DOI: https://doi.org/10.47391/JPMA.045

Dyskeratosis congenita: a case report on a rare disease

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Abstract

Dyskeratosis congenita is a very rare inherited haematological disorder characterised by a classical clinical triad of leukoplakia, skin pigmentation and dystrophied nails. Here is a case of a young patient who presented with brittle nails, lacy hyperpigmentation of the skin and leukoplakia along with pancytopenia. Haematopoietic stem cell transplantation is the only cure for this disease but due to financial constraints of the family it was not possible. The patient was placed on androgen therapy and showed favourable response but later was lost to follow-up.

Keywords: Dyskeratosis Congenita, Pancytopenia, Leukoplakia

Introduction

Dyskeratosis Congenita (DC) is a genetic disorder, the hallmark of which is the typical triad of clinical findings that include abnormal skin pigmentation, nail dystrophy, and leukoplakia. It involves multiple systems, and the patient eventually progresses to bone marrow failure. There is an increased risk of cancer transformation.[1] The median age at diagnosis is between 5-15 years.[2] The basic underlying pathology is shortened length of the telomere for age. Management and treatment depends on individual patient. The only option that has the possibility to cure is haematopoietic stem cell transplantation (HSCT) but if

HSCT is not feasible then androgen therapy can be given. The patient should be monitored at regular intervals for progression of the disease, bone marrow failure and cancer transformation.[3]

It has been observed that most of the very rare diseases are either misdiagnosed or inappropriately managed. Here we report the case of a young girl who presented with the classical clinical triad along with peripheral cytopenias.

Case Report

A 20-year-old girl presented to the Haematology OPD of Fauji Foundation Hospital, Rawalpindi, Pakistan in June 2017 with complaints of shortness of breath and generalised weakness. It was her first visit to the hospital. There were no symptoms of weight loss, fever or change in appetite and she had a regular menstrual cycle. She was not taking any medication. She was a student. Her parents were first- cousins; her siblings — a 12-year-old sister and a 10-year-old brother — were normal and healthy and had no significant finding. Although the patient was concerned about nail dystrophy and hyperpigmentation, she had never been to a doctor for these conditions.

She had pallor. On oral examination she had a white patch on the tongue which could not be rubbed off, and for which she was referred to a dental surgeon. The dental surgeon reported it to be consistent with oral leukoplakia (figure I). Nails of both hands and feet were dystrophied, brittle and had vertical ridges on them (figure II). Her skin looked dirty but on close examination it had hyperpigmented and a few hypopigmented areas (figure III). The examination of the eyes, ears, nose and throat was also normal. Chest was bilaterally clear. Cardiac examination was also within normal range. Ultra Sound Scan of abdomen/pelvis was also within normal range.

Her blood pressure was 120/70 mm Hg, pulse 90/min, respiratory rate was 20/min, and she had no fever. She had pancytopenia. Her WBC count was 3 x 10^9/L (normal reference range: 4-11 X 10^9/L) with an absolute neutrophil count

of 1.1 X 10^9/L (normal reference range: 2-7 X 10^9/L), platelet count was 42 X 10 ^{9}/L (normal reference range:150-400 X $10^{9/}$L) and haemoglobin was 8.8 gm/dL (normal reference range: 12-16 gm/dL). Viral serology for hepatitis B, C and HIV were negative. Serum B12 and folate were normal. Autoimmune profile turned out to be negative. A bone marrow biopsy was conducted, which revealed hypocellular marrow with no abnormal cells. ECG and ultrasound of the abdomen were normal.

