

A RARE CASE OF INCONTINENTIA PIGMENTI WITH SEVERE EXTRACUTANEOUS MANIFESTATIONS

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Abstract

Incontinentia pigmenti (IP) is a complex genodermatosis inherited in an X-linked dominant pattern, associating multistadial cutaneous manifestations with an oculo-dento-cerebral syndrome, which affects only female newborns, as the disorder is lethal in males since intrauterine period. We report on a case of incontinentia pigmenti with an atypical debut consisting of tonic-clonic seizures which had started during the first days of life, associated with severe ocular and neurologic manifestations. The presence and severity of extra-cutaneous features most often command the evolution and the prognosis of the disease.

Keywords: incontinentia pigmenti, genodermatosis, apoptosis

Introduction

Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a genetic disorder inherited in an X-linked dominant pattern, characterized by cutaneous, neurologic, ophthalmologic and dental abnormalities, only present in female new-borns because males do not survive until birth (1). It is a rare disease with a prevalence of 1/50.000 in general population (2). Its pathogenesis seems to be related to the induction of cellular susceptibility to tumor necrosis factor-induced apoptosis in the cells presenting mutations of a gene situated in the Xq28 region of the X chromosome (1)

Clinical case

We report on a case of a female new-born with a birth weight of 3200 g, APGAR 9 score, resulted from a normal pregnancy, hospitalized, without any perinatal pathological history, which since the first 2 days of life presented tonic-clonic generalized seizures that remised after intravenous administration of diazepam. The first seizures were succeeded by the appearance of a cutaneous rash, first presenting as patches and then, after 5 days of life, consisting of vesicles and bullae disseminated on the limbs

and trunk. From the physiological history of the mother, we note primiparity and the existence of an induced abortion.

When addressed our clinic, at the age of 14 days, the patient presented light brown pigmented patches with reticular pattern, vesicles and bullae, as well as verrucous lesions located on the limbs and trunk, arising on place of previous vesicles and bullae. Laboratory findings showed leukocytosis associated with neutrophilia and elevated C-reactive protein (CRP) level; lumbar puncture revealed pleocytosis associated with neutrophilia in the cerebrospinal fluid (CSF) and the transfontanelar ultrasound examination revealed two right choroid plexus cysts and second degree right retinal hemorrhage. Cutaneous cultures proved *Klebsiella spp.* and the skin biopsy revealed suggestive histopathologic aspects asserting the clinical diagnosis of incontinentia pigmenti- verrucous stage.

Under antibiotic treatment (Vancomycin 15 mg/kg/dose administered every 8 hours and Gentamycin 4 mg/kg/dose administered every 24 hours), anticonvulsant (Diazepam 0.3 mg/kg/dose, followed by sodium valproate-Depakine p.o increasing the dose gradually until achieving the maintenance dose of 30 mg/kg/day divided into 3 doses administered every 8 hours) and symptomatic treatment, the evolution was unfavorable, with seizure persistence, subsequent development of generalized porencephalic lesions located in both cerebral hemispheres and progressive deterioration of the medical status that led to exitus at the age of 5 weeks.

Discussion

IP is a genodermatosis inherited in an X-linked dominant pattern that most frequently affects female newborns; it is usually lethal in males since the very intrauterine period (3). In 63% of the cases incontinentia pigmenti is ascertainable since birth or appears during the first week of life, rarely during the first year and even less frequently after the first year. IP is a complex genodermatosis that associates cutaneous changes with an oculo-dento-cerebral syndrome (4).

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Even though a similar case was described in the literature in 1906 by Garrod, the historical credits for the first description of the condition are attributed to Bloch (1926) and Sulzberger (1928). In the past, the disorder has also been called Ashoe-Hansen disease, Bloch-Siemens syndrome, Bloch-Siemens pigmented dermatosis or melanoblastosis cutis linearis (3). Bloch named the disease after he observed that the melanic pigment, instead of passing from the basal layer of the epidermis into the squamous cell layer, is not retained in the epidermis and passes into the dermis, where it is captured by macrophages, producing an effect similar to tattooing, without a real excess in the production of melanin (5)(6)(7).

The pathogenesis of IP is associated with mutations in the gene coding the nuclear factor kB essential modulator (NEMO, NF-kB essential modulator), a 23 kb gene situated on the Xq28 chromosome (2). An important deletion of the 4-10 exons of NEMO (the NEMOΔ4-10 mutation) can be detected through Southern Blot analysis or PCR diagnosis in 85% of the patients with IP, while other mutations such as nucleotide substitutions, various deletions or insertions occur in only a small number of patients (6)(8).

