Multiple Clinical Manifestations and Diagnostic Challenges of Incontinentia Pigmenti—12 Years’ Experience in 1 Medical Center

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Background: Incontinentia pigmenti (IP) is a rare X-linked dominant disorder that involves ectodermal tissues of multiple systems. Previous reports are few in Taiwan. To contribute toward better understanding of IP, we describe and discuss the clinical features of cases that were diagnosed in a medical center during the past 12 years.

Methods: The medical records of all patients with IP between July 1995 and June 2007 were reviewed retrospectively. The demographics, physical findings, pathology reports, molecular study reports, eosinophil counts and outcome were recorded.

Results: A total of 4 patients, 3 female and 1 male neonate, who met the criteria for the diagnosis of IP were enrolled. Among these cases, 3 were not diagnosed with IP at initial presentation but were regarded to have infectious diseases. A definite family history of 3 consecutive generations was proved not only by clinical manifestations but also by molecular study in 1 patient. The patient also had retinal and vitreous body hemorrhage, which rapidly progressed to retinal detachment of the right eye in 2 months. Another patient presenting with stage III hyperpigmentation at birth had an extremely rare finding of left foot deformity. The male patient had unilateral and localized vesicular lesions over his left thigh.

Conclusion: Diagnosis of IP is difficult in the neonatal period. Referral to experienced specialists is necessary. Multiple clinical characteristics of IP and rapid progression of ophthalmologic manifestations can be demonstrated through our study. Furthermore, 3 of the 4 cases in our study are the very first reports in Taiwan. [J Chin Med Assoc 2008;71(9): 455–460]

Key Words: Bloch-Sulzberger syndrome, eosinophilia, incontinentia pigmenti, limb deformity, NF-κB

Introduction

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare X-linked dominant genodermatosis that is usually lethal for males in uterus, while affected females show significant variations in clinical expression. It involves the ectodermal tissues of multiple systems, including the skin and its appendages, teeth, eyes and central nervous system. The most dramatic clinical manifestation of IP is a 4-stage anomaly of skin pigmentation that commences at or before birth: erythema and bullous lesions, verrucous lesions, hyperpigmentation along Blashchko’s lines, and hypopigmented atrophy. Mutations in the gene for NEMO (NF-κB essential modulator) at Xq28 have been shown to cause IP, and a deletion of exons 4–10 is found in 80% of cases. Carrying a NEMO mutation is linked to embryonic lethality in males, while it results in skewed X inactivation in females.

Here, we describe and discuss the clinical features of 4 unrelated newborn patients who were diagnosed in our hospital in the past 12 years. We note the multiple manifestations of IP through these 4 cases. Importantly, 3 of the 4 cases in our study are the very first reports in Taiwan.

Methods

Definitions

Family history was defined as evidence of IP in at least 1 first-degree female relative. Tentative diagnosis was defined as all the diagnoses that had been concluded...
and treated prior to confirmation as IP. Eosinophilia was defined as blood count of eosinophils >500/mm$^3$. Normal development was defined as following normal milestones as the patient grew up. Ocular disorder was defined as retinal anomalies (retinal detachment, vascular anomalies, pigmentary change) or non-retinal anomalies (strabismus, nystagmus, cataract). CNS disorder was defined as having clinical symptoms/signs (seizure, mental retardation, microcephaly, hemiplegia, hemiparesis) or abnormal findings on neuroimages. Skin appendage disorder was defined as alopecia, woolly hair or nail dystrophy. Dental disorder was defined as delayed dentition, hypodontia or conical teeth.

**Study design**

The medical records of the patients with IP, from July 1995 to June 2007, who were identified by ICD-9 coding system, were reviewed retrospectively. The diagnosis of IP was made according to the diagnostic criteria given by Landy and Donnai. The demographics, physical findings, pathology reports, molecular study reports, eosinophil counts and outcome were recorded.

**Results**

A total of 4 patients, 3 female and 1 male neonate, who met the criteria for the diagnosis of IP were enrolled. The presentations and clinical courses are summarized in Table 1. All of them presented with skin anomaly at birth. Only 1 patient had a family history of IP. None of these 4 neonates had low birth weight or were premature. Three of the 4 cases were not diagnosed with IP at initial presentation, and were not diagnosed until they were referred to experienced doctors. Each of them was treated with antimicrobial agents against bacteria or virus, but no improvement in the skin lesions was achieved. Only patient 2 had stage III skin manifestation of IP (Figure 1A) and was diagnosed at presentation. Aside from skin manifestations, skin appendage disorder was the most frequently associated anomaly (75%). All the female patients had alopecia. Also, patient 2 had nail dystrophy over her right little finger, and, of note, had the unique finding of left foot deformity (Figure 1B).

![Image](image_url)
Representative case reports

Patient 1

This full-term female neonate was born by a 33-year-old, G2P1A1, mother with a maternal history of gestational diabetes mellitus. Apgar scores were 8 at 1 minute and 9 at 5 minutes. She was referred to our hospital at 4 days of age with progressive generalized erythematous maculopapular skin lesions, especially over the back, the face and all 4 extremities (Figure 2A). Physical examination showed no fever or other abnormality except for skin rash. White blood cell count (WBC: 9,100/mm$^3$) and eosinophil count (364/mm$^3$, 4% of WBC) were both within normal limits. No definite diagnosis could be made at that time.

