A Retrospective Study of Incontinentia Pigmenti Seen at the National Skin Centre, Singapore Over a 10-year period

Y C Chan,*MBBS, MRCP (UK), Y C Giam,**FAMS, MBBS, M Med (Paed)

Abstract

***Introduction**: Incontinentia pigmenti is a rare X-linked dominant disease which affects the ectodermal tissues, usually lethal in males. **Materials and Methods**: A retrospective analysis of clinical data obtained from the photographic documentation and casenotes of patients diagnosed to have incontinentia pigmenti at the National Skin Centre. The study covered the period from January 1990 to December 1999. **Results**: Twenty-six patients were diagnosed to have incontinentia pigmenti of the Bloch-Sulzberger type; 23 (88.5%) were females and 3 (11.5%) were males. There were 20 Chinese, 3 Malay and 3 Indian patients. Most patients had cutaneous manifestations at birth or within the first week of life. Cutaneous features included vesicles, papules, verrucous plaques and splash-like hyperpigmentation along the lines of Blaschko. The cutaneous lesions were widespread in 21 (81%) and localised in 5 (19%) patients. In some cases, hypopigmented atrophic streaks (2 patients) or whorled scarring alopecia (4 patients) were seen. Extracutaneous manifestations, seen in 5 (19%) patients, included neurological, dental and ocular defects. One Malay girl had severe neurological involvement associated with ocular abnormalities. A positive family history was present in 6 (23%) patients. The 3 male patients were Chinese without any family history. **Conclusions**: Each stage of the disease comes with its own set of differential diagnosis, including infections e.g. herpes virus infection and other types of genodermatoses e.g. linear and whorled nevoid hypermelanosis. The phenomenon of whorled scarring alopecia, hitherto unreported in the literature, corresponded to the lines of Blaschko. In the 3 Chinese male patients, the disorder probably originated from a new mutation. X chromosome inactivation in females during early embryogenesis results in a mosaic population of cells and this explains the linear and patchy manifestations of incontinentia pigmenti.*

***Ann Acad Med Singapore* 2001; 30:409-13**

Key words: Functional X-chromosome mosaicism, Incontinentia pigmenti in males, Lines of Blaschko, Whorled scarring alopecia, X-linked dominant inheritance

Introduction

Incontinentia pigmenti, called Bloch-Sulzberger syndrome, is a rare X-linked dominant disorder involving ectodermal structures. It is a multisystem disorder with cutaneous, ocular, dental, cerebral and skeletal manifestations. Over 700 cases have been reported and 97% are females.[1] It is usually lethal in males and, by 1998, only about 50 males have been reported in the literature.[2] The locus for incontinentia pigmenti has been linked genetically to the factor VIII gene in chromosome Xq28.[3] The gene for NEMO (NF-kappaB essential modulator) has been mapped to a position 200 kilobases proximal to the factor VIII locus. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. Until recently, many geneticists believed that there are two forms of incontinentia pigmenti, type 1 being sporadic and assigned to Xp11 and type 2 being hereditary and assigned to Xq28. This is most likely an erroneous concept. All cases classified so far as "incontinentia pigmenti type 1" appear to belong to the group called hypomelanosis of Ito because vesiculobullous lesions were absent. Skin biopsies, when performed, did not show the typical findings of incontinentia pigmenti.

In 1975, Carney reviewed over 600 published clinical reports of incontinentia pigmenti and provided the most comprehensive survey of the disease.[4] The skin findings in incontinentia pigmenti are the most characteristic clinical features of the disorder. All four cutaneous stages in the form of inflammatory, proliferative, pigmentary and atrophic hypopigmented lesions may exceptionally be seen simultaneously but usually follow each other in this sequence. Alopecia and nail dystrophy are common too. Extracutaneous features of incontinentia pigmenti include dental, ocular and cerebral abnormalities.

In this study, we reviewed the clinical features of patients with incontinentia pigmenti seen at a dermatology tertiary referral centre in Singapore over a 10-year period (from January 1990 to December 1999).

* *Registrar*
** *Senior Consultant*
National Skin Centre, Singapore
Address for Reprints: A/Prof Giam Yoke Chin, National Skin Centre, 1 Mandalay Road, Singapore 308205.

