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CASE REPORT

Reticulated pigmentary changes and Terry's nails in a patient with a TERT variant-associated telomere biology disorder

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Abstract

Telomere biology disorders (TBD) are a complex set of inherited illnesses characterized by short telomeres. Dyskeratosis congenita (DC), which is now considered a severe TBD phenotype, is characterized by reticulated pigmentary changes, nail dystrophy, premalignant oral leukoplakia, and systemic involvement. This case describes a 2-year-old female with reticulated pigmentary changes and Terry's nails who was found to have a TERT variant and short telomeres; she lacked other mucocutaneous and systemic features of TBD. This report describes a unique clinical presentation of TBD and highlights the importance of upholding suspicion for TBD in individuals with limited or subtle features of classic DC.

KEYWORDS

dyskeratosis congenita, leukonychia, reticulate pigmentary disorders, telomere biology disorders, Terry's nails

1 | INTRODUCTION

Telomere biology disorders (TBD) represent a heterogeneous group of conditions characterized by shortened telomeres due to germline variants in telomere-associated genes.[1] Although the condition was initially named dyskeratosis congenita (DC), advances in genomics and clinical telomere length testing has led to the identification of a spectrum of DC-related TBD, in which the umbrella term of TBD is now more preferred.[2] Classic clinical features includes a triad of reticulate hyperpigmentation, nail dystrophy, and oral leukoplakia. Individuals with TBD are also at increased risk of developing bone marrow failure, hematologic and solid organ malignancies, pulmonary fibrosis, hepatic cirrhosis, and various other manifestations.

2 | CASE REPORT

A healthy 2-year-old female was evaluated for asymptomatic pigmentary changes that had been present since birth. She was born at term, was otherwise healthy, and meeting developmental milestones. Her siblings did not have similar skin changes, but her mother had premature hair graying starting in her twenties. Examination of the patient's skin was notable for reticulated hyperpigmented and hypopigmented macules coalescing into patches on the neck, axillae, popliteal fossae, gluteal cleft, lower abdomen, and inguinal folds (Figure 1). There were no abnormal findings of the nails, oral mucosa, or palmoplantar skin on her initial visit. However, one year later, examination of her fingernails revealed new ground glass opacification across almost the entire nail, sparing a two-millimeter distal band of normal pink color, affecting all 10 nails (Figure 2). This was consistent with Terry's nails. There was also erythema on the distal and proximal interphalangeal joints.

The differential diagnosis was initially broad and included genetic reticulate pigmentary disorders such as TBD, Dowling-Degos disease, Galli-Galli disease, and dyschromatosis universalis hereditaria. Given the unique pattern of distribution and age of onset whole exome sequencing of the patient's blood was performed. This identified a variant of uncertain significance (VUS) in TERT (g.1294522A > G, c.479 T > C) (Table 1). Given the association of TERT variants with TBD, telomere length analysis from peripheral blood leukocytes was obtained. This revealed telomere lengths at or below the first percentile, diagnostic of a TBD (Figure 3). Her complete blood count and comprehensive metabolic panel, including liver function tests and albumin levels, were within normal ranges, and she was referred to hematology-oncology for guidance regarding

