Dyskeratosis Congenita: A Rare Case

ABSTRACT

Dyskeratosis congenita (DKC) is a rare genodermatosis which exhibits oral leukoplakia, nail dystrophy, and reticular skin pigmentation as its primary features. Dyskeratosis congenita has increased risk of developing constitutional anemia and malignancies and early diagnosis enables the patient to be monitored and proper interventional therapy to be instituted. Here, we present an interesting and rare case report of DKC. Very few are being reported in our country and we, as physicians, should be aware of DKC, presenting as pyrexia, and anemia.

Keywords: Dyskeratosis congenita, Leukoplakia, Pancytopenia, Telomere.

INTRODUCTION

Dyskeratosis congenita (DKC) is a rare inherited bone marrow failure syndrome characterized by the triad of dystrophy of the nails (90%), reticular skin pigmentation (90%), and oral leukoplakia (80%). It is associated with a higher risk of developing aplastic anemia, myelodysplastic syndrome, leukemia, and solid tumors. Atresia of the lacrimal ducts may occur causing continuous lacrimation. Patients have very short germ line telomeres. Hence, many of the associated symptoms like premature graying are characteristic of geriatrics and the tissues affected are those with a high cell turnover. Dyskeratosis congenita is a rare disease and usually presents to a dermatologist for skin, nail, and hair changes. However, here we present a case who presented with constitutional symptoms to us after careful general examination revealed triad of presentation of this rare disease highlighting the importance of careful head to toe examination in every patient.

CASE REPORT

A 20-year-old male student, resident of Karjat, Maharashtra, presented with chief complaints of fever, weight loss and dyspnea on exertion since the last 6 months. Fever was moderate grade, intermittent and associated with night sweats. He had dyspnea on moderate exertion with no accompanying orthopnea. Considerable weight loss of 12 kg was present in the patient. There was no significant past, family or treatment history. No family member was dealing with history of intrauterine growth retardation, short stature, family history of abnormal toe nails, leukoplakia, neck cancer, hypogonadism, and premature gray hair. On examination, patient was febrile and was dehydrated. His general examination revealed severe pallor, reticular hypopigmentation, and hyperpigmentation on the entire skin and dystrophic nails along with presence of multiple leukoplakias in the oral cavity. There was also presence of graying of hair. On investigations, patient had severe anemia with hemoglobin of 4.2 gm/dl, total leukocyte count of 1100 cells/mm^3 and platelet count of 10,000 c/mm^3. Rests of the laboratory parameters were normal. Patient was subjected for a bone marrow examination and genetic examination. Bone marrow examination revealed a hypoplastic bone marrow and genetic studies could not be done because of financial constraints.

Diagnosis of DKC was made with constellation of presence of skin changes, dystrophic nails, early graying of hair, and pancytopenia. Patient was managed conservatively with intravenous fluid, blood transfusions and antibiotics (Figs 1 to 4).

Fig. 1: Hypopigmented patches on the neck and chest region
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**DISCUSSION**

Dyskeratosis congenita, an inherited syndrome, first described by Zinsser in 1910, is characterized by the triad of reticulated skin hyperpigmentation, nail dystrophy (both occurring in 100% of cases), and white plaques (80% of cases); typically occurring in the oral cavity. Other features occur with lower frequencies and involve virtually every organ system.

The main causes of death are bone marrow failure/immunodeficiency (~60–70%), pulmonary complications (10–15%), and malignancy (5–10%). Dyskeratosis congenita is related to telomerase dysfunction; all genes associated with this syndrome (DKC1, TERC, TERT, TINF2, and NOP10) encode proteins in the telomerase complex responsible for maintaining telomeres at the ends of chromosomes. Patients with DKC have reduced telomerase activity and abnormally short tracts of telomeric DNA compared with normal controls. Telomeres are repeat structures found at the ends of chromosomes that function to stabilize chromosomes, they have critical role in preventing cellular senescence and cancer progression. The defective telomere maintenance in DKC results in chromosomal shortening and gene loss during cell replication which ultimately leads to cell apoptosis, particularly in highly proliferative tissues, such as the hematologic and dermatologic systems.

Two subsets of DKC have been reported:

**Hoyeraal-hreidarsson (HH) syndrome:** The clinical findings are consistent with DKC, plus intrauterine growth retardation, developmental delay, microcephaly, cerebellar hypoplasia, immunodeficiency, and bone marrow failure.

