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Case Presentation

Dyskeratosis Congenita

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Abstract

Importance: Dyskeratosis congenita is a rare disorder that often leads to early death owing to a variety of complications and associated disorders. Early diagnosis and intervention is important in care for patients affected by this disease.

Observations: We describe a patient with dyskeratosis congenita (DC) in a child. Our patient had a 3-year history of transaminitis that was felt to be the result of biopsy proven progressive fibrosis of the liver beginning at age 3. He was referred to the dermatology department because of a chronic, evolving eruption with the hope of establishing a unifying diagnosis. Further examination revealed dystrophic nails, numerous dental caries, and blepharitis. Chromosomal analysis on leukocytes showed significant telomere shortening consistent with DC.

Conclusions and Relevance: Early recognition and long term care is important in patients with DC because of their propensity to develop malignancy, hematologic abnormalities, and infection. Better understanding of this disease may lead to insights into other disorders associated with abnormal telomere maintenance.

Introduction

Dyskeratosis congenita (DC) is a rare genetic disorder affecting 1:1,000,000 people. Classically a clinical diagnosis is made by the presence of the mucocutaneous triad of dystrophic nails, reticular skin pigmentation and oral leukoplakia. It usually presents within the first decade of life, with 80% of classical DC cases progressing to bone marrow failure by age 30. Consequently, cytopenias of different cell lines leave affected patients susceptible to infection and hemorrhage [1-5]. However, advances in the field of genetics have revealed DC to be a genetically and phenotypically heterogeneous disorder caused by de novo or inherited mutations in genes requisite to telomere maintenance. Furthermore, disease transmission has been described as X-linked, autosomal dominant, or autosomal recessive with variable penetrance [1,2,4-6]. As such, the diagnostic criteria have expanded to include combinations of the classic mucocutaneous triad and bone marrow failure with predisposition to malignancy and a variety of neurological, pulmonary, dental, and gastrointestinal anomalies associated with defective telomere maintenance [1-5,7]. The multiple modes of genetic transmission, phenotypic diversity, and variable clinical progression of DC can make diagnosis quite challenging.

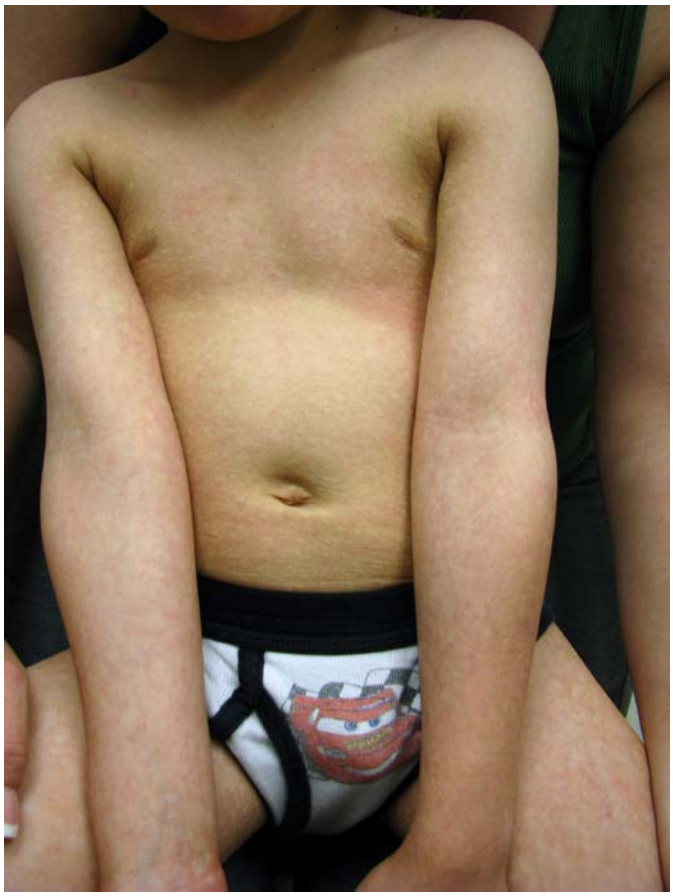
Herein, we describe DC in a child with a 3-year history of transaminitis, which was felt to be the result of biopsy proven progressive fibrosis of the liver beginning at age 3.

Case synopsis

A 6-year-old boy was referred to dermatology for evaluation of a chronic, evolving, reticulated eruption distributed diffusely over his body. The rash had been present for several years and had progressively worsened. The patient also had a history of thin, dystrophic nails on the bilateral hands and feet. Previous skin biopsies had been performed at an outside institution and were read as a non-diagnostic dermatitis.