The condition did not deteriorate until 1 week later, when crops of pustule-like lesions were found over both upper and lower limbs (Figure 2B). Herpes simplex virus infection was ruled out because of a negative herpes simplex virus (HSV)-IgM ELISA test. Skin biopsy showed intraepidermal vesicle formation. The cells in the vesicles contained numerous eosinophils and some neutrophils. Neither bacterial nor viral pathogen was identified. The vesicles regressed gradually without any specific treatment, and they seemed aligned as linear streaks more obviously when the baby was 3 weeks of age. In the meantime, extraordinarily high eosinophil count (14,384/mm$^3$, 58% of WBC) was noted.

Retinal and vitreous body hemorrhage of the patient’s right eye occurred when she was 1 month old. The condition progressed rapidly to local retinal detachment with neovascularization at 3 months of age. Five days later, she was admitted again for panretinal laser photocoagulation to prevent further deterioration. At this admission, verrucous lesions over the little fingers of both hands were found (Figure 2C). In addition, a reticulate pattern of hyperpigmentation was noted over the thighs, axillae, and lateral aspects of the trunk. No more vesicles or pustules existed at that time.

Figure 2. (A) Progressively generalized erythematous maculopapular lesions over the trunk, 4 extremities and face of patient 1 after birth (stage I). (B) Crops of pustule-like lesions over 4 limbs of patient 1 at about 10 days of age (stage I). (C) Verrucous lesions over the little fingers of both hands of patient 1 at 3 months of age (stage II). (D) Note the remains of hyperpigmented spots over the mother’s left axilla (stage III) and hypopigmented spots over the anterior chest (stage IV).
The patient suffered from 1 episode of gastroenteritis with low-grade fever at 4+ months of age. Some fresh vesicles recurred over her trunk and bilateral inguinal areas. Another skin biopsy was performed 1 week later, which revealed hyperkeratosis, acanthosis, focal dyskeratosis, perivascular chronic inflammatory cell infiltrate, and pigmentary incontinence.

Tracing back her family history, the mother also had some skin abnormality with recurrence before she was 1 year old. There still remained some spots of hyperpigmentation over the mother’s left side axilla and hypopigmented spots over the anterior chest and axilla (Figure 2D). Similar skin stigmata could also be found in the grandmother (Figure 3). We noted that both the mother and grandmother had histories of miscarriages with unknown causes; the genders of the fetuses were unknown. With the assistance of DNA diagnosis, all 3 were proved to have the same abnormal 2-kb fragments as 2 positive control patients (Figure 4).

Patient 2
This full-term female neonate was born by a 30-year-old, G1P1 mother after an uneventful pregnancy. No perinatal insult was noted. She was referred to our hospital after birth owing to hyperpigmented skin lesions in streaks or whorl shape over the trunk, face, and 4 limbs. The diagnosis of IP was made immediately by the unique skin manifestations.

Other abnormalities included extremely small nail of the right little finger and alopecia. In particular, left foot deformity with only 3 digits was noted (Figure 1B), for which it was suggested that management be received in the future. However, no eosinophilia was found.

Patient 4
This full-term male neonate was born by a 39-year-old, G1P1 mother after an uneventful pregnancy. Apgar scores were 8 at 1 minute and 9 at 5 minutes. Some vesicular lesions were found over the left lower limb and inguinal area with scaling change at birth. The general appearance, vital signs, activity and intake of the patient were normal. Although some vesicles ruptured and crusted, renascent ones emerged despite topical/systemic antibiotics. The leukocyte count was \(9.47 \times 10^9/L\), with 8% eosinophils (758/mm\(^3\)). C-reactive protein was 0.7 mg/dL.

Fine needle aspiration of vesicle fluid was performed. No bacterial pathogen was identified, either by the culture or smear. Viral isolations of multiple different sites, including vesicle fluid, throat, rectum,
and urine, all showed negative results. The blood ELISA test for HSV was IgG positive and IgM negative. According to the statements of the family, there were some vesicles over the mother’s labia major about 1 week before the delivery. Therefore, perinatal HSV infection was still highly suspected. However, 7 days of acyclovir treatment was not effective. Finally, skin biopsy was arranged and revealed perivascular lymphohistiocytic infiltrate and some eosinophils in the dermis. Dermal melanophages were also found. Thus, the diagnosis of IP was made. Normal karyotype of 46,XY was proved by chromosome analysis.

Discussion

The perinatal incidence of IP has been estimated to be 1 in 50,000 births, but it is probably higher for the following 2 reasons. First, the complex phenotype of IP is difficult to diagnose. Second, the skin lesions are often mistaken for other conditions, such as viral (HSV) or bacterial (bullous impetigo) infections or toxic (erythema toxicum) reactions. Those among our patients who were at first misdiagnosed presented with stage I skin manifestation of IP, including erythema or vesicles/pustules. The only exception was patient 2, who already had linear streaks and whorls of hyperpigmentation (stage III) at birth. The skin anomaly was so unique that it could be easily recognized. Therefore, it depends on the clinician to have a high index of suspicion to diagnose IP, especially in the earlier stages.

