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Case Study

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COLE DISEASE – A RARE CASE REPORT

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ABSTRACT

Cole disease is one of the syndromes with palmoplantar keratoderma (PPK) as an associated feature. PPKs are heterogenous group of disorders characterized by hyperkeratosis of palms and soles. Majority of PPKs are hereditary, some are part of other dermatoses and few are acquired. Cole disease is a rare, autosomal dominant genodermatosis with features of pigmentary anomaly and punctate keratoderma. Exact prevalence is not known. It occurs due to mutation of ENPP1 gene located on chromosome 6q23, encoding ectonucleotide pyrophosphate/phosphodiesterase 1. Presents at birth or early infancy with guttate hypopigmented macules over extremities and keratoderma of palms and soles. There is no treatment for the disease at present and management is purely supportive. This is a report of 23 year old female patient who presented with pigmented, flat lesions over extremities, back and thickening of palmoplantar skin.

KEYWORDS: Cole disease, Palmoplantar keratoderma, Guttate hypopigmentation, ENPP1 mutation.

INTRODUCTION

Cole disease [Online Mendelian Inheritance in Man (OMIM) number – OMIM #615522][1] is a rare autosomal dominant disorder and the first family was described by Cole in 1976.[2] After that, one additional family and one single case have been published.[3,4] It is also known as guttate hypopigmentation and punctate palmoplantar keratoderma (PPK) with or without ectopic calcification.

It occurs due to mutation of ENPP1 gene located on chromosome 6q23. Autosomal dominant being common mode of inheritance, ENPP1 mutation causing recessive Cole disease was identified in a study by Chourabi M et al.[5]

It presents at birth or during early infancy and is characterized by punctate PPK and irregularly shaped, hypopigmented macules distributed over extremities or less typically over the trunk. Calcifications in several organs (tendons, breast, spleen) have been described.[3,6]

CASE HISTORY

A 23 year old female patient presented to our out patient department with whitish and blackish, flat lesions over extremities and back since birth. Patient also complained of thickening of skin over palms and soles. There was no history of fluid filled lesions. She was born out of consanguineous marriage and there were no remarkable events throughout the pregnancy of patient's mother. There was no history of similar complaints in parents and siblings.

Physical examination revealed multiple, well-defined, irregular hypopigmented macules interspersed with few hyperpigmented macules over bilateral forearms extending to dorsal aspect of bilateral hands (Figure 1A), bilateral legs (Figure 1B) and lower back (Figure 1C). Hyperkeratosis was noted over bilateral palms (Figure 2A) and soles (Figure 2B). There were no features suggestive of cutaneous calcification or calcific tendinopathy.

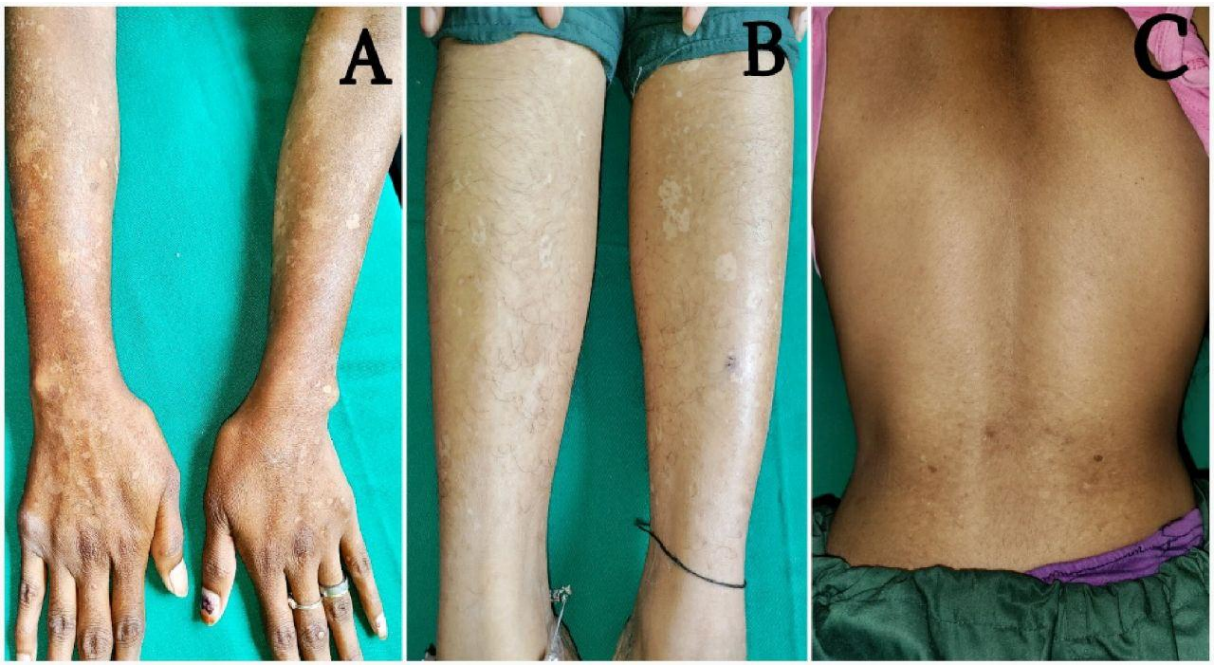

Figure 1: Multiple, well defined, irregular hypopigmented macules interspersed with few hyperpigmented macules noted over forearms (A), legs (B) and back (C).

