

# Incontinentia pigmenti / Bloch–Sulzberger syndrome: a case report

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## Abstract

Incontinentia pigmenti is a rare genodermatosis that almost exclusively affects females. The disease is caused by a mutation of the nuclear factor- $\kappa$ B essential modulator (NEMO) gene in the Xq-28 locus of the X chromosome. The disease can seriously affect various organs, most notably the central nervous system and eyes. Cutaneous manifestation in incontinentia pigmenti is often mild but is an important diagnostic criterion for the disease. Treatment of cutaneous symptoms of incontinentia pigmenti is often not needed because they can spontaneously resolve. However, it should be noted that early diagnosis through parameters such as cutaneous manifestations is important so that prompt diagnosis and intervention for other organs can be made to prevent further fatal complications in the future.

**Keywords:** incontinentia pigmenti, genodermatosis, NEMO gene, children, immunology

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## Introduction

Incontinentia pigmenti (IP), also known as Bloch–Sulzberger syndrome or nuclear factor- $\kappa$ B essential modulator (NEMO) syndrome, is a rare, multiorgan, X-linked dominant disease with an incidence of approximately 0.1/50,000 cases worldwide (1–3). It has a global incidence of 27.6 cases, 65 to 75% of which are caused by sporadic mutations, and the rest are familial (4). The disease was first described by Garrod in 1906, with further description of clinical appearances described by Bloch and Sulzberger in 1928. The disease is more prominent in females because IP is lethal in males and frequently causes spontaneous abortion prior to the second trimester. In rare cases in which male fetuses survive, multiple abnormalities such as somatic mosaicism, Klinefelter syndrome, and hypomorphic alleles can be seen (5). IP is caused by a mutation in the NEMO gene in the Xq28 locus of the X chromosome (1). The NEMO gene is a kinase subunit that activates the NF- $\kappa$ B pathway, which helps prevent TNF- $\alpha$ -induced cell apoptosis by regulating the expression of genes related to the immune system, inflammation reaction, cell adhesion, and apoptosis. This case report presents a 22-day-old infant with a generalized linear rash that was confirmed to be IP through biopsy. The planned treatment for the patient involved other specialties from the pediatrics and neurology department.

## Case report

A 22-day-old female infant was presented to the neonatal intensive care unit with a generalized linear rash since birth accompanied by vesicles. Initially, dark reddish vesicles started to appear on the chest, and then spread across the entire body and ruptured to form crusts. Upon physical examination, the vital signs of the patient were within normal limits. Dermatological examination found generalized hyperpigmented macules, vesicles, and crusts on the trunk and extremities along Blaschko's lines (Fig. 1A and B). The patient was the family's third child, and her mother said that her older brother experienced similar symptoms and died at 20 days. The patient was delivered via normal vaginal delivery.

A punch biopsy of the skin was performed on the right thigh

and showed epidermal hyperkeratosis along with eosinophilic infiltration, inflammation, spongiosis, and exocytosis. In addition, pigment incontinence was also found (Fig. 2). Based on a physical examination and biopsy, the patient was diagnosed with IP. The patient was then referred to the pediatric and neurology departments for further examination and treatment.

