Incontinentia Pigmenti

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Introduction and Pathophysiology

Incontinentia pigmenti (IP; synonym: Bloch-Sulzberger syndrome, OMIM #308300) is an X-linked dominant multisystem genodermatosis lethal in XY males. The name describes the main pathological finding of pigmentary incontinence in the third stage of the disease. IP associates linear skin lesions and anomalies of the teeth, hair and nails. More than 30% of cases present ocular and neurological manifestations. A minority of cases with cardiac impairment have been reported.

IP is characterized by a high genetic penetrance and variable phenotypic expressivity while environmental factors do not appear to impinge on the phenotype. Most cases are sporadic; only 10–25% of cases are familial. IP is caused by loss-of-function mutations in the IKBKG gene (NEMO, nuclear factor-kappa B essential modulator; OMIM #300248) located on the chromosome Xq28. More than 80% of mutations are deletions of exons 4 to 10 leading to the complete loss of NEMO/IKKγ protein, a subunit of the inhibitor of the IKK complex involved in the activation of the NF-kB pathway, which protects against TNFα-induced apoptosis. The remaining cases show microdeletions, missense, nonsense, frameshift and splice-site mutations [1, 2].

Absence of NEMO explains a pro-apoptotic state translated by the destruction of epidermal cells. In the absence of NF-kB protective activity, endothelial cells undergo apoptosis and over-express chemotactic factors specific for eosinophils leading to hypereosinophilia (found in the blood and skin lesions), and extensive inflammation. NEMO deficiency also leads to loss of endothelial cells and thus vasculopathy and ischemia, causing ophthalmologic and neurologic abnormalities. They are related to disruption of TAK1 (Transforming growth factor beta-activated kinase 1), a kinase upstream of NEMO [3]. Small vessel occlusion generates

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underperfusion, precipitating ischemia. Secondary neovascularization results in additional damage. Pulmonary hypertension has also been related to vasculopathy [4, 5].

Prevalence

Incidence of IP is estimated at 1/143,000 births by orphanet with a female to male ratio of 20:1 It shows variable heterozygous mosaicism, explained by the random inactivation of the chromosome X (lyonization) [6]. By definition, most patients are females. IP is lethal in most males during foetal life. Exceptionally, males with somatic mosaicism or XXY karyotype survive [7].

Dermatological Manifestation

Clinical manifestation Skin changes in IP represent the major findings and evolve through 4 stages.

Stage 1 (vesiculobullous) appears at birth or within the first two weeks of live as tense vesicles, pustules or papules on an erythematous base. The lesions show a linear distribution along the Blaschko lines and thus respect the midline (Fig. 6.1a). They occur anywhere on the body but more on trunk and extremities, sparing the face. Each crop of blisters clears within a few weeks. Complete blood count shows marked leucocytosis with up to 65% eosinophils. In 5% of cases, the vesicular stage is thought to occur in utero before birth [8].

In **stage 2 (verrucous),** the lesions become verrucous, wart-like streaks (between 2 to 6 weeks of age), usually found on distal limbs (Fig. 6.1b). Sometimes this stage gets unnoticed. The verrucous streaks clear completely by age of 6 months, being progressively replaced by lines of reticulated hyperpigmentation.

Stage 3 (pigmentary) is the hallmark of IP but its extent is variable. The hyperpigmentation varies from few lesions to extensive skin involvement. The hyperpigmentary streaks appear sometimes directly after disappearance of blisters and