His past medical history was significant for a 3-year history of transaminitis, related to progressive hepatic fibrosis of unknown etiology, and a bicuspid aortic valve that was discovered on a trans-thoracic echocardiogram performed to rule out hepatopulmonary disease. He also had mild asthma, recurrent episodes of blepharitis, dental carries, and a recent evolving anemia. The patient's parents and half-brother were not affected by the aforementioned medical problems, but his mother, in her late 30s, was undergoing treatment for breast cancer.

On physical exam, the patient had a hyperkeratotic, soft grey, reticulated rash distributed over the chest, abdomen, back, shoulders, and proximal upper and lower extremities (Figure 1). All 20 nails were thin with linear ridging; there was proximal nail fold pterygia of some nails (Figure 2). The palms and soles were pink and hyperkeratotic with some fissuring but without evidence of hyperhidrosis. There was mild periocular erythema and blepharitis without obvious conjunctivitis or defect in the lacrimal duct. The patient's oral exam showed carious teeth with numerous crowns and fillings and atrophic scars along the alveolar ridge of the last molars on the bilateral lower jaw without evidence of leukoplakia.



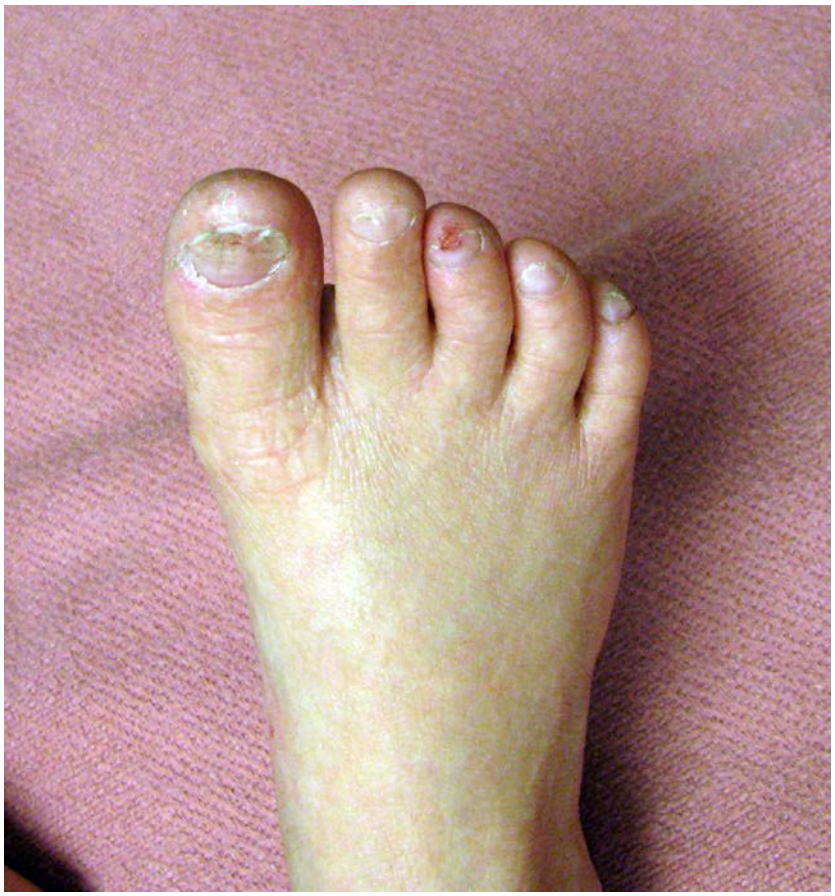


Figure 1. Diffuse, reticulated eruption on trunk and extremities.

Figure 2. Dystrophic toenails

The clinical presentation of grey reticulated skin eruption, dystrophic nails, and dental caries in conjunction with anemia raised suspicion for DC. The direct association with idiopathic hepatic fibrosis prompted review of the relevant literature, which pointed more clearly to this diagnosis. Chromosomal studies done by Repeat Diagnostics Inc. on leukocytes isolated from whole blood showed the patient had telomeres that were less than 1% the expected length in lymphocytes and granulocytes, consistent with DC (Table 1 and Figure 3).

