

## Incontinentia Pigmenti: Case Report

\**Xiuli Li, \*Xiuxiu Wang, Junying Gu, Zhiyu Liu, Yuling Shi*

Department of Dermatology, Tenth People's Hospital, Tongji University, Shanghai, China

### Corresponding author:

Yuling Shi, MD

Department of Dermatology, Shanghai Tenth People's Hospital

Tongji University School of Medicine

301 Middle Yanchang Rd.

Shanghai 200072

China

[tomorrowkexuejia@gmail.com](mailto:tomorrowkexuejia@gmail.com)

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\*Both authors contributed equally to this work

**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/IKBK, 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- $\gamma$ /IKBK (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- $\gamma$  helps activate NF- $\kappa$ B, which controls the expression of multiple genes, including cytokines and chemokines, and protects cells against apoptosis (6-8). A lack of NEMO/IKK- $\gamma$  therefore causes a lack of active NF- $\kappa$ B, 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 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



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



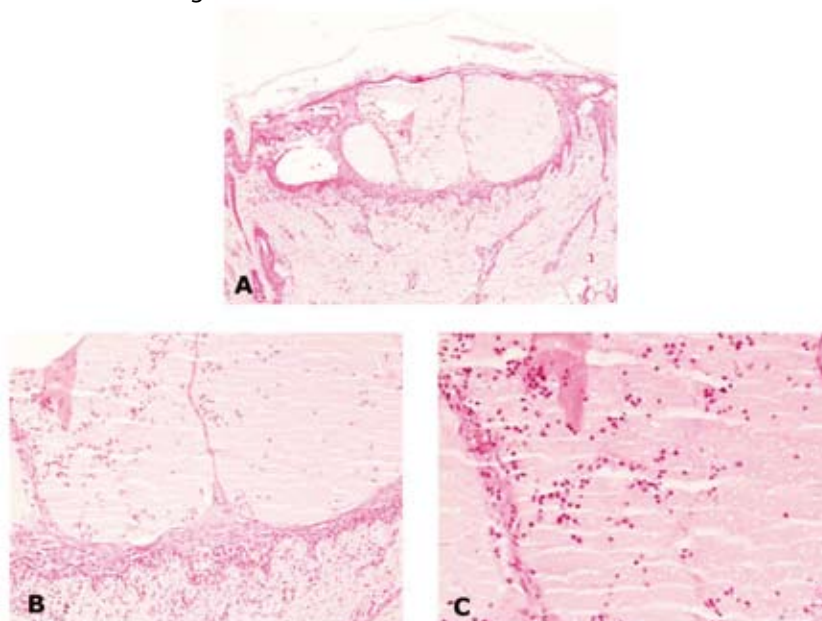
**Figure 2.** Multiple vesicles, firm and yellowish, with inflammatory linear distribution on the left leg.

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 anti-epileptic 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,  $\times 10$ ; B,  $\times 20$ ; C,  $\times 40$ ).



**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.

## CONCLUSION

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).

## References

1. Carney RG. Incontinentia pigmenti – a report of five cases and review of literature. *Arch Dermatol* 1951;64:126-35.
2. Pavithran K, Ramchandran P, Zochariah J. Incontinentia pigmenti. *Indian J Dermatol Venereol Leprol* 1984;50:274.
3. Wiklund DA, William L, Weston L. Incontinentia pigmenti: a four generation study. *Arch Dermatol* 1980;116:701-3.
4. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *J Med Genet* 1993;30:53-9.
5. Jeang KT, Jin DY. Isolation of full-length cDNA and chromosomal localization of human NF-kappaB modulator NEMO to Xq28. *J. Biomed. Sci* 1999;6:115-20.
6. Smahi A, Courtois G, Vabres P, Yamaoka S, Huertz S, Munnich A, *et al.* Genomic rearrangement in NEMO impairs NF-kappa B activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000;405:466.
7. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol* 2002;47:169-87.
8. Nelson DL. NEMO, NFkappaB signaling and incontinentia pigmenti. *Curr Opin Genet Dev* 2006;16:282-8.
9. Carney RG. Incontinentia pigmenti. A world statistical analysis. *Arch Dermatol* 1976;112:535-42.
10. Ardelean D, Pope E. Incontinentia pigmenti in boys: a series and review of the literature. *Pediatr Dermatol* 2006;23:523-7.
11. Thakur S, Puri RD, Kohli S, Saxena R, Verma IC. Utility of molecular studies in incontinentia pigmenti patients. *Indian J Med Res* 2011;133:442-5.
12. Lee Y, Kim S, Kim K, Chang M. Incontinentia pigmenti in a newborn with NEMO mutation. *J Korean Med Sci* 2011;26:308-11.
13. Kim BJ, Shin HS, Won CH, Lee JH, Kim KH, Kim MN, *et al.* Incontinentia pigmenti: clinical observation of 40 Korean cases. *J Korean Med Sci* 2006;21:474-7.
14. Hadj-Rabia S, Froidevaux D, Bodak N, Hamel Teilac D, Smahi A, Touil Y, *et al.* Clinical study of 40 cases of incontinentia pigmenti. *Arch Dermatol* 2003;139:1163-70.

15. Incontinentia pigmenti. DermNet NZ.
16. Clemons E, Clemons D, Lee JA, Berne S. Incontinentia pigmenti in three generations: a case report. *J Am Acad Dermatol* 2008;58:80.
17. Lahari KD. Incontinentia pigmenti. *Br J Dermatol* 1955;67:310-2.
18. Pereira MA, Mesquita LA, Budel AR, Cabral CS, Feltriini Ade S. X-linked incontinentia pigmenti or Bloch-Sulzberger syndrome: a case report. *An Bras Dermatol* 2010;85:372-5.
19. Bentolila R, Rivera H, Sanchez-Quevedo MC. Incontinentia pigmenti: a case report. *Pediatr Dent* 2006;28:54-7.
20. Wu HP, Wang YL, Chang HH, Huang GF, Guo MK. Dental anomalies in two patients with incontinentia pigmenti. *J Formos Med Assoc* 2005;104:427-30.
21. Minic S, Novotny GE, Trpinac D, Obradovic M. Clinical features of incontinentia pigmenti with emphasis on oral and dental abnormalities. *Clin Oral Investig* 2006;10:343-7.
22. Motamedi MK, Lotfi A, Azizi T, Moshref M, Farhadi S. Incontinentia pigmenti. *Indian J Pathol Microbiol* 2010;53:302-4.

