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Authors
Allenspach, Eric J
Bellodi, Cristian
Jeong, David
et al.

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Common Variable Immunodeficiency as the initial presentation of Dyskeratosis Congenita

Eric J. Allenspach, MD, PhD[a], **Cristian Bellodi, PhD**[b], **David Jeong, MD**[c], **Noam Kopmar**[b], **Tomoka Nakamura**[d], **Hans D. Ochs, MD**[a], **Davide Ruggero, PhD**[b], **Suzanne Skoda-Smith, MD**[a], **Akiko Shimamura, MD, PhD**[a,d], and **Troy R. Torgerson, MD, PhD**[a]

[a]Department of Pediatrics, University of Washington and Seattle Children's Hospital, Seattle, Washington [b]School of Medicine and Department of Urology, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California [c]Institute for Asthma and Allergy, P.C. Chevy Chase, Maryland [d]Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Children's Hospital, Seattle, WA, USA

Short Summary

We present a case highlighting the clinical overlap between Common Variable Immunodeficiency (CVID) and Dyskeratosis Congenita (DC). It demonstrates that DC may initially present as an isolated humoral immunodeficiency resembling CVID.

To the Editor

Common Variable Immunodeficiency (CVID) is a heterogenous immunodeficiency characterized by abnormal antibody responses and frequent sinopulmonary infections. Approximately 20% of patients also develop autoimmune or lymphoproliferative symptoms. At present, only a fraction of cases have identifiable genetic defects so CVID remains largely a diagnosis of exclusion (1). We present a patient with childhood-onset humoral immunodeficiency in which the common causes of hypogammaglobulinemia in a young male were excluded. He was therefore diagnosed with CVID. Over time, his clinical course evolved to include aspects of bone marrow failure, leading to a diagnosis of Dyskerytosis Congenita (DC) in early adulthood.

DC is a rare, inherited bone marrow failure syndrome (IBMFS) characterized by shortened telomeres, which are nucleoprotein complexes at the ends of chromosomes, necessary for their integrity, function, and replication (2). The clinical triad of DC (present in ~85% of cases) includes abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia (3). Other features may include malignancy, short stature, pulmonary fibrosis, dental abnormalities, esophageal stricture, and immune deficiency. Although immune defects are often described in pediatric cases, they are typically accompanied by short stature, microcephaly and bone marrow failure with concurrent anemia or thrombocytopenia (4–6).

Corresponding Author: Troy R. Torgerson, MD, PhD, Seattle Children's Research Institute, Center for Immunity and Immunotherapies, 1900 9th Ave., C9S-7, Seattle, WA 98101-1304, troy.torgerson@seattlechildrens.org, Phone: 206-987-7450, Fax: 206-987-7310.

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Our patient with DC uniquely presented with an isolated antibody deficiency for much of his childhood.

The patient was a healthy, full-term, nonconsanguineous infant. His first acute otitis media (AOM) occurred at 4 months of age followed by 4–6 more episodes over the next year, ultimately requiring myringotomy tube placement. At 2 years, he had an uncomplicated varicella infection. At 4 years, he developed a treatment refractory pneumonia, bilateral otitis media, oral thrush, and hepatosplenomegaly. Mild clubbing was also noted. He was normocephalic with height and weight in the 45th and 75th percentile, respectively. An immunologic evaluation at this point revealed low IgG (42 mg/dL), IgA (7 mg/dL), and IgM (7 mg/dL). Complete blood count revealed normal cellularity in all lineages (Table I). Lymphocyte analysis showed 85% T cells with an inverted CD4/CD8 ratio, 10% B cells and 5% NK cells. T cell proliferative responses to tetanus and the mitogen phytohemagglutinin (PHA) were normal.

Immune responses to specific antigen challenge were measured by immunization with the T cell dependent neoantigen, bacteriophage ΦX174. His responses were severely depressed and demonstrated poor T cell dependent amplification after both the primary and secondary immunizations (Figure 1A). There was no measureable class-switching of antigen-specific antibodies from IgM to IgG. Intravenous immunoglobulin (IVIG) therapy was begun at age 4, but sinopulmonary infections continued.

