

Letter to the Editor

Common variable immunodeficiency as the initial presentation of dyskeratosis congenita

To the Editor:

Common variable immunodeficiency (CVID) is a heterogeneous immunodeficiency characterized by abnormal antibody responses and frequent sinopulmonary infections. Approximately 20% of patients also have autoimmune or lymphoproliferative symptoms. At present, only a fraction of patients have identifiable genetic defects, and therefore CVID remains largely a diagnosis of exclusion.¹

We present a patient with childhood-onset humoral immunodeficiency in whom the common causes of hypogammaglobulinemia in a young male subject were excluded; therefore he was given a diagnosis of CVID. Over time, his clinical course evolved to include aspects of bone marrow failure, leading to a diagnosis of dyskeratosis congenita (DC) in early adulthood.

DC is a rare, inherited bone marrow failure syndrome 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 approximately 85% of cases) includes abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia.³ Other features can include malignancy, pulmonary fibrosis, dental abnormalities, and esophageal stricture. Although immune defects are often described in pediatric DC cases, they are typically accompanied by short stature, microcephaly, and bone marrow failure with concurrent anemia or thrombocytopenia.⁴⁻⁶ 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 episode of acute otitis media occurred at 4 months of age, followed by 4 to 6 more episodes over the next year. At 2 years, he had an uncomplicated varicella infection. At 4 years, he had 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 percentiles, respectively. An immunologic evaluation at this point revealed low IgG (42 mg/dL), IgA (7 mg/dL), and IgM (7 mg/dL) levels. 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% natural killer (NK) cells. T-cell proliferative responses to tetanus and the mitogen PHA were normal.

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

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

TABLE I. Hematologic characteristics

Age (y)	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	—	ND	—
CD3 ⁺ T cells (cells/μL)	4094	—	—	—	2582	—	4464	—
CD4/CD8 ratio	0.46	—	—	—	0.74	—	0.75	—
CD56 ⁺ NK cells (cells/μL)	241	—	—	—	26	—	ND	—
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	—

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

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

At age 20 years, he had worsening anemia (hemoglobin, 3.1 g/dL; low folate, 4.7 nmol/L) and became transfusion dependent. Results of Coombs testing (indirect and direct) were negative, and the anemia was unresponsive to IVIG treatment. A bone marrow biopsy specimen was normocellular but was believed 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 years of age, he had dental fistulas and jaw swelling, requiring numerous extractions and abscess drainage. Leukoplakia was noted for the first time. He also had profuse nonbloody diarrhea, but the result of an extensive infectious workup was negative. Colon biopsy showed massive apoptosis of crypt cells, which has been described in patients with DC.

Given his symptoms, telomere length was evaluated by using flow cytometry *in situ* hybridization and found to be very short (<1%) in total lymphocytes (Fig 1, B) 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.

Seven unique gene defects have been associated with DC: *DKC1* (X-linked); *NOPI0*, *TCAB1*, and *NHP2* (autosomal recessive); and *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 with a

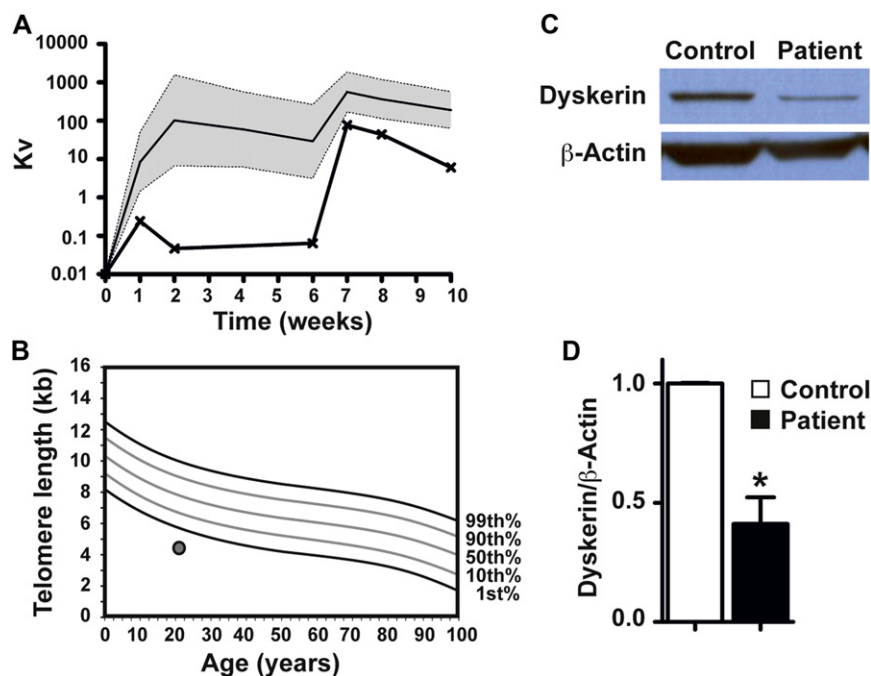


FIG 1. **A**, Response to bacteriophage Φ 174 immunization. Primary and secondary immunizations were administered at 0 and 6 weeks. The shaded area represents the geometric mean $\pm$ 2 SD for 54 healthy control subjects. The patient's antibody responses (X-X) are significantly less than 2 SDs of the control cohort. No immunoglobulin class-switching was observed (data not shown). **B**, Telomere shortening in total lymphocytes. Average telomere length in the patient's total lymphocytes (solid circle) is markedly less than the first percentile of that observed in healthy subjects, as measured by using flow *in situ* hybridization ($n = 2$; courtesy of Repeat Diagnostics). **C** and **D**, Reduced dyskerin expression in the patient's cells. Fig 1, C, Western blot of dyskerin and β -actin protein expression in lymphoblast cell lines from a healthy control subject and the patient. Fig 1, D, Densitometric analysis of relative dyskerin expression (dyskerin/ β -actin) $\pm$ SEM in 2 independent experiments is shown. Statistical analysis was performed with the unpaired *t* test: **P* < .05.

lymphoblast cell line from our patient demonstrated reduced dyskerin protein levels compared with control cells (Fig 1, C and D). Decreased dyskerin protein levels have independently been associated with telomere shortening in patients with X-linked DC,⁸ and polylysine tracts can be used for posttranslational protein modifications, but no direct mechanism has been identified yet to link this mutation to the decreased protein expression in the patient.

Despite IVIG and antibiotic prophylaxis, the patient had progressive chronic lung disease. Chronic interstitial pneumonitis and progressive pulmonary fibrosis is reported in 8% to 20% of patients with DC and likely contributed to the lung disease; it was unresponsiveness to IVIG in this case.^{9,10} The bone marrow failure also progressed, and therefore low-dose oxymetholone (0.5-1 mg/kg) was initiated but stopped after only 2 weeks because of 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 (*Pseudomonas aeruginosa*) and fungal (*Rhizopus zygomycetes*) pneumonia and sepsis 18 days after transplantation.

Patients with DC frequently have early immunologic abnormalities, including decreased B-cell and NK cell numbers, 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 shows, they can 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 inherited bone marrow failure syndrome.

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