



Dyskeratosis congenita, bone marrow failure, and gastric adenocarcinoma: an insight into telomere biology

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Dear Editor,

Bone marrow aspiration and trephine biopsy were sought for evaluation of pancytopenia in a 22-year-old adolescent male who presented with severe weakness, fatigability, and increasing breathlessness for last 6 months. He had a history of two units of packed whole blood transfusion for the above-mentioned symptoms within the last 6 months before coming to our hospital. Remarkably, he also had a history of peculiar skin pigmentation and scalp hair loss and graying, which started when he was 10 years of age. He also had a complaint of occasional loose motions and passing black stool twice in the last month. Physical examination revealed a thin built male with marked conjunctival pallor. There was no edema, clubbing, icterus, lymphadenopathy, hepatosplenomegaly, or sternal tenderness. Skin examination revealed reticulated (hyper- and hypopigmented) macules all over the body, including the palms, soles, and forehead. There was a uniform and marked dystrophy of finger and toe nails. He had gray scalp hairs and sparse eye lashes, predominantly noted on the lateral aspects. Oral examination revealed dental carries and leucoplakic patches involving dorsum of the tongue and the hard palate (Figure 1a-g). His systemic examinations were within normal limits, and radiological evaluation did not show any skeletal abnormalities. He was born to non-consanguineous parents, had normal milestones of development, and had no family history of a similar complaint.

The routine hemogram showed microcytic hypochromic anemia (hemoglobin: 36 g/L, mean corpuscular volume: 70 fL, serum ferritin: 14 ng/mL [ref: 150-450 ng/mL]), total leukocyte count: $3 \times 10^9/L$ with normal differential; absolute neutrophil count: $1.8 \times 10^9/L$; total platelet count: $22 \times 10^9/L$; corrected reticulocyte count: 0.6%; and no abnormal cells in the peripheral blood smear. His stool occult blood test was positive. Upper gastrointestinal endoscopy revealed an antral ulceroprolifera-

tive growth that on histopathological examination was consistent with intestinal type adenocarcinoma. The adjoining gastric mucosa showed atrophy and cystic change with loss of parietal cells, and focal pyloric-type metaplasia. The lamina propria showed paucicellularity, patchy hyalinization, and fibrosis. There was no evidence of *Helicobacter pylori*-associated inflammation, activity, or intestinal metaplasia. The proliferative index (Mib-1) in the tumorous area was 5% in contrast to total absence in the non-neoplastic mucosa, thus suggesting a replicative senescence. Bone marrow aspiration and trephine biopsy findings were consistent with a diagnosis of severe aplastic anemia (marrow cellularity=20% for age; Figure 2a-g). Thus, clinical presentation in correlation with laboratory findings was consistent with the diagnosis of a genodermatosis with bone marrow failure-dyskeratosis congenita (DKC). The patient and their parents were counseled for further management at a higher center but refused any definite therapy and then lost to follow-up. Informed consent was obtained from the parent of the patient, and the identity of the patient was kept confidential.

Dyskeratosis congenita or Zinsser-Cole-Engman syndrome is a rare inherited bone marrow failure syndrome (IBMFS) characterized by diagnostic triad of reticulated skin hyperpigmentation, nail dystrophy, and oromucosal leukoplakia (1). DKC is a disease of defective telomere maintenance, and patients with DKC have premature telomere shortening and subsequent replicative senescence, leading to premature stem cell failure, aging, and cancer predisposition. To date, nearly 14 genes have been identified with DKC of which mutation involving *DKC1*, *TERT*, *TERC*, and *NOP10* genes account for nearly 65% of all cases. While cutaneous hyperpigmentation and nail changes are the earliest manifestation in DKC, there is increased predilection for bone marrow failure, solid and hematolymphoid malignancies, and pulmonary fibrosis, which constitute

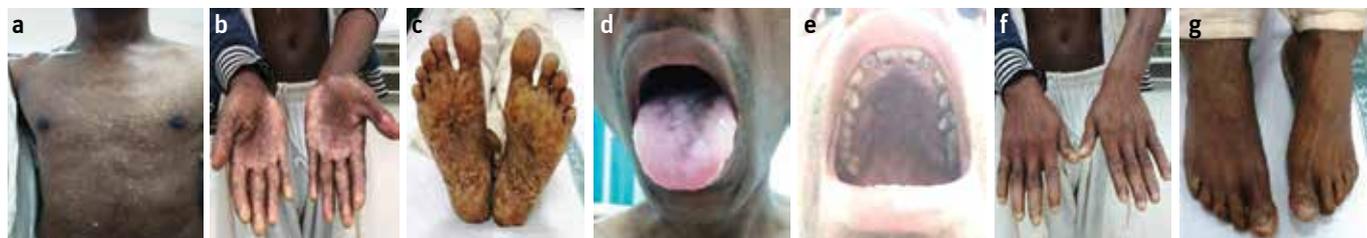


Figure 1. a-g. Phenotypic characteristics of dyskeratosis congenita. The characteristic reticulated hypo- and hyperpigmented macules all over the body, more marked on the trunk (a), palms (b), and soles (c), oromucosal lesions present were leukoplakia involving the dorsum of tongue (d), and hard palate (e), along with presence of dental carries (e), marked dystrophy of all the finger and toe nails (f, g) was quite evident in this case. There was frontal baldness, graying of scalp hairs (more on the temporal aspects), and loss of eyebrows and eyelashes (more so on the lateral aspect; not shown in the figures)

