International Journal of Contemporary Pediatrics
Bajaj U et al. Int J Contemp Pediatr. 2024 Nov;11(11):1658-1661
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20243096

Case Report

Incontinentia pigmenti: a rare cause of skin rash in newborn

Upasana Bajaj, Prasun Bhattacharjee*, Keeranmayee Mishra, Pranay Trivedi, Ashwani Parashar

Department of Pediatrics, Ananta Institute of Medical Sciences and Research Institute, Rajsamand, Rajasthan, India

Received: 30 August 2024
Accepted: 02 October 2024

***Correspondence:**
Dr. Prasun Bhattacharjee,
E-mail: prasunpedia@gmail.com

ABSTRACT

Incontinentia pigmenti (IP) is a genodermatosis caused by mutations in the NEMO gene (Xq28) and is lethal in males. It is an X-linked dominant disorder with multi-systemic involvement. It involves the central nervous system and ectodermal tissues like skin, teeth, hair, nails, eyes, and the commonest manifestations are cutaneous manifestations. Here we present a case of a female newborn with vesico bullous eruption presented at birth. A full-term newborn female patient born by LSCS presented at birth with multiple vesico bullous skin lesions over bilateral upper and lower limbs in a pattern consistent with Blaschko's lines. Maternal HIV, HBsAg, VDRL, and TORCH screening were negative. Systemic examinations were normal. Supportive care and IV antibiotics with IV acyclovir were started but without any response. The sepsis screen, blood, and urine culture were negative. ANA was negative. Wound swab culture and skin culture were negative. Skin biopsy results showed eosinophilic infiltration of the dermis and spongiosis. Genetic testing could not be done. Topical steroids were prescribed. The diagnosis of Incontinentia pigmenti was established based on the patient's skin lesions and biopsy results. The baby improved and was discharged on the 14th day of life on topical steroids and is currently under follow-up. Other dermatologic conditions, like mastocytosis and hereditary epidermolysis bullosa, should be considered in the differential diagnosis of Incontinentia pigmenti. The diagnosis of Incontinentia pigmenti should be confirmed by histopathological examination of biopsy specimens along with genetic testing. It is a systemic disorder, so clinical management should include a multidisciplinary approach.

Keywords: Incontinentia pigmenti, NEMO gene, Skin rash

INTRODUCTION

Incontinentia pigmenti (IP) or Bloch-Sulzberger syndrome is a rare ectodermal dysplastic disorder and genodermatosis that involves multiple organ systems.[1-3] It presents with various cutaneous, dental, skeletal, neurological, and ocular manifestations, which include retinal detachment, blindness, seizures, paralysis, mental retardation, developmental delay, hair loss, and abnormal dentition.[4-6] The IKBKG gene, located at Xq28, which encodes a component of the nuclear factor kappa B (NF-κB) signaling pathway is responsible for this X-linked dominant genetic disease.[7,8] This disease manifests with characteristic skin lesions. Lyonization of the X chromosome contributes to pathognomonic reticular or whorled vesiculo-bullous IP pattern. Mutations in the NEMO gene, which codes for nuclear factor kB (NFkB) essential modulator, are seen in eighty percent of patients with Incontinentia pigmenti.

In the regulation of tumor necrosis factor-induced apoptosis NFkB plays a crucial role and is believed to reactivate pathways in the residual mutant cells by specific triggers (infection, fevers, or vaccinations).[9] Molecular analyses of the NEMO gene and skewed X chromosome inactivation are now possible. However, Incontinentia pigmenti diagnosis is primarily based on the characteristic clinical findings. Almost all the patients

affected with this disorder are females, while the affected male patients were reported to suffer from Klinefelter syndrome.[10] The estimated prevalence of Incontinentia pigmenti is 0.2 cases per 100,000.[11] As per previous reports, the incidence of this disease is 1.2 per 100,000 births. Most of the patients affected with pigment incontinence are females as the affected male patients often die in the uterus.[12-14] This very rare genetic disease with typical skin lesions and often with multisystem developmental disorders, can also involve teeth, eyes, central nervous system, and other organs.[12-14] The typical skin manifestations of this disease are divided into four periods, erythema and blisters, verrucous keratotic papules, plaques, and pigmentation (Blaschko lines).[15,16]

However, the skin lesions are not obvious, and the genetic test results of the parents are not necessarily positive in some occult cases. In such cases, suggestive tests, such as cranial magnetic resonance and retinal examination can be used along with pathological examination and genetic testing which may confirm the diagnosis. IP is a multisystemic disease where the skin manifestations are the hallmark and can be seen even at birth. We present a baby girl with characteristic skin manifestations of IP seen at birth.

CASE REPORT

A female newborn referred soon after birth because of a skin rash was admitted to the Neonatal Intensive Care Unit with vesicular skin lesions on the right forearm, back, and lower extremities. She was born at third conception to a 32-year-old mother, born at term gestation through LSCS (Lower segment Caesarean section) given severe oligohydramnios. Mother had two previous abortions. The Apgar scores of this baby were 8 and 9 in the first and fifth min, respectively.

