Late Recurrence of Inflammatory First-Stage Lesions in Incontinentia Pigmenti

An Unusual Phenomenon and a Fascinating Pathologic Mechanism

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Background: Incontinentia pigmenti (IP) is an X-linked genodermatosis that is manifested by neonatal inflammatory vesicles localized along the lines of Blaschko. These lesions usually clear spontaneously within a few months, leaving hyperpigmentation. Ophthalmologic and neurologic symptoms can be associated with IP. Late recurrences of the first-stage inflammatory lesions after the initial rash are uncommon and have been reported infrequently. The mechanism involved in this phenomenon is unclear. However, the recent identification of NEMO/IKKγ as the gene responsible for IP sheds new light on its pathophysiologic origins.

Observations: We report 5 cases of children who experienced episodes of late reactivation of IP. In all cases, the recurrences occurred on the previously hyperpigmented streaks several months or years after resolution of the initial eruptions. In most cases, the recurrences were preceded by an infectious episode.

Conclusions: These IP recurrences suggest that mutated cells can persist a long time in the epidermis. We theorize that infections trigger the reactivations. The NEMO/IKKγ gene encodes a protein essential in nuclear factor κB activation, which is required for resistance to tumor necrosis factor α-induced apoptosis. We discuss the role of a proinflammatory cytokine such as tumor necrosis factor α as a triggering factor for the reactivation.

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Incontinentia pigmenti (IP) is a genodermatosis that segregates as an X-linked dominant disorder. The gene for IP has recently been identified as NEMO/IKKγ, which encodes for the nuclear factor κB (NF-κB) essential modulator. The disease is usually lethal prenatally in male patients. In affected female patients the disease involves, with high variability, the skin, hair, teeth, nails, eyes, and central nervous system. The skin lesions occur in 4 classic stages: inflammatory, verrucous, hyperpigmented, and scarred. They follow a linear pattern along the lines of Blaschko, reflecting the somatic mosaicism due to the X-chromosome inactivation in female patients.

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 pigmentation fades spontaneously during infancy, and pale hairless patches remain on the skin.

Another consistent feature of IP is the nonrandom X inactivation in peripheral blood leukocytes, suggesting that cells expressing the mutated X chromosome are counterselected. All stages do not necessarily occur; the inflammatory and hyperpigmented stages are the most consistently present. The hyperkeratotic lesions can be absent or unnoticed. Hypopigmentation and atrophy are less frequent, and sometimes several stages overlap. However, recurrence of inflammatory lesions several months and even several years after their initial resolution, when the eruption consists of only hyperpigmented streaks, is an unusual and rarely reported phenomenon. We report 5 cases of late reactivation of the first-stage inflammatory lesions in children observed for IP. The identification of the NEMO/IKKγ gene as responsible for IP sheds new light on the mechanism of the disease, and a hypothesis can be proposed for these late reactivations.
REPORT OF CASES

CASE 1

A 9-month-old girl had sporadic and typical IP. The initial inflammatory and vesicular lesions resolved at age 2 months and followed by the hyperpigmented stage. She had classic IP retinal vasculopathy cured by 2 treatments with laser photocoagulation. Findings of the neurologic examination were normal. At age 9 months, the skin lesions consisted of hyperpigmented streaks, and the vesicles were not umbilicated. Remarkably, the recurrent vesiculobullous lesions were intense on the trunk, where the neonatal eruption was discrete. Three days before the reactivation, the child experienced a rhinopharyngitis and a bronchitis associated with a 39°C fever. The inflammatory lesions cleared in 10 to 15 days. This was the first infectious febrile episode for this child. The child is now 18 months old, and the inflammatory eruption has not recurred.

CASE 2

A 10-month-old girl presented with familial IP on her arms, legs, and trunk. The pigmented stage had started at age 15 days. The skin lesions had been stable since age 6 months. The findings of ophthalmologic examination and cerebral computed tomographic scans were normal. At age 9 months, the child experienced a first recurrence of erythematous papular, verrucous, and pruritic lesions on the trunk, with a linear pattern along the lines of Blaschko (Figure 2). The recurrence was concomitant with a fever, which lasted until the third day of the eruption. These inflammatory skin lesions resolved in 45 days, leaving linear hyperpigmentation. One month later, a second episode of the same type occurred in the same areas 2 days after a fever. This second episode lasted 1 month.

