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Rare disease

Incontinentia pigmenti in the neonatal period

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Summary

Incontinentia pigmenti (IP) is a rare multisystem disease, X linked dominant disorder. As all X linked dominant diseases, it is usually male-lethal. Female newborn admitted to the neonatal intensive care unit on the first day of life was diagnosed as having probable herpetic infection with vesicular skin lesions distributed on upper right limb and inferior limbs. Family history showed that her 22-year-old mother had hypopigmented lesions on the lower limbs and her 13-month-old sister had hyperpigmented lesions on the trunk and limbs. In newborns, herpes infection emerges as the principal diagnosis of vesicular rash, due to the importance of precocious diagnosis and treatment. Other hypothesis must be considered in a newborn with vesicobullous rash, such as IP.

BACKGROUND

Incontinentia pigmenti (IP), also known as Bloch–Sulzberger syndrome, is a rare multisystem neurocutaneous disease, X linked dominant disorder.[1–8] In about 95% of the cases, it occurs in females and is usually lethal in males.[1 4–7] IP has an incidence of 1:40 000 individuals.[7] Initial lesions are usually present at birth.[1 3 6]

We propose to describe and characterise a case of IP with familiar transmission, considering the importance of differential diagnosis in the neonatal period and the rarity of this disease.

CASE PRESENTATION

A female newborn was admitted to neonatal intensive care unit for vesicular skin lesions on the right forearm and lower limbs. She was a healthy, second daughter of a 22-year-old mother, born of an uncomplicated term gestation and normal delivery. Maternal serologies were

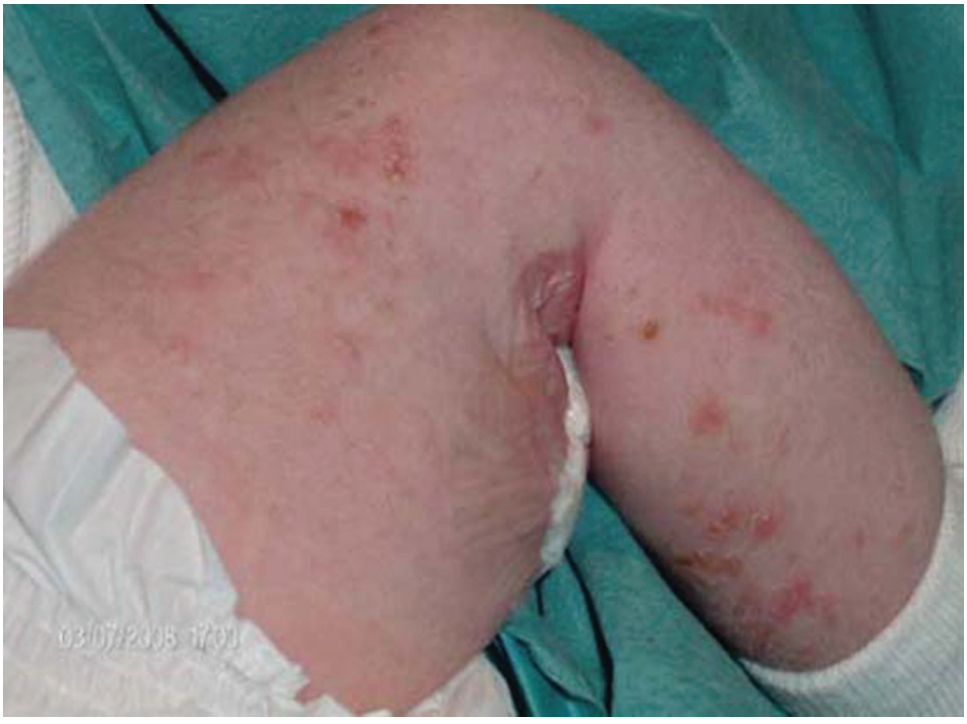

Figure 1 Vesicular lesions on the lower limb of the newborn.