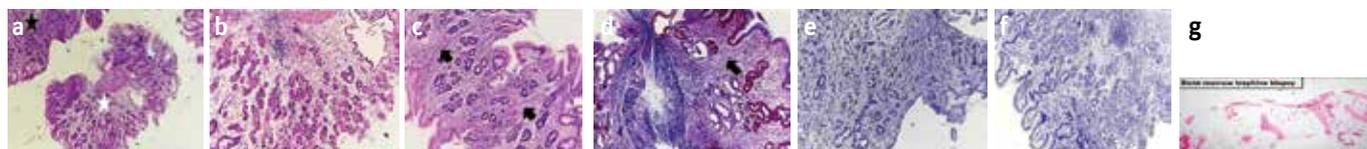


Figure 2. a-g. Gastric mucosal biopsies from distal antrum in a case with dyskeratosis congenita. The non-neoplastic mucosa (white asterisk) adjoining the tumorous bit (black asterisk) is shown in panel (a) (x40), the non-neoplastic mucosa showed atrophy, parietal cell drop out, and cystic dilatation of the glands (b) (x40) and lamina propria fibrosis and hyalinization (c, x200), which were more delineated by Masson Trichrome stain (d) (x200; black arrows). There was no evidence suggestive of *Helicobacter pylori*-associated gastritis. The proliferative index (Mib-1) of the tumorous cells was 5% (e) in contrast to zero in the adjoining mucosa (f), thus suggestive of a replicative senescence (peroxidase-antiperoxidase, x200). The bone marrow trephine biopsy performed for the evaluation of pancytopenia showed markedly reduced hematopoietic cellularity for age (average cellularity=20%) consistent with the diagnosis of severe aplastic anemia (marrow failure; g, x100). Hematoxylin eosin stain (panel - a-c, and g)

the most common causes of early mortality (1-3). Alter et al. (3) reviewed 552 cases of DKC reported in English literature from 1910 to 2008 and found 52 patients (9.4%) with 61 cancers. The median age at which cancer was diagnosed was 29 years (range, 15-68 yrs). Among 61 malignancies, 60 cases were of solid tumors and one case was that of acute myeloid leukemia. Squamous cell carcinomas of head and neck (24/60, 40%) and skin (8/60, 13%) were most common; followed in frequency by anorectum (6/60, 10%) and lungs (4/60, 6.6%) (3). Occurrence of gastric carcinomas in DKC is extremely rare and only 5 such cases (one with Hodgkin lymphoma and squamous cell carcinoma) have been reported in world literature. Four of such cases had a fatal outcome, because of massive gastrointestinal (GI) bleeds, metastasis, or disseminated coagulation following surgery (4-8). None of these cases presented with coexistent aplastic anemia, as in our case.

A combined data from the John Hopkins Telomere Syndrome Registry (N=6 of 38) and 43 additional cases reported in the world literature have reported a substantial link between abnormal telomere biology and GI luminal pathology (9). The GI disease was often the first and most severe manifestation of telomere disease in young children (<10 years of age). Esophageal stenosis at the cervico-thoracic junction, gastric lamina propria fibrosis, atrophic gastritis, parietal cell dropouts, and esophageal intraepithelial lymphocytosis were extremely common, whereas recurrent enteropathy and enterocolitis with striking villous atrophy, extensive apoptosis, and anaphase bridging pointing toward regenerating defect were very commonly reported in the lower GI tract. GI malignancies were rarely reported (9). The present case demonstrated significant

pathology in the adjoining mucosa, which pointed toward a replicative senescence.

The diagnosis of DKC requires the classic triad or the presence of one of the triad plus two or more minor features, such as epiphora, blepharitis, premature gray hairs, alopecia, developmental delay, short stature, cerebellar hypoplasia, microcephaly, esophageal stenosis, urethral stenosis, pulmonary fibrosis, liver disease, avascular necrosis of hips or shoulders, epithelial cancers, myelodysplastic syndrome, and leukemia (4). An algorithmic approach for the diagnosis of a telomeropathy (DKC) has been suggested by Townsley et al. (10). Accordingly, all subjects with an appropriate personal or family history of aplastic anemia/myelodysplasia/acute leukemia, who present with cytopenias, macrocytosis along with dermatologic triad should undergo bone marrow evaluation (for marrow failure) and peripheral blood stress cytogenetic testing for Fanconi anemia. The diagnosis can then be confirmed by measuring the mean telomere content by flow-fluorescent in-situ hybridization (FISH) in peripheral blood lymphocytes; values less than the first percentile compared with age-matched controls accurately identifies individuals with the likely disease (10).

Dyskeratosis congenita should always be considered as a differential diagnosis for inherited bone marrow failure syndrome and evaluated with cytogenetics and/or telomere studies. To the best of our knowledge, the present case is possibly the sixth case of gastric carcinoma (and first such case with coexistent aplastic anemia) to be reported in patients with such bone marrow failure syndrome.

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