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Original Article

Incontinentia pigmenti with remarkable cutaneous manifestations

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Abstract

Background Incontinentia pigmenti (IP) is a genetically determined dysplastic ectodermal disease involving the cutis, hair, teeth, micro-vascular system and the central nervous system. Successive skin manifestations develop in four steps, the first one occurs during early infancy or manifest at birth. IP is a dominant mediated genetic disease of the X chromosome due to abnormalities of the IKBKG gene. The purpose of the study is to report cases of incontinentia pigmenti with variable cutaneous presentation.

Methods Twelve patients with incontinentia pigmenti were evaluated by this case series descriptive study during the period from 2017-2023 years. All demographic and clinical information were recorded. Full cutaneous examination was carried out.

Results The analysis of twelve patients with incontinentia pigmenti showed that all patients were females, with positive family history in one patient and their ages ranged from 2-6 months. Eleven patients showed warty vesicular erythematous rash in a swirled and whorled pattern with some blaschkoid line features in one side of body except one patient showed generalized rash while in one patient the rash was just generalized whorled pigmentation with no blistering warty rash. More than one stage of rash evolution was noticed in 11 patients, often with warty blistering plaques. The warty blistering and the rash was resolved after topical steroid cream.

Conclusion Twelve female infants with incontinentia pigmenti were assessed, mostly with unilateral warty erythematous blistering rash. The sequential stages of the disease were not revealed but in contrast more than one stage was demonstrated at the same time.

Key words
Incontinentia pigmenti; Genetic; Warty blistering rash.

Introduction

Incontinentia pigmenti (IP) is a name derived from the microscopic appearance of the skin during the last stages of the condition.[1] It is a rare disorder of the X chromosome, usually affecting females with classical clinical signs, in Blaschkoid patterns, resulting from inactivation of the X chromosome.[2] In a recent study, Orphanet estimated the newborn prevalence of IP was about 1.2/100 000 in Europeans.[3] IP is usually diagnosed clinically,[4] with isolation of alteration at the *IKBKG gene*, particularly in mild female cases.[5] Skin findings mainly involve Blaschko's lines, that depend on mosaicism of epidermis of the embryoes, this helps early diagnosis of the disease at birth.[6] Physical findings of the kin appear in four phases: The 1st phase can manifest at birth or develop in early life. It manifests as erythematous and inflamed

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cutaneous lesions, blistering and boils, usually involving the scalp and the limbs. It may remit and then relapse from time to time, especially during febrile episodes. These attacks may recur over years, reaching into the adult life. The 2nd phase of hyperkeratotic verrucous papules and plaques can overlap the first and can manifest at birth. Additionally crusts and scabs resolve into hyperpigmented lesions. This stage always involves the extremities. The 3rd stage consists of hyperpigmented whorls and swirls on the trunk, which have a "marble cake" appearance. It may be present at birth, but frequently starts at the ages of six to twelve months and can persists into adolescence. This deep pigmentation can subside after time, but it might persist in many cases.[1,7] The 4th phase appears as hypopigmented streaks, devoid of skin appendages, often involving the lower extremities in early adulthood ages "atrophic stage". Skin features of the third and fourth phases can be misdiagnosed and are suggested to be present at birth, but not obvious.[3]

Incontinentia pigmenti may involve neuronal and ectodermal tissues such as teeth, hair, eyes, and the CNS. Neurological features include seizures and delayed mentality. Provided the low incidence and variability of morphologic criteria, case series studies are an essential way of data for better identification of IP.[8] The aim of this study is to evaluate demographic and clinical features of the twelve females providing the different phenotypes of IP.

Methods

Twelve cases with incontinentia pigmenti were evaluated in Baghdad, Iraq by this case series descriptive study during the period from 2017 to 2023. Demographic and clinical information was recorded. Full cutaneous examination was carried out. Digital photography was done. Biopsies were refused by parents. Topical corticosteroid was applied for warty blistering rash for two months or until resolution. Ethical considerations were followed and written informed consents was obtained from the parents.

Results

The analysis of twelve patients with incontinentia pigmenti showed that all patients were females (100%), with positive family history in one patient (8.3%) and their ages ranged from 2-6 months. Eleven patients (91.6%) showed warty vesicular erythematous rash in a swirled and whorled pattern with some blaschkoid line features in one side of body **(Figures 1-3)**, in one patient the rash was generalized (8.3%). While in one patient the rash was just generalized whorled pigmentation (8.3%) **(Figure 4)**. More than one stage of rash