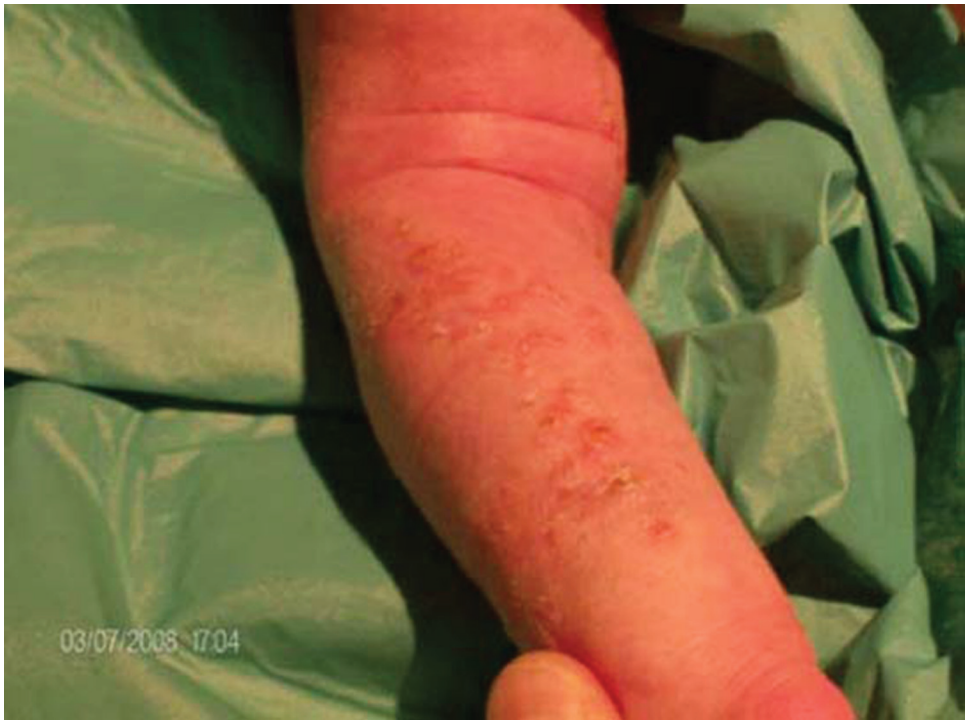

Figure 2 Vesicular lesions on right forearm on the fifth day of life of the newborn.