The NEMO gene encodes a protein called IKKγ, which along with the IKKα and IKKβ proteins form IKK (IκB kinase). IKKα and IKKβ have a catalytic role, while IKKγ has a regulatory role (9)(10).

Normally, NF-kB is inactive and does not activate transcriptions of genes in the nucleus, being confined in the cytoplasm after binding to its specific inhibitory, IκB (IκB inhibitory). IKK will phosphorylate IκB at the level of two serine residues, which leads to the unfolding of the connection between IκB (which will subsequently be

degraded by proteosomes) and NF-kB and allows the latter to migrate unabashed towards the nucleus, where it will bind to the DNA at the level of numerous target genes that present sites for NF-kB attachment and whose transcription will be activated. NF-kB target genes regulate the cellular growth and proliferation and the production of membrane receptors, cytokines and various adhesion molecules. Besides those, an important target of NF-kB at the nuclear level is represented by the IAP genes (inhibitors of apoptosis proteins), genes that encode a set of proteins that block the caspase activity, stopping the apoptosis. Therefore, NF-kB is also involved in cellular survival response, inhibiting the apoptosis triggered on extrinsic pathway by TNF α.

The apoptosis triggered by TNF on extrinsic pathway starts with the binding of tumoral necrosis factor (TNF) to its receptor TNFR-1, event which induces a conformational change of the intracellular domain of TNFR-1, leading to the release of SODD (silencer of death domains), a 60 kDa protein that inhibits the reciprocal interaction between the tanatogenic intracelular domeins of TNFR-1, therefore blocking the accidental activation of the apoptotic pathway. In the absence of SODD, TNFR-1 receptor becomes able to recruit TRADD (TNFR associated death domain), an adaptor protein which itself will recruit and bind other proteins, such as RIP (receptor interacting protein) or TRAF-2 (TNFR associated factor). The latter will activate NIK (NF-kB inducing kinase), which will activate the IKK complex, which will phosphorylate IκB, which in turn will release NF-kB nuclear factor (9). Thus, the alteration of NEMO gene modulates the susceptibility of the cells to apoptosis, which might explain, at least partially, the intrauterine death of males (fig.1) *(2)(6)(10).

