Progressive reticulate skin pigmentation and anonychia in a patient with bone marrow failure

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CASE SUMMARY

History

An 18-year-old man presented to the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, with dyspigmentation and nail dystrophy. His birth history was notable for intrauterine growth restriction (IUGR) and microcephaly. He was hospitalized at 6 weeks of age for respiratory distress and was found to have severe anemia, dilated cardiomyopathy, and cerebellar atrophy (Fig 1). At age 1 year he developed oral leukoplakia and esophageal strictures requiring multiple dilations. By age 3 he developed thrombocytopenia that progressed to multilineage bone marrow failure (BMF). At age 8 years he began undergoing treatment with oxymetholone for BMF. Although mild anemia has persisted, he has not required blood transfusion since he was 6 weeks old. Throughout his early childhood he had mild developmental delay and failure to thrive. He had been followed at the NIH since age 7.

His dermatologic history was notable for skin dyspigmentation and nail dystrophy that progressed during childhood. He also has a history of epiphora treated with lacrimal duct dilation, trichiasis, and keratinization of the conjunctiva, as well as 2 bone fractures. He reported frequent upper respiratory infections and sinusitis despite antibiotic prophylaxis.

At the time of NIH evaluation, the patient was at the 25th percentile for both height and weight. His current medications included oxymetholone for severe BMF, rosuvastatin for dyslipidemia, and clarithromycin and amoxicillin for upper respiratory infection prophylaxis. There was no history of similar skin or hematologic features in first-degree family members.

Physical examination

The patient had a reticulate pattern of skin pigmentation with admixed hypopigmented macules that was most prominent on the lateral neck, axillae, and medial thighs and had become more prominent throughout adolescence (Fig 2). He had bilateral epiphora and eyelash trichomegaly with no edema or erythema of the eyelids. On the medial right cornea there was a small, white hyperkeratotic papule. There was a fixed white plaque on the right buccal mucosa. The patient had micronychia or anonychia of all fingernails and toenails that had also progressed over several years (Fig 3). There was loss of dermatoglyphics on all digits (Fig 4). His hands were xerotic with accentuation of skin lines, but there was no palmoplantar hyperkeratosis.

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Abbreviations used:

BMF: bone marrow failure
DC: dyskeratosis congenita
HCT: hematopoietic cell transplantation
HH: Hoyeraal-Hreidarsson
IUGR: intrauterine growth restriction
NIH: National Institutes of Health
SCC: squamous cell carcinoma
TBD: telomere biology disease

Significant diagnostic studies

Abnormal laboratory values at this visit included a hemoglobin level of 9.8 g/dL (normal range, 13.7-17.5 g/dL), an absolute neutrophil count of 1100/μL (normal range, 1780-5380/μL), and platelet count of 21,000/μL (normal range, 161-347 K/μL). His high-density lipoprotein cholesterol level was 3 mg/dL (<40 mg/dL is considered high risk) and his triglyceride level was 331 mg/dL (normal value < 150 mg/dL). His lymphocyte telomere length (measured at age 7) was significantly below the first percentile for age at 3.1 kilobases (the normal value for age 7 is 9.4 kilobases), and his z score was -6.8, which is substantially below the lower limit of normal (-2.5 standard deviations). Subsequent genetic testing revealed compound heterozygous mutations in the regulator of telomere elongation helicase 1 gene (*RTEL1*).[1]

DIAGNOSIS

Hoyeraal-Hreidarsson (HH) syndrome, a variant of dyskeratosis congenita (DC) (Online Mendelian Inheritance in Man 615190 [https://www.omim.org/]) was the diagnosis.

FOLLOW-UP

The patient is scheduled to undergo allogeneic bone marrow transplantation.

DISCUSSION

DC is a telomere biology disorder (TBD) characterized by very short telomeres; progressive BMF; and the classic clinical triad of reticulate pigmentation, nail dystrophy, and oral leukoplakia. It was originally named Zinsser-Cole-Engman syndrome on the basis of reports from the early 1900s that focused on the dermatologic manifestations of the syndrome.[2-4] Although DC is rare, nearly 1000 cases illustrating both the clinical and genetic diversity of the syndrome have been reported (B.P. Alter, unpublished data).

Mucocutaneous findings are among the earliest and most common manifestations of DC. Approximately 68% of patients with DC manifest at least 2 features of the clinical triad.[5] Additional mucocutaneous features of DC, based on a large cohort of 60 patients with DC who were enrolled in a National Cancer Institute study (NCT-00027274), include epiphora (33%), loss of dermatoglyphics (30%), early gray hair (28%), palmoplantar hyperkeratosis (25%), eyelash loss (23%), scalp hair loss (20%), trichiasis or blepharitis (15%), and hyperhidrosis (5%) (unpublished data).

BMF is common, affecting 50% of patients by 50 years of age, with a lifetime prevalence of up to 86%.[5,6] Patients with DC have an estimated 11-fold increased risk for malignancy, particularly head and neck squamous cell carcinoma (SCC), myelodysplastic syndrome, and acute myeloid leukemia.[7,8] DC is also associated with a high

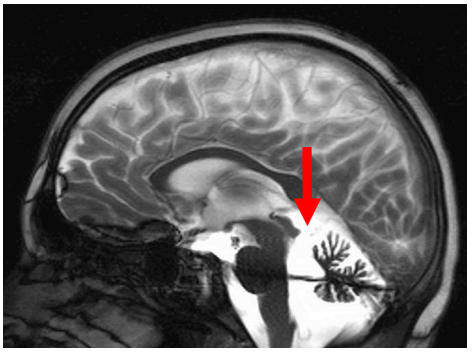

Fig 1. Dyskeratosis congenita cerebellar hypoplasia. Sagittal noncontrast T2-weighted magnetic resonance image of the brain. Red arrow indicates cerebellar volume loss.

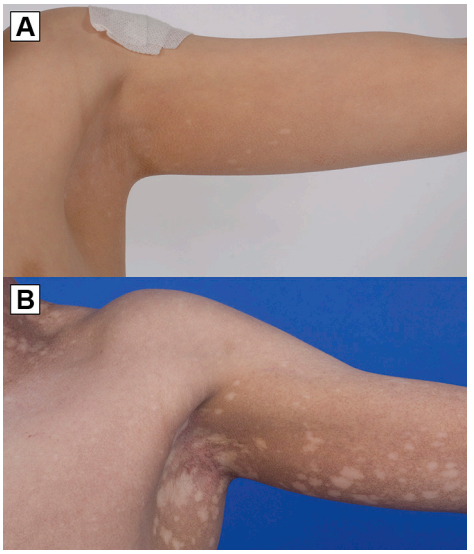

Fig 2. Dyskeratosis congenita skin pigmentation. Progressive reticulate pigmentation with hypopigmented macules at 7 (**A**) and 18 (**B**) years of age.