# Vitamin B12 deficiency secondary to cobalamin F deficiency simulating dyskeratosis congenita

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## INTRODUCTION

Cobalamin F (CblF) deficiency is part of a rare group of intracellular vitamin B12 metabolism deficiencies.[1] It most commonly presents during infancy and childhood, and it manifests as a broad spectrum of phenotypes that include developmental, neurologic, hematologic and, rarely, dermatologic symptoms involving the skin and its appendages.[2] Only a few cases have been reported worldwide.[2] We report a case diagnosed using whole exome sequencing (WES) with an unusual skin manifestation that resembled dyskeratosis congenita.

## CASE REPORT

A 15-year-old Sudanese girl born to first-cousin parents who was the second of 4 otherwise healthy children was noted to have developmental and speech delay, intellectual disability (IQ 70), short stature, microtia, microcephaly, dysphagia, and abnormal dentation. A hematologist followed up with her for years because of pancytopenia and microcytic hypochromic anemia, which failed to respond to several sessions of iron infusion. She was then referred to the pediatric dermatology department for multiple toe and fingernail diffuse hyperpigmentation, graying scalp hairs, and generalized reticulated dyschromia.

The dyschromia began at 4 months of age over the flexure sites, including the antecubital fossa and neck, and progressively evolved to include her entire body, including the palms and soles (Fig 1, *A* and *B*).

*Abbreviations used:*

CblF: cobalamin F
WES: whole exome sequencing

There was no history of recurrent infections, seizures, blistering, or photosensitivity, nor was there any hyper- or hypohidrosis. At presentation to us at the age of 15 years, the laboratory test results were as follows: white blood cells, $2.1 \times 10^9$/L; hemoglobin, 5.8 g/dL; platelets, $130 \times 10^9$/L; B12, 37 pmol/L; folate, 45 nmol/L; and hemoglobin electrophoresis, normal. The results were consistent with pancytopenia and vitamin B12 and folate deficiencies. Her hematologist treated her empirically with a single intramuscular dose of vitamin B12 and daily folic acid tablets for a presumed nutritional deficiency.

We considered dyskeratosis congenita as a possibility and carried out further investigations, including a lung computed tomography scan, an echocardiogram, and an esophageal fluoroscopy, all of which were unremarkable. A skin biopsy found nonspecific results and found that there were many melanophores in the papillary dermis, which was consistent with postinflammatory hyperpigmentation. Follow-up laboratory tests found the resolution of her pancytopenia, and the hematology team did not proceed with a bone marrow biopsy.

Initial molecular testing results using clinical WES were negative for dyskeratosis congenita, and the patient was then recruited, after obtaining informed

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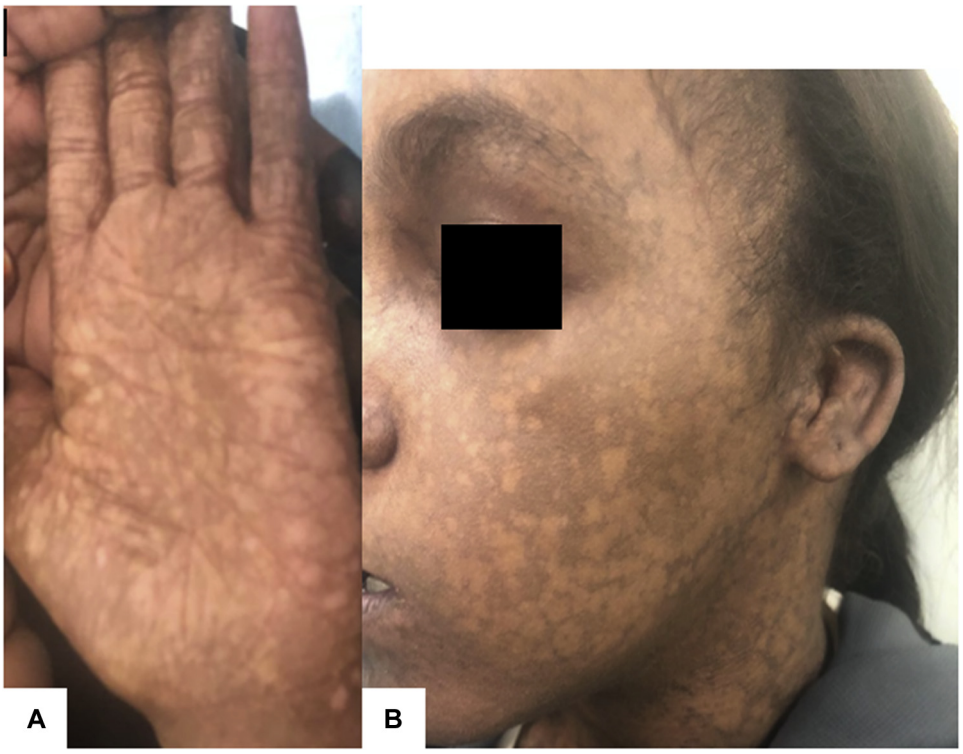