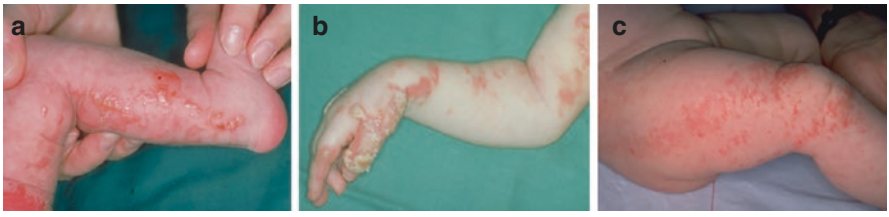

Fig. 6.1 Skin abnormalities in IP: (**a**) vesiculobullous stage: blisters and vesicles on an erythematous base showing a linear distribution on the leg of a new born female; (**b**) verrucous stage: verrucous lesions on a erythematous base on the hand; (**c**) pigmentary stage: the erythematous lesions become progressively hyperpigmented

become progressively darker (Fig. 6.1c). They develop at around 3 months of age and persist usually until early adolescence or adulthood, when they fade slowly and resolve completely by the age of 16. Rarely, lesions persist indefinitely, usually in the groins.

Stage 4 (atrophic/hypopigmented) is characterised by linear macules or patches slightly atrophic and hypopigmented, lacking hair follicles and sweat glands, typically observed on lower legs. They often present before the hyperpigmentation completely disappears. Stage 4 is absent in many patients [9].

IP associates multisystem ectodermal abnormalities which can be present shortly after birth or during childhood [10]. Skin appendages are commonly affected. More than half of patients present hair abnormalities. Cicatricial alopecia on the vertex is seen after the resolution of the blisters but is usually mild and often goes unnoticed, but few patients suffer from severe segmental hair loss. Decreased hair density in children is common. More rarely woolly hair can be identified. Nail dystrophy is found in 40% of patients and ranges from transverse or longitudinal striation and pitting to onychogryphosis and nail disruption. Painful subungual dyskeratotic tumours can be rarely present in adult patients and sometimes are associated with bone deformities of the underlying phalanges [11]. Oral manifestations are found in up to 80% of patients and are characterised by delayed dentition, ano-or hypodontia, conical teeth but also cleft palate, high-arched palate, micrognatia, prognatia or decreased salivary secretion. The dental changes range from mild to severe and occur in 65% of cases [9, 12].

Extracutaneous manifestations include neurologic symptoms in 30% of cases, such as lethargy, seizures and delayed development, associated with local inflammation, ischemia and haemorrhage in the brain [13]. Ocular findings (retinal and non-retinal findings) are common and include proliferative retinopathy, microaneurysms or macular disease [14]. Detachment of the retina and development of vascular retroretineal membrane are common ocular findings, but cataract, nystagmus and optic atrophy were also identified. Skeletal and breast abnormalities may be present [9, 15].

Distinct subtypes. Anhidrotic ectodermal dysplasia associated with immunodeficiency (EDA-ID) is a newly recognized syndrome caused by mutations of the same gene. While the classical IP form is due to amorphic (loss of function) mutations of the IKBKG gene, EDA-ID is induced by milder mutations (hypomorphic) reducing, but not abolishing, NF-kB activation. EDA-ID patients are always males with hemizygous IKBKG mutations. Patients show typical EDA defects (conical teeth, absence of sweat glands, sparse hair, frontal bossing) and a severe immunodeficiency in early childhood. Half of the children die due to severe bacterial infections [16]. Classical IP patients do not show immunodeficiency but a few cases of female patients with **IP and immunodeficiency** have been reported, due to a hypomorphic IKBKG mutation and a delay in X-inactivation skewing [17–19].

Histology. The most specific histological image is obtained in the early inflammatory stage (vesiculobullous), showing spongiosis with intraepidermal vesicles containing eosinophils, and scattered apoptotic keratinocytes (Fig. 6.2). The verrucous stage shows acanthosis with hyperkeratosis and dyskeratosic foci. In the

