

Incontinentia Pigmenti: A Case Report

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Keywords: incontinentia, pigmenti.

Abstract: Incontinentia pigmenti (IP) is an uncommon X-linked dominant genodermatosis, can affects the skin, eyes, teeth, and may be associated with neurological defects. Changes of skin that are always present are usually combined with anomalies in skin appendages and in other organs. A 2 month female baby, with chief complaint brown patches on her body. Her mother said that brown patches on her body since 1 month, at first it was red patch with blister, then dry and left rough mark. Dermatological examination on regio thoracalis anterior et posterior, brachii dextra et sinistra, femoralis dextra et sinistra found linear hiperpigmentation macule, along blaschko line, no scale, no verucosa. Histopathological examination on epidermis there were hiperkeratosis basal cell, no spongiosis and on dermis there were melanin within macrophage along superficial dermis. In this case, there was a skin anomali but with no other organ involvement. This patient is female, with history of her mother miscarriage in second child. Although the skin lesions of IP appear impressive, little treatment is needed as they will gradually clear on their own. Parents should be appropriately counseled about the expected course of the disease. A bland emollient can be applied to inflammatory lesions to prevent ulceration.

1 INTRODUCTION

Incontinentia pigmenti (IP) is an uncommon X-linked dominant genodermatosis, can affects the skin, eyes, teeth, and may be associated with neurological defects. It affects predominantly females and is lethal in utero in male fetuses. Cutaneous manifestations are classically subdivided into four stages: vesiculobullous, verrucous, hyperpigmented, and atrophic. The diagnosis of IP was based on clinical findings and on histopathological analysis of biopsy specimen. IP is a single-gene disorder caused by mutation in the NEMO (nuclear factor kB essential modulator) gene located at chromosome Xq28, which is required for activation of a transcription factor involved in immune, inflammatory, and apoptotic pathways. More than 90% of patients will present in the newborn period with inflammatory vesicles, often following a linear pattern (V-shaped pattern on the back and S-shaped pattern on the anterior trunk) corresponding to the migration of embryonic cells during fetal development (the lines of Blaschko). Classically, these vesicles will subsequently evolve through a verrucous stage, a hyperpigmented stage, and finally, a stage of dermal atrophy and

hypopigmentation. The identification of NF-kB essential modulator (NEMO) as the disease-causing gene, and the skewing of X-chromosome inactivation, are powerful tools for the diagnosis of unusual forms of IP. In 80% of IP cases, the disease is caused by a large-scale deletion of NEMO exons 4 to 10. Nevertheless, the diagnosis of IP is based on a thorough clinical examination. Landy and Donnai have defined criteria that are useful for the clinical diagnosis of IP (Hegde et al., 2006; Hadj-Rabia et al., 2013).

2 CASE

A 2 month female baby, with chief complaint brown patches on her body. Her mother said that brown patches on her body since 1 month, at first it was red patch with blister, then dry and left rough mark. There was no itchy, no pain at the brown patches. There was no history of trauma at the site of the lesion before. History of giving topical, family having the same complaint, eye abnormalities, seizure or epilepsy were denied. No history of having other disease. She is third child, history normal childbirth, 38 weeks of

pregnancy, 3kg birth weight, 50 cm length, no history of having other disease. Her mother said that during pregnancy, she routinely control to the doctor and there were no abnormality. History of consanguineous marriages was denied. Her first brother was not affected. History of consuming drug or medicinal herbs during pregnancy was denied. History of consuming drug or medicinal herbs during pregnancy was denied. Her mother have thin white mark on her wrist. History of mother miscarriage in second child. General examination revealed compos mentis condition, look well with no sign of anemic, icterus, cyanosis, or respiratory distress, no lymph node enlargement. Body weight 3,5 kg, and length 55cm. The pulse rate was 100 per minute, respiratory rate 20 per minute, and body temperature 36.8 °C. There was no abnormality on thorax and abdomen examination. Dermatological examination on regio thoracalis anterior et posterior, brachii dextra et sinistra, femoralis dextra et sinistra found linear hyperpigmentation macule, along blaschko line, no scale, no verrucosa. Blood examination, hemoglobin was 12g/dl, leucocyte was 11.700/cmm with eosinophil 0%, basophil 0%, neutrophil stab 0%, segmen 47%, lymphocyte 44%, monocyte 9%, trombocyte 266.000 and erythrocyte 3,88. Histopathological examination on epidermis there were hiperkeratosis basal cell, no spongiosis and on dermis there were melanin within macrophage along superficial dermis. Patient consult to pediatric department, there were normal growth and development. Consult to ophthalmology department, neurology department, and dentist with no abnormalities found. Patient give therapy emolient baby cream two times daily, and education about patient's condition, possibility of ophthalmologic or neurologic condition, consult if there's any complain and not manipulate the lesion.

3 DISCUSSION

Incontinentia pigmenti [Bloch–Sulzberger syndrome] is a rare X-linked genodermatosis with an estimated prevalence of 0.7/100,000. Changes of skin that are always present are usually combined with anomalies in skin appendages and in other organs. IP appears almost exclusively in females and is usually lethal in males (Hilde et al., 2012; Zhang et al., 2013). The absence of severe systemic complications was noted in 43 of 96 (44.8%) patients with generalized IP and 39 of 43 (90.7%) IP patients with minor cutaneous symptoms (Hadj-Rabia et al., 2011). In this case, there was a skin anomaly but with no other organ

involvement. This patient is female, with history of her mother miscarriage in second child.