CASE 3

An 11-month-old girl presented with a 7-month history of several recurrent linear erythematous, papular, vesicular, or urticarial lesions. The lesions affected especially the extremities of the limbs. Each recurrence was triggered by a febrile episode. The erythematous lesions disappeared within 8 to 10 days, leaving a discrete hyperpigmentation. The diagnosis of IP was suggested by a familial history of IP, the linear pattern of the lesions, and the hyperpigmented evolution of the lesions. The diagnosis was confirmed by histologic examination of a skin biopsy specimen from a hyperpigmented area, which showed some dyskeratotic cells and a melanin incontinence. There was no extracutaneous involvement. The child was lost to follow-up at age 18 months.

CASE 4

An 11-month-old girl presented with sporadic IP, diagnosed neonatally on typical skin lesions associated with seizures. Physical examination at age 3 months revealed pigmented streaks on the lower limbs and atrophic alopecia of the scalp. Between age 4 months and 11 months, the child experienced 6 or 7 recurrences of inflammatory and vesicular lesions affecting the buttocks and the limbs. No neurologic event was observed during the skin reactivation episodes, but the child had been previously treated by valproate. Two recurrences were triggered by viral infections, either gastroenteritis or rhinopharyngitis, both without fever. For the other episodes, no triggering factor was noted in the medical record.

CASE 5

A girl with sporadic, well-documented, and typical IP experienced several episodes of reactivation of inflammatory lesions on the hyperpigmented streaks, about twice

Figure 1. Recurrence of vesicles and patches after a feverish rhinopharyngitis in a 9-month-old girl (case 1).

Figure 2. Recurrence of inflammatory patches on the trunk of a 10-month-old girl accompanying a feverish episode (case 2).
a year, from age 6 months to 7 years (Figure 3). The episodes were sometimes, but not always, associated with fever. The recurrences stopped spontaneously at age 7 years. There was no extracutaneous involvement.

**COMMENT**

We report 5 cases of late recurrences of inflammatory skin lesions in children involving the hyperpigmented areas characteristic of the third-stage of IP. Until now, only a few cases of such late recurrences have been reported, and these were not well explained.5-9 This phenomenon seems to be uncommon but may be misdiagnosed. Our 5 cases were gathered through analysis of a series of 40 children observed for IP in our dermatologic unit. All patients of this series had typical IP disease, according to diagnosis criteria defined by Landy and Donnai.2 We observed recurrence of the first-stage lesions in cases 1, 2, and 4; for the 2 remaining patients, the history of recurrence was reviewed in the specific medical records established for the patients observed for IP. Two patients (cases 4 and 5) experienced several episodes, even until age 7 years in case 5 (ie, a long time after the neonate stage). In most cases, the inflammatory recurrence was clearly preceded by a fever and/or a viral infection, which could then be considered a triggering factor of the reactivation.

Late reactivations have been rarely reported in the literature. Pfau and Landthaler5 described a 7-year-old girl who experienced reactivation of the first-stage skin lesions each time she developed a febrile infection. Barnes6 reported the same phenomenon in accompanying infections with fever in an adult. More recently, the case of an 8-month-old child with an extensive vesiculobullous rash was reported by Van Leeuwen et al,7 but the existence of a fever in the preceding days was not mentioned. Bessemse et al8 described a 20-year-old patient who developed, from the age of 11 years, exacerbations of inflammatory lesions accompanied by persistent hyperkeratotic and verrucous lesions restricted to the hyperpigmented linear areas. No triggering factor was noted. Nagase et al9 reported the recurrence of a linear vesiculobullous rash following a laser treatment for hyperpigmented areas. As in our cases, no resurgence of extracutaneous involvement, ophtalmologic or neurologic, was experienced in any of these cutaneous exacerbations.

