

CASE REPORT

Incontinentia Pigmenti: Three New Cases That Demonstrate it is not Only a Matter of Women

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Abstract. *Incontinentia pigmenti* is a rare, dominantly X-linked genodermatosis characterized by multisystemic involvement that is lethal prenatally in the majority of affected males and shows great clinical variability when it is expressed in women. Recently it has been shown that mutations of the gene NEMO/IKK-g located in Xq28 cause the expression of the disease, being only one mutation responsible for approximately 80% of the cases. The diagnosis of *incontinentia pigmenti* is performed based on clinical features and family history with the support of histological findings. Nevertheless, as the gene responsible for the phenotype of the disease has been identified, a genetic study may be employed for doubtful cases. We report three cases of this entity (two women and one man) in different clinical stages of development that show the broad clinical spectrum we may encounter in the clinic.

Key words: *incontinentia pigmenti*, hereditary bullous disease.

INCONTINENTIA PIGMENTI: TRES NUEVOS CASOS QUE DEMUESTRAN QUE NO ES SÓLO COSA DE MUJERES

Resumen. La *incontinentia pigmenti* es una genodermatosis infrecuente con carácter multisistémico que sigue un patrón de herencia dominante ligado a X, por lo que resulta letal en la mayoría de varones afectados intraútero y muestra gran variabilidad clínica cuando se expresa en mujeres. Recientemente se ha encontrado que las mutaciones del gen NEMO/IKK- γ localizado en Xq28 causan la expresión de la enfermedad, siendo una única mutación la responsable de aproximadamente un 80% de los casos. La *incontinentia pigmenti* interesa a varias especialidades médicas, aunque son la clínica cutánea y la historia familiar las que marcan el diagnóstico, ayudadas de los hallazgos histológicos. No obstante, la identificación reciente del gen responsable del fenotipo de la enfermedad permite la resolución de muchos casos dudosos mediante estudio genético.

Presentamos a continuación tres nuevos casos de esta patología (dos mujeres y un varón) en diferentes estadios evolutivos, que muestran el amplio espectro clínico con el que esta patología puede llegar a nuestra consulta.

Palabras clave: *incontinentia pigmenti*, enfermedad ampollosa hereditaria.

Introduction

Incontinentia pigmenti (IP) is a rare genodermatosis with multisystem involvement. Currently, only IP2 (the hereditary form) is recognized. The cases previously described as IP1 (the sporadic form) are, in fact, pigmentary mosaicism and not genuine cases of IP as currently understood.^{1,2} We

present 3 cases of IP involving 2 girls and 1 boy with different symptoms and disease courses.

Case Description

Patient 1

A 3-day-old girl brought to term via normal pregnancy and childbirth, without a family history of interest, was referred to us for the assessment of vesicular lesions initially diagnosed as herpes and unsuccessfully treated with intravenous acyclovir. The physical examination revealed erosive vesicular

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lesions that alternated with scabby lesions, forming longitudinal lines on the legs (Figure 1), and V-shaped transverse ones on the posterior trunk. The lesions evolved over time, and at 3 weeks there were hyperkeratotic lesions and other erosive vesicular lesions on the legs, while others with a verrucous appearance simultaneously developed in the acral area of the arms. Furthermore, over a short period, the patient developed strabismus and retinopathy that finally culminated in detached retina. Clinicopathological study showed eosinophilic spongiosis and eosinophil-filled vesicles consistent with a diagnosis of IP.

Patient 2

Girl, 6 months old, referred to our clinic for assessment of hyperpigmented macules with swirling plaque on the anterior trunk and V-shaped plaque on the posterior trunk (Figure 2). These formed a linear arrangement on the arms and legs, with hyperkeratotic plaque and verrucous acral lesions. According to preceding reports from the referral hospital, previous generalized vesicular lesions had been present, but these were currently in remission. Her mother had suffered 2 prior miscarriages of male fetuses in the fifth and sixth months of pregnancy, respectively. The patient also presented 2 other types of clinical symptoms: ophthalmic, with retinopathy currently under study; and neurological, with generalized convulsive episodes that correlated with venous malformations in the parieto-occipital territory visualized with magnetic resonance imaging.

Patient 3

The last patient was a male baby, with no relevant family history, referred to us at 6 days old for linear papulovesicular lesions on the left leg. In the following weeks, these remitted to be replaced by other hyperpigmented lesions with more obvious superficial scale in the popliteal fossa (Figure 3). A differential diagnosis was made with other entities—mainly inflammatory linear verrucous epidermal nevus—and a histological study was performed. The findings revealed eosinophilic spongiosis, eosinophil-filled vesicles and focal dyskeratosis (Figure 4), compatible with the diagnosis of IP. The karyotype was normal and at 3-year follow-up the patient remained asymptomatic with spontaneous involution of the cutaneous lesions.

