A Case Report of Incontinentia Pigmenti in a Newborn with Positive Family History Extending Over Three Generations

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ABSTRACT

Background: Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare X-linked dominant genodermatosis that presents at the time of birth or soon after birth with cutaneous manifestation. This disorder may also affect the ectodermal tissues, such as the central nervous system, skeletal system, eyes, hair, nails, and teeth. The dermatological findings occur in four successive phases.

Case report: Herein, we presented the case of a two day-old female newborn with inflammatory vesiculopustular lesions on the right forearm and lower limbs, who was in a good general condition. The patient had a history of similar disease in three other members of her family, who had dental abnormalities as the most common non-cutaneous manifestation. This case report highlighted the importance of a detailed diagnostic workup for the newborns with pustular skin disease.

Conclusion: IP is a rare, x-linked dominant genodermatosis with multiple organs involvement. Dermatological abnormalities are the most prominent manifestation. The diagnosis is based on the clinical findings, the presence of positive family history of skin vesiculopustular lesions support the diagnosis. The skin lesions do not require specific treatment and prognosis depend to other organs involvement.

Keywords: Bloch-Sulzberger syndrome, Incontinentia pigmenti, Newborn, Pustular lesions, X-linked

Introduction

Incontinentia pigmenti (IP) or Bloch-Sulzberger syndrome is a rare genodermatosis that can have several cutaneous, dental, skeletal, neurologic, and ocular manifestations, including retinal detachment, seizures, paralysis, developmental delay, hair loss, and abnormal dentition. The locus of the IP mutation was shown to be present on Xq28 (IP online Mendelian inheritance of man [OMIM] No 308300) in 1989. Dermatological abnormalities are the most prominent manifestations of this disorder, developing through four stages, including vesicular stage, verrucous stage, hyperpigmentation phase, and atrophic phase (1, 2).

Although this condition is lethal for the affected males in utero, it presents overwhelmingly in the females as a result of mutant X chromosome inactivation. Lyonization of the X chromosome contributes to the reticular or whorled vesiculobullous pathognomonic pattern of IP. Eighty percent of the IP patients carry mutations in the NEMO gene, which codes for nuclear factor kB (NFkB) essential modulator. The NFkB is crucial for the regulation of tumor necrosis factor-induced apoptosis. Reactivation is believed to occur when specific triggers (possibly infection, fevers, or vaccinations) reactivate pathways in the residual mutant cells (3).

It is now possible to perform molecular analysis of the NEMO gene and skewed X chromosome inactivation. However, the diagnosis of IP is typically based on the characteristic clinical findings. Almost all the patients inflicted...
with this disorder are female; nevertheless, the affected male patients were reported to suffer from klinefelter syndrome (4).

The prevalence of IP was estimated to be 0.2 cases per 100,000 based on the data of 386 diagnosed IP patients, who were reported in the available literature published during 2000-2013 (5). Dental anomalies represent the most common non-cutaneous manifestation of IP in more than 80% of the patients. The frequently reported dental anomalies include hypodontia, microdontia (pegged and conically-shape teeth), delayed eruption, and accessory cusps, which could affect both primary and permanent dentitions (6).

**Case report**

A female newborn was admitted to the Neonatal Intensive Care Unit with vesicular skin lesions on the right forearm and lower extremities. She was a healthy child and the first baby of a 20-year-old mother, born of an uncomplicated term gestation through normal delivery. The Apgar scores were 8 and 9 in the first and fifth min, respectively. She had a birth weight of 3,200 g, length of 50 cm, and head circumference of 36 cm.

The newborn was hospitalized on the second day of her life due to multiple skin vesicular lesions, with some serous surrounding erythema as well as large and multiple Mongolian spot on the abdomen and leg with a non-linear distribution (figures 1-4). Given the suspicion of neonatal herpes and bacterial infections, acyclovir, vancomycin, and cefotaxime were prescribed. By the eight days of life, new lesions appeared with the same characteristics in linear distribution on the limbs. The patient was a well-appearing newborn since birth. The maternal serologies were negative for herpes and cytomegalovirus.

**Laboratory and clinical examinations**

Based the initial screening, the peripheral white blood cell count and eosinophilia were 23,300/mm³ and 18%, respectively. Furthermore,
the blood, urine cultures and C-reactive protein were negative. Additionally, the bacteriological test and PCR using cerebrospinal fluid were also negative for herpes simplex virus types 1 and 2. Skin lesions smear showed eosinophils and neutrophils of 60% and 40%, respectively.

The skin biopsy revealed orthokeratosis, severe spongiosis with exocytosis of eosinophils, and occasional dyskeratotic cells. In addition, the infiltrate containing eosinophils and melanin incontinence were observed in the superficial dermis (figures 5 and 6). On the neurological examination, the motor and mental maturation were normal. Visual fixation and optical tracking were also found to be normal. Furthermore, the results of the ophthalmologic observation performed by an ophthalmologist on the 20th day of age were reported to be normal. Likewise, the findings of the brain magnetic resonance imaging (MRI) were normal (Figure 7).

The mother examination revealed the presence of hyperpigmented linear lesions on the back and
concealed teeth (figures 8-10). Her family history revealed a sister, which led to the consideration of IP diagnosis, and also a maternal grandmother with a history of erythematous, vesiculopapular, and pustular skin lesion on the hand and foot, followed by dermal atrophy. She had also clinical manifestations of dental caries, early dental extraction, and hyperpigmentation on the abdomen with normal visual acuity and normal mental status (figures 11 and 12).