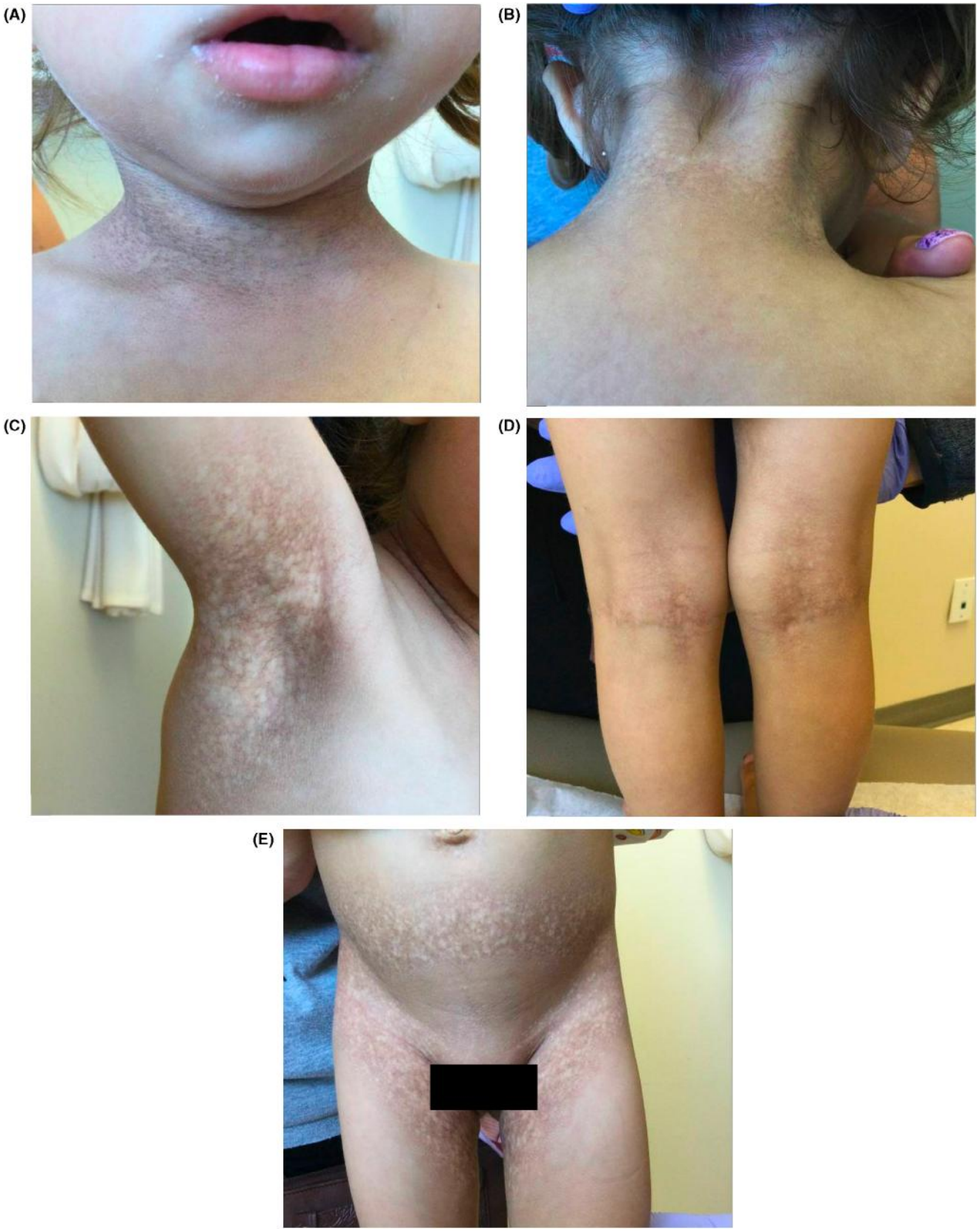

FIGURE 1 Reticulated hypopigmented and hyperpigmented macules coalescing into patches on the patient's (A) anterior neck, (B) posterior neck, (C) right axilla, (D) popliteal fossa, (E) lower abdomen and inguinal folds.

malignancy screening. She was also evaluated by genetics and both parents underwent genetic testing. Whole exome sequencing of her mother's blood revealed the same TERT variant, and telomere length analysis indicated that her mother's telomeres were shortened (Figure 4).

