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Surviving male with incontinentia pigmenti: a case report

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Summary. Incontinentia pigmenti, or Block–Sulzberger Syndrome, is an X-linked dominant disorder with characteristic skin, hair, eye and tooth abnormalities. It is classically considered a male-lethal disorder with recurrent miscarriages of male foetuses. A few cases of surviving males with incontinentia pigmenti have been reported in the medical literature. This article reports the medical and dental findings of a boy diagnosed with incontinentia pigmenti.

Introduction

Incontinentia pigmenti (IP), or Block–Sulzberger Syndrome, is an X-linked dominant disorder characterized by abnormalities of ectodermal tissues including skin, eye, tooth and hair as well as neurological deficiencies [1]. IP is classically considered a male-lethal disorder, and many women with IP have recurrent early miscarriages [2,3]. Most cases of IP are due to a recurrent genomic rearrangement that deletes part of the gene for NF-kappaB essential modulator (NEMO) [4]. Male foetuses with this mutation usually die *in utero*. Mosaicism, 47,XXY karyotype, or hypomorphic alleles are possible reasons for the survival of males with IP [3].

The name of the disorder is derived from the observation of incontinence of melanin from the epidermis into the dermis [2]. The disease is characterized by an erythematous skin eruption with linear vesiculation that is present at birth or shortly after. Weeks to months after the onset of the disorder, verrucous growths are noted on one or more extremities which last for a few months. Finally, the classic IP lesions appear as hyperpigmented, brown, whorled macules mainly on the trunk. The pigment may fade over time and atrophic depigmentation and dermal scarring may occur. Other manifestations include alopecia, neurological abnormalities, ophthalmic defects, and musculoskeletal disorders [1,2].

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There have been some previous reports of the dental findings in patients with IP. Almost all have been reports of females. Reported dental anomalies have included hypodontia, conical teeth, notch shaped incisors, and delayed eruption [5–9]. Delayed root resorption of primary teeth may also be observed in some cases [7]. This article reports the medical and dental findings of a boy affected with IP.

Case report

The patient (JL) was a Chinese boy who was 8 years old when first seen and had been followed up in a University paediatric clinic since he was 3 months old. He was delivered by Caesarian section because of being post-term and failure of medical induction of labour. His weight at birth was 2·9 kg. There was no family history of hereditary disease. His mother has a history of allergic rhinitis but no history of miscarriage. JL is the only child in his family.

JL was diagnosed with incontinentia pigmenti at three months of age with a history of typical inflammatory vesicles mainly on the extremities shortly after birth, followed later by linear verrucous and hyperkeratotic lesions on the extremities. Even as young as 5 months of age he was noted to be 'hyperactive', which has persisted, with signs of frustration, quick temper and aggressive behaviours being evident. Genetic advice was obtained when he was 1 year old. Chromosomal studies revealed a normal karyotype 46XY. JL was admitted to hospital when he was two years old due to febrile convulsion with

transient left hemiparesis. Because of hyperactivity and complaints from teachers (no classmates wanted to sit next to him), his paediatrician prescribed methylphenidate HCl 5 mg a.m. when he was 7 years old. His mother discontinued the medication after one month as she felt that her son was just naughty instead of having behavioural problems. JL has been followed by an ophthalmologist since he was $2^1/_2$ years old and no abnormalities have been detected so far. The dermatologist prescribed aqueous cream and light mineral oil baths for his skin lesions.

Previous dental history shows that JL was diagnosed with hypodontia. At age 1 year, the paediatrician noted that no teeth had erupted. When he was 7 years old, a clinical examination and panoramic radiograph showed that he was in the late primary dentition stage, with congenitally missing:

$$\frac{5 \mid A15}{54D \mid A1}$$ (15; 61, 21, 25; 71, 31; 84, 44, 45) (Fig. 1)

Negligible root resorption of the primary teeth was evident.

JL was first been seen by us when he was 8 years old. He was in the early mixed dentition with mandibular right permanent central incisor and all first permanent molars erupted (Fig. 2). Carious lesions were found on distal surfaces of mandibular left primary first molar and maxillary right primary central incisor. His maxillary right primary lateral incisor was notch-shaped and macrodontic. Pigmentation was evident mainly on his trunk and limbs (Fig. 3).