Discussion

The IP is an X-linked dominant disorder, which is usually male-lethal as all X-linked dominant diseases. IP is a rare multisystem disease, which is characterized by the abnormalities of the tissues and organs embryonically derived from the ectoderm and neuroectoderm. The pigment melanin is usually located in the melanocytes of the basal epidermal layer; however, this pigment is seen in the superficial layer in the IP (7). As indicated in our case and her affected family members, the female predominance suggests an X-linked dominant transmission.

The skin changes occurring in IP represent the major criteria of this disorder. These variations typically occur at birth or during the first weeks of life and continue to adulthood while distributing...
along Blaschko’s lines. All four members of this family had positive history of skin vesiculopustular lesion. Eosinophilia (as high as 65%) occurs in 65-88% of the cases with IP in the first phase, reverting in 4-5 months of age; however, in our patient, eosinophilia was mild (18%). Eosinophilia has been classified as a major diagnostic criteria of IP. Since eosinophilia is not pathognomonic for IP, it may only support the IP diagnosis (8).

Landy and Donnai proposed the diagnostic criteria for IP in 1993. These criteria were divided into two groups of negative family history and positive family history in a first-degree relative. In the absence of familial history, the presence of at least one major criterion is required, while the presence of minor criteria supports the diagnosis of IP. The complete absence of minor criteria leads to uncertainty in diagnosis (Chart 1). On the other hand, in case of positive family history, the presence of any criterion strongly supports the diagnosis of IP (Chart 2) (9).

Histopathological findings change according to the phase of the lesions. The first phase may be manifested with intraepidermal spongiosis with eosinophilic, neutrophilic, and rarely basophilic inflammatory infiltration. Large dyskeratotic cells are also usually present in this phase (7). The histopathological findings in our patient were compatible with the early phase.

Central nervous system is the most affected system after the skin in the IP patients, which is involved in about 10-40% of the cases and entails such symptoms as motor and cognitive developmental delay. Central nervous system disorder can have a major impact on the patient’s quality of life. There may be a correlation between the severity of ophthalmologic findings and the neurological phenotype (9). Our patient showed normal clinical neurologic and brain MRI results. Furthermore, there was no neurologic involvement in her family members.

Ocular diseases such as strabismus, microphthalmia, and pigmentary retinal changes may affect about 30-70% of the IP patients (9, 10). Vision loss has been associated with vascular occlusions, secondary extraretinal neovascularization, fractional retinal detachment, and foveal hypoplasia (10). However, our patient showed normal ophthalmologic findings.

Some reports suggest that abnormalities found in maternal dentition can act as a sensitive indicator of the nature of problems expected in the offspring, as shown in our patient’s mother and grandmother. The IP also entails hair abnormalities (e.g., alopecia, sparse hair, as well as hypoplasia of eyebrows and eyelashes), which have been reported in 28-38% of the patients inflicted with this disorder. Scarring alopecia, usually on the vertex, is the most common
manifestation of hair involvement (9). The IP can also involve nail and lead to such abnormalities as

**Chart 1. Diagnostic criteria for IP in the absence of familial history (Landy and Donnai, 1993)**

<table>
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<th>Major criteria</th>
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<tr>
<td>- Typical neonatal vesicular rash (e.g., erythema, vesicles, eosinophilia)</td>
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<td>- Typical hyperpigmentation (especially on the trunk, following the lines of Blaschko, disappearing in adolescence)</td>
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<td>- Linear atrophic alopecic lesions</td>
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<table>
<thead>
<tr>
<th>Minor criteria</th>
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<tr>
<td>- Dental abnormalities</td>
</tr>
<tr>
<td>- Alopecia</td>
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<tr>
<td>- Wooly hair, nail abnormalities</td>
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<td>- Retinal disorders</td>
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**Chart 2. Diagnostic criteria for IP in the presence of familial history (Landy and Donnai, 1993)**

<table>
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<th>Criteria</th>
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<tr>
<td>- Suggestive history or evidence of typical rash</td>
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<td>- Cutaneous manifestations of IP: hyperpigmentation, scarring lesions, atrophic lesions, and linear atrophic lesions with absence of hair and alopecia on the vertex</td>
</tr>
<tr>
<td>- Dental abnormalities</td>
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<tr>
<td>- Wooly hair</td>
</tr>
<tr>
<td>- Retinal disorders</td>
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<td>- Multiple abortions of male fetuses</td>
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dystrophy and fibromas. Nevertheless, no hair or nail involvement was observed in the family members of our case.

The diagnosis of IP is based on the clinical findings and differential diagnosis including neonatal herpes simplex infection, impetigo, neonatal bullous dermatoses, and autoimmune blistering. The skin lesions of IP do not require specific treatment, since spontaneous resolution of the lesions usually occurs. Although the bacterial superinfection should be prevented, the use of topical and systemic antibiotics for vesicular lesions is not recommended (9).

Regarding the scattered case reports conducted in Iran, there is limited data in this regard. As previously reported, despite the considerable progress that has been made in detailing the basic pathology of the IP disorder, there is a wide gap between the research and clinical care in this regard. Moreover, the paucity of the IP patients in each single diagnostic center makes it difficult to provide an overall epidemiological report. Therefore, the integration of scattered resources may be crucial for the success of future scientific accomplishments (11).

**Conclusion**

IP is a rare, x-linked dominant genodermatosis with multiple organs involvement. Dermatological abnormalities are the most prominent manifestation. The diagnosis is based on the clinical findings, the presence of positive family history of skin vesiculopustular lesions support the diagnosis. The skin lesions do not require specific treatment and prognosis depend to other organs involvement.

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**Conflicts of interests**

The authors of this manuscript certify that they have no financial or other competing interest concerning this article.

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