A Case of a Surviving Male Infant with Incontinentia Pigmenti

Ji Young Song, M.D., Chan Ho Na, M.D., Byoung Soo Chung, M.D.,
Kyu Cherl Choi, M.D., Bong Seok Shin, M.D.

Department of Dermatology, Chosun University Medical School, Gwangju, Korea

Incontinentia pigmenti (Bloch-Sulzberger's disease) is an X-linked dominantly inherited disorder which is usually lethal in hemizygous males, but rarely found in male infants. It can be explained by the presence of an extra X chromosome (Klinefelter's syndrome), hypomorphic mutations, and somatic mosaicism. We herein report a rare case of incontinentia pigmenti with typical course of skin manifestation in normal karyotype (46, XY) male infant.
(Ann Dermatol (Seoul) 20(3) 134~137, 2008)

INTRODUCTION

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger's disease, is a rare X-linked dominant genodermatosis caused by a mutation in nuclear factor-κB (NF-κB) essential modulator (NEMO) gene on the X chromosome, localized to Xq28. IP predominantly affects female infants (in excess of 37 : 1), and is usually lethal in males in utero[1,2]. The survival of affected males is attributed to the presence of an extra X chromosome (Klinefelter's syndrome), hypomorphic mutations, and somatic mosaicism[3-5]. Only two cases of IP in male infants without karyotype study have been reported in the Korean dermatologic literature since 1982[6,7]. This study reports a rare case of incontinentia pigmenti in normal karyotype (46, XY) male infant.

CASE REPORT

A 3-day-old boy was referred to our department for the evaluation of skin finding presented at birth. The lesion showed erythema, linear vesiculations, and focal crust on the trunk and leg, predominantly over the left side (Fig. 1A, B).

At the time of birth, several vesicles and erythematous papules developed over the left trunk and thigh along Blaschko's lines. Blistered skin was replaced by a crusted lesion on the fifth day after birth (Fig. 1C). Then, hyperkeratotic papules and verrucous lesions occurred consecutively on the fifteenth day (Fig. 1D).

The patient was the second child born on normal full term delivery to the patients. His parents and his elder brother were healthy, and had no other comparable dermatoses.

There was no remarkable abnormality except for the skin lesions on physical examination. Laboratory tests including complete blood count, blood chemistry analysis, urinalysis, VDRL, bacterial culture, and TORCH serology (for toxoplasmosis, rubella, cytomegalovirus and herpes simplex) were in the normal range or negative. Also, radiologic findings in brain MRI, echocardiogram, and chest, abdomen, both extremities X-rays appeared normal. Chromosome analysis from peripheral blood leukocytes showed a normal male karyotype (Fig. 2), nonetheless, due to the refusal of parental consent, molecular analysis was not executed.

A skin biopsy was taken from one of the blistered areas on the left thigh. Histopathologically, epi-

Fig. 1. (A, B) On the third day, linear distribution of clustered vesicles on the left lower extremity and trunk along the Blaschko's lines. (C) On the fifth day, blistered skin replaced by crusts and scaling. (D) On the fifteenth day, hyperkeratotic verrucous papules and plaques developed at the site of previous blistering.
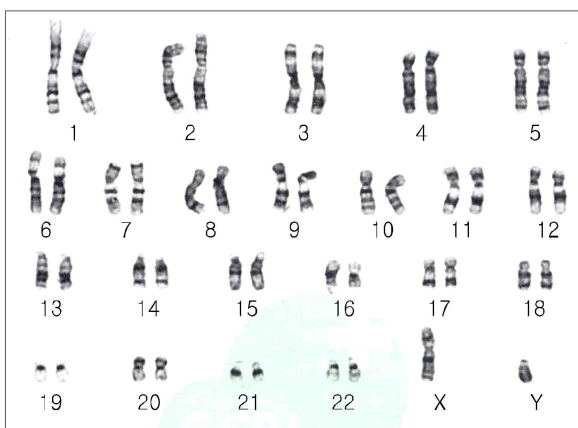