Lymphocytes			Granulocytes			CD45RA+ (Naïve T)			CD45RA- (Memory T)			CD20+ (B Cells)			CD57+ (NK Cells)		
MTL	MTLN	INT	MTL	MTLN	INT	MTL	MTLN	INT	MTL	MTLN	INT	MTL	MTLN	INT	MTL	MTLN	INT
(kb)	(kb)		(kb)	(kb)		(kb)	(kb)		(kb)	(kb)		(kb)	(kb)		(kb)	(kb)	
7.3	9.5	VL	**7.2**	10.0	VL	**7.3**	9.7	L	**6.9**	8.8	L	**7.7**	9.6	L	**6.6**	9.5	L

MTL = Patient Median Telomere Length
MTLN = Normal MTL at age (50th percentile)
INT = Telomere length interpretation

VH = Very High (≥ 99 percentile)
H = High (≥ 90 and < 99 percentile)
N = Normal (≥ 10 and < 90 percentile)
L = Low (≥ 1 and < 10 percentile)
VL = Very Low (< 1 percemtile)

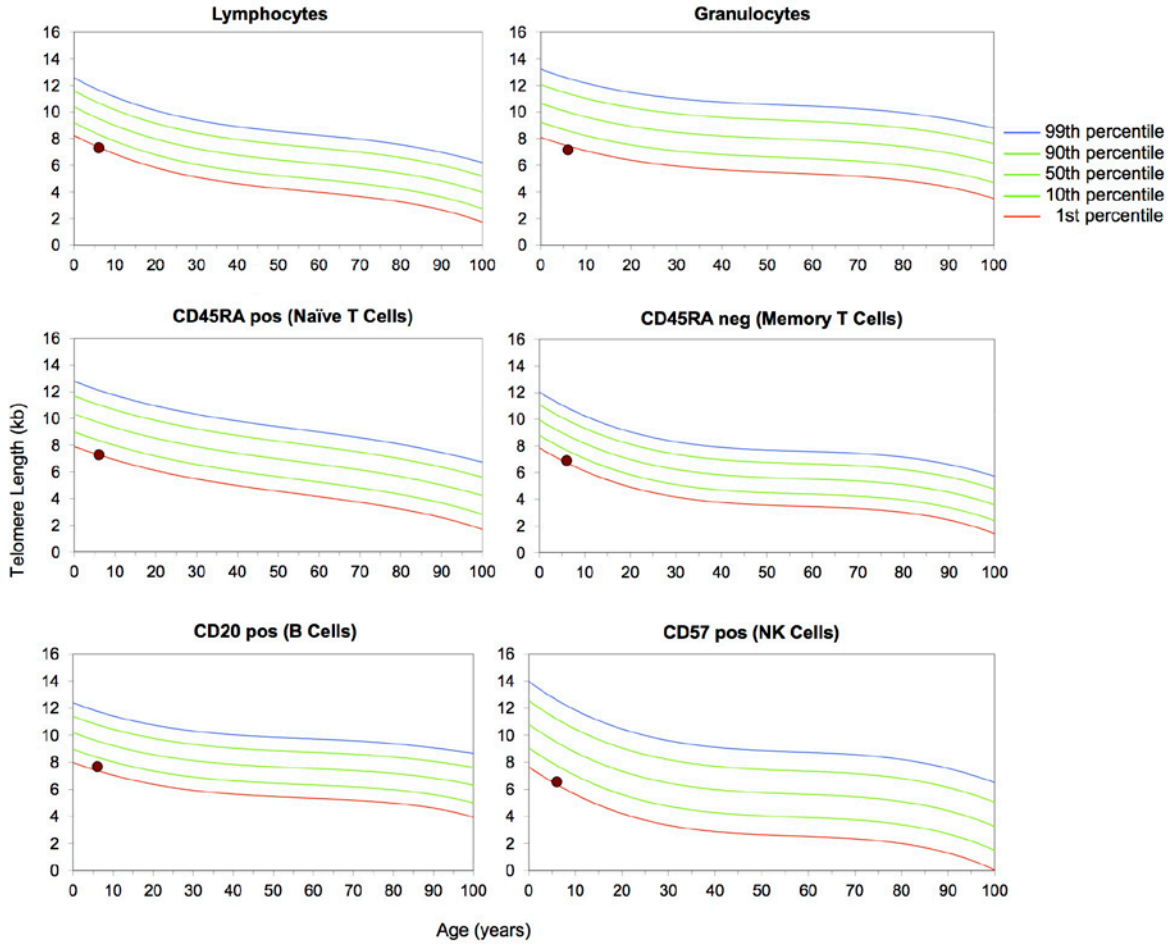


Figure 3. Plot of telomere length in various cell populations tested

Table 1. Telomere length measurements: All values are expressed in kilo base pairs (kb).