**Revesz syndrome:** Findings similar to HH, plus a specific finding in the eye, called “exudative retinopathy”.

The typical symptoms of DKC involve the skin, nails, and mucous membranes, as well as bone marrow failure. The cutaneous presentation is abnormal skin pigmentation with tan-to-gray hyperpigmented or hypopigmented macules and patches in a mottled or reticulated pattern, which may clinically and histologically resemble graft vs host disease. The typical distribution involves the sun-exposed areas, including the upper trunk, neck, and face as seen in our patient.

Other cutaneous findings may include alopecia of the scalp, eyebrows, and eyelashes, premature graying of the hair, hyperhidrosis, hyperkeratosis of the palms and soles, and adermatoglyphia (loss of dermal ridges on fingers and toes). Nail dystrophy, the first component of the syndrome to appear, is seen in approximately 90% of patients, with fingernail involvement often preceding toe nail involvement. Progressive nail dystrophy begins with ridging and longitudinal splitting. Progressive atrophy, thinning, and distortion eventuate in small, rudimentary, or absent nails. In mild cases ridging and longitudinal fissuring occur. In our patient all the toe and finger nails were dystrophic from birth itself.

Though mucosal leukoplasia commonly involves the buccal mucosa, tongue, and oropharynx, it may also be seen in areas like esophagus, urethral meatus, glans penis, lacrimal duct, conjunctiva, vagina, anus, etc. Constriction...
and stenosis can occur at the later mentioned sites, with subsequent development of dysphagia, dysuria, phimosis, and epiphora. The leukoplakia may become verrucous, and ulceration may occur. Leukoplakia of the buccal mucosa and hyperpigmentation of the tongue were found in our patient. Bone marrow failure is a major cause of death, with approximately 70% of deaths related to bleeding and opportunistic infections as a result of bone marrow failure. Approximately 90% have peripheral cytopenia of one or more lineages. In some cases, this is the initial presentation with a median age of onset of 10 years. There was no hematological abnormality in our patient.

Individuals with DKC may also be presented with gastrointestinal system findings like hepatosplenomegaly and cirrhosis and pulmonary complications, including pulmonary fibrosis and abnormalities of pulmonary vasculature. Other symptoms, such as an increased prevalence and severity of periodontal disease, increased incidence of dental caries as in this patient, mandibular hypoplasia, osteoporosis, and scoliosis may be seen in these types of patients. Abnormalities of the CNS like low intelligence, small sella turcica and intracranial calcifications have also been reported. Patients have an increased prevalence of malignant mucosal neoplasms, particularly squamous cell carcinoma of the mouth, nasopharynx, esophagus, rectum, vagina, or cervix. These often occur within sites of leukoplakia and tend to develop in the third decade of life. The prevalence of squamous cell carcinoma of the skin is also increased. Other malignancies reported include Hodgkin lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma.

Dyskeratosis congenita is usually diagnosed by taking in to account the findings on physical examination and with the help of telomerase length testing and mutation analysis. The type of DKC with X-linked inheritance shows mutations in the gene called DKC1, whereas DKC with autosomal dominant inheritance may be due to mutations in other genes called TERC, TERT, and TINF2 and autosomal recessive type of DKC is characterized by abnormal genes called NOP10 (also known as NOLA3). The diagnosis of DKC in our patient was supported by the presence of characteristic triad of pigmentary and atrophic changes of the skin nail dystrophy and leukoplakia on the buccal mucosa. In addition, he had variety of minor manifestations like multiple caries teeth, gingivitis, hyperpigmentation of tongue, gastric ulcer, skeletal abnormalities, and features of premature aging as have been described in earlier reports.

Currently, there is no curative treatment for DKC. The variation in presentation makes it difficult to treat, with bone marrow failure/imunodeficiency being the main cause of premature mortality. Use of the anabolic steroid oxymetholone and hematopoietic growth factors, such as erythropoietin (epoetin alpha), granulocyte macrophage colony—stimulating factor and granulocyte colony—stimulating factor (filgrastim) can produce improvement in the hematopoietic function. Although the mechanism of action of oxymetholone is not well understood, it is thought to function by promoting the growth of hematopoietic progenitors indirectly through the effect of cytokine production and by supporting hemopoietic production in times of stress. The only long-term cure for the hemopoietic abnormalities is allogeneic hematopoietic stem cell transplantation, but this is not without risk. There is still significant mortality associated with bone marrow transplants for DKC patients when compared with other bone marrow failure syndromes. One of the main reasons for this is the high level of pulmonary/vascular complications that present in these patients probably as a result of the underlying telomere defect.

### CONCLUSION

The advances in understanding of DKC have increased remarkably over the last 10 years but there are still huge advances to be made. The long-term survival, however, is unknown at present but the initial response is encouraging as a more effective treatment for DKC.

### REFERENCES