**Fig 1.** **A**, Palmar dyschromia with accentuated hyperpigmentation of the palmar creases. **B**, Reticulated dyschromia over the face and neck along with microtia.

consent, into a research study prior to performing WES, which found the following homozygous loss-of-function variant: *LMBRD1*: NM018368:Exon12: c.1156C>T:p.R366X. This finding was consistent with CblF deficiency. The patient was placed on a lifelong regular replacement regimen of intramuscular hydroxocobalamin (1000 $\mu$g/mL, 3 times weekly) and 1 mg folic acid daily. Her laboratory test results and her cutaneous symptoms continued to improve (Fig 2, *A* and *B*).

## DISCUSSION

Cobalamin (vitamin B12) is a water-soluble vitamin that is obtained from animal sources.[1] It plays important roles in development, growth, and cellular differentiation.[3] Although deficiency of the vitamin is primarily an adult disease caused by gastrointestinal and malabsorptive disorders, it is now more frequently encountered in children who are born in strictly vegetarian households or who have a mutation in one of the genes associated with the vitamin's intrinsic pathways.[4,5]

Since the first report by Rosenblatt et al,[5] only a few cases of CblF deficiency have been reported. It is a disorder that is inherited in an autosomal recessive manner secondary to a mutation in *LMBRD1*,[2,5] and it is 1 of 8 known intracellular vitamin B12 pathway defects. Normally, CblF acts as a cofactor in the intracellular vitamin B12 metabolism pathway that transports unbound cobalamin from lysozyme into the cytoplasm after receptor-mediated endocytosis. When it is mutated, it interrupts the release of cobalamin and impairs the formation of adenosylcobalamin and methylcobalamin, resulting in combined hyperhomocysteinemia and methylmalonic aciduria.[6]

The clinical spectrum is highly nonspecific, but the clinical phenotype often involves neurologic deficits in the form of seizures, hypotonia, or torticollis, which occur alongside developmental and hematologic abnormalities. Other features include failure to thrive, congenital heart disease, intrauterine growth retardation, stomatitis, glossitis, feeding difficulties, gastric upset, dental anomalies, microcephaly, facial dysmorphism, hepatic dysfunction, rash, pes equinovarus, tracheoesophageal fistula, arthritis, recurrent infection, recurrent apnea, encephalopathy, cleft palate, and unilateral renal agenesis.[2] Hematologic findings of megaloblastic anemia in cobalamin deficiency are thought to be attributed to folate entrapment and impaired DNA synthesis.[7] This patient had microcytic hypochromic anemia, a feature that might be explained by concomitant anemia caused by chronic disease. Of the 18 reported cases, all involved patients younger than 13 months, except for one 11-year-old patient