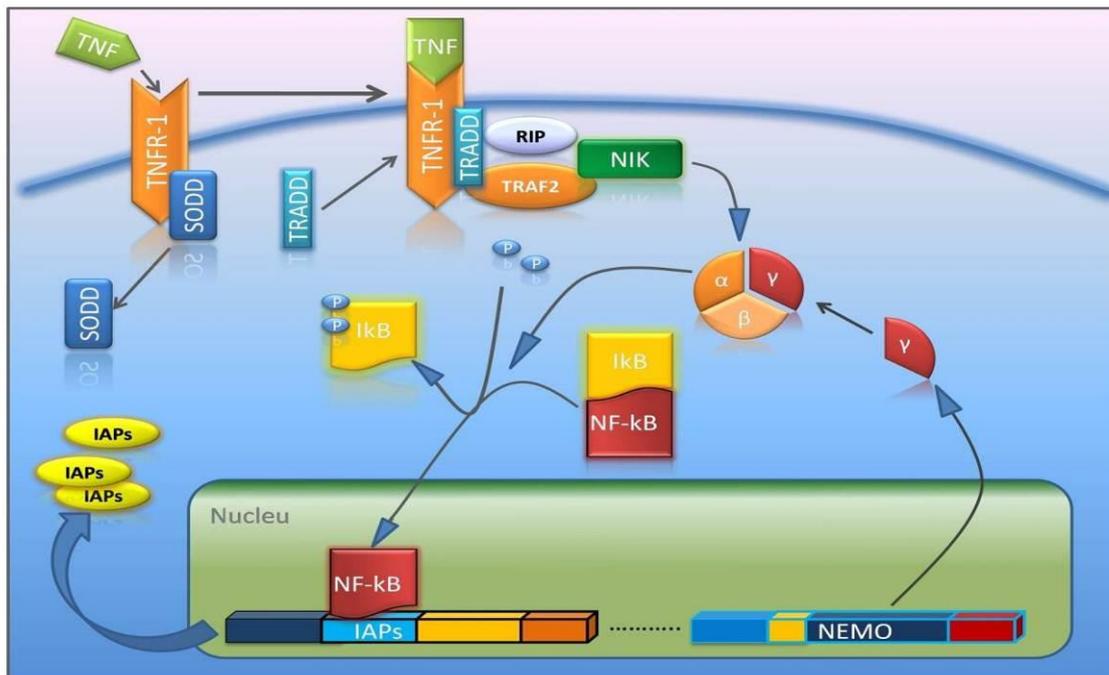


Fig. 1- Nuclear factor kB regulation and mechanism of action; TNF-Tumor Necrosis Factor, TRNFR-1 – TNF-Receptor 1, SODD –Silencer of Death Domains, TRADD-TNFR-associated Death Domain, RIP-Receptor Interacting Protein, TRAF-2- TNFR Associated Factor 2, NF-kB – Nuclear Factor kB, P-phosphate groups, NIK- NF-kB Inducing Kinase, IκB –Inhibitory of kB, NEMO-gena NF-kB essential modulator, IAPs-Inhibitors of Apoptosis Proteins.

Moreover, it has been demonstrated that the NEMO deletion only determines inflammation in the keratinocytes exposed to TNF and that the induced absence of TNFR-1 (TNF receptor 1) cancels the appearance of inflammation, aspect which contributes to the hypothesis according to which the cells which present mutations of the NEMO gene are destroyed by TNF induced apoptosis. The subsequent destruction of the cells may explain, at least partially, the healing of the lesions and the multistadial aspect found in the evolution of the disease (9). Another role in the pathogenesis of the disorder is attributed to eotaxin, a chemokine whose cutaneous expression is stimulated by TNF; eotaxin has an eosinophil chemotaxis role, their accumulation and the degranulation in the epidermis explaining, among others, the formation of vesicle-bullae following the action of their proteolytic enzymes on the desmosomes and tonofilaments (3)(11)(12).

IP is classically considered a lethal disease in males, with few exceptions. Male patients with clinical features resembling the ones that appear in females with IP- more accurately the four characteristic dermatologic stages and ocular anomalies- are extremely rare and generally have a 47XXY karyotype (Klinefelter syndrome) (10)(13). Also, the postzygotic mutation and somatic mosaicism have been recognized as mechanisms which can explain the survival of males with IP (13)(14)(15). In the case we are presenting, the patients' mother was primipar and had presented, two years before, a provoked abortion, with no history of previously lost pregnancies.

Cutaneous manifestations in IP are frequently the first observed and are classified in 4 stages:

Stage 1- vesicular or inflammatory stage: occurs in 90% of the patients, usually at birth or during the first week of life; there have also been described cases in which the lesions had appeared after the age of one year. This stage is characterized by the development of erythematous patches and vesicles/bullae with a linear pattern and inflammatory

base, which can transform to pustules by superinfection. In most cases the trunk and the extremities are affected. Vesicles usually disappear spontaneously after a few months (3)(16)(17).

Stage 2- verrucous stage: is seen in 70% of patients, usually appearing between the weeks 2 and 6 of life. As the vesicles dry, verrucous, hyperkeratotic, papules and plaques with a linear pattern, and rarely, lichenoid papules develop in their place. In 92% of cases the lower limbs are affected. The lesions disappear in 80% of the patients by the age of 6 months (3)(17).

Stage 3: is seen in 98% of the patients and is characterized by the development of streaks of brown or gray pigmentation along the Blaschko lines, often resembling "chinese letters"; they most often involve the trunk and limbs and do not derive from the lesions that characterize the previous stages. The nipples, axillas and genitals are frequently hyperpigmented; the hyperpigmented areas do not usually correlate to the areas affected in the previous stages. The onset of the stage is generally at the age of 16-26 weeks and the lesions persist for years or decades, until puberty or adulthood (3)(16).

Stage 4- the cutaneous features arise after the resolution of vesicle-bullae and verrucous lesions, often before the disappearance of hyperpigmentation and consist of hypopigmented and atrophic areas, lacking sudoripary secretion. Generally the lesions are located on the limbs; these lesions are permanent and can often be the only sign of cutaneous involvement in adults (3)(16).

Our patient presented a typical progression of the cutaneous features, with the appearance of vesicle-bullae on the limbs and trunk during the first days of life and their healing with the occurrence of verrucous lesions at the age of 14 days (fig.2).

Extracutaneous abnormalities are associated in approximately 80% of the cases (table 1) (3)(4)(16)(18)(20).



Fig. 2 – Clinical appearance at the age of 14 days: vesicles and bullae, as well as verrucous lesions located on the upper limbs and the distal third of the lower leg; light brown pigmented patches with reticular pattern located on the trunk and the lower limbs.