Subjects and Methods

A retrospective analysis of all patients with incontinentia pigmenti seen at the National Skin Centre (NSC) from January 1990 to December 1999 was conducted. Referrals to the NSC were from hospital paediatricians, private dermatologists and general practitioners. There were records of a total of 37 patients. Detailed clinical information was available in 26 patients. The diagnosis of incontinentia pigmenti was clinically established in all 26 cases. Skin biopsies were performed in 9 patients, including the 3 male patients. Incomplete information existed on the remaining 11 patients. We report the clinical features as seen in the group of 26 patients for whom information is complete.

Results

The 26 patients consisted of 23 (88.5%) females and 3 (11.5%) males. There were 20 Chinese, 3 Malay and 3 Indian patients. They presented at the NSC from the first week of life to 15 years of age. Fifteen patients were seen in the first week of life, 4 between the ages of 1 week and 1 year, and 7 after the age of 1 year. Six had a positive family history. Analysis of these 6 pedigrees revealed that the female carriers had children in a sex ratio of approximately 2 girls to 1 boy (the rough ratio of 5:2 had to be corrected for the female index patient). The 3 male patients were sporadic cases.

Twenty-three patients had cutaneous lesions at birth or within the first week of life, the remaining 3 patients could only recall the onset as being "since young". The cutaneous lesions were widespread and bilateral in 21 patients and localised, usually to one limb, in 5 patients. There are 4 clinical stages in incontinentia pigmenti. The first stage consisted of grouped vesicles and bullae on an erythematous base, in swirls and patches along the lines of Blaschko on the limbs and the trunk (Fig. 1). In 15 patients, they were seen from birth to 3 months of age. One exception, a Chinese girl with histopathologically confirmed incontinentia pigmenti, continued to develop vesicles till the age of 4.5 years. The second stage, verrucous papules and plaques on an erythematous base in linear patches or swirls along the lines of Blaschko, were seen from birth to the age of 3 years in 11 patients (Fig. 2). The third stage, brown pigmentation in streaks and whorls along the lines of Blaschko, were seen from birth to the age of 20 years in 23 patients (Fig. 3). The fourth stage, hypopigmented streaks along the lines of Blaschko, were seen in 2 patients only, at the ages of 3 and 12 years, respectively.

A remarkable and so far less well-known feature, scarring alopecia, was present in 4 patients and mainly on the vertex of the scalp with a whorled pattern (Fig. 4).

Extracutaneous abnormalities were seen in 5 patients (Table I) i.e., in 19% of the 26 patients. One Malay girl manifested neurological signs, being afflicted with cerebral palsy and hypotonia at birth, and subsequently developed strabismus and retinal detachment of the left eye. She had widely-spaced notched conical teeth and a whorled pattern of scarring alopecia. Her mother had likewise widely-

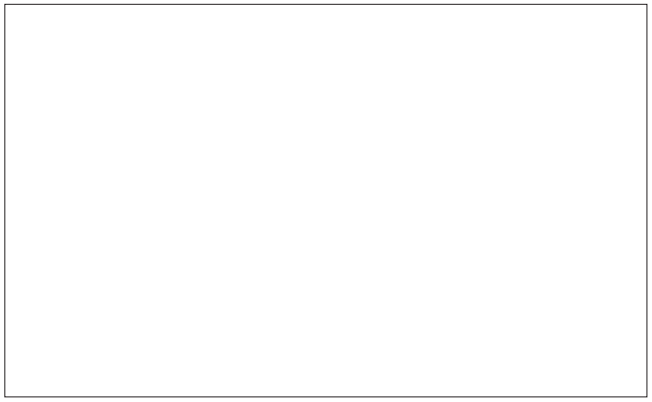

Fig. 1. Vesicles and bullae on an erythematous base along the lines of Blaschko on the legs.