Lymphocytes		
MTL	**MTLN**	**INT**
7.3	9.5	*VL*

Granulocytes		
MTL	**MTLN**	**INT**
7.2	10	*VL*

CD45RA+		
MTL	**MTLN**	**INT**
7.3	9.7	*L*

CD45RA-		
MTL	**MTLN**	**INT**
6.9	8.8	*L*

CD20+		
MTL	**MTLN**	**INT**
7.7	9.6	*L*

CD57+		
MTL	**MTLN**	**INT**
6.6	9.5	*L*

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N = Normal (≥ 10 and < 90 percentile)
L = Low (≥ 1 and < 10 percentile)
VL = Very Low (< 1 percentile)

Comment

In the early 1900's, DC was described as a genetic condition characterized by the mucocutaneous triad of abnormal reticulated skin pigmentation, dystrophic nails, and oral leukoplakia, usually presenting within the first decade of life [2]. It was soon realized that affected individuals often experienced bone marrow failure by age 30 placing patients at increased risk of infection and bleeding disorders, now recognized as the primary cause of mortality in DC patients [2, 4, 5, 7]. Because of this truly multi-system disease process, DC patients are often faced with a number of other somatic ailments including increased risk of malignancy, pulmonary fibrosis, cerebellar hypoplasia, conjunctivitis, blepharitis, and gastrointestinal complications including esophageal strictures and cirrhosis [2, 4, 5, 7]. Genetic studies have found DC to represent a phenotypically diverse family of diseases caused by defects in the genes responsible for telomere maintenance [1-3, 6, 7].

Telomeres are structures composed of DNA and protein that protect the ends of chromosomes. Each telomere consists of a series of TTAGGG repeats bound by a protein cap, shelterin [2-4, 6]. Telomeres protect the structural integrity of chromosomes by preventing the ends of chromosomes from being recognized as breaks in DNA, without which chromosomes are at increased risk of breakage and fusion with other chromosomes. Thus, cells are predisposed to premature senescence and malignant transformation [2, 3, 6]. Studies have shown that over the course of many cell replications, telomere length decreases, which is thought to be a major factor for the increased incidence of cancer with increasing age. However, individuals with DC have telomere lengths <1% the expected length compared to age-matched controls; this is likely responsible for the 11-fold increase in cancer among DC patients [1-3, 5, 6].

The first gene associated with DC, *DKC1* on Xq28 encoding a component of telomerase called dyskerin, was identified in 1986 [5]. Further characterization of patients with X-linked DC showed that the same mutation can have a highly variable presentation. Although more common in males, dyskerin mutations can also affect females. Since 1986, genetic mutations have been identified in 8 genes of the telomere maintenance complex including telomerase reverse transcriptase (*TERT*) and the RNA component of telomerase (*TERC*) [1, 2, 5, 7]. Reports have characterized de novo mutations in addition to familial mutations that segregate in an X-linked, autosomal dominant or autosomal recessive fashion with variable penetrance. The commonality among all mutations is that they adversely affect telomere length [2, 3, 6]. Consequently, screening patients for specific mutations has been supplanted by telomere flow-FISH assays that combine flow cytometry and fluorescence in-situ hybridization to evaluate telomere length. This is a sensitive and specific method that identifies more than 90% of cases of DC [6].

It is estimated that approximately 7% of DC patients will be affected by hepatic disease and this is often blamed on transfusion-associated hemochromatosis related to the treatment of anemia [8]. Studies also suggest that the livers of affected individuals are more susceptible to insults such as alcohol and smoking than the general population [2]. Hepatic disease has also been characterized in DC patients after bone marrow transplantation for aplastic anemia [8]. In 2008 a study of 150 individuals with telomerase dysfunction and interstitial pneumonia identified four patients who also had cryptogenic cirrhosis diagnosed later in life [9]. Furthermore, Calado and colleagues conducted a study associating *TERT* and *TERC* mutations and hepatic disease; however, the youngest individual in that study was 20 years of age [8].

As the spectrum of disease in DC patients is broad, follow-up and treatment protocols vary widely. However, early diagnosis and referral to specialty care is important in DC patients given their proclivity toward aplastic anemia and its complications, increased risk of cancer, pulmonary fibrosis, and dental caries.. Our patient was initially brought to medical attention for transaminitis that led to the diagnosis of progressive liver fibrosis at age 3. He was seen by a dermatologist early in life because of his chronic skin eruption. However, the eruption continued to worsen and evolve until his diagnosis at age 6, at which point he also had an evolving anemia and extensive dental caries. Although more investigation is warranted, we feel that a unifying diagnosis of DC should be considered in children with hepatic dysfunction and chronic rash to facilitate early multi-disciplinary care in DC patients. Our patient is now being followed at the National Institute of Health where there is active research to better classify and understand the diseases of telomere maintenance.

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