Incontinentia Pigmenti: Case Report

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SUMMARY Incontinentia pigmenti or Bloch-Sulzberger syndrome is a rare X-linked dominant disorder with characteristic skin, hair, eye, dental and neurologic abnormalities mostly affecting females. We report a case of a female newborn exhibiting characteristic cutaneous and neurologic findings with one-year follow-up.

KEY WORDS: incontinentia pigmenti, NEMO/IKBKG, newborn

INTRODUCTION

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare X-linked dominant genodermatosis. It is a multisystem, ectodermal and mesodermal disorder accompanied by dermatologic, dental and ocular features and in a minority of cases may be associated with neurologic deficit (1-4). Mutation of NEMO (NF-kappa-B essential modulator), also known as IKK-γ/IKBKG (inhibitor of nuclear factor kappa-B kinase subunit gamma) gene located on chromosome Xq28 is believed to play a role in the pathogenesis (5). NEMO/IKK-γ helps activate NF-κB, which controls the expression of multiple genes, including cytokines and chemokines, and protects cells against apoptosis (6-8). A lack of NEMO/IKK-γ therefore causes a lack of active NF-κB, which makes cells more prone to apoptosis.

In this report, we describe a case of IP in a female infant with dermatologic and neurologic signs of early onset neonatal seizures and verrucous skin lesions.

CASE REPORT

A of 19-day-old female infant was born at full-term by normal vaginal delivery with no history of consanguinity in the parents. The baby was referred to the hospital for evaluation of seizures and abnormal skin lesions. According to her parents, the infant developed partial seizures in the arms, legs and face about 10 times before coming to the hospital. Each time, the seizures lasted for 1 to 2 minutes. The girl was also reported to have erythematous vesicular eruptions on the upper and lower extremities since she had been 12 days old. Skin lesions were noticed to be of a linear pattern, mostly seen on the limbs, and developed increasingly over the next 7 days (Figs. 1 and 2). The mother denied the presence of any skin rash at birth. There was no history of fever or cold since the infant's birth.

The mother was a healthy G2P1 with a history of spontaneous abortion. She denied any similar sign in family members. However, the mother presented

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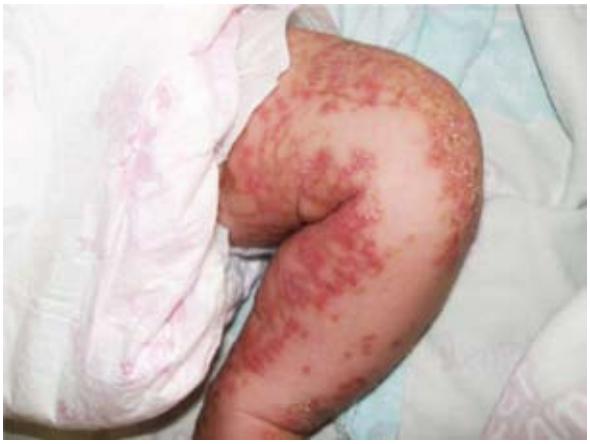

Figure 1. Linear vesiculobullous skin eruption with erythematous base on both legs on the first day of the patient's presentation to the hospital.

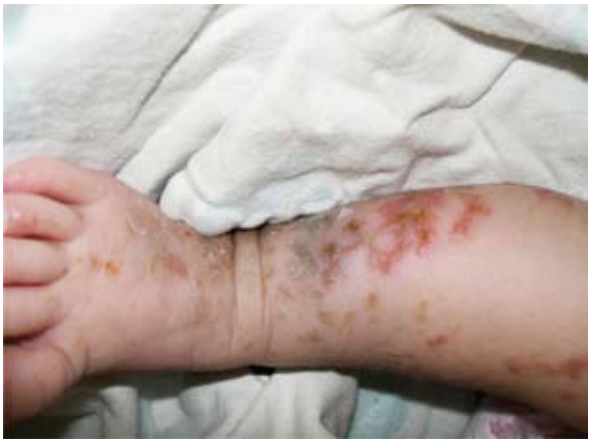

Figure 2. Multiple vesicles, firm and yellowish, with inflammatory linear distribution on the left leg.

some faint hypopigmented atrophic linear lesions on both thighs, which she believed had appeared in her childhood.

Laboratory tests revealed no abnormalities in whole blood count, C-reactive protein, serum electrolytes and glucose, although eosinophil count was as high as 32% (normal range, 0-10%). The infectious cause was excluded (VDRL test performed in the child and her parents was non-reactive). Electroencephalogram (EEG) showed epileptiform discharges with sharp waves and sharp, slow complex waves in the right hemisphere. However, computed tomography (CT) scans of the brain appeared normal. Other systemic examination including ocular and skeletal system revealed nothing abnormal. Histopathology of a skin biopsy showed spongiotic dermatitis with massive intraepidermal eosinophilia in the presence of eosinophil-filled intraepidermal vesicles, as well as infiltrate of lymphocytes in superficial dermis (Fig. 3).