3 | DISCUSSION

Although reticulate dyspigmentation in TBD commonly arises within the first decade of life, only one prior report has described this skin finding to be present since birth.[3] The mechanism of telomere dysfunction resulting in pigmentary changes in TBD has not been identified. However, telomeres play a crucial role in protecting chromosome ends and ensuring genomic stability.[1] We postulate that dysfunction in these mechanisms may lead to abnormal and premature skin dyspigmentation. For example, mutations in the TERT gene that specifically alter the TERT protein in the skin, rather than in the blood or other tissues, lead to an increased occurrence of solar lentigines, which are indicative of aging skin.[4] Conversely, changes in the promoter of the TERT gene, which do not alter the protein structure but instead increase the transcription of the normal TERT protein, are associated with a higher risk of melanoma.[5]

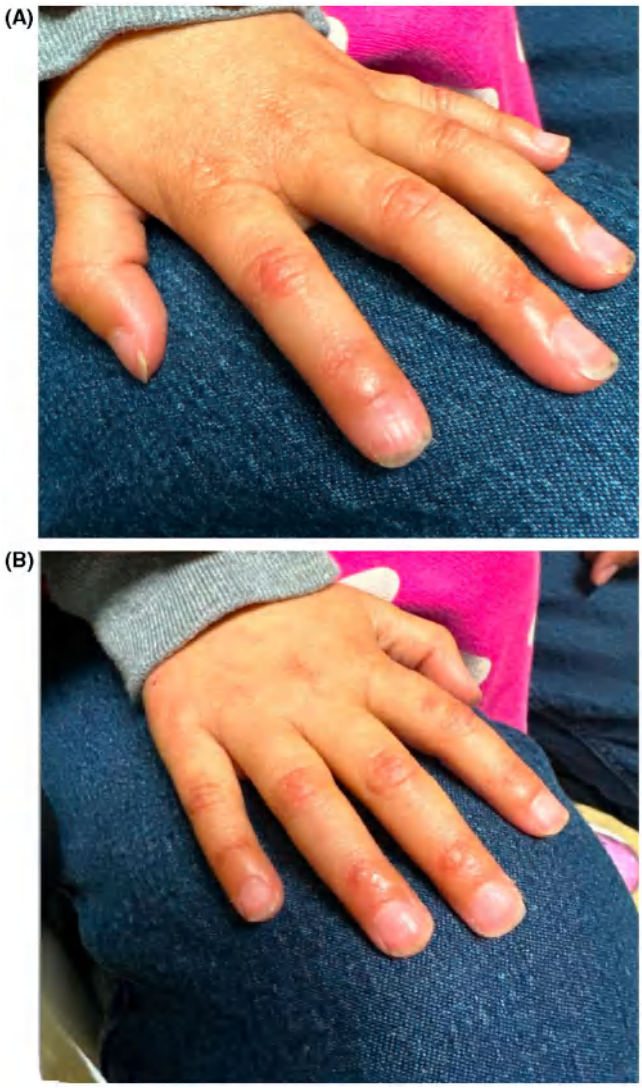

FIGURE 2 The patient's (A) left and (B) right hands exhibit a glass-like opacity covering most of the nail bed, except for a 2-mm distal band displaying a normal pink color.

Nail manifestations of TBD typically include atrophy, splitting, ridging, and complete absence of nails.[6] Interestingly, this case involves a patient with Terry's nails, a condition not previously associated with TBD. Terry's nails are characterized by proximal leukonychia or a ground glass-like appearance with a reddish or brown distal band covering less than 20% of the nail bed. Initially identified as a dependable physical examination finding in cirrhosis, Terry's nails have also been observed in cases of chronic renal failure, congestive heart failure, adult-onset diabetes mellitus, and normal aging.[7] Given that this patient's chemistry panel and liver function tests were normal, we postulate that her nail findings may represent premature aging associated with her TBD. This patient also exhibited erythema over her distal and proximal interphalangeal joints, resembling nailfold redness and Gottron papules; however, no other clinical signs of dermatomyositis were present including other skin manifestations, muscle weakness, or pulmonary symptoms. This patient's distinctive combination of congenital reticular skin pigmentation and Terry's nails underscores the broad spectrum of diverse phenotypes linked to TBD.