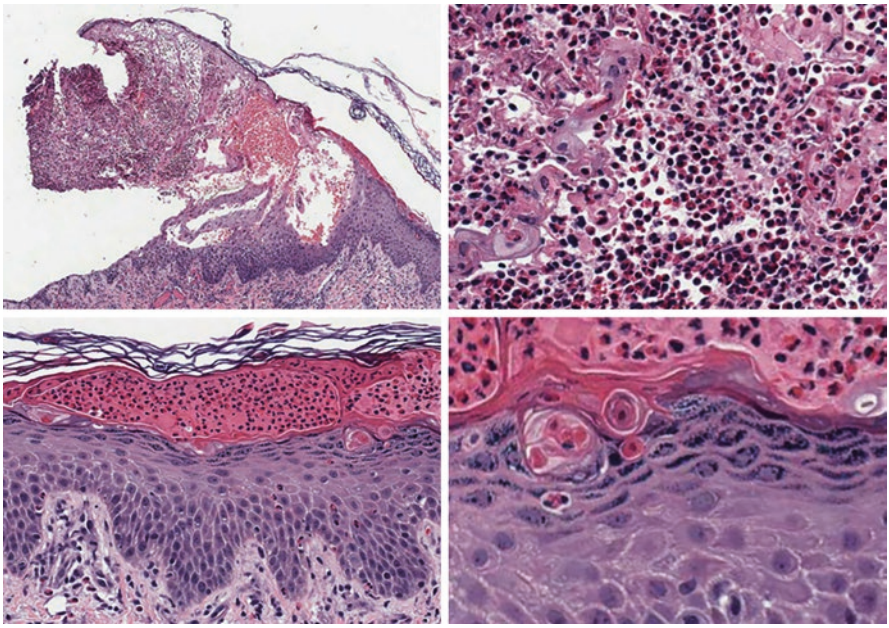

Fig. 6.2 Histology of IP: inflammatory stage, showing spongiosis with intraepidermal vesicles containing a massive eosinophilic infiltrate and scattered apoptotic keratinocytes

hyperpigmented stage the main finding is the pigmentary incontinence, while the fourth stage shown a thin epidermis and the absence of the skin appendages.

Differential diagnosis. IP in the early stage should be differentiated by **infectious diseases** (herpes simplex, varicella, staphylococcal infection) by performing Tznack smears, PCR for HSV and/or Varicella-Zoster virus and bacterial cultures. Differentiation from an **epidermal nevus** in the second stage is done by biopsy. The third stage should be distinguished from **hypomelanosis of Ito (pigmentary mosaicism)**, a skin condition characterized by linear hypo- or hyperpigmentation along the Blaschko lines, not preceded by inflammation. 30% of patients with hypomelanosis of Ito present brain or musculoskeletal abnormalities [20]. **Naegeli-Franceschetti-Jadassohn** syndrome is an autosomal dominant disorder characterized by reticulated hyperpigmentation in association with palmo-plantar keratoderma and hypohidrosis [21] (Table 6.1).

Cardiological Manifestations

Few cases of IP have been reported in association with cardiopulmonary abnormalities, notably a primary pulmonary hypertension (PHTN) of variable severity. Pulmonary hypertension was reported in nine children worldwide [4, 15, 22–28]. The infants develop PHTN shortly after birth, leading to respiratory distress with cyanoses and diminished consciousness, necessitating neonatal intensive care with intubation and mechanical ventilation. Cardiac anomalies such as tricuspid valve

Table 6.1 Differential diagnosis of IP

Stage	Clinical finding	Differential diagnosis
Stage 1 (vesiculobullous)	Vesicles and/or pustules on erythematous base	Impetigo Herpes simplex Varicella
Stage 2 (verrucous)	Wart-like streaks	Linear epidermal nevus X-linked-dominant chondrodysplasia punctate Warts Molluscum contagiosum
Stage 3 (pigmentary)	Hyperpigmentation	Hypomelanosis of Ito Pigmentary mosaicism Naegeli-Franceschetti-Jadassohn syndrome
Stage 4 (atrophic/ hypopigmented)	Hypopigmentation and atrophy	Vitiligo Ectodermal dysplasia

insufficiency, abnormal shunt of the right pulmonary artery to superior vena cava, right ventricular hypertrophy, dilated right ventricle, patent foramen ovale or atrial sept defect, and in most cases neurological and ophthalmological abnormalities are associated [4].