Bronchiectasis was diagnosed at the age of 10. Sweat chloride testing was negative. At 12, his lung function worsened requiring hospitalization every 3 months for IV antibiotics and pulmonary toilet. At 14, he was noted to have pansinusitis, gingivitis, dental caries, frequent diarrhea, abdominal pain and dysphagia. Gastrointestinal biopsies showed histologic pan-inflammation in the gastric, duodenal, terminal ileal, and colonic mucosa. He was started on mesalamine for suspected enteritis and iron supplements for a mild microcytic anemia (Table I). By the age of 15, he developed B and NK cell deficiency (Table I). He continued to require frequent hospital admissions for sinopulmonary infections.

At age 20, he developed worsening anemia (hemoglobin 3.1 g/dL; low folate (4.7 nmol/L)) and became transfusion-dependent. Coombs testing (indirect and direct) was negative and the anemia was unresponsive to IVIG treatment. A bone marrow biopsy was normocellular but was felt to be consistent with pure red cell aplasia. No viral inclusion bodies were identified and no Parvovirus was detected. He continued to require frequent blood transfusions. At 21, he developed dental fistulas and jaw swelling requiring numerous extractions and abscess drainage. Leukoplakia was noted for the first time. He also had profuse, non-bloody diarrhea but an extensive infectious workup was negative. Colon biopsy showed massive apoptosis of crypt cells, which has been described in DC.

Given his symptoms, telomere length was evaluated by flow cytometry *in situ* hybridization and found to be very short (<1%) in total lymphocytes (Figure 1B) and in naive (CD45RA+/CD20−) and memory (CD45RA−/CD20−) T lymphocytes (data not shown) (7). There were insufficient numbers of CD20+ B cells for telomere analysis. Genetic testing for DC was initiated.

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Seven unique gene defects have been associated with DC: *DKC1* (X-linked); *NOP10*, *TCAB1*, and *NHP2* (autosomal recessive); *TERT*, *TERC*, and *TINF2* (Autosomal dominant). Mutations in these genes account for only 50% of all patients with the clinical phenotype of DC. Gene analysis (excluding *TCAB1*) revealed a mutation in exon 15 of the *DKC1* gene (c. 1512_1514 dupGAA). The duplication adds a lysine residue to a polylysine tract at the C-terminus of the protein. Western blotting using a lymphoblast cell line from our patient demonstrated reduced dyskerin protein levels compared to control cells (Figure 1C & D). Decreased dyskerin protein levels have independently been associated with telomere shortening in X-linked DC (8).

Despite IVIG and antibiotic prophylaxis, the patient had progressive chronic lung disease. Chronic interstitial pneumonitis and progressive pulmonary fibrosis is reported in 8–20% of patients with DC and likely contributed to the lung disease and unresponsiveness to IVIG in this case (9,10). The bone marrow failure also progressed so low dose oxymetholone (0.5–1mg/kg) was initiated but stopped after only 2 weeks due to liver toxicity and extreme sensitivity to the steroid. He underwent bone marrow transplantation using a reduced intensity conditioning regimen and a matched unrelated donor. Unfortunately, he died of overwhelming bacterial (*Psuedomonas aeruginosa*) and fungal (*Rhizopus zygomyces*) pneumonia and sepsis 18 days post-transplant.

A retrospective review of the patient's chart revealed a report of denuded tongue epithelium and white cobble-stoned palmar epithelium at age 5, nail dystrophy at age 6, and esophageal strictures at age 8 that were effectively treated. None of these features were persistently or recurrently noted. In retrospect however, some of these findings are rare in CVID and although subtle, were likely early manifestations of DC.