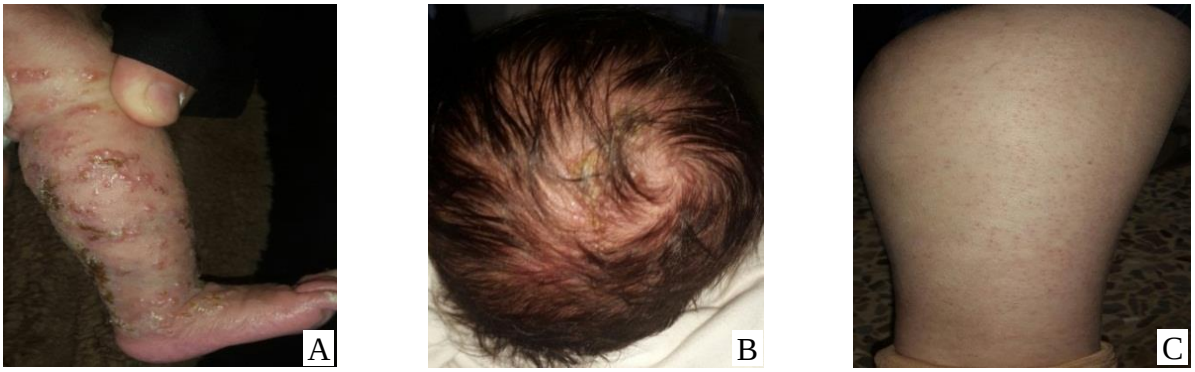

Figure 1 An infant with IP showing an erythematous blistering rash affecting the right leg (A) and scalp(B). (C) The mother of the same infant showing her right leg with atrophic hypopigmented rash of IP.

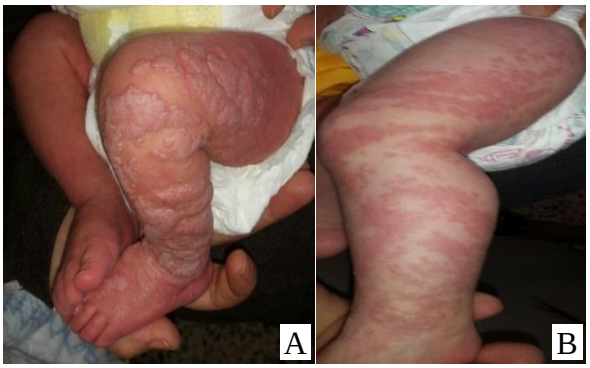

Figure 2 An infant with IP showing warty blistering plaque of the left leg(A),then resolution of rash by topical steroid therapy (B).

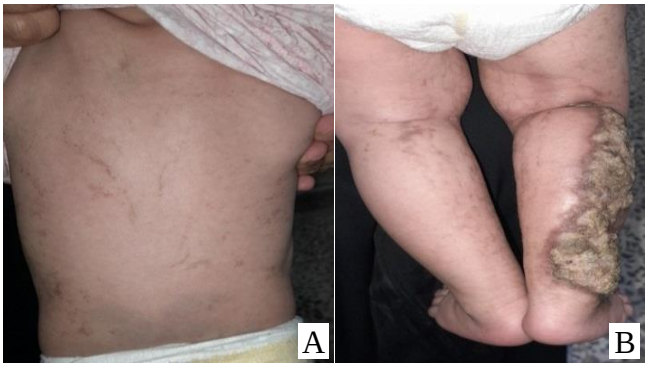

Figure 3 An infant with IP showing generalized whorled pigmented rash (A) with warty blistering plaque (B).

evolution was noticed in 11 (91.6%) patients, often with warty blistering plaques. A remarkable thing was the clinical absence of visual and neurological deficits and seizures in our patients, and also the lack of significant hair or nail abnormalities at the time of examination. The therapeutic trial showed that the warty blistering rash was resolved after topical corticosteroid cream.

Discussion

Skin findings are critical signs for the diagnosis of IP. In all phases, these manifestations occur as lines on the limbs or whorled shapes on the trunk. These may affect the face and scalp, and there is no specific sequence of appearance. Different lesions can appear simultaneously and the later phases might persists once they occur.[1]

This present study showed that all patients were females (100%). This is explained as the disease is X-linked dominant and the diseased males die in utero; or very rarely carry postzygotic mutation leading to mosaicism, or with a Klinefelter syndrome 47, XXY karyotype.[1]

The patients' ages, in the present work, were ranged from 2 to 6 months that was much younger than in a case series by Hübner S *et al.* where he found a median age of thirty patients was 3 years that ranged from eight days to forty seven years at the time of the last observation. A positive family history of IP in this study was found in one patient (8.3%), while Hübner S *et al.* reported first degree relatives in (26.6 %). This considerable difference could be due to different sample sizes or populations of these studies. Eleven patients in the present study

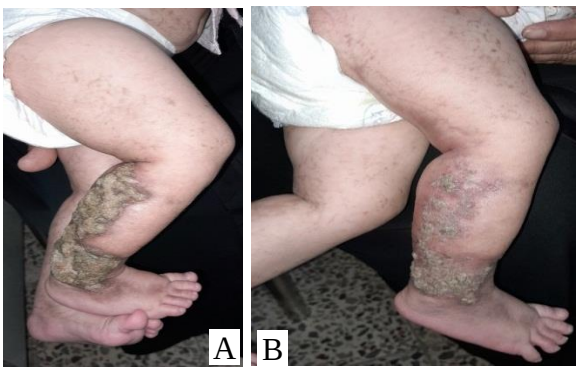

Figure 4 The same infant after topical therapy of plaque showing improvement of rash.

