Recurrent Inflammation of Incontinentia Pigmenti in a 30-year-old Woman

Hsuan-Wen Hsiao 1 Chi-Liang Chang 2 Hsuan-Hsiang Chen 2 Yi-Hua Liao 2

Incontinentia pigmenti (IP) is an X-linked dominant disorder with a complex multisystemic and developmental phenotype. Classically, the skin lesions occur perinatally in four successive stages: inflammatory vesicular (stage 1), verrucous (stage 2), hyperpigmented (stage 3), and scarring (stage 4), along the lines of Blaschko, reflecting the somatic mosaicism of X-chromosome inactivation in female patients. In general, the lesions of stage 1 IP begin perinatally and clear completely within the age of 4 months. We report a rare case of late recurrence of first stage lesions of IP in adulthood. This 30-year-old woman with a history of IP presented with multiple erythematous papules on pigmented patches distributing along the lines of Blaschko. Histological findings exhibited dyskeratosis in the epidermis along with perivascular and interstitial infiltrations composed of lymphocytes and eosinophils, consisting with the diagnosis of IP. In addition, we also review the recurrent cases with IP previously reported in the literature. (Dermatol Sinica 26: 242-247, 2008)

Key words: Incontinentia pigmenti, Recurrence

INTRODUCTION

Familial incontinentia pigmenti (IP) is an X-linked dominant genodermatosis. It is ordinarily lethal in males, while heterozygous females survive attributed to functional mosaicism. The skin findings of IP are characteristically along the lines of Blaschko, and progress through different stages (vesicular, verrucous, hyperpigmented, and atrophic). Extracutaneous manifestations include ophthalmologic (strabismus, cataracts, optic atrophy, retinal vascular pigmentary abnormalities, microphthalmia), odontologic (partial anodontia, delayed dentition, cone/peg-shaped teeth, impactions), and neurologic defects (seizures, spastic paralysis, motor and mental retardation, microcephaly). The mutated gene in patients with IP has been mapped to Xq28 and encodes the NF-κB essential modulator, NEMO/IKKγ. Approximately 80% of IP patients were revealed to carry an identical deletion mutation of exons 4 to 10 of the NEMO gene. NEMO mutations abolish NF-κB signal pathway and lead to increased cellular sensitivity to apoptosis.

CASE REPORT

A 30-year-old woman was diagnosed of sporadic incontinentia pigmenti 4 days after birth, presenting with reticulated brownish
Recurrent Incontinentia Pigmenti patches, which corresponded to the stage 3 lesion of IP, along the lines of Blaschko on both forearms, hands, popliteal fossae and legs. No associated neurological, ocular or dental defects had been found. The skin lesions of hyperpigmented streaks persisted and kept stable since then. She visited our clinic in April 2005 for evaluation of pruritic erythematous papules for 1 week. Physical examination revealed multiple linearly arranged, edematous, and erythematous papules, which only affected the streaky pigmented patches of the right hand, right forearm (Fig. 1A, B) and some scattered on both popliteal fossae. No vesicular lesions were found. She had multiple oral ulcers and sore throat 3 days before the onset of skin rash, but no associated fever had been noted. A skin biopsy was obtained from an erythematous papule and its nearby hyperpigmented region over the right forearm. Histologically, it showed acanthosis and clumps of dyskeratotic cells in the epidermis along with perivascular and interstitial infiltrations containing lymphocytes, histiocytes and eosinophils in the dermis. In addition, some melanophages were also found intermingled with the infiltrates (Fig. 2A, B). Combining the past history, physical examination and histological findings, recurrence of first stage

Fig. 1
Multiple linearly arranged, edematous and erythematous papules on the streaky pigmented patches of the right forearm (A) and right hand (B).

Fig. 2
(A) Acanthosis and clumps of dyskeratotic cells in the epidermis (H&E, original magnification x200) along with (B) perivascular and interstitial infiltrations composed of lymphocytes and eosinophils (H&E, original magnification x200).
lesions of incontinentia pigmenti was diagnosed.

**DISCUSSION**

IP is an X-linked dominantly inherited disorder characterized by abnormalities of the central nervous system, teeth, eyes, and skin. Classically, the skin lesions occur perinatally in four successive stages. The first stage begins perinatally and lasts from 2 weeks to 4 months. It gives rise to inflammatory vesicles and patches and is accompanied by massive eosinophilic granulocyte infiltration into the epidermis. Subsequently, verrucous and keratotic lesions occur between the second and sixth months of life. They usually appear on the distal part of the limbs as the blisters begin to heal and then disappear, leaving areas of hyperpigmentation. The hyperpigmented streaks and whorls often persist for years, clearing later in childhood or after puberty.