The caries lesions were restored and fissure sealants were applied on all first permanent molars. JL has been reviewed three monthly. A notch-shaped maxillary right permanent central incisor erupted when he was nine years old (Fig. 4). The mandibular left permanent lateral incisor erupted between the mandibular left primary lateral incisor and canine and was

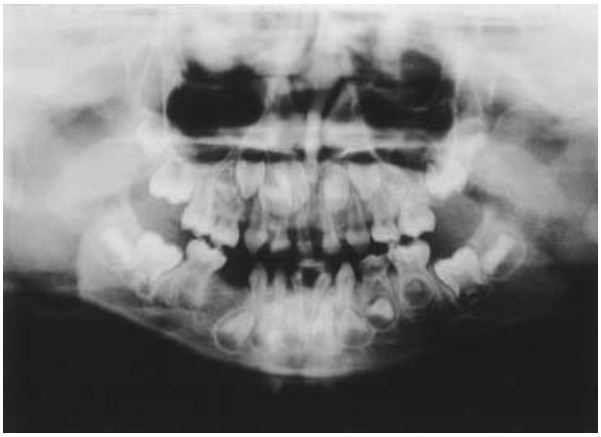

Fig. 1. Radiograph taken at 7 years old showing congenital absence of 15, 21, 61, 25, 31, 71, 84, 44 and 45.

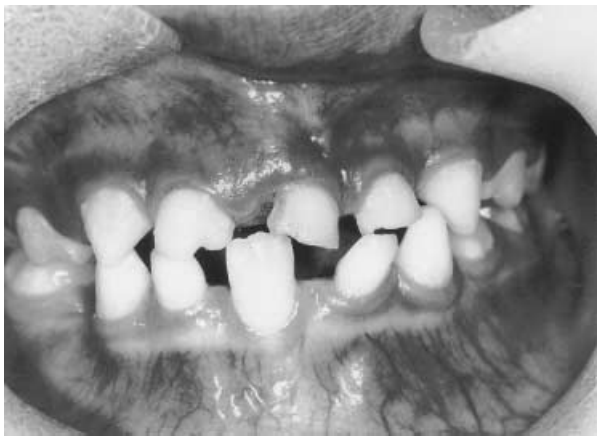

Fig. 2. Frontal view of patient's dentition at 8 years old showing notch-shaped maxillary right primary lateral incisor.

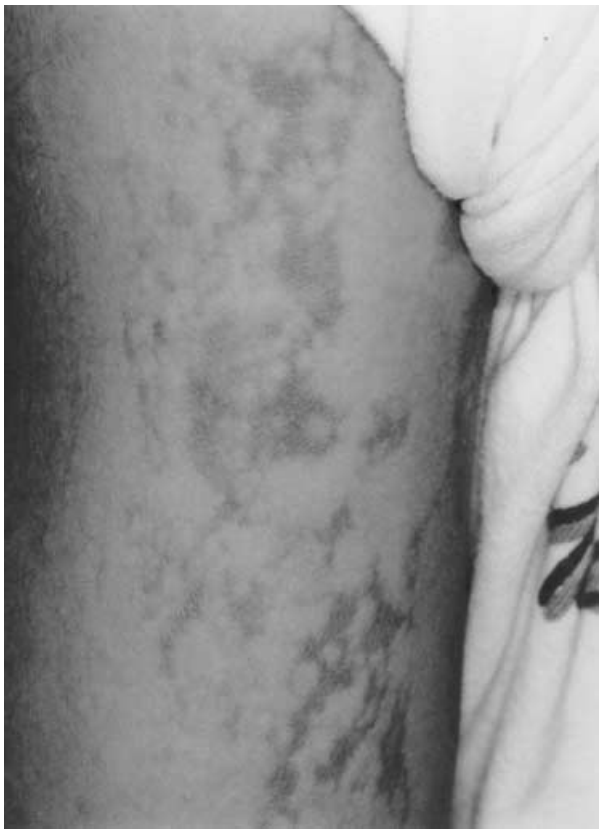

Fig. 3. Photograph of patient's right arm showing typical pigmentation.

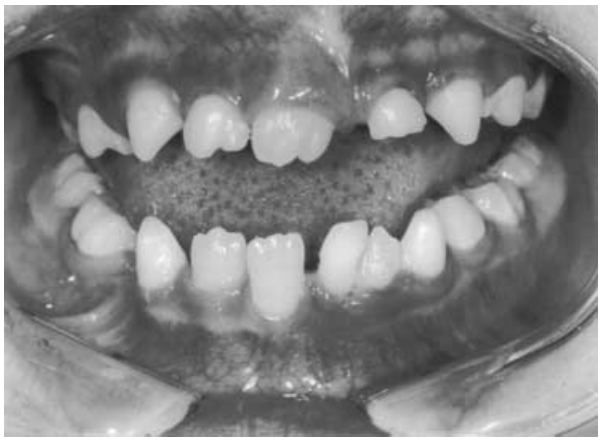

Fig. 4. Frontal view of patient's dentition at 9 years old showing notch-shaped maxillary right permanent central incisor and conical shaped mandibular left permanent lateral incisor.