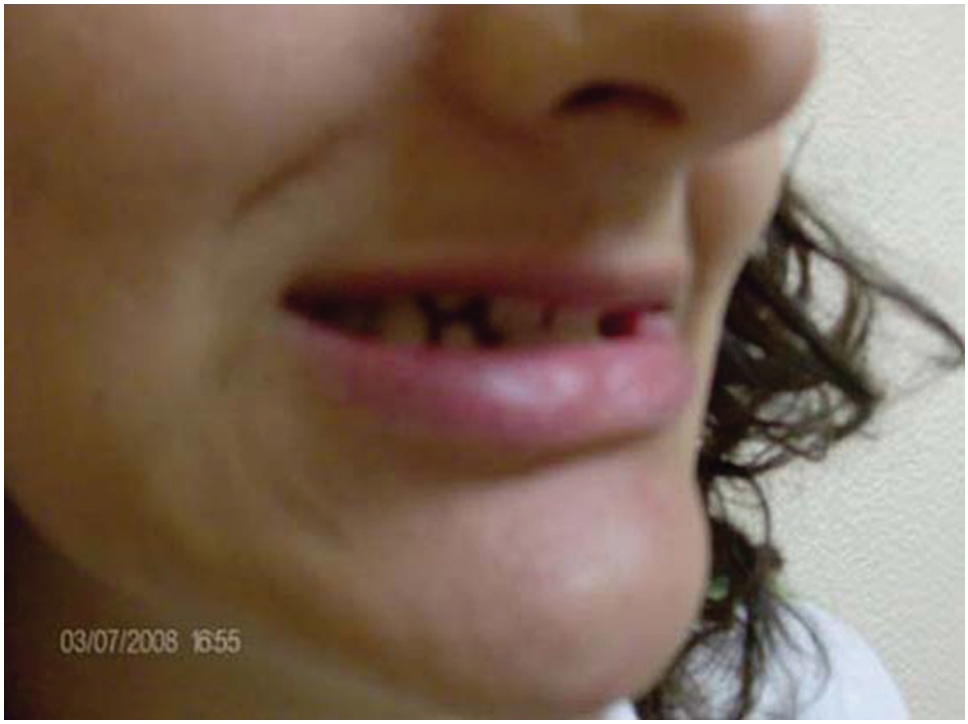

Figure 3 Newborn's mother – conical shaped teeth.

negative with rubella immunity and group B streptococcus screening was negative. The Apgar score was 9 in the first minute and 10 in the fifth minute. At birth: weight 3450 g (50th percentile), length 50 cm (50th percentile) and head circumference 34.5 cm (50th percentile). The newborn was hospitalised in the first day of life with multiple vesicular lesions (about 100 vesicles), with some serous, surrounding erythema and linear distribution (figure 1). Given the suspicion of neonatal herpes, acyclovir was started.

By the fifth day of life, new lesions appeared with the same characteristics and linear distribution on the limbs (figure 2). She was always a well-appearing newborn since birth.

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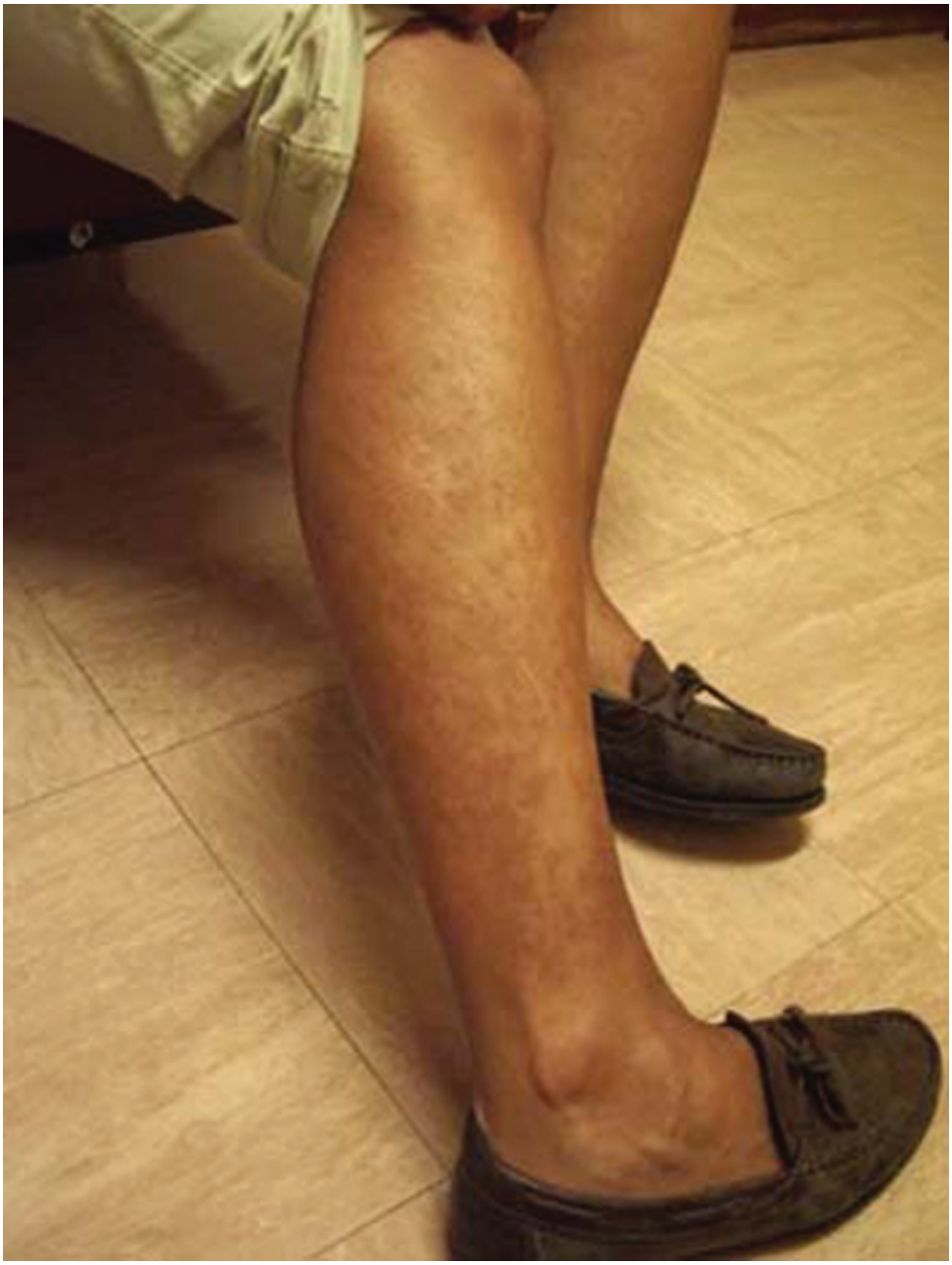