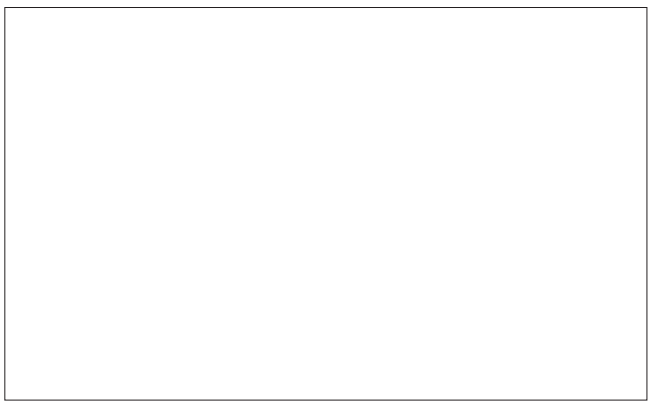

Fig. 2. Verrucous plaques along the lines of Blaschko on the foot.

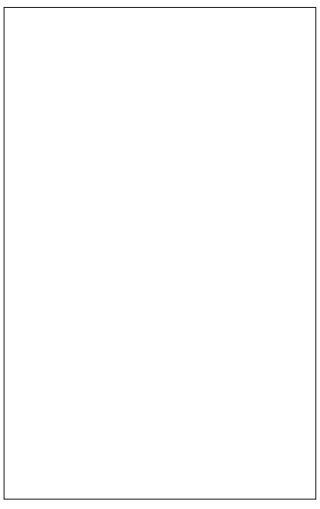

Fig. 3.

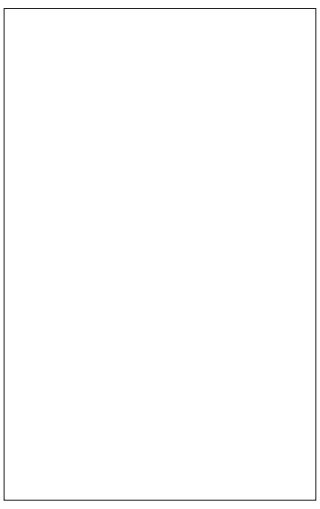

Fig. 4.

Fig. 3. Hyperpigmentation along the lines of Blaschko on the back.
Fig. 4. Whorled scarring alopecia.

TABLE I: EXTRACUTANEOUS ABNORMALITIES

Extracutaneous abnormalities		No. of patients
Dental	peg/notched teeth	2
	delayed deciduous teeth eruption	1
	hypodontia, adontia, enamel hypoplasia	
Central nervous system	cerebral palsy	1
	hypotonia	1
	childhood seizures	2
	microcephaly and mental retardation, hydrocephalus	
Eye	retinal detachment	1
	Strabismus	1
	cataracts, glaucoma, optic atrophy, neovascularisation	

Note: abnormalities in italics have been reported in the literature but were not seen in our patients.

spaced, notched teeth and scarring alopecia. Two other children had neurological involvement in the form of seizures. One boy had febrile fits and one girl had fits in childhood.

The 3 male patients were all Chinese and had no family history of incontinentia pigmenti; careful examination of their mothers did not reveal any abnormalities. All 3 presented in the first week of life with vesicles and subsequently developed papules and hyperpigmentation. One of them had scarring alopecia and febrile seizures; cytogenetic analysis revealed a normal 46, XY karyotype. All 3 patients had skin biopsies done during the vesicular stage. All 3 biopsies showed spongiotic vesicles with eosinophils in the epidermis and a predominantly eosinophilic infiltrate in the upper dermis.

Discussion

In this review, we would like to highlight the differential diagnosis of incontinentia pigmenti, the exceptional occurrence in males, and the concept of a selective process eliminating the functionally aberrant cell clone during early childhood. In particular, we emphasize the presence of linear and whorled scalp lesions reflecting functional X-chromosome mosaicism and being described for the first time in incontinentia pigmenti.

The differential diagnosis includes those diseases that may present with a vesiculobullous eruption at birth or shortly after, such as neonatal infections e.g. herpes simplex, varicella zoster, bullous impetigo and genodermatoses e.g. epidermolysis bullosa (especially of the Dowling-Meara type), bullous congenital ichthyosiform erythroderma. The verrucous lesions in the second stage may resemble a linear epidermal nevus. Diseases that manifest with splashed pigmentation in older infants, such as linear and whorled nevoid hypermelanosis, the Franceshetti-Jadassohn syndrome, dermatopathia pigmentosa reticularis and post inflammatory hyperpigmentation, should be considered in the differential diagnosis of incontinentia pigmenti in its third stage. Hypomelanosis of Ito can result in hypopigmentation resembling the fourth stage.