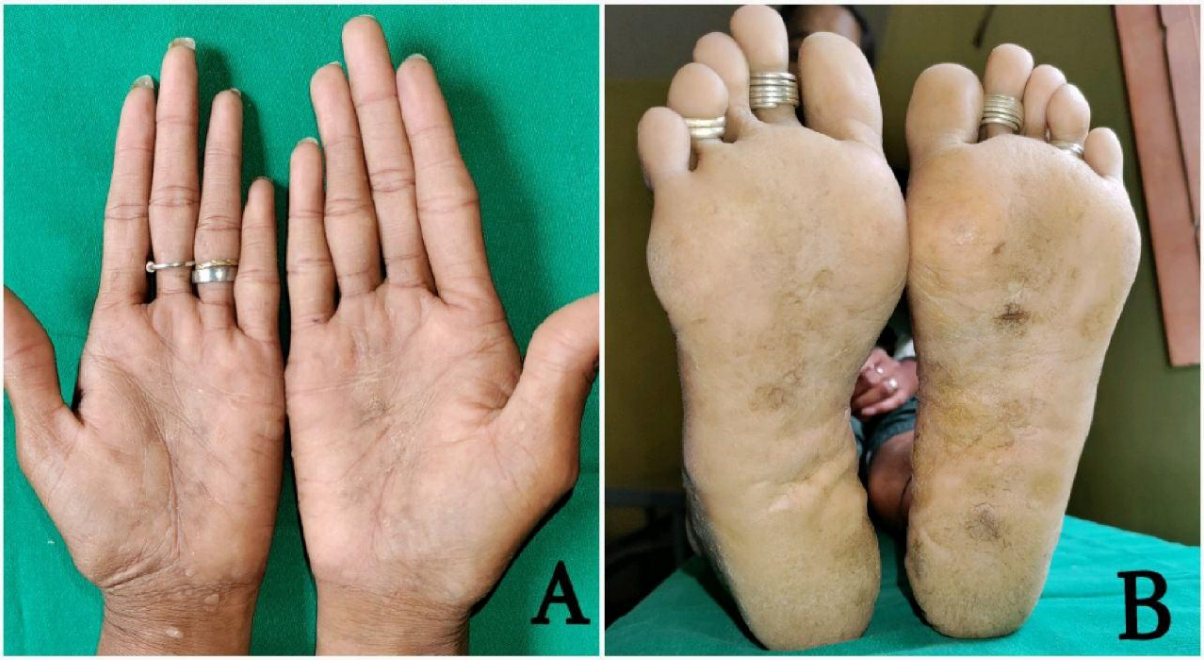

Figure 2: Hyperkeratosis of palms (A) and soles (B).

Skin biopsy revealed hyperkeratosis, hypergranulosis and acanthosis. Hyperpigmented areas showed increased pigmentation in epidermal basal layer (Figure 3A) and hypopigmented areas showed reduced pigmentation (Figure 3B). Dermis showed slit-like capillaries with surrounding non-specific inflammation.