Figure 4 Newborn's mother – hypopigmented lesions on the lower limbs.

INVESTIGATIONS

The initial screening revealed mild eosinophilia (9.7%, 2100/µl). The blood and urine cultures were negative. The bacteriological test and PCR using cerebrospinal fluid were also negative for herpes simplex virus 1 and 2.

In this phase, the mother observation showed residual hypopigmented linear lesions, cone shaped teeth (figures 3 and 4) and diminished visual acuity. She also referred her own neonatal hospitalisation with a 'skin disease'. A 13-month-old sister had hypopigmented linear lesion on the back and lower limbs (figure 5). Her family history revealed a male fetal loss in the maternal side of the family (figure 6) and also a maternal grandmother with clinical manifestations similar to the mother, which led to the consideration of IP diagnosis.

The newborn skin biopsy showed lymphocytic infiltration with perivascular and interstitial eosinophilia in superficial dermis, some eosinophils exocytosis and dyskeratotic keratinocytes in the epidermis, compatible with IP diagnosis (figure 7).

Ophthalmologic observation in the second day of hospitalisation revealed multiple haemorrhages in different retinal quadrants.

Genetic testing revealed genetic mutation in NEMO/IKK-γ in the newborn, mother and sister, consistent with a diagnosis of type 2 IP.