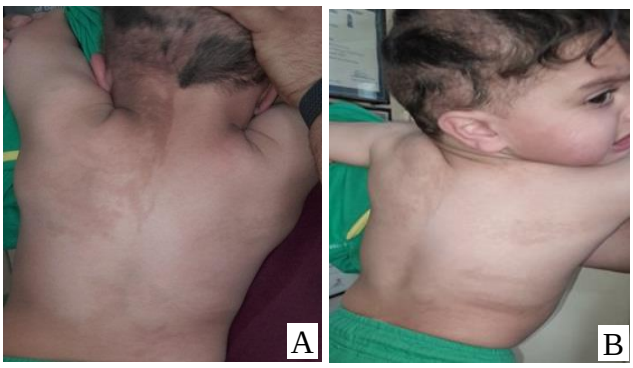

Figure 5 An infant with IP showing only generalized whorled hyperpigmented patches on both sides of the body.

showed warty vesicular erythematous rash in a swirled and whorled pattern with some blaschkoid line features in one side of the body except in one patient the rash was generalized. This might be attributed to diverse postzygotic mutations, which is in agreement to typical presentations of the disease and can be explained by the observation of overlap of the clinical phases in many cases.[1,10] The findings of redness and blisters (phase I) as the first clinical features in 90 % of the cases, hyperkeratotic lesions (phase II) in (85%) of Hübner S *et al*. series can be comparable to the observations of a mixture of different phases of IP in our patients. Another factor was the relatively younger and narrow age range (2-6 months) of the patients in this present trial might lead to this finding, because most of the phases can be presented shortly after birth and during early infancy. Only in one patient the rash was just pigmentation (8.3%), this was much lower than in Hübner S *et al*. series where atrophic or hypopigmented skin lesions were present in 20%, probably due to different sample sizes (12 versus 30), or different age of presentation of the patients in these studies. In this work, the more than one stage of rash evolution noticed in 11 (91.6%) patients (often warty blistering plaques) can be elucidated due to previous misdiagnoses and management or delayed medical consultations by the parents of children with IP. This led to progression of the disease and appearance of the second, third and fourth stages.

An interesting clinical observation was that the the warty blistering rashes were resolved after using topical steroid cream. This could also be a contributing factor in delayed presentation of some patients. A remarkable thing was the absence of visual and neurological deficits and seizures in our patients, and the lack of significant hair or nail abnormalities.

Conclusion

Twelve female infants with incontinentia pigmenti were assessed, mostly with unilateral warty erythematous blistering rash. No sequential stages of the disease were recorded but in contrast more than one stage was noticed simultaneously.

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References

1. Carey JC, Cassidy SB, Battaglia A, Viskochil D, editors. Cassidy and Allanson's management of genetic syndromes. John Wiley & Sons; 2020 Oct 22.
2. Döffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-κB signaling. *Nature Genetics*. 2001;**27(3)**:277-85.
3. Pavan S, Rommel K, Mateo Marquina ME, Höhn S, Lanneau V, Rath A. Clinical practice guidelines for rare diseases: the orphanet database. *Plos One*. (Number 1). 2020 [cited 2020, May 21].
4. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *J Med Genetic*. 1993;**30(1)**:53.
5. Minić S, Trpinac D, Obradović M. Incontinentia pigmenti diagnostic criteria update. *Clinical Genetics*. 2014;**85(6)**:536-42.
6. Senner S, Eicher L, Nasifoglu S, Wollenberg A. Linear patterns of the skin and their dermatoses. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2020;**18(4)**:341-64.
7. Sigl J, Vodopiutz J, Tanew A, Radakovic S. An unusual presentation of incontinentia pigmenti. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2020;**18(2)**:133-5.
8. Fusco F, Paciolla M, Conte MI, Pescatore A, Esposito E, Mirabelli P, Lioi MB, Ursini MV. Incontinentia pigmenti: report on data from 2000 to 2013. *Orphanet J Rare Dis*. 2014;**9**:1-5.

9. Kenwrick S, Woffendin H, Jakins T *et al*. Survival of male patients with incontinentia pigmenti carrying a lethal mutation can be explained by somatic mosaicism or Klinefelter syndrome. *Am J Hum Genet*. 2001;**69**:1210–7.
10. Hübner S, Schwieger-Briel A, Technau-Hafsi K, Danescu S, Baican A, Theiler M, Weibel L, Has C. Phenotypic and genetic spectrum of incontinentia pigmenti–a large case series. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2022;**20(1)**:35-43.