Fig. 2. Chromosome analysis from blood showed a normal male karyotype (46, XY).
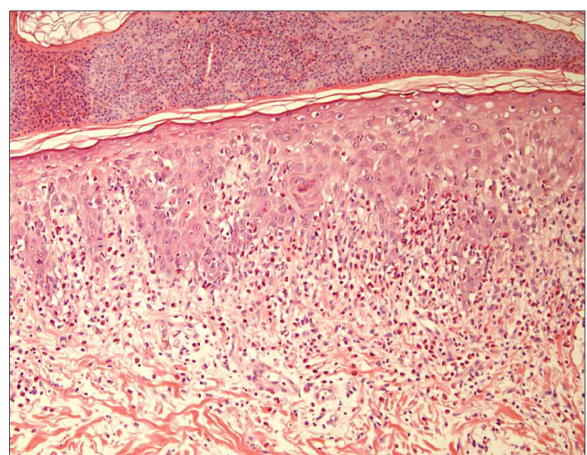

Fig. 3. Histologic feature showing dyskeratotic cells throughout the spongiotic epidermis, basal liquefaction degeneration, and inflammatory infiltration composed predominantly of eosinophils (H&E, ×100).

dermal hyperkeratosis, spongiosis, dyskeratotic cells throughout the epidermis, basal liquefaction degeneration, and inflammatory infiltration composed predominantly of eosinophils were noted (Fig. 3).

The patient was diagnosed as IP, and received antibiotic treatments to control secondary infection. After 2 months, the lesion disappeared with residual hyperpigmented streaks on the left thigh.

DISCUSSION

Although a case resembling IP was first described by Garrod in 1906, IP was characterized as a clinical syndrome by Bloch in 1926. In 1927, Sulzberger reported Bloch's case in details, and then proposed as Bloch-Sulzberger's disease[2].

In general, boys with single X chromosomal gene abnormality are so severely affected as to be lethal in utero, therefore there is an increased incidence of spontaneous abortion in affected women, presumably of male fetuses[8,9].

The major cause of IP is loss-of-function mutation of NEMO protein, most consisting of a deletion of exons 4~10 in heterozygous females[3,10]. The gene mutated in IP is mapped to Xq28 and encodes the NEMO. NEMO is a regulatory component of the IKB kinase complex required for NF-κB activation. Therefore, it is central to many immune, inflammatory responses, and apoptotic pathways. Disruption of NEMO gene leads to diminished NF-κB activity which increases the susceptibility of cells to apoptosis[11,12].

It is quite rare for male patients with IP to survive. Survival occurs in approximately 2~3% of all the reported cases[13]. It can be explained by three potential mechanisms: abnormal karyotype (Klinefelter's syndrome, 47, XXY), hypomorphic mutations, and somatic mosaicism. The third is the most reliable explanation for the survival of male patients. It results from a postzygotic mutation occurring during the blastocyst stage of embryogenesis and does not completely abolish NF-κB activity, which allows survival[3-5,14]. Thus, the presence of somatic mosaicism results in mild features of known genetic disorders, and better outcomes afterward[15]. Skin findings of live born male patients are generally not greater than those in affected females and many male patients have disease expression limited to cutaneous involvement of one or two

limbs[2]. According to Scheuerle[9], live born males with IP are inferred to be of generally good health and not at increased risk of neonatal or infantile mortality, because multiple hospitalizations or life threatening illness have not been reported. The clinical features of IP are associated with ectodermal tissue abnormalities including skin, hair, nails, teeth, eyes, and central nervous system. Skin finding is characterized by typical linear lesions subdivided into 4 stages with variable timings: Perinatal inflammatory vesicles (stage 1), verrucous patches with hyperkeratosis (stage 2), a distinctive pattern of streaky hyperpigmentation following Blaschko's lines (stage 3), and finally atrophy, hairlessness, and scarring (stage 4)[13,16]. These represent the death of cells carrying the mutated gene along lines of embryonic cellular migration[12]. However, some of the stages may occur concurrently with others, or not at all.