The inheritance patterns of TBD vary based on the specific gene variant, and can manifest as X-linked recessive, autosomal dominant, or autosomal recessive. Among 19 genes that have been associated with TBD, TERT variants are the most frequently reported.[6] TERT, or telomerase reverse transcriptase gene, encodes the catalytic subunit of telomerase. This enzyme is important for the addition of telomere repeats, which allows for maintenance of telomere length at the ends of chromosomes. Variants in TERT are typically inherited in an autosomal dominant pattern, with homozygotes or compound heterozygotes developing more severe disease.[8] Patients with TERT variants exhibit a low penetrance and variable clinical presentation ranging from the classic mucocutaneous triad to isolated aplastic anemia.[6,9]

Although the TERT variant this patient was found to have reported as a VUS, her clinical findings and telomere length studies confirm that this is likely a pathogenic variant affecting telomerase activity. Furthermore, the VUS identified in this case leads to a valine to alanine substitution in amino acid position 160 (V160A). This is located in the N-terminus, where mutations leading to alterations in TERT Q169 have been previously shown to decrease telomerase

TABLE 1 Whole exome sequencing showing a variant TERT.

Gene	Genomic change (hg19)	Zygosity	Coding change	Protein change
TERT	chr5:g.1294522A > G	Heterozygous	NM_198253.2:c.479 T > C	p.Val160Ala