Discussion

Incontinentia pigmenti is a multisystem disorder of X-linked dominant inheritances, as demonstrated by the fact



Figure 1. Erythema and vesiculation on an inflamed base with longitudinal linear distribution on the legs (stage 1). Hyperkeratotic verrucous plaque on the knee (stage 2).



Figure 2. Hyperpigmented macules with Blaschko line distribution on the back (stage 3).



Figure 3. Erythema and linear papulovesicular lesions on the left leg.

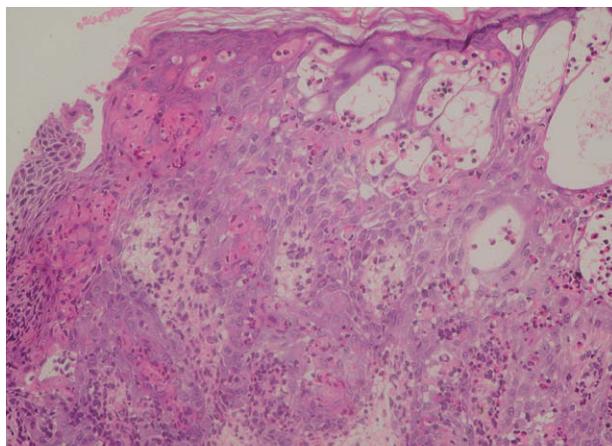


Figure 4. Eosinophilic spongiotic dermatitis, eosinophil-filled intraepidermal vesicles and multiple dekeratinized cells; all these are typical histological findings of stage 1. (Hematoxylin-eosin, $\times 20$).

that mainly women are affected and that it is carried by female lineages.¹⁻³ As in other hereditary X-linked diseases, the clinical variability observed in women is attributed to the so-called lyonization phenomenon. Incontinentia pigmenti is lethal in most affected males in utero, culminating in miscarriage in a large number of cases.⁴ It has recently been found that this disease is caused by mutations in the nuclear factor- κ B-essential modulator (NEMO) gene (an essential modulator in the pathway protecting cells against apoptosis induced by the tumor necrosis factor family), located on segment Xq28; in fact, a single mutation is responsible for 80% of cases, and thus genetic counseling can be made available to a large number of patients.⁵ At present, the 3 cases described are pending the results of the genetic study.

Cases of IP are rare in males, and thus a complete genetic study is recommended, with the aim of identifying any of the 3 mechanisms that facilitate survival⁴: *a*) an extra X chromosome (for example, 47,XXY, implying a state of functional heterozygosity); *b*) somatic mosaicism; and *c*) hypomorphic alleles, which are less deleterious mutations in different domains of the NEMO gene, that would induce different phenotypes, such as anhidrotic ectodermal dysplasia plus immunodeficiency⁶ or anhidrotic ectodermal dysplasia plus immunodeficiency plus osteopetrosis and lymphedema). According to several authors, these phenotypes form a continuum with IP. The natural history of the disease in surviving males is not well understood. Contrary to what might be expected, and according to the limited literature published to date, mortality is not greater among affected males compared to affected females, although more studies with greater numbers of patients are needed to clarify this point.⁷

The typical clinical signs of this disease consist of 4 stages: vesicular (90% of cases), verrucous (70%), hyperpigmented

(98%) and atrophic (42%), as previously reported.^{1,2,8-10} The different stages are not water-tight, but can overlap; nevertheless, the lesions can change location as the disease progresses from one stage to another, preferentially affecting the trunk and the arms and legs in the vesicular phase, and the arms and legs, mainly in acral areas, in the hyperkeratotic stage. When making a retrospective diagnosis,^{11,12} especially in relatives of probands, attention should be focused on lesions in the last 2 stages. Thus, hyperpigmented macules, in addition to presenting as large bands following a Blaschko line distribution, can present in a more subtle way as hyperpigmented macules scarcely a few centimeters in diameter, usually located in the axillary, inguinal or mammary region. Similarly, pale, hairless, atrophic bands, preferentially found on the back of the legs (characteristic of the last stage), may escape notice if the patient is not thoroughly examined. Series that include a greater proportion of adults, mainly through retrospective diagnosis, report a greater rate of occurrence of this stage and fewer neuroophthalmic complications; thus, other series may have overestimated such complications because they only included pediatric cases.³

There may be several types of extracutaneous involvement; dental involvement stands out, not only because it is the most frequent, but also because its permanent character often helps corroborate retrospective diagnosis.^{1-3,12} However, neuroophthalmic symptoms, as described in our first 2 cases, are definitive keys to prognosis.^{13,14} Ophthalmic involvement is often present with normal vision and is thus underdiagnosed, but presentation is usually asymmetrical and severe and is associated with neurological pathology. Retinal manifestations, together with neurological ones, usually present in the first year of life; however, nonretinal manifestations present later.