The cutaneous lesions in the first stage represent the population of NEMO-deficient cells that fail to activate NF- κ B, leading to apoptosis, as NF- κ B normally protects against tumor necrosis factor-induced apoptosis. Epidermal cells expressing the defective NEMO gene give rise to typical skin lesions along the lines of Blaschko, reflecting the embryonic migration path of the affected keratinocytes. The number of NEMO-deficient cells decreases secondary to apoptosis and is replaced by cells expressing the normal allele. Subsequently, the inflammatory and vesicular stage ends. The hyperproliferation in the second stage is likely due to compensatory proliferation of normal NEMO keratinocytes. Hyperpigmentation in the third stage results from incontinence of melanin pigment from the destroyed epidermis into the dermis (Hilde et al., 2012).

The differences in effect that are found among tissues in an individual, and among the same tissues in different individuals, point out the profound effect of selection for cells in which the normal X-chromosome escapes inactivation and becomes the active X-chromosome in this disease. Some tissues appear to undergo this selection early in development and are therefore spared any apparent phenotype at the time of birth. Other tissues, such as hair roots and tooth bulbs, undergo selection after birth during proliferation. This leads to abnormalities such as anodontia and alopecia, in which cells harboring the NEMO mutation fail to proliferate. These cells are apparently unaffected by the NEMO mutation until directed to generate teeth or hair, which they are unable to do. Those cells with an active normal X-chromosome contribute to these tissues, resulting in patchy alopecia, and oddly shaped when the tooth bud is made up of a mix of mutant and normal cells or normal teeth (Hadj-Rabia et al., 2011).

Recently, NEMO was implicated as the primary effector molecule for signaling the presence of DNA damage to the NF κ B complex. Cells that undergo DNA damage must determine whether to undergo apoptosis, a decision that is mediated by a number of components of the DNA damage-sensing and repair pathway. Huang et al. recently determined that NEMO is the principal molecule that provides this signaling from the nucleus to the cytoplasm, thereby enabling the release of NF κ B released into the nucleus to stimulate transcription of anti-apoptotic genes. The ATM (ataxia telangiectasia mutated) kinase phosphorylates NEMO and assists its association with the IKK complex in the cytoplasm.

The details of NEMO alteration in the nucleus are also being explored; it has been found to be associated with PIDD (p53-inducible death-domain-containing protein) and RIP1 (receptor-interacting protein 1) in a complex that facilitates its sumoylation, a mark of activation. The cell death causes lethality in male embryos and skewed X-inactivation in female patients, as a result of elimination of cells with an active mutant X-chromosome. In order to explain the survival of some male patients with IP, three mechanisms have been proposed (Nelson, 2006).

Cutaneous manifestations: Stage 1, inflammatory or vesicular stage: development of papules, vesicles and pustules on an erythematous base, distributed linearly along the lines of Blaschko. Stage 2, verrucous stage, is characterized by plaques and warty papules linearly arranged over an erythematous base, also following the lines of Blaschko. Stage 3 or hyperpigmented stage : development of linear or whorled lesions, with a brownish pigmentation, which may be accompanied by atrophy, occurs in 90-98% . Stage 4, known as atrophic or hypopigmented, is characterized by areas of hypopigmentation, atrophy and absence of hair. develop during adolescence, persist into adulthood (Berlin et al., 2002).

On this case, histopathological examination showed on epidermis there were hiperkeratosis basal cell, no spongiosis. On dermis there were melanin within macrophage along superficial dermis. There were some lymphocyte. No eosinophil. This is more like the third stage of IP.

Other dermatologic findings, the inflammatory lesions of IP can produce scarring alopecia, primarily of the vertex of the scalp. Up to 38% of affected individuals report this finding. Like atrophic skin lesions, vertex alopecia is a persistent marker for IP (Zou et al., 2007).

Laboratory findings, perhaps one of the most striking findings during the first cutaneous stage of IP is the marked peripheral blood leukocytosis and eosinophilia. Eventually, the counts return to normal during the subsequent stages. Immunoglobulin levels and lymphocyte subpopulation counts are within normal limits (Zou et al., 2008).

Although the skin lesions of IP appear impressive, little treatment is needed as they will gradually clear on their own. Parents should be appropriately counseled about the expected course of the disease. A bland emollient can be applied to inflammatory lesions to prevent ulceration. If ulceration occurs, antibiotic ointment and non-adherent sterile dressings should be used to cover the affected areas. Subungual tumors may spontaneously resolve, but can be treated

with surgical excision or curretage to ameliorate the associated pain (Bruckner, 2004; Julie et al., 2013; Mini'c et al., 2014).

Parents should also be counseled about the possibility of delayed eruption of the teeth and other dental abnormalities. Significant absence of the teeth may impact not only the ability to eat and speak, but also facial development and cosmesis. The early involvement of a dental team familiar with these problems is important (Bruckner, 2004; Julie et al., 2013; Mini'c et al., 2014).

4 CONCLUSION

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