Patients with DC frequently have early immunological abnormalities, including decreased B and NK cells, dysgammaglobulinemia and frequent infections. The immune defects have typically been reported in the setting of other characteristic clinical symptoms of DC (4–6) but as this case illustrates, they may precede these symptoms. This case demonstrates that DC can present with a significant humoral immunodeficiency and that in the absence of other obvious clinical manifestations, a diagnosis of CVID can lead to premature diagnostic closure without early screening for IBMFS.

References

1. Orange JS, Glessner JT, Resnick E, Sullivan KE, Lucas M, Ferry B, et al. Genome- wide association identifies diverse causes of common variable immunodeficiency. J Allergy Clin Immunol. 2011; 127:1360–7. [PubMed: 21497890]
2. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev. 2010; 24:101–22. [PubMed: 20417588]
3. Kirwin M, Dokal I. Dyskeratosis congenita: a genetic disorder of many faces. Clin Genet. 2008; 73:103–12. [PubMed: 18005359]
4. Jyonouchi S, Forbes L, Ruchelli E, Sullivan KE. Dyskeratosis congenita: a combined immunodeficiency with broad clinical spectrum – a single-center pediatric experience. Pediatr Allergy Immunol. 2011; 22:313–9. [PubMed: 21284747]

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5. Khan S, Pereira J, Darbyshire PJ, Holding S, Doré PC, Sewell WA, et al. Do ribosomopathies explain some cases of common variable immunodeficiency? Clin Exp Immunol. 2010; 163:96–103. [PubMed: 21062271]

6. Knudson M, Kulkarni S, Ballas ZK, Bessler M, Goldman F. Association of immune abnormalities with telomere shortening in autosomal-dominant dyskeratosis congenita. Blood. 2005; 105:683–8.

7. Alter BP, Baerlocher GM, Savage SA, Chanock SJ, Weksler BB, Willner JP, et al. Very short telomere length by flow fluorescence in situ hybridization identifies patients with dyskeratosis congenita. Blood. 2007; 110:1439–47. [PubMed: 17468339]

8. Parry EM, Alder JK, Lee SS, Phillips JA 3rd, Loyd JE, Duggal P, et al. Decreased dyskerin levels as a mechanism of telomere shortening in X-linked dyskeratosis congenita. J Med Genet. 2011; 48:327–33. [PubMed: 21415081]

9. Dokal I. Dyskeratosis congenita in all its forms. Br J Haematol. 2000; 110:768–79. [PubMed: 11054058]

10. Giri N, Lee R, Faro A, Huddleston CB, White FV, Alter BP, et al. Lung transplantation for pulmonary fibrosis in dyskeratosis congenital: Case report and systemic literature review. BMC Blood Disorders. 2011; 11:3. [PubMed: 21676225]