Based on all these findings, definitive diagnosis was IP. The seizures were treated with phenobarbital and no special treatment was administered for her skin lesions. The seizures ceased after 2 days of antiepileptic treatment. She stayed in the hospital for another 10 days for observation and no other central nervous system reflection abnormality was detected. Then the patient was discharged from the hospital,

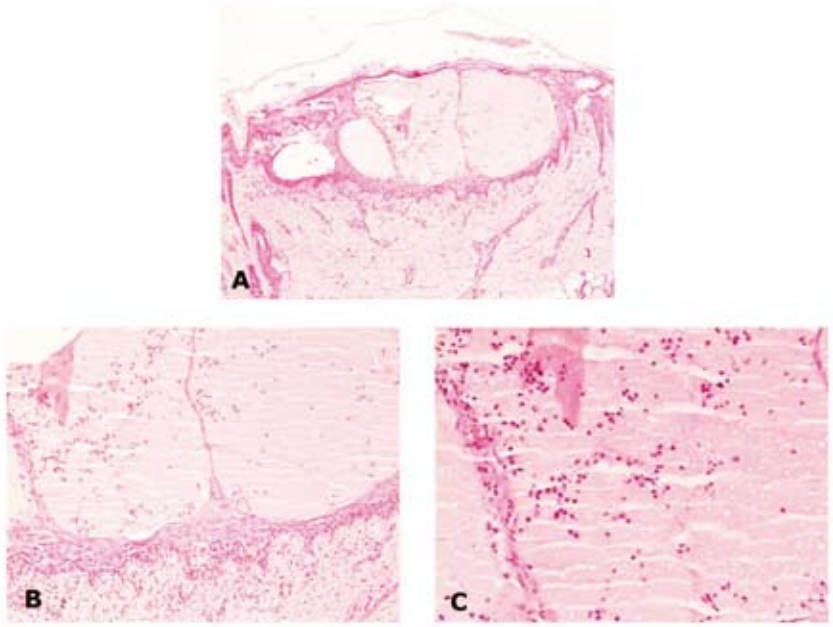

Figure 3. Histopathology of the skin biopsy showed spongiotic dermatitis with massive intraepidermal eosinophilia in the presence of eosinophil-filled intraepidermal vesicles, as well as the infiltrate of lymphocytes in superficial dermis (A-C); (hematoxylin and eosin staining; original magnifications: A, ×10; B, ×20; C, ×40).

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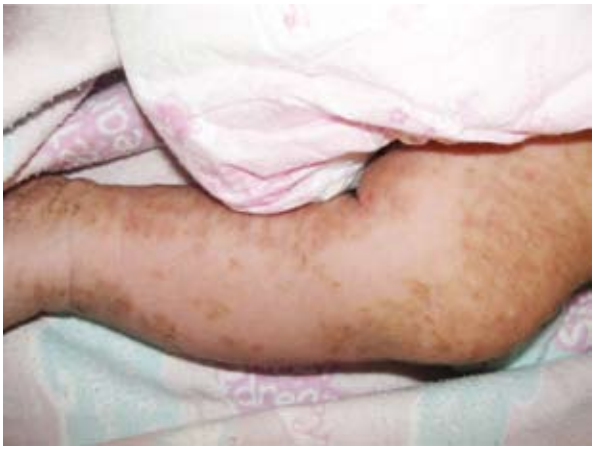

Figure 4. Hyperpigmented lesions on the left leg following the lines of Blaschko ten days after the patient's admission to the hospital.

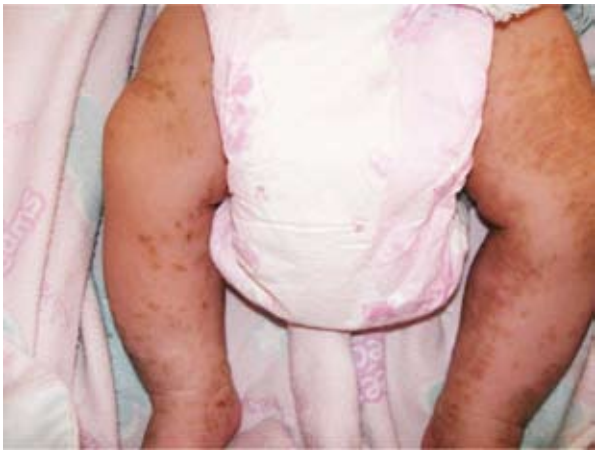

Figure 5. Verrucous lesions with hyperpigmented streaks of the leg ten days after the patient's admission to the hospital.

while her skin lesions mostly became verrucous with additional hyperpigmented streaks (Figs. 4 and 5). There were no new skin rashes.

