

Case Report

An unusual case of incontinentia pigmenti in a male neonate

男性新生兒中的色素失禁症罕有個案

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Incontinentia pigmenti, also known as Bloch-Sulzberger syndrome, is a rare X-linked dominant genodermatosis classically described to be lethal in male foetuses. Few cases of male survivors have been reported in medical literature. Male survival is thought to be due to hypomorphic alleles, a 47, XXY karyotype or somatic mosaicism. We describe a case of a 2-week-old Chinese male neonate who presented at our centre.

色素失禁症，也被稱為布洛克-蘇茲貝格綜合徵是一種罕見的性聯顯性遺傳性皮膚病，在經典描述中對男性胎兒是致命的。據醫學文獻報導，男性倖存者非常之少。男性病者能存活的機轉包括有低表現量的等位基因，47,XXY核型及體細胞嵌合體。本報告描述了一位兩週大的華籍男性嬰兒的個案。

Keywords: Bloch-Sulzberger syndrome, genodermatosis, incontinentia pigmenti, NEMO gene

關鍵詞：布洛赫-蘇茲貝格綜合徵、遺傳性皮膚病、色素失禁症、NEMO 基因

Introduction

Incontinentia pigmenti (IP), or Bloch-Sulzberger syndrome, is characterised by distinct cutaneous lesions with associated hair, nail, teeth, eye and neurological abnormalities. The skin lesions typically occur in four stages, and may initially

present with erythematous, blistering lesions following Blaschko's lines of ectodermal embryologic development. Mutations in the gene for NF-kappa B essential modulator (*NEMO*) have been found in 85% of patients with IP.¹ Females survive due to functional mosaicism, while male foetuses inheriting this mutation usually die in utero. The few surviving males reported in medical literature were accounted for by hypomorphic mutations, abnormal karyotypes and somatic mosaicism.²

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Case report

A 2-week-old Chinese male neonate presented at the National Skin Centre, Singapore, with scaly

and pustulo-vesicular rashes in the groin, buttocks and axillae since birth (Figure 1). Most of the lesions were linearly distributed along the lines of Blaschko. He was otherwise feeding and growing well. The patient was delivered at full term via normal vaginal delivery with no obstetric complications. He was the only child in his family. His mother did not have any previous history of spontaneous abortions or miscarriages, and she did not have any hypopigmented skin areas. There was no known family history of genetic, dermatologic, neurologic or ophthalmologic conditions.

Initial differential diagnoses by the paediatrician included herpes simplex infection, immunobullous conditions and neonatal lupus. A Tzanck smear showed numerous eosinophils. The Gram stain, fungal smear and herpes isolation were all negative. Histopathological examination revealed multi-loculated distended intraepidermal blisters filled with serous fluid and numerous eosinophils (Figures 2 and 3). The dermis showed superficial perivascular and interstitial infiltrates composed of a mixture of eosinophils, lymphocytes and histiocytes. This was consistent with a diagnosis of IP.

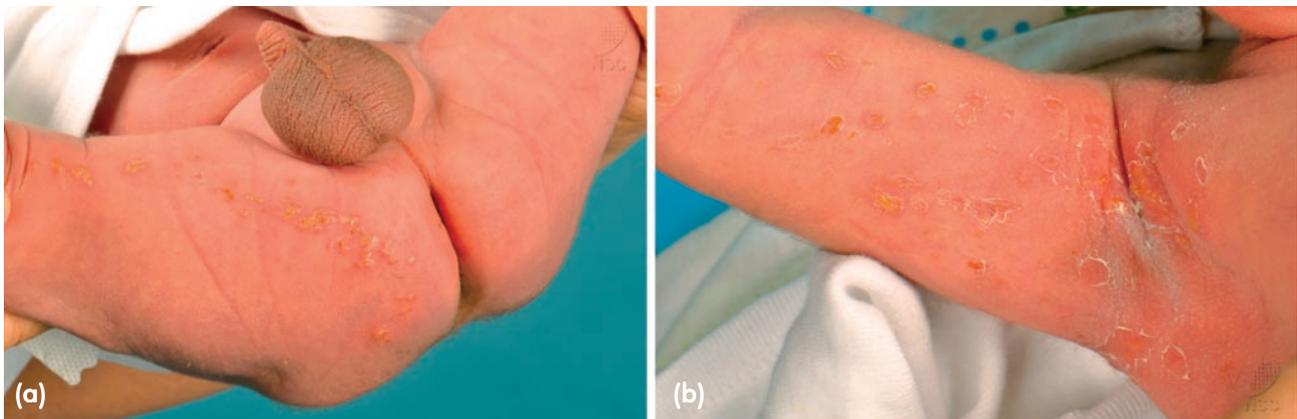


Figure 1. (a) Pustulo-vesicular rashes at the groin area. These lesions were linearly distributed along lines of Blaschko. (b) Similar lesions in the axilla.

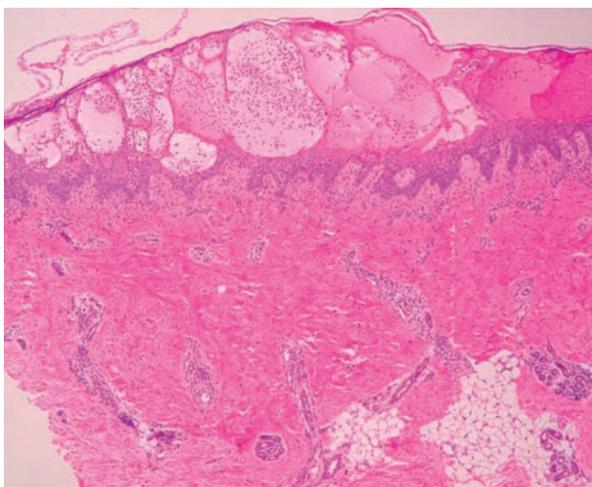


Figure 2. Multi-loculated distended intraepidermal blisters (H & E Stain, x 40).