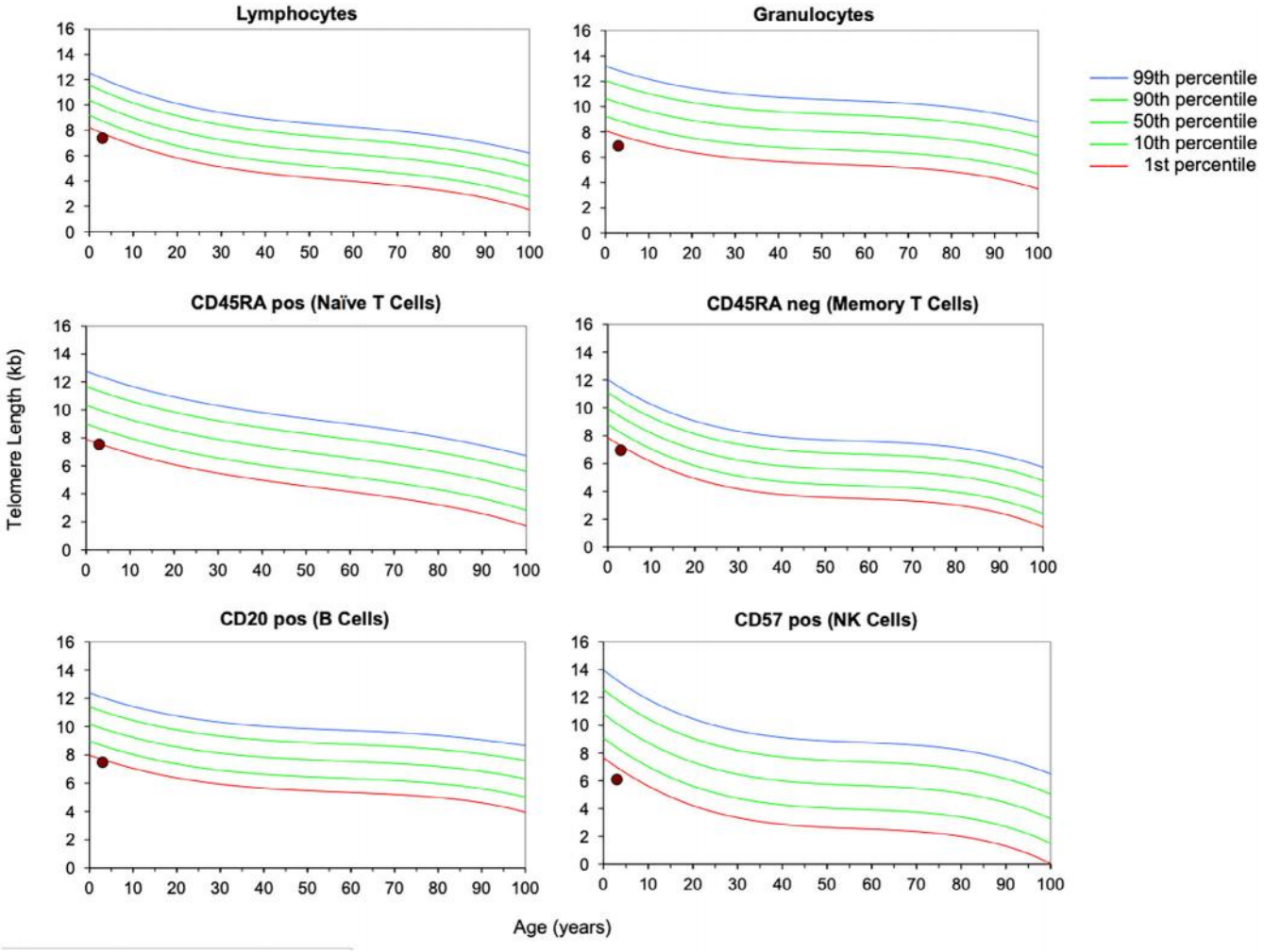

FIGURE 3 Telomere length analysis of the patient's peripheral blood.

activity due to its critical role in DNA primer binding.[10] Given the proximity of V160 to Q169, it is likely that this variant may also have a similar role.

Notably, the patient's mother carried the same TERT variant, but her only TBD-associated manifestation was premature hair graying. This can be attributed to the disease anticipation phenomenon, which is observed in patients with TERT variants. Disease anticipation is unique to autosomal dominant disorders and refers to a pattern in which a genetic condition becomes apparent earlier in life and has progressively more severe manifestations in successive generations. This is a result of shorter telomeres in subsequent generations, leading to a younger onset and greater severity of premature hair graying and other clinical manifestations.[11–13] Analysis of patients with de novo haploinsufficiency of TERT demonstrated that although heterozygous gene deletion leads to shorter telomeres within one generation, several generations must pass for telomeres to become short enough to be clinically apparent.[11] As a result, parents of affected patients may be asymptomatic carriers of the abnormal gene.

Recognizing and diagnosing TBD poses challenges due to their diverse presentations, contributing to its underdiagnosis. Additionally, the absence of established diagnostic criteria and the incomplete identification of all TBD-related gene variants further complicate diagnosis.[1] Current guidelines are limited to DC, which is only one condition within a spectrum of TBD. As a result, these guidelines may not adequately capture cases where patients exhibit subtle findings and genetic testing or telomere length testing may not be pursued.[14] The diagnosis of TBD typically relies on recognizing suggestive clinical findings, followed by the identification of a pathogenic gene variant through genetic testing and subsequent telomere length analysis. Telomere length testing can be performed using automated multicolor flow cytometry combined with fluorescent in situ hybridization (flow FISH). This method is clinically available in certified labs using commercial flow cytometers that rapidly determines the telomere lengths in subsets of nucleated blood cells.[15] Management of TBD involves multidisciplinary care to treat presenting features and monitor for potential complications. This includes ongoing surveillance for bone marrow failure, myelodysplastic syndrome, hematologic malignancies, and pulmonary fibrosis. Notably, providers should consider regular skin cancer screenings in individuals with TBD. Squamous cell carcinomas are among the most frequent solid tumors in individuals with

