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

Suzanne C. Ward, B.E.¹, Sharon A. Savage, M.D.², Neelam Giri, M.D.², Blanche P. Alter, M.D., M.P.H.², and Edward W. Cowen, M.D., M.H.Sc.¹

¹Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

²Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

Keywords

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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 (Figure 1). At age 1 year he developed oral leukoplakia and esophageal strictures requiring multiple dilations. By age 3 he developed thrombocytopenia which progressed to multilineage bone marrow failure (BMF). At age 8 years he was started on treatment with oxymetholone for BMF. While mild anemia has persisted, he has not required blood transfusion since 6 weeks of age. Throughout his early childhood he had mild developmental delay and failure to thrive. He had been followed at the NIH since age 7 years.

Correspondence should be addressed to: Edward W. Cowen, MD, MHSc, Dermatology Branch, NCI, NIH, Bldg 10 Rm 12N240A, MSC 1908, 10 Center Dr, Bethesda, MD 20892-1908, cowene@mail.nih.gov, Tel: 301-480-7196, Fax: 301-480-7175.

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NOTE

Drs. Alter, Giri and Savage are leading authorities on dyskeratosis congenita and other inherited bone marrow failure syndromes. For more information on the NCI Inherited Bone Marrow Failure Syndrome protocol, visit www.marrowsfailure.cancer.gov. Clinicians can refer interested patients to the Inherited Bone Marrow Failure Syndromes Study Recruitment Office at 1-800-518-8474.

His dermatologic history was notable for skin dyspigmentation and nail dystrophy which 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 (URIs) and sinusitis despite antibiotic prophylaxis.

At the time of NIH evaluation, the patient was at the 25th percentile for both height and weight. 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, most prominent on the lateral neck, axillae, and medial thighs which had become more prominent throughout adolescence (Figure 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 finger and toenails that had also progressed over several years (Figure 3). There was loss of dermatoglyphics on all digits (Figure 4). His hands were xerotic with accentuation of skin lines, but there was no palmoplantar hyperkeratosis.

Significant diagnostic studies

Abnormal laboratory values at this visit included hemoglobin 9.8 g/dL (normal 13.7–17.5 g/dL), absolute neutrophil count 1100/μL (normal 1780–5380/μL), and platelets 21 K/μL (normal 161–347 K/μL). High density lipoprotein (HDL) cholesterol was 3 mg/dL (<40 mg/dL considered high risk) and triglycerides were 331 mg/dL (normal <150 mg/dL). Lymphocyte telomere length (measured at age 7) was significantly below the 1st percentile for age at 3.1 kb (normal for age 7 is 9.4 kb); the Z-score was –6.8, substantially below the lower limit of normal of –2.5 SD. Subsequent genetic testing revealed compound heterozygous mutations in the regulator of telomere elongation helicase 1 (*RTEL1*) gene.¹

Diagnosis

Hoyeraal-Hreidarsson (HH) syndrome, a variant of dyskeratosis congenita (DC, Online Mendelian Inheritance in Man #615190).

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 based on reports from

the early 1900s which focused on the dermatologic manifestations of the syndrome.²⁻⁴ While DC is rare, nearly 1000 cases have been reported which illustrate both the clinical and genetic diversity of the syndrome [Alter BP, unpublished data].

Mucocutaneous findings are among the earliest and most common manifestations of DC. Approximately 68% of DC patients manifest at least 2 features of the clinical triad.⁵ Additional mucocutaneous features of DC, based on a large cohort of 60 patients with the DC enrolled in a National Cancer Institute study (NCT-00027274), include epiphora (33%), loss of dermatoglyphics (30%), early grey 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 (MDS), and acute myeloid leukemia (AML).^{7,8} DC is also associated with a high risk of pulmonary fibrosis, as well as gastrointestinal, hepatic, genitourinary, ophthalmologic, and other clinical manifestations (Table I). DC displays variable penetrance; patients present with a spectrum of features, including some patients who appear clinically unaffected.