In 1977, Happle proposed functional X-chromosomal mosaicism as the genetic mechanism underlying cutaneous anomalies that were seen in a number of X-linked skin diseases such as incontinentia pigment.[5] Moreover, he recognized that these cutaneous anomalies followed the lines of Blaschko and thus he could tie in the development of the lines of Blaschko with a datable embryonic event. Convincing proof for the concept of functional X-chromosomal mosaicism was later provided by his group from functional sweat studies in female carriers of the X-linked gene defect hypohidrotic ectodermal dysplasia, showing on the back of the patient a gross, fountain-like mosaic typical of the lines of Blaschko. It is now recognised that during early embryogenesis of a mammalian female organism, X chromosome inactivation, or lyonisation, results in a mosaic population of cells; some cells have an active paternal X chromosome, others have an active maternal X chromosome.[6] It has been hypothesised that the segmental and streaked manifestations of incontinentia pigmenti may be consequential to tissue mosaicism from random X inactivation, with the normal X chromosome active in uninvolved skin, and the incontinentia pigmenti X chromosome active in involved skin.[7]

Incontinentia pigmenti is a X-linked dominant disease seen almost exclusively in females. The mutation is lethal for affected hemizygous males.[8] Several longitudinal studies show that females with incontinentia pigmenti have about twice the number of daughters as sons; this sex ratio was illustrated in our series. This is likely due to the increased incidence of spontaneous abortions of male fetuses.[9-11] Affected girls survive because of two functionally different cell clones resulting from lyonisation. These phenotypes display the mosaicism pattern type 1a, which consists of narrow bands along the lines of Blaschko.[12]

An unusual and hitherto unreported feature, scarring alopecia, was present in 4 patients and mainly on the vertex of the scalp with a whorled pattern (Fig. 4). It appears to correspond to Blaschko's lines on the scalp.[13]

Extracutaneous abnormalities were seen in 5 patients (Table I). They represent 19% of the 26 patients and this rate is much lower than the 80% noted in Carney's review. Severe neurological manifestations have been reported and include seizures, mental retardation, spasticity, hemiparesis and encephalopathy.[4] Francis and Sybert[14] noted that neurological involvement usually occurred early in life and was associated with eye involvement. Carney's rather high percentage of extracutaneous lesions may reflect

a bias of ascertainment.

The exceptional occurrence of incontinentia pigmenti in males can be explained in the following ways showing three possibilities. Firstly, these men may have a 47,XXY constitution (Klinefelter's syndrome),[15] and they are able to survive because of their extra normal X chromosome. The disease would reflect functional X-chromosome mosaicism as found in females. Secondly, they may reflect genomic X-chromosomal mosaicism resulting from an early post-zygotic mutation involving Xq28. Thirdly, they may originate from a gametic half-chromatid mutation.[16] This is transmitted to the zygote and semiconservative replication will result in a chromosome with two chromatids carrying different base pairs (Fig. 5). After cleavage, one cell may carry a complete mutation. In this case, the skin involvement would usually be widespread, systematised and bilateral. Our 3 male patients, like the males reported in the literature, are considered to be sporadic cases and are likely to have resulted from new mutations. Only 1 had extracutaneous manifestation (febrile fits) and cytogenetic analysis in this individual revealed a normal karyotype. Unfortunately, cytogenetic analysis was not done on the other 2 male patients. Assuming that all 3 males had normal XY karyotypes, we can propose that they exemplify genomic X chromosomal mosaicism due to either an early post-zygotic mutation or a gametic half-chromatid mutation. The latter situation may also arise in the male patient's gonads. Hence, these men may potentially transmit the disease to their daughters and must be appropriately counselled. Based on the existing literature, males appear to have a higher rate of mental retardation than the general population, but there does not appear to be a correlation between the severity of skin involvement and mental status.[2] Our 3 male patients were neither more severely affected nor show any signs of mental retardation.