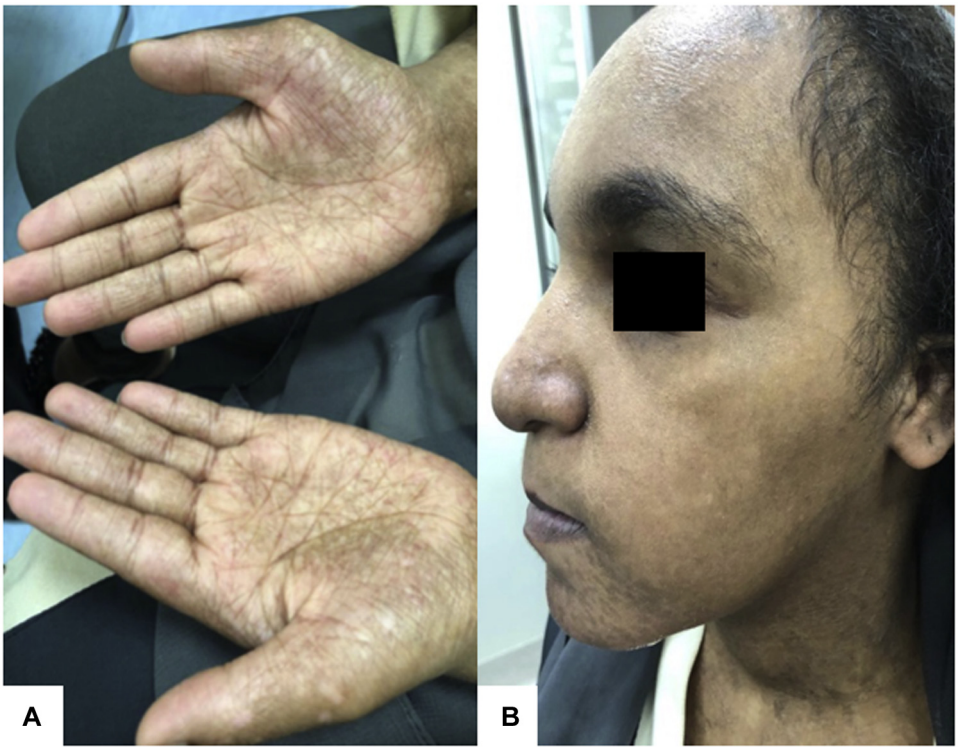


**Fig 2.** Improvement of dyschromia 1 year after vitamin B12 replacement. **A**, Palms. **B**, Face and neck.

who was reported by Macdonald et al[2]; this patient had no skin manifestations.[2,8] No other patient had cutaneous findings except one with a nonspecific description.[2]

Cutaneous manifestations of vitamin B12 deficiency encompass a group of reversible but nonspecific findings. These include localized, generalized homogenous, reticulate, or honeycomb hyperpigmentation; angular stomatitis; glossitis, poliosis; and total melanonychia.[4,9] The skin changes possibly result from imbalances in melanocyte homeostasis, whereby tyrosinase is activated, reactive oxygen species are increased, and glutathione is decreased.[10] Classically, CblF deficiency is diagnosed with a high index of suspicion alongside urine organic acid and plasma analysis.[1] In our patient, WES was needed to establish the diagnosis because of the unusual presentation of unique diffuse dyschromia involving the palms and soles, diffuse finger and toenail hyperpigmentation, and graying of the scalp hairs, which were suggestive of reticulated and dyspigmentation genodermatosis, particularly dyskeratosis congenita, especially when one considers the accompanying microcephaly and hematologic features. However, the early onset of symptoms, lack of oral leukoplakia, and nail dystrophy combined with a marked improvement in response to cobalamin replacement therapy and confirmatory testing with WES, assisted in negating this differential diagnosis.[1]

This study highlights the importance of familiarity with CblF deficiency because it requires lifelong replacement therapy, unlike nutritional vitamin B12 deficiency. Moreover, CblF deficiency should be added to the list of differential diagnoses for diffuse reticulated dyschromia. Finally, this case report shows the importance of using WES to make a quick and accurate diagnosis for complex and vague cases.

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