Evaluation and Management of Hematopoietic Failure in Dyskeratosis Congenita

Suneet Agarwal, MD, PhD

KEYWORDS

• Dyskeratosis congenita • Telomeres • Bone marrow failure
• Bone marrow transplantation • Aplastic anemia

KEY POINTS

- Genetic discovery in the rare inherited bone marrow failure syndrome dyskeratosis congenita (DC) has revealed a spectrum of diseases caused by mutations in genes regulating telomere maintenance.
- Defects in telomere maintenance provide a molecular framework for understanding hematopoietic stem cell failure in DC.
- Timely diagnosis of an underlying telomere biology disorder greatly affects patient management and is facilitated by telomere length testing and genetic testing.
- Prospective trials and coordinated efforts are driving therapeutic advancements for hematopoietic failure in DC.

INTRODUCTION

Dyskeratosis congenita (DC) is a rare, inherited bone marrow failure (BMF) syndrome characterized by variable manifestations and ages of onset, and predisposition to cancer. Genetic discoveries in the past 20 years have revealed DC as one of a spectrum of diseases caused by mutations in genes regulating telomere maintenance, collectively referred to here as telomere biology disorders (TBDs). Hematologic disease is a frequent finding in patients with DC and in children presenting with TBD. Timely diagnosis of an underlying TBD in patients with BMF affects treatment and has been facilitated by increased awareness and availability of diagnostic tests in recent years. This article summarizes the pathophysiology, evaluation, and management of hematopoietic failure in patients with DC/TBD.

Division of Hematology/Oncology, Harvard Medical School, Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston Children's Hospital, 1 Blackfan Circle, Karp 07214, Boston, MA 02115, USA
E-mail address: suneet.agarwal@childrens.harvard.edu

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A SPECTRUM OF TELOMERE DISEASES

DC in its classic form was described more than 100 years ago and is characterized by manifestations regarded as the diagnostic triad of reticular skin pigmentation abnormalities, oral leukoplakia, and dystrophic nails. These symptoms are now recognized as the outward manifestations of a systemic degenerative disease with myriad disorders emerging variably over the lifespan.[1] Hematologic disease is frequent: clinically significant BMF manifested in 50% of patients with DC by age 50 year in one prospective cohort, whereas 90% of patients with DC developed at least a single lineage cytopenia by the fourth decade of life in a registry study.[2,3] Patients with DC have increased risks of myelodysplastic syndrome (MDS) (>500 times) and acute myeloid leukemia (AML) (~73 times) compared with the general population.[4] The elucidation of gene mutations in classic DC led to the discovery of a broad and variable spectrum of disease, affecting individuals of all ages.[5,6] Early-onset, multisystem disorders manifesting as Hoyeraal-Hreidarsson syndrome, Revesz syndrome, or Coats plus disease are caused by mutations in genes also disrupted in patients presenting with classic DC.[7–10] In contrast, some patients without overt syndromic features diagnosed in childhood or adulthood with idiopathic aplastic anemia or familial MDS/AML carry germline mutations in the same telomere biology genes implicated in DC.[11–14] Still other patients with TBDs may remain asymptomatic from a hematologic standpoint throughout life, but present in the fifth to seventh decades of life with progressive and ultimately fatal hepatic or pulmonary fibrosis.[15,16] An increasing awareness of the highly variable presentation of TBD and the availability of clinically validated telomere length and genetic testing have led to refined estimates of the rarity of TBD. Although early-onset phenotypes with multisystem disease such as DC are generally said to affect ~1 in 1 million children, the prevalence of the broader spectrum of TBD that includes adults with late-onset manifestations may be 10 to 100 times higher.[17] In these individuals, recognizing subtle hematologic defects in the absence of overt symptoms can have important clinical consequences, such as anticipating complications of medical therapy for other TBD-associated disorders (eg, organ transplant for lung or liver disease), and assessing their suitability as bone marrow donors for affected family members.[18,19]

TELOMERES IN STEM CELL SELF-RENEWAL

Telomeres are repetitive protein-DNA structures that protect the ends of chromosomes (**Fig. 1**). Hundreds to thousands of copies of the hexanucleotide repeat TTAGGG are complexed with shelterin proteins (TRF1, TRF2, RAP1, TIN2, POT1, TPP1) to prevent the recognition of free DNA ends as double-stranded breaks. The ends of linear DNA cannot be replicated by DNA polymerase, and therefore telomere length decreases with each cell cycle. At a critically short telomere length, senescence is triggered and cells stop dividing.[20,21] Adult self-renewing cells such as hematopoietic stem cells (HSCs) counteract telomere-associated senescence by activating telomerase (encoded by the *TERT* gene), a ribonucleoprotein that replaces hexanucleotide repeats by reverse transcription of an RNA template (encoded by the *TERC* gene). The balance of replication-associated telomere attrition and telomerase-mediated repeat addition is an important determinant of stem cell self-renewal capacity and therefore tissue regenerative capacity throughout the lifespan. Telomere length can be considered an endowment from a tissue-specific stem cell that determines the number of times its telomerase-negative, differentiated progeny can divide.

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