With the aim of identifying typical and subtle cases, in 1993 Landy and Donnai proposed some diagnostic criteria to help guide the clinician⁹ (Table). Much emphasis was placed on a family history of the disease such that, when present, minor criteria become major criteria and support the diagnosis of IP, just like traditional cutaneous criteria. On the other hand, if there is no recognizable family background of the disease, at least one major cutaneous criterion is necessary to establish the diagnosis and some minor criteria are needed to support it. The histological changes of the different stages are characteristic, although nonpathognomonic,¹⁵ and play an important role in diagnosis by supporting clinical findings. Generally, a genetic study is appropriate to provide genetic counseling, confirm doubtful cases, and those presented by males.

There are no authentic protocols on the management of IP regarding treatment, but existing guidelines can be very useful.¹ Thus, cutaneous symptoms spontaneously resolve, and supportive treatment only is provided. The early diagnosis and treatment of dental pathology are essential

Table. Diagnostic Criteria for Incontinentia Pigmenti

No Evidence of IP in First-degree Female Relatives
<i>Major Criteria:</i>
– Typical neonatal rash: erythema and vesicles with eosinophilia
– Typical hyperpigmentation following Blaschko lines, mainly on the trunk, that resolve during puberty
– Linear, hairless, atrophic lesions
<i>Minor Criteria:</i>
– Dental anomalies
– Alopecia
– Nail anomalies
– Retinal disease
Evidence of IP in First-degree Family Member
– Presence of typical neonatal rash, hyperpigmentation, atrophic hairless lesions
– Male-pattern baldness
– Dental anomalies
– Retinal pathology
– Recurrent miscarriage of male fetuses

Source: Landy SJ, Donnai D.⁹

Abbreviation; IP, incontinentia pigmenti.

to prevent secondary complications, with radiological studies from 2 years old onward. Corrective surgery should be performed if needed. In addition, thorough neurological exploration is indispensable at diagnosis, using imaging techniques if anomalies are detected, as described in the second clinical case presented. Finally, strict ophthalmologic monitoring is recommended,¹⁴ more frequently during the first year (the period during which retinal pathology usually appears) and less frequently during the ensuing 3 to 4 years.

In conclusion, IP is a rare X-linked dominant disorder, and thus most reported cases occur in females; cases in males are rare. Although a multidisciplinary approach is needed to manage this entity, diagnosis is mainly based on cutaneous symptoms, assisted by histological and genetic studies. We want to emphasize the importance of late cutaneous symptoms (third and fourth stages) and dental symptoms, since these allow us to make retrospective diagnoses in a large number of cases.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: A review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol.* 2002;47:169-87.
- Hadj-Rabia S, Froidevaux D, Bodak N, Hamel-Teillac D, Smahi A, Touil Y, et al. Clinical study of 40 cases of incontinentia pigmenti. *Arch Dermatol.* 2003;139:1163-70.
- Phan TA, Wargon O, Turner AM. Incontinentia pigmenti case series: clinical spectrum of incontinentia pigmenti in 53 female patients and their relatives. *Clin Exp Dermatol.* 2005;30:474-80.
- The International Incontinentia Pigmenti (IP) Consortium. Survival of male patients with Incontinentia Pigmenti carrying a lethal mutation can be explained by somatic mosaicism or Klinefelter Syndrome. *Am J Hum Genet.* 2001;69: 1210-7.
- The International Incontinentia Pigmenti (IP) Consortium. Genomic rearrangement in NEMO impairs NF- κ B activation and is a cause of incontinentia pigmenti. *Nature.* 2000; 405:466-72.
- Mansour S, Woffendin H, Mitton S, Jeffery I, Jakins T, Kenwick S, et al. Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. *Am J Med Genet.* 2001;99:172-7.
- Scheuerle AE. Male cases of incontinentia pigmenti: case report and review. *Am J Med Genet.* 1998;77:201-18.
- Carney RG. Incontinentia pigmenti: a world statistical analysis. *Arch Dermatol.* 1976;112:535-42.
- Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *J Med Genet.* 1993;30:53-9.
- Chan YC, Gima YC. A retrospective study of incontinentia pigmenti seen at the National Skin Centre, Singapore over a 10-year period. *Ann Acad Med Singapore.* 2001;30:409-13.
- Wiklund DA, Weston WL. Incontinentia pigmenti. A four-generation study. *Arch Dermatol.* 1980;116:701-3.
- Spallone A. Incontinentia pigmenti (Bloch-Sulzberger syndrome): seven case reports from one family. *Br J Ophthalmol.* 1987;71:629-34.
- O'Brien JE, Feingold M. Incontinentia pigmenti. A longitudinal study. *Am J Dis Child.* 1985;139:711-2.
- Holmström G, Thorén K. Ocular manifestations of incontinentia pigmenti. *Acta Ophthalmol Scand.* 2000;78:348-53.
- Weedon D. Disorders of pigmentation. In: *Skin Pathology.* Edinburgh: Churchill Livingstone; 2002. p. 333-4.