Table 1. Extracutaneous abnormalities:

- central nervous system (30% of cases) abnormalities: microcephaly, hydrocephaly, seizures, epilepsy, motor disturbance, mental deficiency, aseptic encephalomyelitis, EEG abnormalities;
- dental abnormalities (80% of patients) include partial anodontia, delayed eruption of dentition, conial or pegged teeth, anomalous crowns, etc.
- bone anomalies (20% of patients): skull deformities, kyphoscoliosis, hip dislocation, etc
- congenital cardiopathy : rare
- other anomalies: nanism, cleft lip and palate, ear anomalies, spina bifida.
- ophthalmologic findings: are frequent, usually asymmetric, and include: nystagmus, strabismus, microphthalmia, conjunctival pigmentation, corneal scars, irregular iris pigmentation, congenital cataracts, retinal detachment, optic nerve atrophy, vitreous anomalies or hemorrhages, persistent hyaloid artery, myopia.
- nail features: nail dystrophy and pitting that appear in 7-40% of the patients during childhood and usually disappear as the years go by (3).

In our patients' case, she presented neurological anomalies since birth, respectively generalized tonic-clonic convulsions and ophthalmologic abnormalities consisting of retinal hemorrhage which accompanied the cutaneous features, represented by a patch eruption that transformed during the first days of life into a vesicular and then verrucous eruption.

The diagnosis is initially based on clinical criteria (18). The skin biopsy is useful, showing changes that vary depending on the stage of the cutaneous features. In this particular case, the histopathologic examination proved

moderate hyperorthokeratosis and focal parakeratosis including polymorphonuclear cells (eosinophils) forming abscesses located in stratum corneum, moderate acanthosis and papillomatosis and frequent transepidermal dyskeratotic keratinocytes; moderate spongiosis with focal eosinophil exocytosis, dermal edema, capillary ectasia, minimum inflammatory infiltrate with frequent eosinophils and minimal vacuolar degeneration of the basal layer of epidermis were also observed and are consistent with the diagnosis of incontinentia pigmenti- verrucous stage (fig.3).

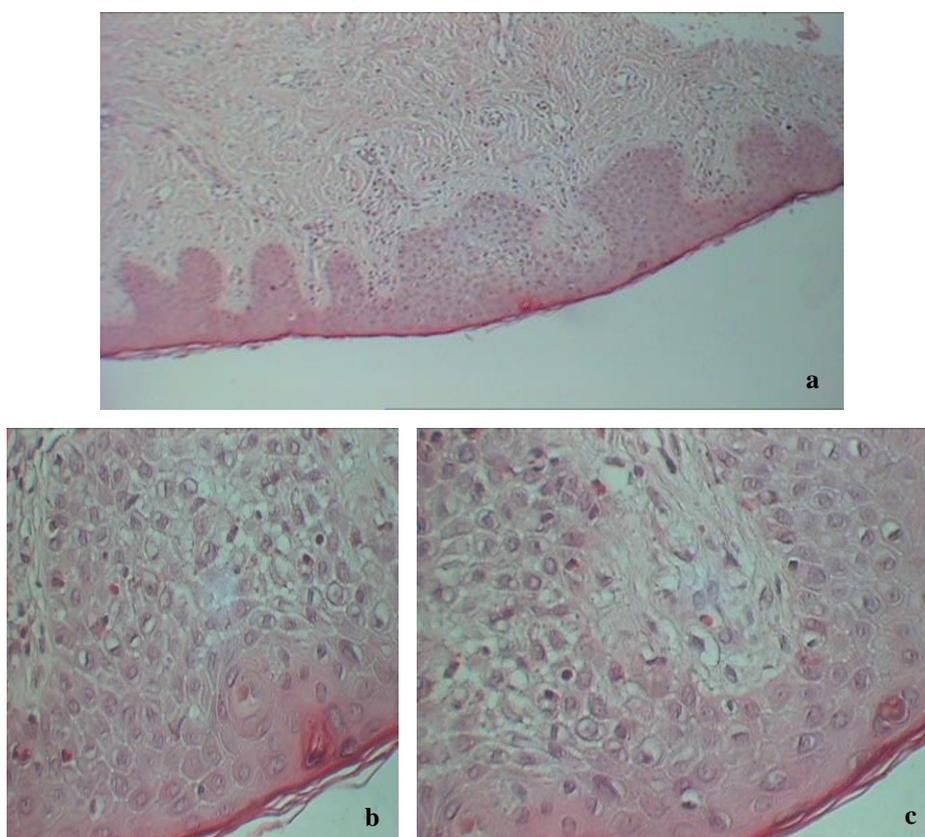


Fig. 3 – Histopathological examination of skin lesions, H-E, magnification 10X(a), 20X (b) and 40X (c) – detailed explanations in the text.