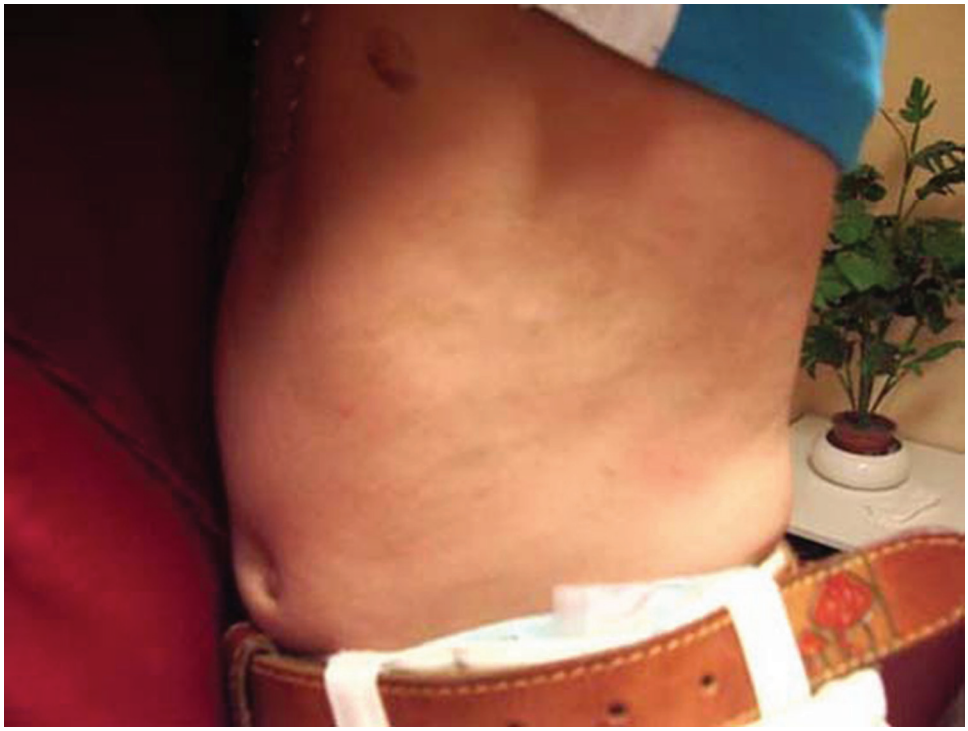

Figure 5 Newborn's sister – hyperpigmented lesions on trunk.

DIFFERENTIAL DIAGNOSIS

Infections such as herpes simplex infection or pyodermitis was excluded as well as other diseases with dermatologic involvement.

OUTCOME AND FOLLOW-UP

Nearly 2 months after admission, the infant had linear hyperpigmented patches on the lower limbs and trunk (figure 8).

DISCUSSION

IP is a rare genodermatosis characterised by abnormalities of the tissues and organs embryologically derived from ectoderm and neuroectoderm.[1–3 6–8] The designation of IP is derived from the accumulation of melanin in the deep dermis as a free pigment and melanophages.[3–4 6] Originally described by Garrod in 1903 and Bloch in 1926, its pathogenesis has been clarified in 1928 by Sulzberger and cutaneous location by Happel in 1985.[2 3 5–6 9]

It is most often found in females with familial transmission in 50% of the cases.[6–7 9] IP type 1 or hypomelanosis, can occur in most cases as a sporadic mutation through Xp11.21.[3] The genetic mutation found in our case, responsible for IP type 2, corresponds to NEMO/IKK-γ, in Xq28, which encodes a protein in the signalling pathways of apoptosis and inflammatory responses.[1 4–6 8] In Klinefelter syndrome (47, XXY), IP can be manifested in males, presenting as X linked recessive trait disease[3 5–8] and it may also occur in males who have mosaicism and hypomorphic mutation, which is associated with reduced level of gene expression and partial loss of function.[4–5 8] As in our case, female predominance and male spontaneous abortions of affected women suggest an X linked dominant transmission.[5–6 8]

Clinical presentation includes a wide spectrum of skin, neurologic, ophthalmologic and dental abnormalities.[2 7 8] Classically, skin lesions evolve through four stages: vesicobullous eruption, verrucous lesions, hyperpigmented and hypopigmentation macules.[1 3–8] The first phase, vesicobullous, typically occurs in the first 2 weeks of life with erythematous streaks, plaques, pustules or vesicles linearly distributed on the extremities, trunk and scalp.[1 3 4 6 9] The skin lesions follow Blaschko's lines, which represent the routes of embryonic cell migration.[4] Eosinophilia occurs in 65% of cases in the first phase, reverting in 4–5 months of age.[3–4 7] Histologically, this phase is characterised by eosinophilia with dyskeratotic keratinocytes.[1 3 5 9] The second phase, characterised by hyperkeratotic verrucous lesions on an erythematous base affects the distal extremities.[1 3 4 6 9] Histologically, it is characterised by acanthosis, papillomatosis and dyskeratosis that last several weeks.[1 2 4–5] Phase three, hyperpigmentation, the hallmark of IP, usually appears between 3 and 6 months of age, manifests during months or years and it is characterised by hyperpigmented lesions asymmetrically distributed along Blaschko's lines.[1 2 4–6] The presence of dermic melanin is a typical finding.[2] Finally, the phase of hypopigmentation may start from childhood to adolescence, is permanent and consists of hairless, anhidrotic patches and streaks, with or without atrophy, on the flexor surface of the lower legs.[3 4] The newborn may exhibit any of those stages, because the former can occur in uterus.[1 6 8]