In addition, females who carry loss-of-function mutations would be expected to often have severe clinical signs, including neurologic: spastic paralysis, convulsion, and mental retardation; ophthalmologic: strabismus, cataracts, microphthalmos, cataract and optic atrophy; and odontologic defects: partial anodontia, delayed impaction, and crown malformations, presenting at birth or during the first few weeks of life[10,11,13,14].

The severity of IP is related to ocular and neurological impairment, in particular, blindness and psychomotor retardation, not skin lesions[1,17]. The latter generally disappear spontaneously, and no treatment is necessary other than the control of secondary infection. However, other complications should be sought carefully and, if possible, treated quickly as soon as the diagnosis of IP is established. Also, urgent consultations with ophthalmic, neurologic and dental subspecialists are often needed.

In conclusion, in a survival case of male infant with IP, careful evaluation, chromosomal analysis, and family counseling should be performed to rule out alternative diagnoses and for better clinical outcomes.

REFERENCES

1. Hadj-Rabia S, Froidevaux D, Bodak N, Hamel-Teillac D, Smahi A, Touil Y, et al. Clinical study of 40 cases of Incontinentia pigmenti. Arch Der-

matol 2003;139:1163-1170.

2. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. J Am Acad Dermatol 2002;47:169-187.

3. Pacheco TR, Levy M, Collyer JC, Parra NP, Parra CA, Garay M. Incontinentia pigmenti in male patients. J Am Acad Dermatol 2006;55:251-255.

4. Lenz W. Half chromatid mutations may explain incontinentia pigmenti in males. Am J Hum Genet 1975;27:690-691.

5. Ormerod AD, White MI, McKay E, Johnston AW. Incontinentia pigmenti in a boy with Klinefelter's syndrome. J Med Genet 1987;24:439-441.

6. Park SS, Kook HI. A case of Incontinentia pigmenti in male. Korean J Dermatol 1982;20:487-489.

7. Kim BJ, Lee DH, Shin HS, Won CH, Lee JH, Kwon OS. Incontinentia pigmenti in male infant. Korean J Dermatol 2006;44:624-626.

8. James WD, Berger TG, Elston DM. Genodermatoses and congenital anormaly. Andrew's disease of the skin. 10th ed. Philadelphia: Elsevier, 2006:547-549.

9. Scheuerle AE. Male cases of incontinentia pigmenti: case report and review. Am J Med Genet 1998;77:201-218.

10. Fusco F, Bardaro T, Famiani G, Mercadante V, Miano MG, Falco G. Molecular analysis of the genetic defect in a large cohort of IP patients and identification of novel NEMO mutations interfering with NF-kB activation. Hum Mol Genet 2004;13: 1763-1773.

11. Goldberg MF. The skin is not the predominant problem in Incontinentia pigmenti. Arch Dermatol 2004;140:748-750.

12. Mayer EJ, Shuttleworth GN, Greenhalgh KL, Sansom JE, Grey RH, Kenwrik S. Novel corneal features two males with incontinentia pigmenti. Br J Ophthalmol 2003;87:554-556.

13. Carney RG. Incontineatia pigmenti-A world statistical analysis. Arch Dermatol 1976;112:535-542.

14. Mckee PH, Calonje E, Granter SR. Pathology of the skin with clinical correlation. 3rd ed. Philadephia: Elsevier Mosby, 2005:702-704.

15. Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. Lancet 2000;356:830-832.

16. Elder DE, Elenitsas R, Johnson BL, Murphy GF. Lever's histopathology of the skin. 9th ed. Philadelphia: Lippincott Williams & Wlikins, 2005:168-169.

17. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger's disease). J Med Genet 1993;30: 53-59.