HH is a severe variant of DC, first described in 1970.⁹⁻¹² Defining features of HH include IUGR, microcephaly, cerebellar hypoplasia, developmental delay, BMF and immunodeficiency, all of which may precede development of DC clinical triad features. Patients with HH typically develop BMF within the first decade of life.¹³

A diagnosis of DC should be considered in patients manifesting features of the classic mucocutaneous triad. However, as mentioned, the complete triad is not seen in all patients and features may develop over time. The diagnosis of DC/TBD should also be considered in the setting of non-alcoholic liver fibrosis, idiopathic pulmonary fibrosis, aplastic anemia, AML, or early-onset head and neck or anogenital SCC.^{7,14} Telomere length measurement by multicolor flow cytometry and fluorescence *in situ* hybridization (flow-FISH) in leukocyte subsets is >90% sensitive and specific for DC.^{15,16}

Genetic testing may be employed after appropriate genetic counselling. A causative pathogenic variant is identified in 70–80% of patients with DC. Telomere length in leukocyte subsets aids in the diagnosis in the 20–30% of patients without an identifiable genetic cause.¹⁸ DC may be inherited as an autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XLR) trait, or may arise *de novo*. Pathogenic variants in at least 12 genes have been implicated in the pathogenesis of DC and related TBDs (Table II). Each gene has a role in the synthesis or maintenance of telomeres. Five of the 12 DC genes have been reported in patients with HH.¹³

Management of DC requires a multi-disciplinary approach and is determined by each patient's constellation of findings. Initial work-up is detailed in Table 1. BMF, the major cause of mortality, can be definitively treated with allogenic hematopoietic cell transplantation (HCT). If no donor is available or HCT is contraindicated, androgens (*e.g.*, oxymetholone, danazol) may be beneficial.^{17,18} Routine surveillance is an important

component of caring for individuals with DC as understanding the trajectory of the clinical manifestations can be useful in management. Complete blood counts (CBC) should be measured annually to screen for BMF, MDS, and hematologic malignancy. Annual pulmonary function tests (PFT) are indicated for all patients over 8 years old to screen for pulmonary fibrosis. Annual cancer screening by a dermatologist, otolaryngologist, and gynecologist, biannual dental examination, and monthly self-checks for head and neck SCC are also recommended.¹⁸ Lifestyle interventions include avoidance of sunlight, alcohol, and tobacco products.^{19,20}

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ABBREVIATIONS AND ACRONYMS

AD	autosomal dominant
AML	acute myelocytic anemia
AR	autosomal recessive
BMF	bone marrow failure
CBC	complete blood count
DC	dyskeratosis congenital
Flow-FISH	multicolor flow cytometry and fluorescence in situ hybridization
HCT	allogenic hematopoietic cell transplantation
HDL	high density lipoprotein
HH	Hoyeraal-Hreidarsson syndrome
IUGR	intrauterine growth restriction
MDS	myelodysplastic syndrome
NCI	National Cancer Institute
NIH	National Institutes of Health
PFT	pulmonary function test
RTEL1	regulator of telomere elongation helicase 1
SCC	squamous cell carcinoma
TBD	telomere biology disease

URI	upper respiratory infection
XLR	X-linked recessive

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KEY TEACHING POINTS

- Dyskeratosis congenita (DC) is a telomere biology disorder associated with bone marrow failure and the classic clinical triad of reticulate hyperpigmentation, nail dystrophy, and oral leukoplakia. Patients may not manifest all features of the triad, or may present with other mucocutaneous findings include epiphora, loss of dermatoglyphics, palmoplantar hyperkeratosis, early greying and/or hair loss, and hyperhidrosis.
- Hoyeraal-Hreidarsson syndrome is a severe variant of DC characterized by additional findings of intrauterine growth restriction, microcephaly, cerebellar hypoplasia, developmental delay, and immunodeficiency.
- DC may be suggested by detection of very short telomeres, and confirmed by genetic testing when positive. Early diagnosis aids in the initiation of lifestyle interventions, treatment of bone marrow failure, screening for malignancies, hematopoietic cell transplantation donor selection, and genetic counseling for family members.