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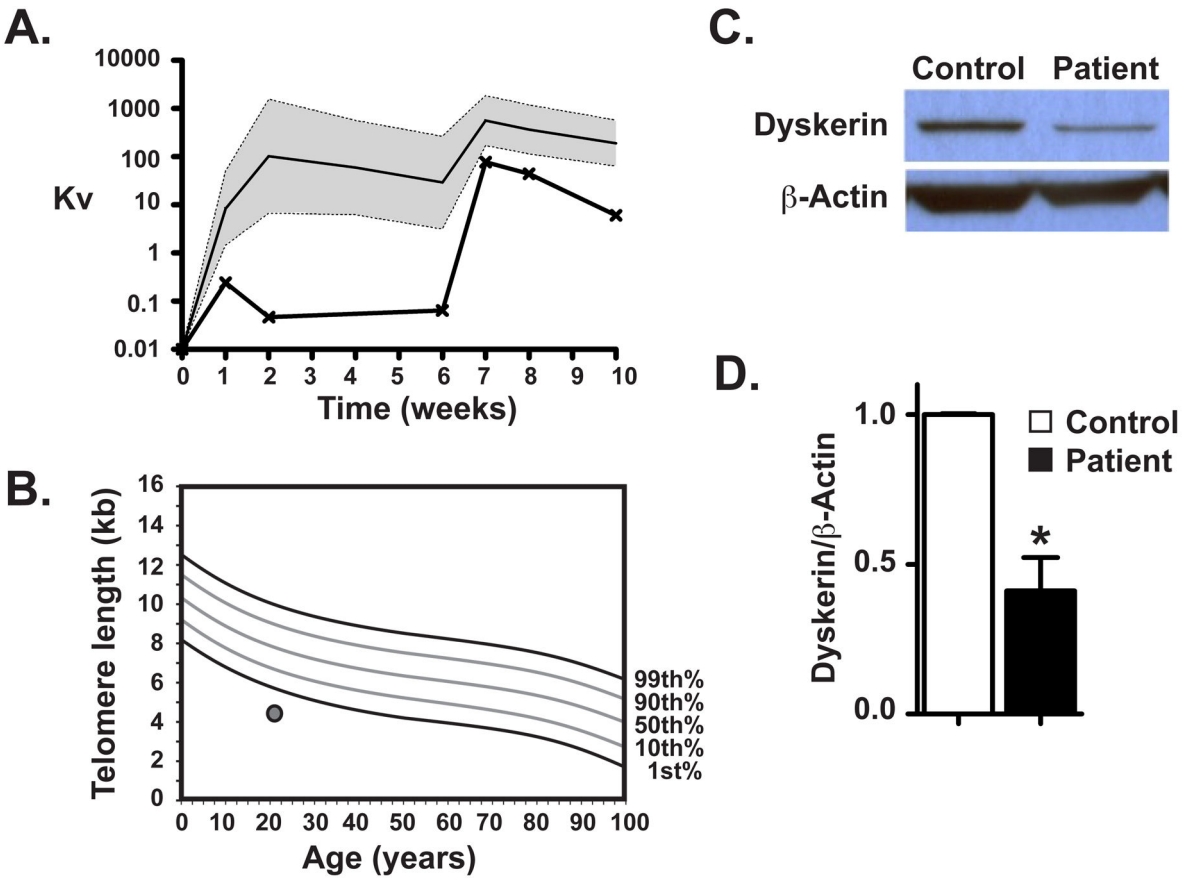

FIGURE 1.

A) Response to Bacteriophage Φ174 Immunization Primary and secondary immunizations were given at 0 and 6 weeks. The shaded area represents the geometric mean ± 2 SD for 54 normal control individuals. The patient's antibody responses (X-X) are significantly below 2 SD of the control cohort. No Ig class-switching was observed (data not shown). **B) Telomere shortening in total lymphocytes.** Average telomere length in the patient's total lymphocytes (filled circle) is markedly below the 1st percentile of that observed in normal individuals as measured by flow *in situ* hybridization (n=2; courtesy of Repeat Diagnostics) (7). **C & D) Reduced dyskerin expression in the patient's cells.** C) Western blot of dyskerin and β-actin protein expression in healthy control and patient lymphoblast cell lines. D) Densitometric analysis of relative dyskerin expression (dyskerin/beta-actin) ± SEM in two independent experiments is shown. Statistical analysis was performed using unpaired t-test * P<0.05.

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Table I

Hematological characteristics

Age (years)	**4**	**6**	**11**	**14**	**15**	**16**	**20**	**20**
WBC (10^3 cells/μL)	11.2	11.6	9.4	7.8	8.5		8	7.9
ANC (10^3 cells/μL)	5.04	5.56			5.01		2.24	
ALC (10^3 cells/μL)	4.81	4.75			2.63		4.8	
CD19+ B cells (cells/μL)	530				36		n.d.	
CD3+ T cells (cells/μL)	4094				2582		4464	
CD4/CD8 ratio	0.46				0.74		0.75	
CD56+ NK cells (cells/μL)	241				26		n.d.	
Platelets (10^3 cells/μL)	367		300	327	400		292	
Hemoglobin (g/dL)	12.6	12.8	11.4	11.1	10.6	10.2	6	3.1
MCV	78	75		65	64	70	98	

WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; MCV, mean corpuscular volume; n.d., none detected

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