At present, the girl is aged 16 months and undergoing complete medical follow-up on a regular outpatient basis including checkups at departments of pediatrics, dermatology, ophthalmology, and rehabilitation medicine.

DISCUSSION

Incontinentia pigmenti is inherited in an X-linked dominant manner. Therefore, more than 95% of the patients are female infants (9). In males, it is usually lethal and most of the affected male fetuses result in miscarriage or stillbirth (4). 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 (10). In our case, although there was no information on the fetus's sex, the history of miscarriages might be a result of IP. Incontinentia pigmenti is hereditary in 10%-25% of cases (11).

Dermatologic findings are often the first observed sign of IP and are present in nearly all patients (7). In most cases, the onset of skin changes is before 6 weeks of age (4). Progressive cutaneous manifestations are the main clinical feature of the disease and classically evolve through 4 stages. However, their sequence is irregular and some of may overlap with others or not appear at all. Stage 1 (vesicular stage) is presented at birth or within the first 2 weeks in 90% of patients and is characterized by a rash of erythematous blisters, which often appear to be grouped along the lines of Blaschko. Biopsy characteristically exhibits spongiotic dermatitis with massive intraepidermal and dermal eosinophilia (7). Stage 2 (verrucous stage) occurs in about 70% of patients. Eruption of hyperkeratotic verrucous papules and plaques develops over the healing blisters. It usually appears within 2 months and disappears within 6 months. Hyperkeratosis, dyskeratosis, acanthosis and papillomatosis are present in this stage (11,12). Stage 3 (hyperpigmented stage) is classically the hallmark of IP. Nearly 98% of patients experience stage 3. Pigmentation ranges from blue-grey or slate to brown, and occurs in streaks or whorls. It generally develops within the first few months of life and tends to fade by adolescence. Melanophages in the dermis and vacuolization of basal cells is the most common finding (4,13). Stage 4 (atrophic/hypopigmented stage) occurs in adolescence and persists into adulthood. Pale, hairless patches or streaks, sometimes scar-like lesions are mostly found on lower legs. Such changes are mostly permanent and often the only sign of skin involvement in adult patients. It presents as atrophy and thinning of the epidermis with the absence of skin appendages (4,14-16).

The vesicular stage is most often observed at birth or within the first two weeks of life in IP, which coincides with our case. The patient presented with stage 1 and gradually developed to stages 2 and 3. According to the follow-up, we believe that the hyperpigmented stage is still the current clinical presentation of the patient. Since the patient is only 16-month-old, she may still develop into stage 4.

Cutaneous lesions may also be accompanied by defects of cutaneous appendages in the form of vertex alopecia, ridged, pitted, or dystrophic nails

(17). Extracutaneous manifestations occur in various ways in about 70%-80% of IP patients. Dental abnormalities are the most common types and affect more than 80% of patients with delayed dentition, partial anodontia, cone or peg shaped teeth or absence of teeth. Some 30%-50% of patients exhibit neurologic deficiency, identified as seizures, mental retardation, developmental delays, spastic paralysis, ataxia and motor dysfunction (18-20). Ocular abnormalities are also observed in around 30% of patients including strabismus, cataracts, optic atrophy, retinal dysfunction, uveitis, nystagmus and blindness. Skeletal and structural anomalies have occasionally been reported as well, such as somatic asymmetry, skull deformities, spina bifida, dwarfism, syndactyly, extra ribs, primary pulmonary hypertension, and cardiopulmonary failure. Keratotic tumors in late adolescence may involute spontaneously. Several cases of IP have been associated with cancer in childhood (21,22).

In our case, seizure was one of the first manifestations of the disease but no other signs were present. However, the presence of central nervous system involvement in the neonatal period is believed to be a poor prognostic sign. Anomalies may not appear at the initial evaluation but later on. Therefore, long-term follow-up with dermatology, pediatrics, neurology, ophthalmology and dentistry is crucial.

There are no standardized diagnostic criteria for IP yet. The diagnosis relies mostly on the characteristic skin lesions and other clinical findings. Therefore, timely recognition of IP by pediatricians and dermatologists is crucial. Skin biopsy and molecular genetic testing of the NEMO gene may help confirm the disease. Family history or a history of multiple miscarriages also supports the diagnosis of IP.

There is not specific treatment for IP yet. Although skin lesions are the most common manifestations and one of the most important aspects of the diagnosis, they are actually less damaging to the patients and tend to heal spontaneously. The management of systemic abnormalities is based on symptomatology. Support and corrective treatment should be used whenever possible.

CONCLUSSION

Long-term and close cooperation between dermatologists, pediatricians, neurologists, genetic counselors, and even dentists is crucial for better understanding of IP and prediction of the occurrence of the potential anomalies later in life (13).

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