopsies there was no melanin incontinence or inflammatory cells, and the elastic network was normal. Recently, eotaxin – an eosinophil-selective chemokine – has been identified in the epidermis of skin lesions of patients with IP [20].

Differential diagnosis

In the blistering stage, other blistering skin conditions should be excluded, such as common infections caused by *Herpes simples virus* (HSV) or *Staphylococcus aureus* (*Bullous impetigo* – BI). Skin lesions caused by HSV are characterized by closely grouped vesicles, which rupture easily leaving erosions, often covered with honey-like crusts due to the secondary bacterial infection. *Herpes simples virus* infection is usually not accompanied by systemic symptoms or any organ abnormalities. *Bullous impetigo*, and its generalized form – staphylococcal scalded skin syndrome (SSSS) – is a serious skin infection, due to action of exfoliative toxins produced by *S. aureus* which leads to the formation of pus-filled blisters. Lesions in BI are usually diffuse and accompanied by systemic symptoms. Nikolsky's sign may be observed and a very intense systemic treatment is necessary (systemic antibiotics *i.v.*). In the warty stage, IP may be confused with epidermal birthmarks (nevi) or warts. Epidermal birthmarks are not preceded by the onset of vesicles. In the pigmentary stage, sites of hyperpigmentation are uniquely arranged in whorls, which is why IP is unlikely to be confused with other causes of hyperpigmentation/discoloration of the skin [1-4].

Discussion

Incontinentia pigmenti is a familial, X-linked dominantly inherited, neurocutaneous syndrome. The perinatal incidence of IP is estimated at a level of 1 to 50 000 births, but it is probably higher. The disease is difficult to diagnose by non-dermatologists as it is sometimes confused with usually infectious conditions, such as HSV, BI or erythema toxicum [1, 17, 21]. The underlying defect in IP is a mutation in the essential modulator gene (NEMO), which results in the loss of activity of the regulatory component of the IκB kinase (IKK) complex encoded by the NEMO/IKKγ gene. Deletion of exons 4 - 10 is observed in 80% of patients with IP [8, 17, 21]. Thus, nonfunctional IKK abolishes activity of nuclear factor-κ B (NFκB), preventing the transcription of various target genes. NEMO seems to be involved in epidermal development and differentiation. This is why dysregulation of NFκB is suspected to play an important role in the pathogenesis of skin diseases, such as psoriasis, sunburn, Lyme disease, allergic contact dermatitis, autoimmune diseases and skin cancers [21].

Various phenotypes of patients with IP offer a great opportunity for expanding the current knowledge of the function of this transcription factor. It has been shown experimentally that the NFκB pathway is important in limb morphogenesis as well as odontogenesis and retinogenesis. This is why, apart from characteristic skin lesions, arranged in a linear pattern along the lines of Blaschko and evolving through 4 distinct stages, other systems are usually involved [1-4, 17, 18, 22-24]. Systems that may be involved in IP include as follows:

- the teeth – delayed eruption, microdontia, hypodontia, dysplasia,

- CNS – seizures, spasticity, mental deficiency, microcephaly,
- the eyes – uveitis, keratitis, cataract, retinal dysplasia, strabismus, retinal detachment, retrolental dysplasia, blue sclerae, pigment retinopathy,
- the musculoskeletal system – hemiatrophy, extra rib, hemivertebrae, kyphoscoliosis, syndactyly, short arms and legs,
- the hair – alopecia.

The high rate of neurological disturbances and blindness in the population of neonates with IP remains the most important challenge for clinicians. For that reason, newborns with the suspicion of IP should be carefully diagnosed by the ophthalmologist and neurologist as these disorders decrease the quality of life significantly. The variety of neurological symptoms is very wide, including recurrent strokes and acute disseminated encephalomyelitis [22-25]. Current results of neuroradiologic and histopathologic observations indicate that vascular anomalies in CNS might be responsible for neurologic complications in IP [23, 26, 27].

Chromosomal instability seen in IP patients may increase the risk of malignancy in young children [28]. Due to mutation in the NEMO gene, which protects against TNF-α-induced apoptosis, IP is considered as a pre-apoptotic state leading to male lethality and cell destruction in females. This may account for the dyskeratosis observed in the histological examination of verrucous lesions in the course of IP. Moreover, the late manifestation of IP, STIP, may clinically resemble keratoacanthoma, which is a pre-malignant condition, or even SCC [14-16]. In adolescents and young adults with IP, recurrent cases of SCC have also been described [29, 30].

Treatment options

There is no specific treatment. Most of the therapeutic methods are claimed to be ineffective as they do not hasten the resolution of any of phases in the course of IP. However, vesicubullous lesions which appear due to inflammatory infiltration of the epidermis (mainly with eosinophils) are expected to respond to topical treatment with corticosteroids. It was proved that topical steroids reduced the expression of eotaxin in the epidermis of patients with IP [20, 31]. Topical use of steroids and antiseptic agents (diflucortolone valerate, chlorquinaldol 1%) was observed to contribute to resolution of vesicular lesions [20, 31]. Furthermore, tacrolimus (0.1% ointment), a topical calcineurin inhibitor, has been reported recently to be an effective agent in the treatment of IP [32, 33]. According to Jessup *et al*., tacrolimus halted the progression of the disease through its subsequent disfiguring stages [32]. Even though systemic and topical antibiotics may show anti-inflammatory effects on the level of the skin, they are not effective in the course of IP, except for lesions with secondary bacterial infection [1, 8]. In patients with solitary STIP, the first-line treatment is surgical excision, though multiple new lesions appear in other locations. Moreover, the treatment with 5-fluorouracil injections with a good clinical outcome has also been reported [20]. Finally, therapy with retinoids is also worth considering as reports of resolution of lesions and growth of nails after the systemic treatment with acitretin (25 mg for 2 months) as well as topical application of retinoic acid were reported [16, 34, 35]. All-trans-retinoic acid (ATRA) regulates synthesis of NFκB components and activates apoptosis of various cell lines. Acitretin, which is a synthetic analog of retinoic-acid-receptor, prevents the formation of STIPs probably by inducing NEMO-independent mechanisms [36, 37].

Although skin lesions are the least damaging aspect of Bloch-Sulzberger syndrome, the proper diagnosis is very important, thus a careful head-to-toe clinical examination is critical in the evaluation of a child with suspected IP. Dermatological examination and diagnosis is the first step in the multidisciplinary approach including pediatricians, ophthalmologists, neurologists, dermatologists and dental consultants, which is recommended in patients with the suspicion of IP.

Photographs were used courtesy of Dr. Aleksandra Dańczak-Pazdrowska and Dr. Leszek Bartoszak.

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