Figure 1. Dyskeratosis Congenita. Cerebellar hypoplasia
Sagittal non-contrast T2-weighted MRI of the brain. Arrow indicates cerebellar volume loss.

Figure 2. Dyskeratosis Congenita. Skin pigmentation

Progressive reticulate pigmentation with hypopigmented macules at (a) 7 years and (b) 18 years of age.

Figure 3. Dyskeratosis Congenita. Progressive nail dystrophy
Micronychia at (a) 7 years of age and complete anonychia at (b) 18 years of age.

Figure 4. Dyskeratosis Congenita. Adermatoglyphia
Complete loss of dermatoglyphics on distal fingers.

Table I

Clinical manifestations of dyskeratosis congenita.

Organ system	Manifestations ^{5,6,18,21,22,23}	Initial work-up ¹⁸
Gastrointestinal	Esophageal stenosis, liver fibrosis	Clinical evaluation, baseline liver function tests
Genitourinary	Hypogonadism, urethral stenosis, anogenital SCC	Assessment for urethral stenosis (males), gynecologic examination starting at age 16 or when sexually active (females), endocrinology evaluation for hypogonadism
Hematologic	Progressive bone marrow failure, myelodysplastic syndrome, acute myelogenous leukemia	Clinical evaluation, baseline complete blood count, consider bone marrow aspirate/biopsy at diagnosis, HLA-typing in anticipation of possible hematopoietic cell transplant
Neurologic	Developmental delay, microcephaly	Clinical evaluation, consider brain MRI
Ophthalmologic	Epiphora, blepharitis, abnormal eyelashes	Ophthalmologic examination
Oral	Oral leukoplakia, head/neck SCC, periodontal disease, taurodontism, short tooth roots	Baseline oral evaluation for leukoplakia and head/neck SCC
Orthopedic	Short stature, osteoporosis, avascular necrosis of the hips and shoulders	Consider baseline bone mineral density scan
Pulmonary	Pulmonary fibrosis, pulmonary arteriovenous malformations	Baseline pulmonary function tests, consider bubble echocardiography
Skin, hair, and nails	Reticulate pigmentation, nail dystrophy, adermatoglyphia, palmoplantar hyperkeratosis, hyperhidrosis, premature greying, hair loss (scalp and/or eyelashes)	Baseline dermatologic exam

Table II
Genetic heterogeneity of dyskeratosis congenita

Genes are listed in approximate descending order of frequency. Around 30% of DC patients have an unknown genetic cause.

Gene name	Symbol	Inheritance
Dyskerin pseudouridine synthase 1 ^{a,b}	<i>DKC1</i>	XLR
Telomerase RNA component ^b	<i>TERC</i>	AD
TRF1 interacting nuclear factor 2 ^{a,b}	<i>TINF2</i>	AD, <i>de novo</i> ^c
Telomerase reverse transcriptase ^{a,b}	<i>TERT</i>	AD, AR
NOP10 ribonucleoprotein	<i>NOP10</i>	AR
NHP2 ribonucleoprotein	<i>NHP2</i>	AR
CST telomere replication complex component 1	<i>CTC1</i>	AR
Regulator of telomere elongation helicase 1 ^{a,b}	<i>RTEL1</i>	AD, AR
Shelterin complex subunit and telomerase recruitment factor	<i>ACD</i>	AD, AR
Poly(A)-specific ribonuclease ^{a,b}	<i>PARN</i>	AR
WD repeat containing antisense to TP53	<i>WRAP53</i>	AR
Nuclear assembly factor 1 ribonucleoprotein ^b	<i>NAF1</i>	AD

^a Gene has also been implicated in the pathogenesis of HHS

^b Gene associated with pulmonary fibrosis, emphysema and telomere biology defect.

^c *De novo* occurrence of pathogenic variants in any DC gene may occur, although the majority reported, to date, have occurred in *TINF2*.