In female patients, the clinical findings may sometimes likewise be subtle, reflecting extreme lyonisation. This may explain why a positive family history was present in only 6 (23%) of our patients. The mothers of these 6 patients had either a history of the characteristic skin changes, dental abnormalities or scarring alopecia. The dental abnormalities and scarring alopecia are permanent and can be used as markers to ascertain affected adult women. In our series, one mother and a grandmother had whorled scarring alopecia. The mothers of these 6 patients had children in a female to male ratio of 2:1, which corresponds to the expected ratio in a X-linked dominant, male-lethal disorder (Fig. 6).

Four sequential stages are classically described in incontinentia pigmenti: inflammatory, proliferative, pigmentary and atrophic. It is not uncommon to find a coexistence of two or even three stages in 1 patient; this phenomenon was documented in 14 of our patients. Crops of vesicular lesions are rarely seen beyond one year of life; one of our patients had vesicular lesions till the age of 4.5 years. Presumably, the functionally aberrant clones can be eliminated by the normal cell clones but this may be incomplete; thus, the presence of vesicles in a linear mosaic form in late childhood or even adulthood has been reported.[17]

About 14% of patients showed the typical whorled hyperpigmentation as the initial and solitary clinical expression of incontinentia pigmenti; even fewer patients are born with this pigmentation.[4] Two of our patients presented at the age of 1 week and 3 months**,** respectively, with the typical hyperpigmentation since birth. They had

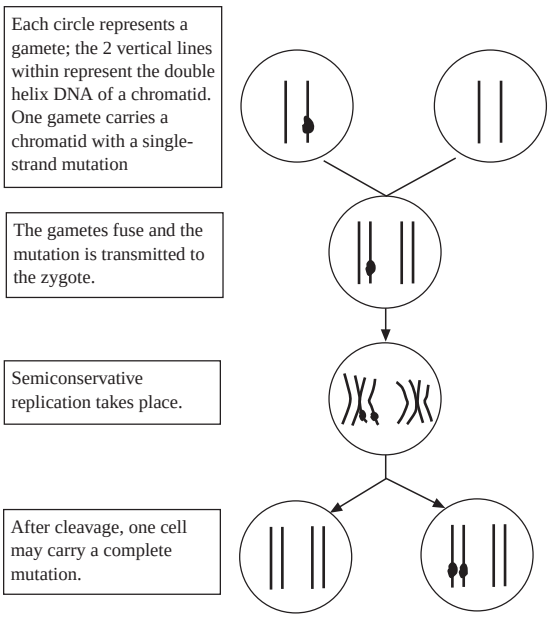

Fig. 5. Gametic half-chromatid mutation.

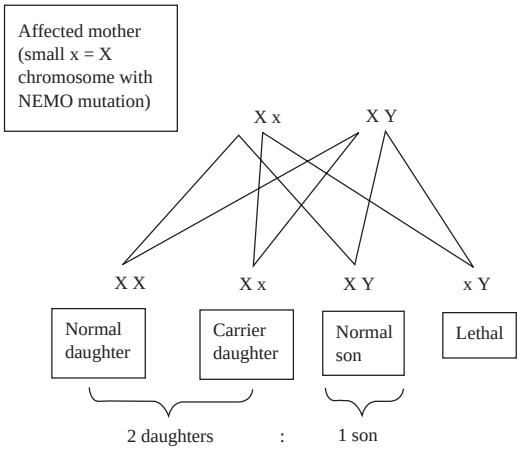

Fig. 6. X-linked dominant, male-lethal inheritance.

no history of and showed none of the other stages of incontinentia pigmenti on follow-up. Most likely one or more of the first two stages may have occurred already *in utero*. The diagnosis of incontinentia pigmenti should be carefully reconsidered in these patients as differentiation from linear and whorled nevus may be difficult. A helpful clinical sign is that the latter does not disappear with time, whereas incontinentia pigmenti tends to clear.