Central nervous system is the most affected system after the skin in about 10–40% of patients.[1–4 8] Seizures are the most frequent neurologic complication and commonly arise in the first weeks of life and are associated with poorer prognosis.[1 4] Other symptoms include motor and cognitive development delay, microcephaly, spasticity, ataxia, cerebral microangiopathy and haemorrhagic strokes.[1–8]

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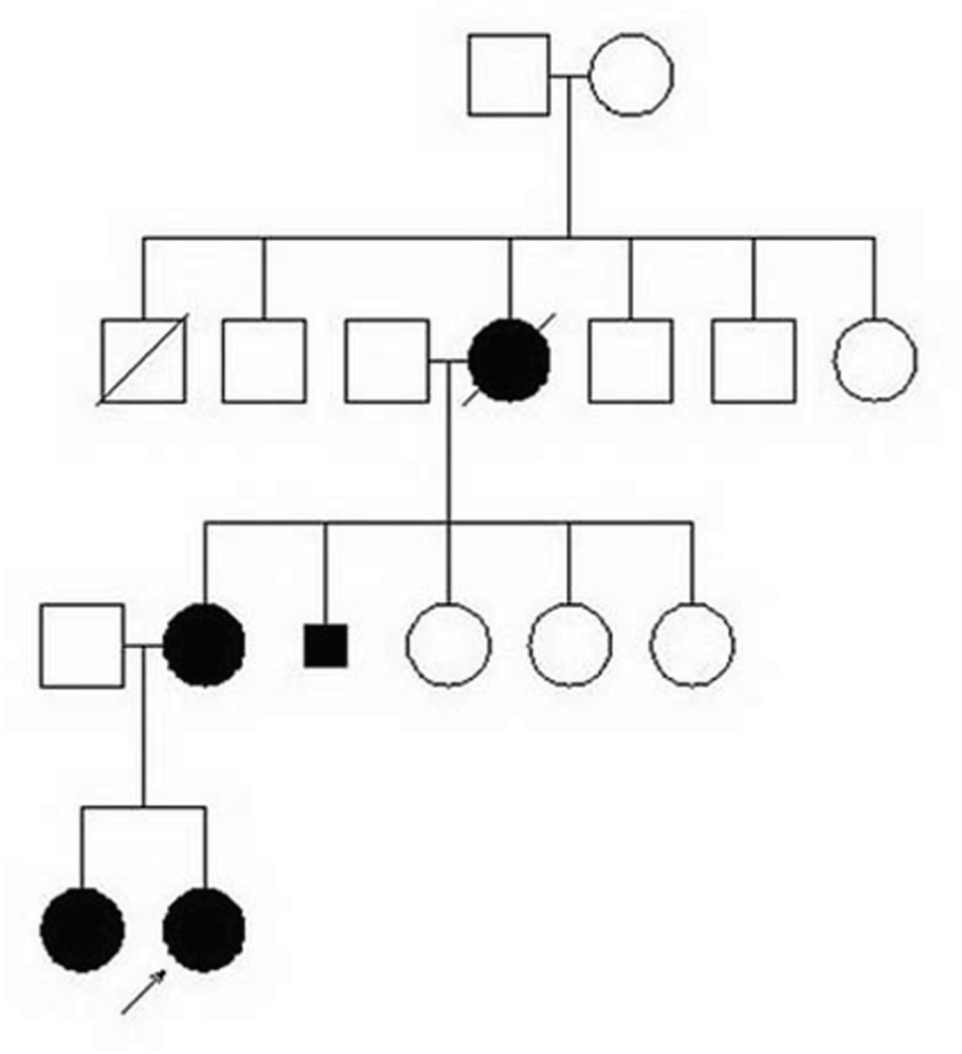

Figure 6 Genealogical tree where it can be seen the mother, sister and maternal grandmother involvement as well as the male abortion.