However, it is not necessary for all 4 stages to occur. The inflammatory and hyperpigmented stages are most consistently present. The hyperkeratotic lesions can be absent or unnoticed. Hypopigmentation and atrophy are less frequent, and sometimes several stages overlap.

In general, the lesions of stage 1 IP begin perinatally and clear completely within the age of 4 months. Rarely, recurrence of inflammatory papulovesicular lesions consistent with IP stage 1 have been described (Table 1). All cases except one developed the recurrent lesion on the previously affected area. In most cases, the recurrence was preceded by fever and/or a viral infection, and few cases had recurrence after ruby laser or estrogen therapy. Nevertheless, some recurrent cases had no preceding systemic illness or trauma. The majority of previously reported patients experienced one to several episodes of recurrence in their pre-school age, and only 2 cases had late recurrence in their adulthood. In our patient, the presence of an infection may trigger the recurrence of the inflammatory lesions, but the reason for the extremely delay in onset of the recurrent inflammatory stage is unclear.

The mutated gene responsible for IP has been identified as NEMO/IKKγ (Xq28), encoding a regulatory component of the IκB kinase (IKK) complex--IKKγ which is responsible for activating the NF-κB signaling pathway. The NF-κB transcription factor complex can act to implement immune and inflammatory responses and to prevent apoptosis. The inhibitory IκB-molecules sequester NF-κB in the cytoplasm. In response to stimuli such as proinflammatory cytokines or viruses, IKK phosphorylates IκB and targets it for degradation. The removal of IκB enables NF-κB to translocate into the nucleus, where it activates the transcription of various target genes. Thus, the absence of NEMO renders IKK nonfunctional and consequently abolishes NF-κB activity. Most IP patients carry loss-of-function mutations in NEMO and thus lack NF-κB function in their mutant cells. The loss of NEMO activity leaves mutant cells vulnerable to apoptosis when exposed to tumor necrosis factor-alpha (TNF-α). The cell death causes lethality in male embryos and skewed X-inactivation in female patients, as a result of elimination of cells bearing an active mutant X-chromosome with gradual replacement by cells expressing the nonmutated X chromosome. The mechanisms of recurrent IP remain unknown. It is proposed that, after the initial episode of first stage IP, most IKKγ-deficient cells have been destroyed. However, the persistence of residual IKKγ-mutated cells within the hyperpigmented areas could later be affected while exposure to some apoptosis-inducing events, including fever or infections. This hypothesis is supported by that most recurrences arise from previously affected area after some kind of insult. However, there...
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are still few recurrent cases emerging from previously spared skin.\textsuperscript{10, 15} That the first eruption in some area was so mild that we could not perceive the subtle changes and mistook it for spared skin was assumed. Recurrent episodes of IP are generally short-lasting and easily managed by topical steroids, probably because of smaller numbers of residual

