

Incontinentia Pigmenti: A Newborn with Characteristic Skin Lesions and Bilateral Optic Atrophy: Case Report and Review of Literature

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Abstract- Incontinentia Pigmenti (IP) is a rare X-linked dominant disorder with skin, eye, central nervous system (CNS) and tooth abnormalities. According to the reported cases, it is estimated that there have been nearly 900-1200 affected individuals. In this article, the literature is reviewed and a case of IP with characteristic skin lesions and optic atrophy is presented.

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Introduction

Bloch-Sulzberger disease or Incontinentia Pigmenti (IP) syndrome is a heritable, multi system ectodermal disorder, with characteristic dermatologic, central nervous system (CNS), dental and ocular abnormalities (1,3).

Over 80 percent of patients are caused by mutation, resulting in defective activation of nuclear factor-kappa B (NF- κ B, the transcription factor); an important pathway in the proliferative and apoptotic cellular mechanisms (2-4).

The condition influences dominantly female newborns. When male is affected, it is mostly lethal; and causes spontaneous abortion. However, cases have been reported of male patients with Klinefelter syndrome or with a mosaic karyotype for it (5,6).

Clinical manifestations of IP are classically divided in to the following 4 stages:

The first phase is apparent at birth or in the first few weeks of life. It appears with erythema, vesicles and blisters typically in a linear pattern; predominantly on the limbs. In this phase, blood eosinophilia as high as 65% of the white blood cells is common.

Second phase: The blisters become keratotic and dry, creating verrucous plaques.

Third phase: Hyperpigmentation that is mostly evident on the trunk than the limbs.

Fourth phase: Cutaneous atrophy and hypopigmentation, are as late manifestations of IP

(2,3,7,8).

All stages do not essentially occur in one patient. The inflammatory and hyperpigmented stages are the most common form of these cutaneous lesions (4,9,10).

Diagnosis of IP is made on clinical presentations (2,3). In 1993, Landy and Donnai recommended clinical diagnostic criteria for IP (11). The criteria based on whether the patient has a first degree with IP or not. If this relative exists, then only one of the following is required for the diagnosis of IP:

- Evidence or history of characteristic skin lesions
- Hairless, pale, atrophic linear skin streaks
- Dental anomalies
- Multiple male miscarriages
- Retinal disease

If there was not any affected first degree relative, diagnostic criteria are divided into major and minor classes.

Major criteria

Skin lesions that happen in stages from infancy to adult hood:

- Erythematous lesions followed by vesicles anywhere on the body (except the face), usually in a linear pattern.
- Hyperpigmented streaks and whorls distribute in Blaschko's lines, happening mostly on the trunk (sparing the face) and becoming pail in adolescence.
- Hairless, Pale, atrophic linear streaks or patches

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Incontinentia pigmenti: a rare multi systemic disorder

Minor criteria

- Hypodontia or anodontia, microdontia, abnormally shaped teeth
- Alopecia, coarse hair
- Mild nail ridging or pitting, hypertrophied curved nails
- Retinal abnormalities

If there are no affected individuals in the first degree relative, one major criterion and two or more minor criteria are required for diagnosis. If there wasn't any minor criterion, diagnosis other than IP should be considered (7,11).

We present a case of IP in a female infant with vesicubullous and verrucous skin lesions, presented when she was only one week old. Rarity of this syndrome with ocular and CNS abnormalities is the reason of reporting.

Case Report

A full term girl was born by vaginal delivery with a

weight of 2415 gram and OPGAR score of 8 at first minute. Physical examinations showed a neonate with no anomalies.

Her parents were not related. Her mother didn't report any complication during her prenatal care. She is 34 years old (Gravida3, Para 2, Ab1, D1) with a history of abortion in the second month of gestational age, two years ago. After 3 months, she became pregnant again, but her female fetus died in uterus in 34th weeks of gestational age without any reason (in autopsy no abnormal finding was reported).

Our case was first lived-child of this family. In this neonate, maculopapular rash was found on the back and the limbs, in the second day of life. Five days later, she developed linear vesicubullous lesions on proximal part of her limbs, which were extended to the distal parts during a few days. Some of bullous lesions were postulated (Figure 1).

Face, neck, mouth and upper chest were not affected. Hyperpigmented macules were presented on both thighs and lower trunk.



Figure 1. Linear vesicubullous lesions on the right upper limb.



Figure 2. Verrucous lesions and residual hyperpigmentation in left lower limb.



Figure 3. Hyperpigmented macules mostly in Blaschko's lines on the trunk.



Figure 4. Hyperpigmented verrucous lesion in the right sole.

After rupture of vesicles, these regions became darker than around areas during healing.

After one month of life, hyperpigmentation in lower trunk and verrucous lesions in lower limbs were the most prominent feature (Figures 2 and 3) and verrucous lesion in the right sole was appeared (Figure 4).

There was no similar case in her relatives. ECG and echocardiographic study showed no significant problem.

Ophthalmological evaluation showed bilateral optic atrophy. Because of possible associated abnormalities, brain MRI was requested.