Physical examination revealed a pulse rate of 150 beats per minute, respiratory rate of 50 breaths per minute, blood pressure of 60/40 mm of Hg, temperature of 37° C, and oxygen saturation of 99% on room air. She had a birth weight of 2600 g, a length of 49 cm, and a head circumference of 35 cm. Other systemic examinations were normal. She was admitted to the Neonatal intensive care unit (NICU) on the first day of her life with a diagnosis of newborn with generalized rash for evaluation.

Maternal HIV, HBsAg, VDRL, and TORCH screening were negative. A sepsis screen was sent. Wound swab culture and skin culture were negative. Sepsis screen, blood, and urine culture were negative. ANA was negative. The baby was treated with intravenous Antibiotics and other supportive measures immediately. Given multiple skin vesicular lesions, with some serous surrounding erythema with a non-linear distribution and given the suspicion of neonatal herpes and bacterial infections, acyclovir, vancomycin, and cefotaxime were prescribed but without any response (Figure 1).

RESULTS

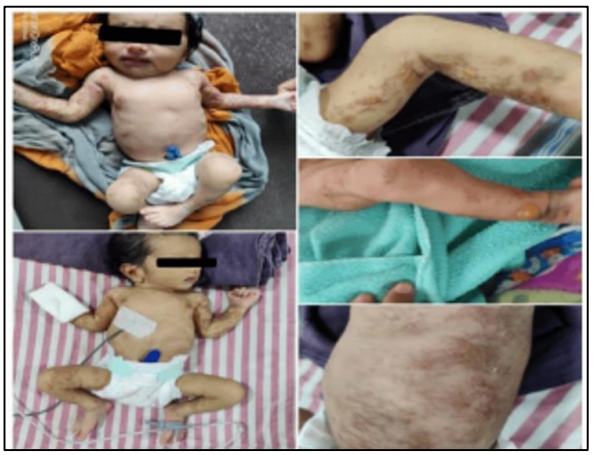

Figure 1: Clinical images of the present newborn showing the characteristic rash and its distribution.

By the eighth day of life, new lesions appeared with the same characteristics in linear distribution on the limbs. The patient was a well-appearing newborn since birth except for the rash. After consulting with a dermatologist skin biopsy from one of the blisters on the lower extremity was taken. A histopathological examination was done. Skin biopsy results showed eosinophilic infiltration of the dermis and spongiosis (Figure 2).

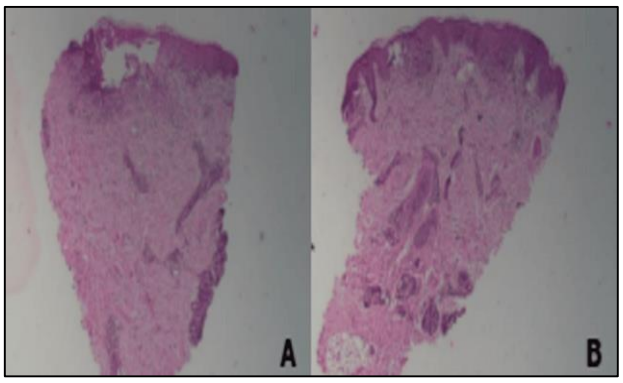

Figure 2: Histopathology images of skin lesion biopsy A) Shows superficial perivascular spongiotic dermatitis with several dyskeratotic cells in the upper epidermis. The dermis shows sparse superficial perivascular infiltrate of lymphocytes and a few eosinophils. The epidermis shows spongiosis with occasional eosinophils and numerous scattered dyskeratotic cells. B) Shows superficial perivascular spongiotic dermatitis with several dyskeratotic cells in the upper epidermis. The dermis shows sparse superficial perivascular infiltrate of lymphocytes and a few eosinophils. The epidermis shows eosinophilic spongiosis and numerous scattered dyskeratotic cells.

Genetic testing could not be done. The diagnosis of IP was established based on the patient's skin lesions and biopsy results. The baby improved and was discharged on

the 14th day of life on topical steroids and is currently under follow-up.

DISCUSSION

At present history of the disease, characteristic manifestations, and evolution of skin lesions are the internationally accepted criteria for the diagnosis of Incontinentia pigmenti (IP).[17] Typical skin lesions include erythroid blisters in the neonatal period which contain eosinophils, pigmentation with a linear distribution on the trunk, and linear skin atrophy.[17-19] The characteristic skin manifestations are divided into four periods. In the first stage, lupus erythematosus blisters are seen, and it occurs usually between birth to 2 weeks of age.[20] These blisters occur along the inside of the limbs and the trunk with a linear lateral distribution and are characterized by pimples, erythema, blisters, and rash. The blister fluid contains eosinophils in large numbers, and it is usually sterile.