Radiographic findings include cortical malformations such as heterotopy, hemimegalencephaly, focal cortical dysplasia and periventricular and white matter lesions.[1]

In about 30% of patients, ocular disease may occur such as strabismus, microphthalmia, pigmentary retinal changes, retinal vessels anomalies with areas of ischaemia, retinal detachment, proliferative retinopathy, cataracts and optic nerve atrophy.[1–9]

Additional findings include abnormalities of hair (alopecia, sparse hair, hypoplasia of eyebrows and eyelashes), dental (delayed tooth eruption, hypodontia, defects of dentition and peg-shaped teeth) and nails (dystrophy resembling onychomycosis, subungual fibromas associated with underlying bone deformities of the phalanges).[2–9] Less common manifestations are supernumerary nipples or breasts and skeletal deformities.[3 4]

IP is considered a chromosomal instability condition which is associated with an increased risk for developing malignancies such as chronic myelogenous leukaemia, Wilms' tumour or retinoblastoma.[4 6] Laboratory findings of IP include leukocytosis in the first phase and peripheral eosinophilia.[1 2 4–5]

The diagnosis of IP is based on clinical findings and differential diagnosis includes infectious disorders, such as neonatal herpes simplex infection, among other diseases with dermatologic involvement.[1 4 6 10]

Skin lesions do not require specific treatment, although measures to prevent bacterial superinfection are necessary.[3 4]

The newborn described is in the first phase of the disease, her sister in the third and the mother in the fourth stage, shows the progressive evolution of the disease. Ocular anomalies were noted, manifested by multiple retinal haemorrhages, although with no other affected organs in the neonatal period. The mother, however, had extracutaneous involvement, ophthalmologic and dental abnormalities. Although the diagnosis is clinical, histopathological analysis of skin biopsy allowed IP confirmation. Differential diagnosis is mainly with herpes simplex virus infection, pyodermitis and IP.

This case shows the difficulty of IP diagnosis in the neonatal period. Given the high morbidity and mortality of herpes infection, a precocious treatment with acyclovir is extremely important until definitive diagnosis.

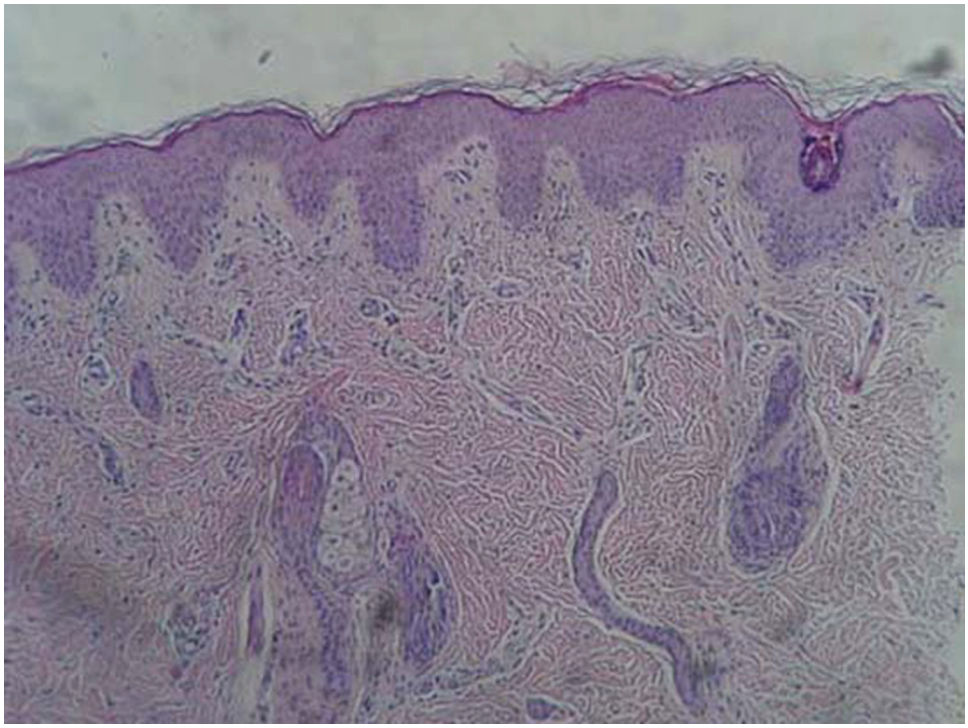

Figure 7 Skin biopsy showed lymphocytic infiltration with perivascular and interstitial eosinophilia in superficial dermis, some eosinophils exocytosis and dyskeratotic keratinocytes in the epidermis.