The recent identification of NEMO/IKKγ as the gene responsible for IP may shed light on the pathophysiology of IP and the phenomenon of reactivation. The IkB kinase (IKK) γ is one of the subunits of the IKK complex implied in the NF-κB activation, an essential pathway in the antiapoptotic and proliferative cellular mechanisms.10-15 In unstimulated cells, NF-κB remains inactive while sequestered in the cytoplasm through interaction with molecules of the IkB family. Stimuli such as proinflammatory cytokines or viruses lead to phosphorylation of IkB by the IKK, causing its rapid degradation and, accordingly, the release of free NF-κB, which can thereby reach the nucleus and activate its target genes.10

Incontinentia pigmenti has been recently ascribed to mutations in the NEMO/IKKγ gene. The mutated NEMO/IKKγ encodes a nonfunctional protein, unable to activate the NF-κB pathway.1 Therefore, cells in which the mutant X chromosome remains active are devoid of NF-κB activation and become more sensitive to apoptosis and hyperproliferation.11-15 Makris et al16 have proposed a model based on their observations in transgenic IKKγ-positive and -negative mice. They suggest that IKKγ-deficient cells may undergo rapid hyperproliferation and necrosis, leading to increased proinflammatory cytokine production in the neighboring IKKγ-positive cells. Indeed, most of the cytokines whose expression was found to be elevated in the transgenic mice’s skin (interleukin 1, tumor necrosis factor (TNF) α, interferon γ, and transforming growth factor β) are under NF-κB control. Therefore, they cannot be produced by the IKKγ-deficient cells.

The signaling mechanism underlying this proinflammatory response has not yet been identified. Makris et al16 propose the role of a heat-shock protein released by the necrosis of the IKKγ-negative cells. It has recently been shown that a secreted 70-kd heat-shock protein can act as a cytokine and activate NF-κB, resulting in a proinflammatory cytokine production, which might account for the granulocyte infiltration and the inflammation observed at the first stage of IP.17

Another effect of the proinflammatory cytokines might be the enhancement of apoptosis in the mutated cells. Indeed, histologic examination of skin biopsy specimens from patients with IP shows numerous apoptotic cells. TUNEL assays (terminal deoxynucleotidyl transferase–mediated biotin-deoxyuridine 5-triphosphate nick-end labeling) performed in the epidermis of the IKKγ-positive and -negative transgenic mice reveal a large increase in the frequency of these cells.18 The inconti-
nence of melanin from basal keratinocytes might be the result of apoptosis (and necrosis) of the IKKγ-deficient cells. The cells in which the mutant X chromosome is active are then gradually eliminated through apoptosis, leading to the classic progressive resolution of the skin lesions. However, Makris et al16 suggest that all of the IKKγ-deficient cells might not be eliminated through a first cycle. The phenomenon of recurrence observed in our patients could be explained by the persistence of some residual IKKγ-deficient cells, which might give rise to another cycle of hyperproliferation, inflammation, and apoptosis.16 Several cycles could thus occur, until the mutated cells are completely eliminated.

In the observation reported by Van Leeuwen et al17 most of the recurrent inflammatory lesions occurred on the trunk, a site that was relatively spared during the first episode. Our first patient presented with lesions on the trunk. It can be supposed that a large number of IKKγ-deficient cells had persisted in the site of mild first eruption. Remarkably, when a biopsy specimen from a hyperpigmented linear skin lesion was obtained, in a few cases of our series of 42 patients with IP, histologic examination revealed some apoptotic cells, emphasizing that the pigmented streaks are not only residual but still active lesions. The classic absence of recurrent inflammatory phenomenon could be due to an insufficient number of persistent IKKγ-deficient cells.

The triggering of reactivation by infections, fever, or both remains to be explained. The role of a proinflammatory cytokine such as TNF-α might be imagined, which would enhance hyperproliferation, necrosis, and apoptosis in the persistent IKKγ-deficient cells, abnormally sensitive to TNF-α-induced apoptosis.13-15 We did not perform any skin biopsies on a recurrent inflammatory lesion in our 5 patients. However, Pfau and Landthaler3 analyzed skin biopsy specimens from recurrent inflammatory lesions and found numerous dyskeratotic cells and focal ballooning of basal keratinocytes concordant with apoptotic cells.

The mechanisms of these cutaneous reactivations will certainly be better understood in the future. The possibility of numerous persistent IKKγ-deficient cells, highly reactive to particular triggering factors, raises the possibility that such reactivations could occur in organs other than the skin, for instance, the brain and eyes. The demonstration of the role of triggering factors of organ damage (eg, TNF-α) could facilitate the planning of early effective therapeutic strategies.

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