Histopathological findings of skin in the first stage suggest typical eosinophilic sponge edema. The second stage appears after 2-6 weeks of birth and is characterized by verrucous keratosis papules and plaques, which are distributed on the extremities. The third stage starts at 12 to 26 weeks after birth and is characterized by pigmentation in the form of stripes or vortices along the Blaschko line on the trunk.[18,19] The fourth stage occurs at any stage from early adolescence to adulthood and is characterized by pale atrophic plaques or hypopigmentation.[19,20] These four stages of skin lesions can occur sequentially or simultaneously. in the literature, positive head imaging has also been reported apart from typical skin symptoms of IP.[21,22] The dominant lesions in conventional MRI in patients with IP are widespread, sometimes confluent punctate, and patchy changes in the periventricular and subcortical white matter. Unlike other neurological conditions, in IP neurological lesions do not change over time or no new neurological lesions develop.[21,22] Therefore, cranial magnetic resonance examination has a certain significance for neonatal IP.

Our patient showed normal clinical neurologic and brain MRI results. Furthermore, there was no family history of neurologic disease in our case. Ophthalmologic abnormalities, especially retinopathy is seen in approximately 20-77% of IP patients. These ophthalmologic lesions are mainly retinal vascular abnormalities, including abnormal vascular anastomosis, peripheral retinal avascular areas, vascular loop-like changes, and decreased blood flow density in the macular area. Strabismus, cataracts, optic nerve atrophy, retinal pigment epithelial abnormalities, retinal detachment, and microphthalmia are the other ophthalmic abnormalities reported in IP patients. However, our patient showed normal ophthalmologic findings. Hair abnormalities like alopecia, sparse hair, and hypoplasia of eyebrows and eyelashes have been reported in 28-38% of the patients with this disorder. The most common manifestation of hair is scarring alopecia, usually on the vertex.[22] Nail abnormalities, such as dystrophy and fibromas were also reported in IP. In our case which is a newborn, no such nail or hair changes are seen as of now and both the parents had no hair or nail involvement. IP is a rare X-linked dominant genetic, ectodermal dysplastic disorder involving multiple organ systems. Mutations in the IKBKG gene, located at Xq28 which encodes a component of the nuclear factor kappa B (NF-κB) signaling pathway, cause this disorder.[22] This disease is characterized by skin lesions and may also involve teeth, eyes, hair, CNS and the musculoskeletal system. It can lead to blindness, convulsions, and mental retardation.

In the current literature, no reason was found for the negative genetic tests of the parents of the affected child, while our studies speculated that it might be due to somatic mosaicism or mild gene mutations. So genetic testing is not necessary for those with low incomes, due to its high cost. In addition, in the early stages, typical skin lesions like erythema, blisters, papules, and verrucous plaques along the Blaschko line do not manifest, which can easily lead to misdiagnosis of herpes. Therefore, for accurate diagnosis of the disease (IP) magnetic resonance imaging (MRI) and retinal examination should be performed on time after the evidence of typical clinical manifestations, followed by invasive tissue biopsy and genetic testing of the pedigree.

The differential diagnosis of Incontinentia pigmenti includes neonatal herpes simplex infection, impetigo, neonatal bullous dermatoses, and autoimmune blistering. The skin lesions of IP resolve spontaneously, so specific treatment is not required. Topical and systemic antibiotics are not recommended for vesicular lesions, to prevent bacterial superinfection. Incontinentia Pigmenti diagnosis can be confirmed by the mutation analysis of the IKBKG gene. But in resource-poor settings of our country, even in the absence of genetic studies, the combination of suspicious Blaschko skin lesions, eosinophilic skin infiltration in biopsy, and CNS manifestations with MRI changes of vasculopathy are enough to diagnose IP, as per the recent update in the IP diagnostic criteria.[23]

There is a wide gap between the research and clinical care despite the considerable progress in detailing the basic pathology of the IP disorder. Moreover, it is difficult to provide an overall epidemiological report of IP disorder because of the paucity of IP patients in every single diagnostic center. Therefore, for successful future scientific accomplishments integration of scattered resources may be crucial.[23]

CONCLUSION

Incontinentia pigmenti (IP) is a rare genetic disorder characterized by X-linked dominant inheritance and affects multiple systems. It is important to distinguish it from other dermatological conditions like hereditary epidermolysis bullosa and mastocytosis. In addition to

genetic testing, the histopathological examination of skin lesions is instrumental in confirming the diagnosis of IP. A multidisciplinary approach is essential for improved outcomes and future research into this clinical condition. Dermatologists, pediatricians, neurologists, genetic counsellors, and dentists should be well-informed about the different manifestations, available diagnostic tests, treatment possibilities, and the prognosis of this multisystemic disease.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Bajaj U, Bhattacharjee P, Mishra K, Trivedi P, Parashar A. Incontinentia pigmenti: a rare cause of skin rash in newborn. Int J Contemp Pediatr 2024;11:1658-61.