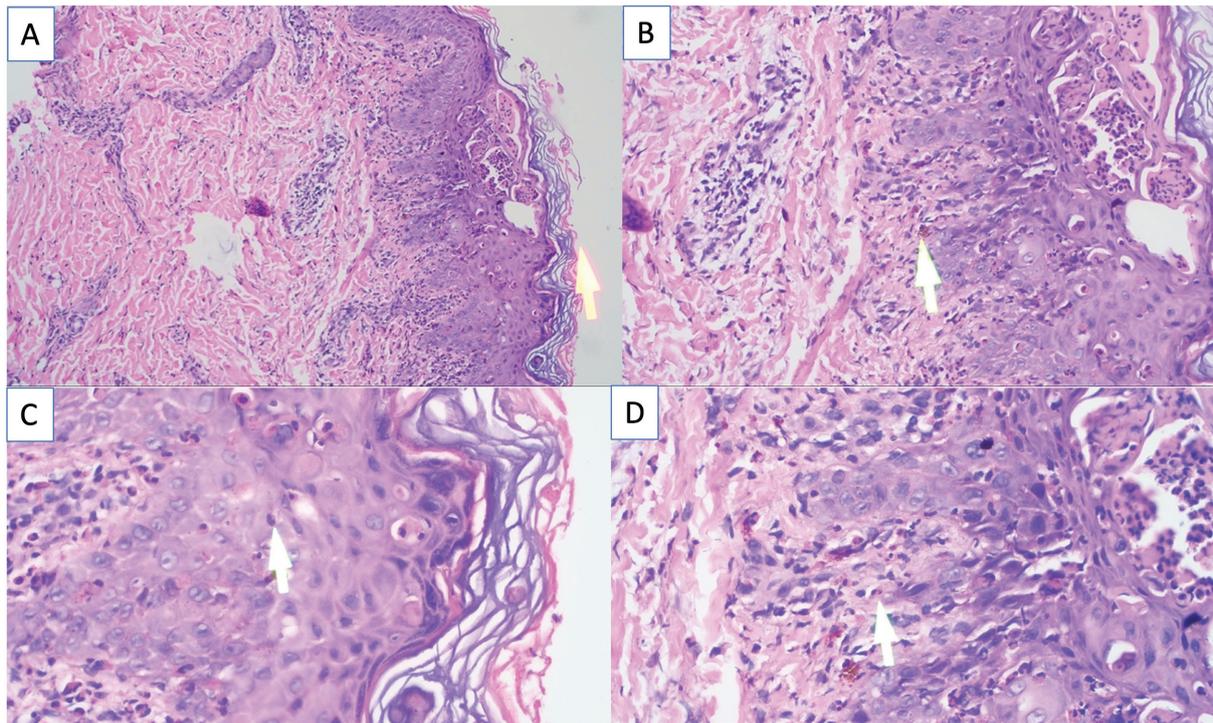
## Discussion

IP is an X-linked inherited multiorgan genetic disease that can affect the central nervous system (CNS) and ocular and musculoskeletal tissue. Cutaneous manifestation of the disease is often mild. However, it is an important diagnostic tool for IP. The disease is caused by a mutation to an inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase subunit gamma (IKBKG), located on Xp28. The result of this mutation is increased susceptibility of cells to undergo apoptosis (6). The disease is more prominent in females because being an X-linked disease makes it lethal to



**Figure 1** | (A, B) Generalized hyperpigmented macules, vesicles, and crusts along Blaschko's lines.

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**Figure 2** | (A–D) Epidermal hyperkeratosis with eosinophilic infiltration, spongiosis, and eosinophilic exocytosis with focal pigment incontinence.

males. There are four stages of cutaneous manifestation in IP. The patient in this report showed the first stage of cutaneous lesions characterized by generalized vesiculobullous eruption that appeared after birth. This is in accordance with the literature, which states that the initial lesions will appear in the 1st week of life (6). Stage II of the cutaneous manifestation of IP shows verrucous eruption particularly on the extremities, which can last for weeks to months. Stage III of IP is the hyperpigmentation stage, which manifests as linear or whorled hyperpigmentation along Blaschko's lines, which in most cases will spontaneously resolve or can last to adulthood. Stage III is the most common cutaneous manifestation of IP, with 98% of patients experiencing it, most predominantly on the intertriginous areas and trunk (4, 7, 8). The inflammation process during this stage leaves trapped melanin deposits in the dermis, which gives the condition the name *incontinentia pigmenti* (4, 8). Stage IV of IP is the hypopigmented stage; this stage usually occurs in adolescence to adulthood and can be permanent. Clinical manifestation includes hypochromic macules to alopecia (7). The prevalence of this stage is between 30 and 75%. Atrophy of the skin can be mild, and it is often misdiagnosed or undiagnosed (9). It is important to note that these four stages can overlap and will not necessarily occur in order (7). Eosinophilic infiltration is characteristic for IP and can be seen in approximately 30 to 60% of all IP cases. It is caused by a mutation in Xp28 that increases the apoptotic activity of cells.

Aside from cutaneous manifestation, 30 to 75% of patients may also experience ocular abnormalities such as early active retinal vasculopathy, optical nerve damage, or asymptomatic corneal abnormalities, which can lead to nystagmus, strabismus, retinal detachment, and blindness (10). CNS abnormalities are less frequent, with their manifestation determined by the phenotype. The most common symptom is seizure, with 42% of patients experiencing it, along with microcephaly, motor impairment in 26% of cases, and intellectual disabilities and learning difficulties in

20% of cases. Most CNS manifestations can be seen within the 1st year of life (10).

The definitive diagnosis of IP is made with identification of the NEMO gene. However, when this is not possible, such as in this case, typical clinical presentation in addition to a familial history of a similar condition in another child and histopathological analysis can be used for the diagnosis of IP. As previously mentioned, cutaneous lesions of IP are often self-limiting, and they require no specific treatment. The focus of treatment is to prevent secondary infection after the vesicles rupture (11). The use of topical corticosteroids, tacrolimus, and other anti-inflammatory agents can also be considered (5). Further examination of the patient is needed, especially regarding dental, CNS, and ocular abnormalities, to prevent long-term and potentially fatal complications (12).

Due to the wide array of multiorgan involvement in IP, it is important to provide genetic counseling for parents and the patient in the future regarding cosmetic appearance and possible psychological and psychomotor difficulties. In addition, because IP is an X-linked disorder and therefore lethal in males, it is important to counsel the patient in the future by taking into consideration the social and cultural aspects of having children (7).

## Conclusions

IP is a rare X-linked multiorgan genodermatosis with cutaneous, ocular, and CNS involvement. Cutaneous manifestation is the most common and visible finding and is therefore important for early diagnosis. Treatment of IP warrants multispecialty care and genetic counseling.

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