The typical transition from inflammation to verrucous hypertrophy and hyperpigmented skin areas in incontinentia pigmenti suggests a gradual replacement of defective cells by normal cells. This would imply a process eliminating the cell population with the active X chromosome carrying the incontinentia pigmenti gene. This hypothesis has been supported by demonstrating that the same X chromosome is preferentially active in fibroblasts grown from normal and hyperpigmented skin of an affected girl.[18]

Histologically, the vesicular lesions are characterised by eosinophilic spongiosis, intraepidermal vesicles, often surrounded by dyskeratotic cells, and a predominantly eosinophilic infiltrate in the dermis. The verrucous lesions show hyperkeratosis, papillomatosis, acanthosis and scattered dyskeratotic cells. The pigmented lesions show an accumulation of melanophages in the superficial part of the dermis.

A skin biopsy taken in the vesiculobullous phase is often helpful in establishing the diagnosis.

For the skin disorder, no treatment is needed except for the control of secondary infection of the vesiculobullous lesions. Meticulous dental hygiene is advisable and dental intervention in affected patients can minimise cosmetic disability related to the dental abnormalities. Neurologic consultation should be sought if the patient is symptomatic and ophthalmologic consultation at the time of diagnosis is advisable. Female members of the family should be examined for signs of incontinentia pigmenti.

Genetic counselling should be offered to all families. For a woman with incontinentia pigmenti, one pregnancy in four will probably result in a spontaneous abortion. Statistically, half of her daughters will have incontinentia pigmenti. Of the affected daughters, about 30% will have more pronounced manifestations than her mother and about 94% will have at least as many defects as her mother.[4] If a woman without a history or symptoms of incontinentia pigmenti gives birth to a child with this disorder, this may reflect either a new mutation in the child or the presence of extreme lyonisation in the mother. Males who have incontinentia pigmenti as a result of a new mutation may transmit the disease to their daughters.

REFERENCES

1. Spitz J L. Genodermatoses. Baltimore: Williams and Wilkins, 1996:64.
2. Scheuerle A E. Male cases of incontinentia pigmenti: case report and review. Am J Med Genet 1998; 77:201-18.
3. Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, et al. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. Nature 2000; 405:466-72.
4. Carney R G. Incontinentia pigmenti: A world statistical analysis. Arch Dermatol 1976; 112:535-42.
5. Traupe H. Functional X-chromosomal mosaicism of the skin: Rudolf Happle and the lines of Alfred Blaschko. Am J Med Genet 1999; 85:324-9.
6. Lyon M. Gene action in the X-chromosome of the mouse (Mus musculus L.). Nature 1961; 190:372-3.
7. Happle R. Lyonization and the lines of Blaschko. Hum Genet 1985; 70:200-6.
8. Wettke-Schäfer R, Kantner G. X-linked dominant inherited diseases with lethality in hemizygous males. Hum Genet 1983; 64:1-23.
9. Iancu T, Komlos L, Shabtay F, Elian E, Halbrecht L, Book J A. Incontinentia pigmenti. Clin Genet 1975; 7:103-10.
10. Wiklund D A, Weston W L. Incontinentia pigmenti: a four-generation study. Arch Dermatol 1980; 116:701-3.
11. O'Brien J E, Feingold M. Incontinentia pigmenti: a longitudinal study. Am J Dis Child 1985; 139:711-2.
12. Happle R. Mosaicism in human skin: Understanding the patterns and mechanisms. Arch Dermatol 1993; 129:1460-70.
13. Happle R, Fuhrmann-Rieger A, Fuhrmann W. Wie verlaufen die Blaschko-Linien am behaarten Kopf? Hautarzt 1984; 35:366-9.
14. Francis J, Sybert V. Incontinentia pigmenti. Semin Cutan Med Surg 1997; 16:54-60.
15. Prendiville J S, Gorski J L, Stein C K, Esterly N B. Incontinentia pigmenti in a male with Klinefelter's syndrome. J Am Acad Dermatol 1989; 20:937-40.
16. Lenz W. Half chromatid mutations may explain incontinentia pigmenti in males. Am J Hum Genet 1975; 27:690-1.
17. Barnes C M. Incontinentia pigmenti: report of a case with persistent activity into adult life. Cutis 1978; 22:621-4.
18. Wieacker P, Zimmer J, Ropers H H. X inactivation patterns in two syndromes with probable X-linked dominant, male lethal inheritance. Clin Genet 1985; 28:238-42.