Patient 1 of our series is a perfect teaching model of IP. The case illustrates that IP that follows X-linked dominant inheritance pattern is expressed not only through the typical skin manifestations found merely in females in 3 consecutive generations, but also has the same genetic defect in all of them. The mother and the grandmother both had histories of miscarriages. Furthermore, the patient had experienced 3 different stages of skin lesions with overlaps. Mild, short-lived recurrence of blisters had developed during episodes of febrile illness. She had dramatically high eosinophil count (14,384/mm³, 58% of WBC) during which time linear streaks of vesicles appeared. Interestingly, as low as 2% eosinophils was noted at presentation, while erythema was the only skin manifestation then. To our knowledge, there can be as much as 79% eosinophils associated with IP. Moreover, the majority of patients with eosinophilia expressed “vesicular” skin lesions in some reports. It is rational to postulate that the yield of eosinophilia in IP depends on the time of when the data were acquired. However, severity of skin lesion has no significant relation with eosinophil count.

The severity of skin abnormality and the frequency of recurrence in patient 1 were much greater than those of her mother. Of note, patient 1 had severe and early onset of retinal and vitreous body hemorrhage of the right eye, which rapidly progressed to local retinal detachment, while her mother and grandmother did not have any ocular problem. As mentioned above, all of them had the same genetic defect. What could explain this variability in clinical expression? It seems that IP may relate to an interesting hereditary characteristic: anticipation, which refers to worsening severity or earlier age at onset with each succeeding generation for an inherited disease. However, it remains for large-scale studies to confirm our observations.

Since IP is an X-linked dominant disorder, it is usually lethal in males. However, numerous reports in the literature have described the survival of male patients with IP and their clinical manifestations. The International IP Consortium proposed 3 mechanisms for the possible explanations: the 47,XXY karyotype (Klinefelter syndrome), somatic mosaicism, and hypomorphic alleles. Therefore, chromosome analysis and molecular diagnosis should be suggested for any male IP patient. Unlike the 3 female patients whose skin abnormalities were generalized, the male in our series (patient 4) presented at birth with vesicles localized over his left lower limb and inguinal area. Pacheco et al reported that in 8 of 9 male patients, lesions were localized to 1 extremity at presentation. In the 9th, lesions involved more than 1 extremity, but were localized to 1 side of the body. Such features, that males tend to have more localized disease or unilateral involvement than females, were also observed in other reports. However, early unilateral involvement does not predict a milder course because unilateral skin lesions and multisystem abnormalities may develop later.

IP results from mutations in NEMO (NF-κB essential modulator), as previously noted. NEMO encodes the regulatory component (IKKγ) of the IkB kinase (IKK) complex required for activating the NF-κB signaling pathway. IKK is composed of 3 polypeptides: the catalytic subunits of IKK-α and IKK-β, and the regulatory subunit of IKKγ. The NF-κB transcription factor complex can act to implement immune and inflammatory responses and to prevent apoptosis. Therefore, the absence of NEMO renders IKK nonfunctional and consequently abolishes NF-κB activity, which causes the mutant cells’ vulnerability to apoptosis.

We would like to emphasize an unusual finding of IP, congenital left foot dysplasia, in our patient 2.
Hayes et al had reported a female case of IP associated with acheiria, which means congenital absence of 1 or both hands. Limb abnormality with a small stump of the hand or foot is also seen in some craniofacial syndromes such as Saethre-Chotzen syndrome. The correlation between NF-κB and IP has been discussed above, and it is interesting that NF-κB seems to also play an important role in the formation of the apical ectodermal ridge that is essential for limb outgrowth. Limb dysmorphism like reduction in limb size or loss of distal elements of digits will be observed when NF-κB activity is blocked experimentally in chick embryo limb buds. Furthermore, inhibition of NF-κB activity has been known to result in reduction in expression of the TWIST gene that underlies Saethre-Chotzen syndrome. Therefore, these 2 incontinentia pigmmenti (IP) and limb abnormality in 1 of the human craniofacial syndromes, could be brought together through NF-κB. However, some authors have declared that the kinase-independent part of IKK-α, not NF-κB activity, is responsible for epidermal differentiation required for proper morphogenesis of mesodermally-derived skeletal elements. Perhaps this may explain why limb abnormality occurs so infrequently in comparison with other manifestations of IP.

In conclusion, the diagnosis of IP is sometimes difficult, especially in the neonatal period. Referral to more experienced specialists is crucial to diagnose it correctly. IP is an X-linked dominant disorder, as demonstrated through our patient 1. Also, our patient 2 had an extremely rare finding of limb deformity, which we believe is only the second report in the literature. The only male patient in our series presented with unilateral and localized skin abnormality, which much differs from female IP patients. These 3 cases mentioned above are all the very first reports in Taiwan.

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References