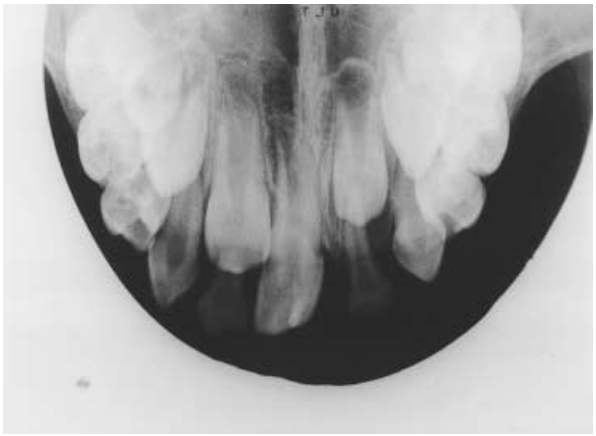

Fig. 5. Maxillary occlusal radiograph taken at 9 years old showing delayed resorption of maxillary left primary lateral incisor.

conical in shape. The mandibular right permanent lateral incisor was also erupted and was normal. Further caries was detected on the mesial surface of the maxillary right primary second molar and it was restored. The maxillary left primary lateral incisor was extracted as it showed delayed root resorption (Fig. 5). JL continues to be reviewed regularly and referral to other dental specialists such as orthodontist and prosthodontist will be made at the appropriate time.

Discussion

Incontinentia pigmenti is a rare X-linked dominant condition. The diagnosis has traditionally been made on clinical grounds. Segregation analysis suggests it is lethal in males [10] and therefore girls are almost exclusively affected and account for more than 95% of cases [7,11]. Female cases of IP survive because of the moderating effects of Lyonization [12]. Over 80% of individuals with IP have been shown to have alterations of NEMO protein, which is the essential regulatory component of the IKappaB kinase (IKK) complex. It is required for NF-kappaB activation by various stimuli such as tumour necrosis factor alpha and interleukin 1 [13]. In addition to being important for immune cell differentiation and function, NF-KappaB responses are required to regulate apoptosis in certain cell types. Many of the clinical signs of IP, such as delayed tooth eruption, can be related to the functions of the NF-KappaB pathway [12].

A few cases of males with IP have been reported in the medical literature [2,3,12,14,15]. Some of them have hypomorphic mutation and presented with atypical phenotypes of IP including features of hypohidrotic ectodermal dysplasia and severe immunodeficiency, in addition to the typical IP skin lesions [2,12,16]. Female carriers of these mild mutations may be asymptomatic or have clinical signs of IP [3]. Surviving males with typical IP are very rare. Some of these patients have been found to have Klinefelter Syndrome, and the 47,XXY karyotype established a heterozygous genotype that is compatible with survival [3,14]. Recently, a few male cases of typical IP and normal karyotype have been found to possess both wild-type and deleted copies of the NEMO gene, and were therefore mosaics for the common mutation [3]. Mosaicism, 47,XXY karyotype, or hypomorphic alleles are therefore possible reasons for the survival of males with IP [3]. In this case, the patient has been shown to have a normal 46,XY karyotype, has no clinical features of hypohidrotic ectodermal dysplasia or immunodeficiency, and so his survival may also be due to mosaicism. However, this cannot be confirmed without further genetic analysis.

Controversy exists whether IP belongs to the ectodermal dysplasia group of conditions [6–8,17]. Both disorders present with hypodontia and conical teeth, yet there are subtle differences in systemic manifestations. It has recently been suggested that both disorders may be genetically related [13,18]. Other differential diagnoses of IP include Naegeli (Franceschetti–Jadassohn) syndrome and hypomelanosis of Ito [17]. Naegeli syndrome is characterized by reticular skin pigmentation, heat intolerance and enamel defects [19]. Hypomelanosis of Ito would present as

swirling areas of alternating hyper- and hypopigmentation, and teeth are not commonly affected [20,21]. However, the skin lesions in both conditions are never preceded by inflammatory vesiculations, which is characteristic in IP.

Dental anomalies have been reported in most patients with IP [6–8]. Dental findings in JL included hypodontia, notch shaped and conical shaped incisors, delayed eruption, and delayed resorption of primary teeth, which have been typically reported in other patients with IP. In this case, the boy does not have the hair, eye, central nervous or musculoskeletal abnormalities that have been reported in 20–40% of patients with IP [8]. Although JL has been diagnosed with attention deficit hyperactivity disorder (ADHD), he accepted dental treatment reasonably well with normal behaviour management techniques. Patients with IP, like other patients with severe hypodontia, require the combined care of paediatric dentists, orthodontists and prosthodontists [5,6,22,23]. This is planned for JL as specific problems arise in his developing dentition and occlusion.

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