Neuroimaging is recommended when neurological or ophthalmological anomalies are suspected. In our patients' case, the eye fundus examination proved the presence of retinal hemorrhage (fig. 4) and the transfontanelar

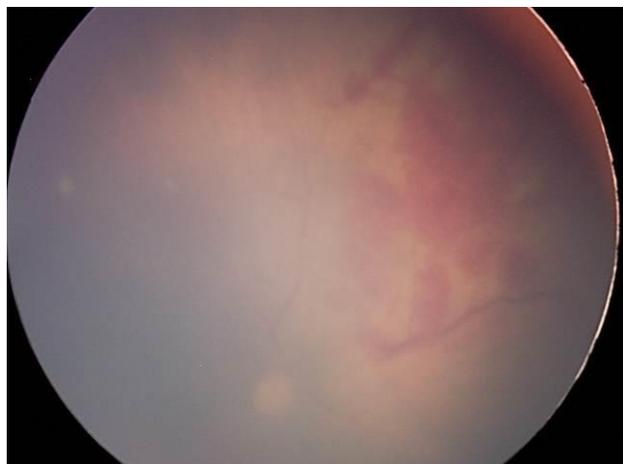


Fig. 4 – Eye fundus examination of right eye proving the presence of second degree retinal hemorrhage.

ecography revealed disseminated porencephalic lesions, bilateral hydrocephaly and the presence of two right choroid plexus cysts (fig.5).



Fig. 5 – Transfontanelar ultrasound examination: bilateral hydrocephaly, bilateral disseminated porencephalic lesions and the presence of two choroid plexus cysts.

Besides these investigations, the study of the NEMO gene can prove or disprove the diagnosis; the genetic analysis of NEMO could be helpful for the rapid prenatal confirmation of the IP diagnosis and for detecting carriers, but the patients' parents refused testing (19).

Depending on the stage of the disorder, this disease must be differentiated from epidermolysis bullosa, epidermolytic hyperkeratosis, scabies, impetigo, bullous mastocytosis, varicella, herpes simplex virus infection, linear porokeratosis, acropustulosis of infancy, linear epidermal nevus, segmental vitiligo, hypomelanosis of Ito and Pallister-Killian syndrome.

The management of the patients during the neonatal period or when the vesicular stage occurs consists of applying strict hygiene measures for avoiding superinfection, but there is no specific treatment. The lesions will be kept dry and will be protected from eventual physical trauma. The vascular retinal changes are the first to progress during the first months of life, for which reason monthly perinatal screening is recommended. Xenon photocoagulation or cryotherapy promote the regression of the neovascular lesions specific for the disease. The central nervous system disorders are associated with long term negative prognosis (16)(18).

In our patients' case we have administered antibiotic therapy using Vancomycin 15 mg/kg/dose every 8 hours and Gentamycin 4 mg/kg/dose for the treatment of meningitis, anticonvulsant treatment using Diazepam 0.3 mg/kg/dose, followed by sodium valproate (Depakine) in gradually increasing dose until achieving the maintenance dose of 30 mg/kg/day as well as symptomatic and local treatment for

the skin lesions. In spite of all this, the patient developed generalized porencephalic lesions in both cerebral hemispheres, with progressive alteration of the medical status and death at the age of 5 weeks.

Although the vesicle-bullae characteristic for the disease are the first ones noticed by the parents who bring the patient for a consult, they only affect the long term aesthetic prognosis. On the other hand, the ophthalmologic and psychomotor changes are serious complications that darken the prognosis of the disease (19)(20).

Case particularity

The case particularity consists of the co-existence of cutaneous features with extra-cutaneous ophthalmologic and neurologic abnormalities in a rare case of incontinentia pigmenti, as well as the fact that the neurological manifestations preceded the appearance of skin lesions.

Conclusions

Incontinentia pigmenti is a serious genetic disorder, whose prognosis depends on the presence and severity of extra-cutaneous features. The early recognition of the disease by the neonatologist, paediatrician or general practitioner and the pediatrician collaboration with the dermatologist can improve the prognosis of the disorder. The treatment most often implies interdisciplinary collaboration, the dermatologist occupying a central role in the case management. Even so, in the cases which associate neurologic and ophthalmologic abnormalities the evolution can be dreadful, in spite of sustained medical treatment.

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