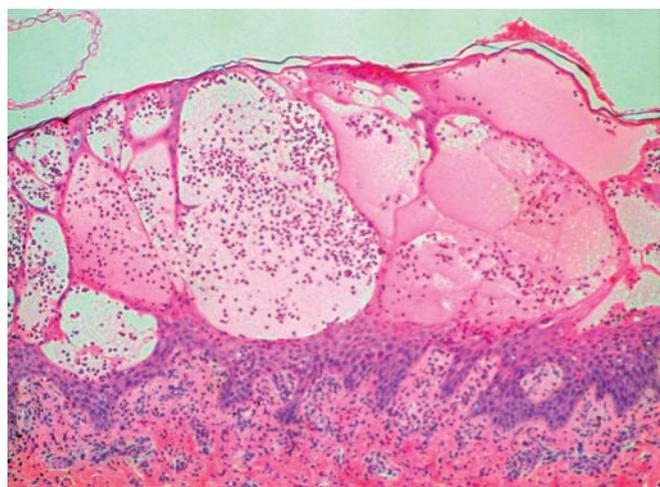


Figure 3. The blisters were filled with serous fluid and contained eosinophils (H & E Stain, x 100).

At four weeks of age, most of the pustules and vesicles had resolved and were replaced by scabs. Genetic studies were carried out to look for the *NEMO* gene mutation. The blood results were negative, whilst the DNA in the skin biopsy specimen was inadequate for amplification. This is due to the small size of the specimen leading to a low DNA load in the paraffin section. We plan to perform a skin scrape of the lesional cells to increase the yield for genetic testing upon his next visit. The parents were offered genetic counselling and informed of the possible extradermal complications. Referrals were made to the neurologist, ophthalmologist and dentist.

Discussion

The diagnosis of incontinentia pigmenti is made based on the clinical appearance of typical cutaneous lesions and its characteristic distribution along the Blaschko lines. Histopathological features include a spongiotic dermatitis with eosinophilic infiltrate and large dyskeratotic cells during the vesicular stage.³

Initial differentials for an infective cause such as herpes simplex, bacterial impetigo and cutaneous candidiasis were ruled out by the negative smear or culture. There was no maternal history suggestive of immunobullous conditions that could have occurred via transplacental passage and the patient was negative for IgG antibodies to immunobullous conditions such as neonatal bullous pemphigoid. Neonatal lupus was considered; however, there was an absence of annular lesions or maternal history of lupus.

Clinical features

Cutaneous features of incontinentia pigmenti can be grouped into four stages, namely vesicular, verrucous, hyperpigmented and atrophic/hypopigmented stages. Extracutaneous manifestations include hair, nail, teeth, eye and

neurological abnormalities. A review of 40 male patients indicated tooth abnormalities to be the most common (40%), followed by hair, eye and central nervous system anomalies (30%).⁴ Dental abnormalities often present as a delay in the eruption of teeth, missing or small teeth and peg-shaped or cone-shaped teeth. There may be alopecia, retinal vascular abnormalities, cataracts or uveitis. Complications involving the central nervous system include seizures and mental retardation. At the time of presentation, our patient did not have any apparent extracutaneous manifestations and we have made the appropriate referrals for follow-up.

The male clinical phenotype of IP remains largely unknown. Studies suggest that affected males generally go through the same clinical process as females. However, a notable difference is that males tend to have more localised presentations⁵ and may even have unilateral cutaneous and extracutaneous manifestations. These unilateral presentations do not appear to represent a milder phenotype; the majority of patients in this subset subsequently develop bilateral skin lesions.⁴ This could possibly be due to an incomplete expression of an unstable pre-mutation that is otherwise silent in a normal male during embryogenesis.⁶

Molecular studies

Incontinentia pigmenti is a genodermatosis associated with mutations in the *NEMO* gene on chromosome Xq28. Hsiao et al screened for the *NEMO* gene mutation in a population of Chinese patients with IP, and found that the mutation was present in 66.7% of patients.⁷ In another study conducted by Fusco et al in a cohort of Italian patients, *NEMO* gene mutation was found in 60-80% of these patients.⁸ Hence, the frequency of *NEMO* mutations in IP is comparable in both Western and Asian populations.⁷ Since the majority of cases arose from de novo mutations in patients with no prior family history, the Asian population is equally susceptible to IP.⁷

There are three possible mechanisms that presumably allow for survival in male patients with IP: hypomorphic mutations, abnormal karyotypes and somatic mosaicism.² Male patients with hypomorphic mutations in the *NEMO* gene usually have ectodermal dysplasia and immunodeficiency.^{9,10} A previous study on 48 male patients with IP showed 7% of the study population having a 47,XXY karyotype.¹¹ Karyotyping was not performed in view of the cost effectiveness of the test. We intend to monitor the patient closely for any manifestations of the other mechanisms.

Treatment

There is no definitive treatment for incontinentia pigmenti. Patients should be monitored for complications of local skin lesions, e.g. secondary infections. In addition, continuing evaluation under multidisciplinary care is required for the possibility of extracutaneous abnormalities that appear after infancy.⁴ Annual eye screening should be commenced, full neurological examination and MRI brain should be performed.

Conclusion

In summary, we have discussed a male patient with incontinentia pigmenti who presented with cutaneous lesions which were characteristically distributed along Blaschko lines. Due to a negative family history of skin diseases, it is likely due to a mosaic disorder caused by somatic mutations. We emphasise the need for continuous follow-up to monitor for subsequent development of extracutaneous manifestations.

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