<table>
<thead>
<tr>
<th>Cases</th>
<th>Extracutaneous abnormality</th>
<th>Number of recurrence</th>
<th>Age of recurrence</th>
<th>Triggering factors</th>
<th>Distribution of stage 3 or 4 lesions</th>
<th>Recurrence on previously affected site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes 1978\textsuperscript{11}</td>
<td>Teeth</td>
<td>Several</td>
<td>Between 2m/o and 11y/o</td>
<td>No</td>
<td>Trunk and extremities</td>
<td>Yes</td>
</tr>
<tr>
<td>Bessems 1988\textsuperscript{12}</td>
<td>Teeth/alopoeia</td>
<td>3</td>
<td>2 y/o, 11y/o, 20 y/o</td>
<td>No</td>
<td>Trunk and extremities</td>
<td>Yes</td>
</tr>
<tr>
<td>Sahn 1994\textsuperscript{13}</td>
<td>Teeth</td>
<td>Several</td>
<td>Between 1m/o and 12m/o</td>
<td>No</td>
<td>Trunk and extremities</td>
<td>Yes</td>
</tr>
<tr>
<td>Pfau 1995\textsuperscript{6}</td>
<td>No</td>
<td>Several</td>
<td>Between 1m/o and 7y/o</td>
<td>Infection/fever</td>
<td>Flexor sides of the lower limbs</td>
<td>Yes</td>
</tr>
<tr>
<td>De Argila 1996\textsuperscript{14}</td>
<td>White substance*</td>
<td>Several</td>
<td>Between 2m/o and 18m/o</td>
<td>No</td>
<td>Limbs and lateral areas of the torso</td>
<td>Yes</td>
</tr>
<tr>
<td>Nagase 1997\textsuperscript{9}</td>
<td>No</td>
<td>1</td>
<td>3 y/o</td>
<td>Ruby laser</td>
<td>Trunk and limbs</td>
<td>Yes</td>
</tr>
<tr>
<td>Van Leeuwen 2000\textsuperscript{8}</td>
<td>No</td>
<td>1</td>
<td>8 m/o</td>
<td>No</td>
<td>Not mentioned</td>
<td>No</td>
</tr>
<tr>
<td>Bodac 2003\textsuperscript{3}</td>
<td>Retinal vasculopathy</td>
<td>1</td>
<td>9 m/o</td>
<td>Infection/fever</td>
<td>Not mentioned</td>
<td>Yes</td>
</tr>
<tr>
<td>case 2</td>
<td>No</td>
<td>Several</td>
<td>Between 9 and 12m/o</td>
<td>Fever</td>
<td>Arms, legs and trunk</td>
<td>Yes</td>
</tr>
<tr>
<td>case 3</td>
<td>No</td>
<td>Several</td>
<td>Between 4 and 11m/o</td>
<td>Fever</td>
<td>Limbs</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>case 4</td>
<td>Convulsions</td>
<td>6</td>
<td>Between 4 and 11m/o</td>
<td>Infection</td>
<td>Lower limbs</td>
<td>Yes</td>
</tr>
<tr>
<td>case 5</td>
<td>No</td>
<td>Several</td>
<td>Between 6m/o and 7y/o</td>
<td>Fever</td>
<td>Not mentioned</td>
<td>Yes</td>
</tr>
<tr>
<td>Patrizi 2004\textsuperscript{4}</td>
<td>Teeth</td>
<td>Several</td>
<td>(1) Since birth to 5 m/o (2) 17 m/o</td>
<td>(1) Infection (2) Estrogen therapy</td>
<td>Flank, abdomen and inguinal folds</td>
<td>Yes</td>
</tr>
<tr>
<td>Llombart 2005\textsuperscript{7}</td>
<td>Teeth</td>
<td>4</td>
<td>Between 4-18 m/o</td>
<td>Infection/fever</td>
<td>Four limbs</td>
<td>Yes</td>
</tr>
<tr>
<td>Darne 2007\textsuperscript{10}</td>
<td>No</td>
<td>1</td>
<td>5 y/o</td>
<td>No</td>
<td>Trunk and limbs</td>
<td>Yes</td>
</tr>
<tr>
<td>Our case</td>
<td>No</td>
<td>1</td>
<td>30 y/o</td>
<td>Infection</td>
<td>Both forearms, hands, and legs</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Brain MRI: A partial alteration in the signal located at the periventricular white substance which may be the result of small vessel occlusive phenomenon.
IKKγ-deficient cells.

With the development of the identification of NEMO and NF-κB signal transduction, we acquire a better apprehension on the pathophysiology of IP; however, it still takes more efforts to unveil the mystery of the phenomenon indeed.

REFERENCES
色素失調症是一種性聯顯性遺傳的疾病，臨床表現可能會侵犯多重器官系統。典型的皮膚表現發生在周產期並可區分為四個階段：發炎水泡(第一期)，疣狀增生(第二期)，色素沉著(第三期)和疤痕形成(第四期)，而這些病灶都沿著 Blaschko's line 分布。它代表了女性患者身上一種嵌合型 X 染色體異常的現象。一般而言，第一階段的病灶在周產期時出現並在四個月大之前消退。我們在此報告一個罕見在成人時期復發的色素失調症病例。這是一個過去有色素失調症病史的 30 歲女性，在沿著 Blaschko's line 分布的深色斑塊上出現多個紅色丘疹。組織學上顯示表皮角化不良表現，伴隨著真皮層中出現血管周圍及組織間隙中有淋巴球及嗜伊紅性白血球浸潤。結合病史、臨床與病理表現，此病例被診斷為復發性色素失調症。此外，我們也回顧過去文獻上所報告過的復發性病例。（中華皮誌：26: 242-247, 2008）