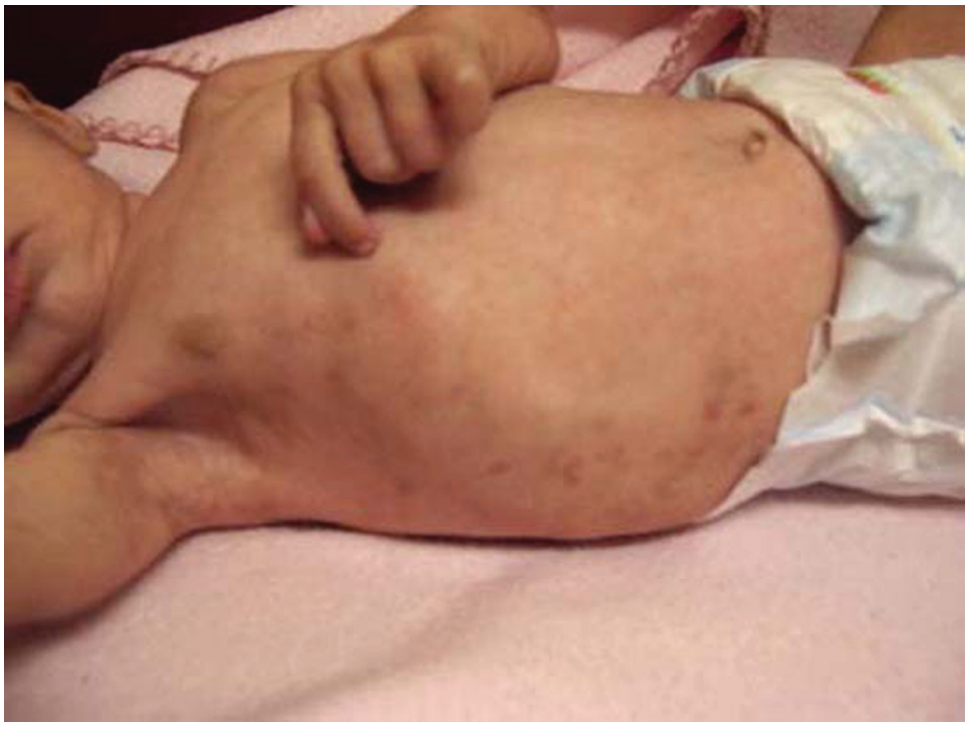

Figure 8 Two-month-old infant with linear hyperpigmented patches on the lower limbs and trunk.

The mode of transmission and clinical manifestations described require a multidisciplinary follow-up throughout life, as well as genetic counselling and eventual prenatal diagnosis.[4 9] The prognosis is generally good and the worse prognosis is associated with neurologic, dental or ophthalmologic complications.[4 6]

In the literature there are some similar cases described. However, this case includes a positive genetic study of the infant, sister and mother and also a positive family history involving four affected members in three generations.

IP must be considered as a diagnosis in a newborn with vesicular skin lesions distributed linearly and after exclusion

of infection. Family history of similar skin lesions and male gender abortion also supports this diagnosis.

Learning points

- IP should be considered in any female newborn who presents with crops of linear vesicles on the trunk and lower extremities in the first few weeks after birth.
- IP is a potential masquerader of herpes simplex infection or pyodermitis.
- Family history can have a very important role in the diagnosis of IP.
- Multiorganic involvement of IP demands a multidisciplinary follow-up.

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Competing interests None.

Patient consent Obtained.

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