Independent of PHTN, a case of a 32-year old female with IP complicated with endomyocardial fibrosis [27] and tetralogy of Fallot in a 5-year old boy associating IP and a trisomy 14 mosaicism [26] were reported. A case of IP associated with congenital absence of portal vein system and nodular regenerative hyperplasia of the liver has been recently reported [29]. Cardiac complications are rare in IP patients but the prognosis of these patients requires cardiological and pulmonary evaluation in order to recognise such abnormalities.

Diagnosis/Investigations

Diagnostic criteria originally established in 1993 [9] were recently revised [30] (Table 6.2). Clinical diagnostic requires at least two major criteria or one major and one or more minor criteria (see Table 6.2). Eosinophilia supports the diagnosis, occurs in stages I and II and represents up to 65% of total leucocytes. Magnetic resonance imaging of the brain and electroencephalogram should be obtained if neurological symptoms are present. Cardiac echography shows a persistent pulmonary hypertension. In some cases, dilated right ventricle and tricuspid regurgitation can be visualised. Computed tomography (CT) angiogram might show signs of pulmonary artery hypoplasia. Cardiac catheterisation can identify a distal pulmonary artery stenosis [4].

Diagnosis of IP is established by suggestive clinical and histological findings, and confirmed by the demonstration of a IKBKG gene mutation. For most patients, a targeted mutational analysis of DNA extracted from peripheral blood is sufficient to detect the common IKBKG deletion, present in 80% of cases. Targeted mutational analysis detects a 11.7 kb deletion removing exons 4 to 10. Other patients

Table 6.2 Diagnostic criteria for IP after Minc et al. [30]

Major criteria	Minor criteria
Typical stages of skin eruption along Blaschko's lines: 1. Vesiculobullous 2. Verrucous 3. Hyperpigmented 4. Atrophic/hypopigmented	Typical skin histological findings Alopecia Abnormal hair (sparse hair, wooly hair, anomalies of the eyebrows and eyelashes) Dental anomalies Palate anomalies Ocular anomalies CNS anomalies Nipple and breasts anomalies Multiple males miscarriages
In absence of IKBKG data: Two major criteria or one major and one minor In presence of typical IKBKG mutation: Any single major or minor criteria IP in a first degree female relative: a major or at least two minor criteria	

need extensive sequence analysis. In suspected male patients, genetic testing is performed on DNA from lesional skin to detect the mosaicism, together with karyotyping and fluorescence in situ hybridization to identify the XXY aneuploidy. In females, X-chromosome inactivation studies may be performed to identify skewed lyonization. Prenatal diagnosis is possible via multiplex polymerase chain reaction analysis on DNA from tissue obtained by amniocentesis or chronic villus sampling in fetuses with a family history of IP [31].

Treatment

There is currently no treatment for the disease as a whole. Medical care is limited to symptom management and requires a pluridisciplinary approach (dermatologic, genetic, ophthalmologic, neurologic, dental, and cardiologic). Skin lesions initially require gentle wound care and antiseptics to prevent infections and excessive scarring. Topical corticosteroids have been successfully used [32]. Stage two requires emollients. Systemic and topical retinoids could be beneficial [33, 34].

Patients presenting PHTN benefit from diuretics at the beginning. If the child survives, phosphodiesterase-5 inhibitors can be used [4]. Dental malformation benefit from orthodontic care. Retinal neovascularization responsible of ophthalmologic manifestations is treated similarly to retinopathy of prematurity with cryotherapy or laser treatment. Retinal detachment requires surgical repair. Early experimental use of intravitreal anti-vascular endothelial growth factor (VEGF) may be a promising treatment [35].

Prognosis and Complications

Skin lesions lead to hypo−/hyperpigmentation and scarring. Besides the extremely rare cardiological complications, eye and brain are the most affected extracutaneous organs in terms of complications and definitive functional loss. The natural history

of retinal impairment leads to retinal detachment. Neurological disease is associated with a considerable morbidity and are often cause of death in IP patients. Prognosis of patients with cardiological manifestations is very poor. Four of reported cases died by age of 5 months because of severe PHTN [22, 23, 25, 28].

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