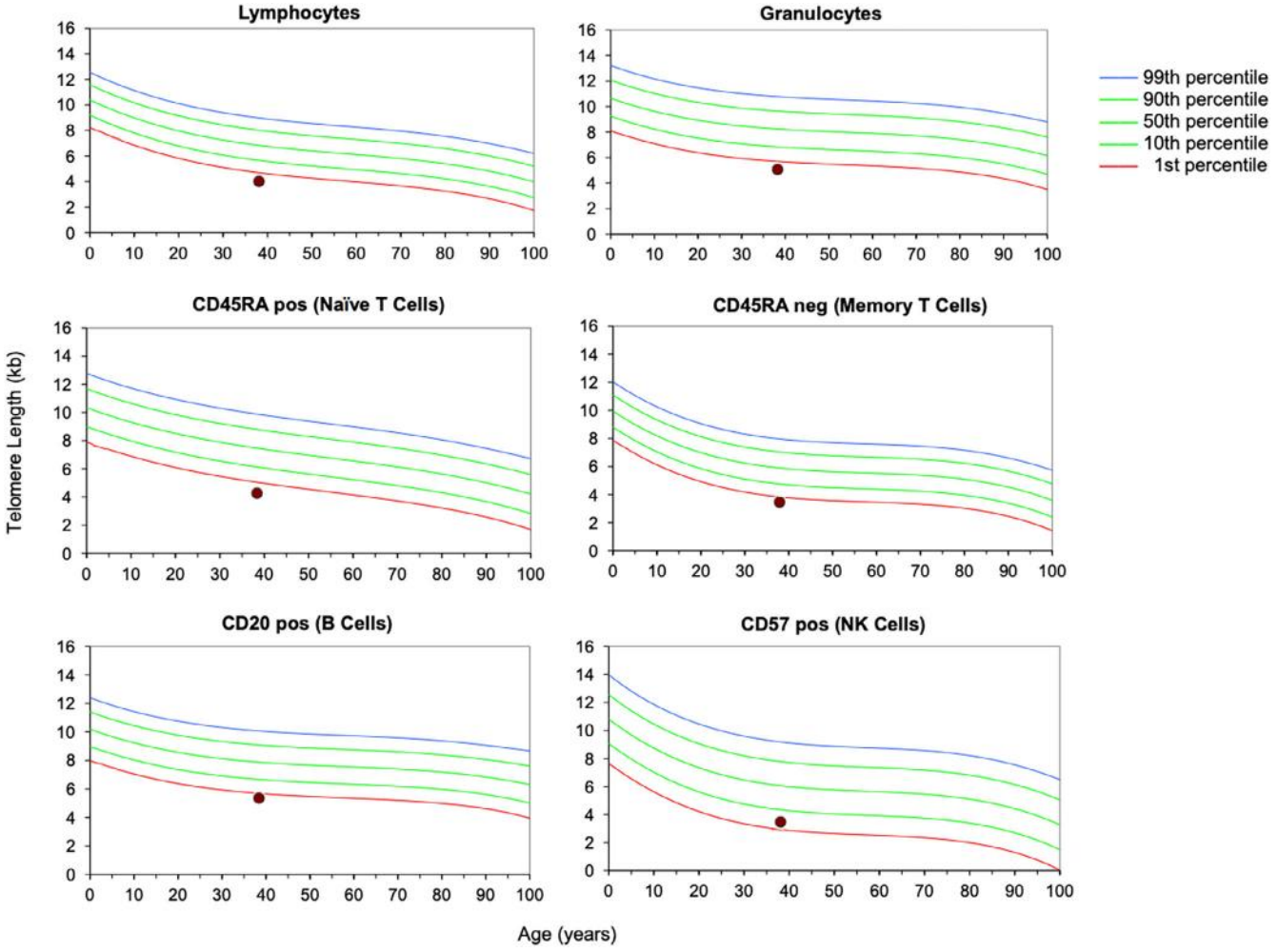

FIGURE 4 Telomere length analysis of the mother's peripheral blood.

TBD, with a median age of diagnosis at 21 years.[16] Patients should also receive genetic counseling, and first-degree family members should consider genetic testing.

This case describes a unique presentation of TBD, with pigmentary changes isolated to the neck and flexural surfaces since birth as well as eventual development of Terry's nails. It also identifies a variant previously classified as of unknown significance (VUS) in TERT (g.1294522A > G, c.479 T > C) as a pathogenic variant. Furthermore, this report highlights the importance of maintaining suspicion for TBD in individuals exhibiting limited or subtle features. Genetic testing and telomere length testing are essential in confirming diagnosis, as they aid in identifying potential genetic variants associated with the disorder. Further research is needed to establish criteria that encompass both clinical and genetic factors of TBD, which would facilitate early identification and risk stratification of affected individuals.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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