In MRI that obtained after first month of life, hypersignal intensities were found in periventricular white matter and centrum semiovale. Dysgenesis of corpus callosum was reported. Follow up MRI imaging at 7th week of life, revealed no more additional abnormalities.

Laboratory studies revealed significant eosinophilia (58% of total WBC count, absolute eosinophil count was 30000) that is a common finding in vesiculobullous

phase. Other hematologic tests were within normal limits. Flow cytometric immunophenotyping analysis on peripheral blood performed for R/O hematologic malignancies. It revealed a lymphoid population about 40% of all leukocytes, composed of mature T and B lymphocytes and positive periodic acid shift in myeloid cells.

As she became older, eosinophilia was reduced and 2 months after birth, there was no eosinophilia in laboratory studies.

During follow up, she had recurrent seizures at 3 months of life and was hospitalized because of severe aspiration pneumonia subsequently. She died due to respiratory failure on the 4th day of admission, despite of supporting care and adequate treatment.

Although genetic studies and skin biopsy were not performed (the neonate parent didn't consent to the tests), according to the major criteria of IP diagnosis, clinical features and laboratory data were compatible with the diagnosis of IP.

Discussion

After the first explanations of IP by Bloch and Sulzberger, various cases of IP have been reported (8). The clinical manifestations have a wide distribution, ranging from fine cutaneous and dental changes, to severe neurological and ophthalmological manifestations.

92% of patients have the unique linear configuration skin rash by the age of 2 weeks (12). In the first year of life, the diagnosis of IP is difficult and there are many differential diagnoses, depending on the phase of the disease progression.

In the first phase, vesiculobullous lesions may be confused with those of bullous impetigo, herpes simplex or mastocytosis, but the linear pattern of lesions in IP is characteristic for this syndrome (2,3,13).

The second phase may be mistaken for epidermolytic hyperkeratosis and hyperkeratosis in the base of lichen striatus and skin infections. The third phase can be misdiagnosed with X linked chondrodysplasia punctata, nevoid hypermelanosis, dermatopathia pigmentosa reticularis and in the fourth phase can be confused with hypomelanosis of Ito and congenital cutis aplasia (6,14). The first and the third phase are more common than the other phases (7,9,15).

Even though dermatologic manifestations are the most important criteria for the diagnosis of IP, they have no prognostic value (16). Our patient initially presented with vesiculobullous lesions in the limbs that turned in to verrucous plaque and hyperpigmented macules mostly in Blaschko's lines on the trunk. The association of linear blisters and verrucous lesions on the child extremities in the first month of life, in association with eosinophilia is characteristic of IP (17). In one study, 88% of the patients with the diagnosis of IP had eosinophilia, with absolute eosinophil count (AEC) ranged between 55 and 15400/ml (7). In our patient, AEC was 30000/ml.

About 80% of affected individuals have ectodermal anomalies. The severity of this syndrome is related to neurological and ocular impairments (11,18). Ocular anomalies such as neovascularization, strabismus, microphthalmia, optic atrophy, cataract and retrolenticular masses happen in up to 30% of affected children (2,3). In Kim *et al.* study, ocular disorders and anomalies was observed in 66.7% of the patients and retinopathy was the most prevalent ophthalmologic problem (19). In Karth *et al.* study, retinal detachment

was the most commonly diagnosed eye finding in these patients (20). Prevalence of optic atrophy was reported about 5% in this syndrome (21-23).

CNS manifestations including seizure, spasticity and microcephaly are found in one third of the patients (2,3). The pathogenesis of the CNS involvement is still unknown, but small vessels occlusion, inflammatory mechanisms or both, has been suggested (24-27). Neonatal seizure and structural anomalies are at high risk for motor and cognitive impairments (28). Seizure is the most common CNS related manifestation of IP (7,19,28). In Hadj-Rabia *et al.* study, neurological impairments were found to be frequent (32%) and severe; causing death in 2 cases. In their study, hypoplasia of corpus callosum was noted in 17% of patients (7). Our patient's MRI revealed hypoplasia of corpus callosum and periventricular vasculitis. She had several episodes of seizure during the third month of life and finally she died because of respiratory failure and severe aspiration pneumonia due to seizure.

Since several cases of IP have been associated with ocular problems or cancer in childhood, long term follow up is necessary (29-31). It is important to detection of the rare neurological and ophthalmological involvements as early as possible.

Recently we heard about a new born baby girl in this family. So we called and ask them for visiting their 3 months infant. She had vesiculobullous skin lesions, which had been appeared right after birth. These lesions were in a similar pattern as the previous affected infant, but with less severity. Her general physical examination was normal and in her ophthalmological examination, there was no pathologic finding. It seems that this infant was the second lived-birth of IP in this family. Unfortunately, we didn't have the parent's agreement for more evaluations.

There are a few cases of familial IP in the literature. Spallone reported 14 cases of this syndrome in the three generation of one family (32) and Phan *et al.*, reported 18 cases of female cases of IP that were relatives of 25 female probands (9). In conclusion, IP should be considered in the differential diagnosis of patients with cutaneous lesions, optic and CNS involvements, such as those clinical features, seen in our patient.

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