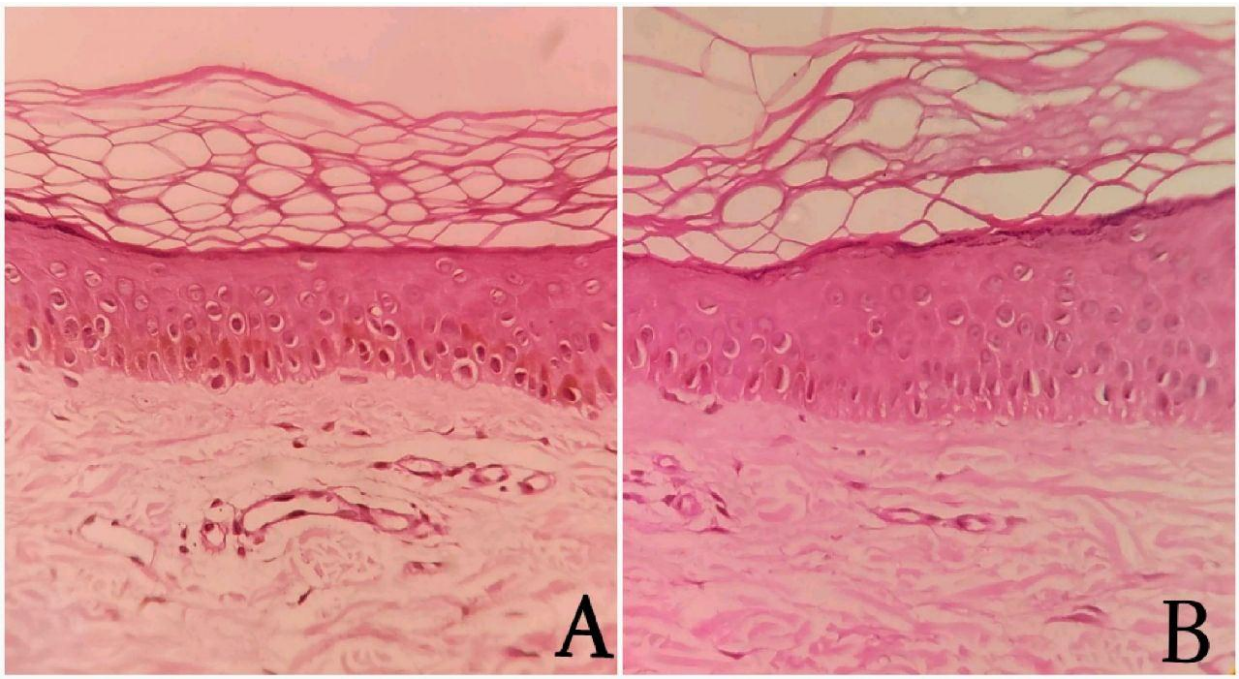

Figure 3: Histopathological examination of skin biopsy. (A) Hyperpigmented areas showed increased pigmentation in epidermal basal layer. (B) Hypopigmented areas showed reduced pigmentation in epidermal basal layer.

Complete hemogram, blood sugar, serum calcium, Renal Function Tests, Liver Function Tests, urine routine were normal. No abnormality was revealed on chest X-ray, ultrasonography of abdomen. A diagnosis of Cole disease was done based on clinical and histological findings. Patient was counselled regarding the nature of the disease and was treated for hyperkeratosis of palms and soles.

DISCUSSION

PPKs represent a heterogenous group of hereditary and acquired disorders of cornification characterized by prominent hyperkeratosis of skin on palms and soles.[7] They may represent a component of other genodermatosis. Based on clinical pattern of involvement, simple working classification divides PPKs into three major types - diffuse PPK, focal PPK and punctate PPK.

Cole disease is a rare inherited disorder caused due to mutation of ENPP1 gene,[8] which encodes for ectonucleotide pyrophosphate/phosphodiesterase 1.[7] ENPP1 has role in melanosome transfer from melanocyte to keratinocyte, keratinocyte development and generates extracellular organic pyrophosphate which is a major inhibitor of mineralization. Hence, its mutation may lead to pigmentary anomaly, keratoderma and abnormal calcium deposits.

ENPP1 is composed of eight domains including phosphodiesterase, nuclease and somatomedin-B-like (SMB) domains.[9] Through interaction between SMB domain and insulin receptor, ENPP1 inhibit insulin signalling and abnormal insulin signalling plays a role in pathogenesis of Cole disease. An Indian family with Cole disease with a novel pathogenic variant in ENPP1 in the SMB2 domain was reported in a study by Arti Nanda.[10]

Cole disease is characterized by congenital or early childhood onset of irregularly shaped, sharply demarcated hypopigmented macules on the extremities and punctate PPK. Abnormal accumulation of calcium in tendons (calcific tendinopathy) can cause pain during movements. Ectopic calcification may also occur in skin (calcinosis cutis) or breast tissue.

Histopathological examination, immunohistochemistry (IHC) markers for impaired melanogenesis like Melan A (Mel-A), tyrosinase (TYR), microphthalmia associated transcription factor (MITF), tyrosinase-related protein-1 (TRP-1), human melanoma black 45 (HMB-45) are helpful for diagnosis. ENPP1 gene mutation can be detected by whole exome sequence analysis[11] and Next generation sequencing with additional Sanger sequencing.

Management is purely supportive as there is no definitive treatment for this disorder. Treatment of keratoderma is difficult. Simple measures like saltwater soaks, paring and careful selection of footwear can be advised. Patients may respond to topical therapy with emollients, keratolytics, retinoids.

CONCLUSION

To conclude, even though pigment anomalies in this case were similar to dyschromias, presence of punctate keratoderma suggests that it is a separate entity and

diagnosis of Cole disease was made. This report might help the clinicians not to miss a diagnosis of Cole disease even in cases presenting without any positive family history as seen in our patient.

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