Her cytogenetic report lacked any structural or numerical chromosomal abnormality. Chromosomal breakage studies did not show any evidence of Fanconi anaemia. Pancytopenia along with a classical triad of oral leukoplakia, dystrophied nail and hyperpigmentation of the neck/chest led to the diagnosis of DC. The main diagnosis was DC, and although the definitive treatment for DC is bone marrow transplant, it could not be done due to financial constraints of the family. The patient was started on Danazol at a dose of 1 mg/kg/day with monitoring of her liver function tests as it could cause liver impairment. She followed-up after three weeks and her haemoglobin was 10.2 gm/dl and platelets had risen to 68 × 10^9/L. She reported a feeling of wellbeing and improvement in her dyspnoea. One month later she had her second follow-up visit and showed further improvement her haemoglobin was 11.2 gm/dL and platelet count was 96 X 10 ^{9}/L on this visit. The patient's blood counts improved but leukoplakia and nail dystrophy did not show any signs of improvement. She later lost to follow-up.

Discussion

The clinical diagnosis of DC is based on the presence of four major features which include the mucocutaneous triad and bone marrow failure. There are associated multisystem features of the disease; for example, developmental delay or mental retardation, pulmonary disease, periodontal disease, epiphora, oesophageal stricture, premature hair greying, hyperhidrosis, or malignant transformation.[4]

Differential diagnoses of DC include Fanconi Anaemia and Shwachman-Diamond syndrome. DC is considered a type of aplastic anaemia and the differential diagnosis is with Fanconi anaemia. However, in contrast to DC, Fanconi anaemia is an autosomal dominant condition with concomitant skeletal and renal abnormalities but there no nail dystrophy or oral leukoplakia is seen in Fanconi anaemia.[5]

Shwachman-Diamond syndrome is another rare cause of pancytopenia, inherited in an autosomal recessive manner, and usually presents in the first year of life with exocrine pancreatic insufficiency and bone marrow failure. There is no exocrine pancreatic insufficiency in DC and Shwachman-Diamond syndrome lacks the typical DC triad.[6]

Dyskeratosis congenita (DC) has autosomal dominant, autosomal recessive and X-linked mode of inheritance. Ten genes have been identified out of which X-linked DKC1 has the most frequent mutation, occurring in approximately 40% of patients.[1] It encodes the nucleolar protein dyskerin which is involved in telomere maintenance and the biogenesis of ribosomes. The underlying pathology of shortened telomeres in DC is due to mutations in the telomere stabilising component. As a result, there is a defect in the renewing and regenerating capacity of the haematopoietic stem cell.[3]

The median age at diagnosis of DC is approximately 15 years. The diagnosis of classical DC requires that out of the triad of dysplastic nails, lacy reticular pigmentation of the upper chest and/or neck, and oral leukoplakia, at least two features are present .[2]

Almost 90 percent of the patients with DC present with dystrophic nails. Our patient reported to have involvement of fingernails before toenails. The dystrophy of the nails could progress to such an extent that it might result in the complete absence of nails.[7]

Mucosal leukoplakia is a common occurrence in DC involving the tongue and buccal mucosa.[7] The leukoplakic areas have an increased risk of cancerous transformation.[7]

DC is a multisystem disorder. Pulmonary complications can lead to fibrosis of the lungs and alterations in the pulmonary vasculature. Other systemic complications include liver diseases, neurological ataxia due to cerebellar hypoplasia and ocular and neurological abnormalities, developmental delays and microcephaly.[8]

Majority of the DC patients presents with peripheral cytopenia. Bone marrow failure in DC patients is a result of defective dyskeratin that results in a defective regenerating ability of the haematopoietic stem cells.[1] Bone marrow failure is a major cause of death leading to bleeding and infections.[1] In one study, the patient presented with recurrent dysphagia and on further examination was found to have the classical triad which led to the diagnosis of DC. Although dysphagia has been reported in DC, it is not a very usual finding; however, our patient did not have any such complaint. [9, 10]

Ophthalmological consultation is important as DC patients are at the risk of developing conjunctivitis, retinopathy, blepharitis, pterygium, and epiphora, which occurs as a result of lacrimal duct stenosis. Ophthalmological complications occur in almost 50 percent of DC patients, with epiphora being the commonest.[1] Our patient was seen by an ophthalmologist and thus far has normal eye examination.

DC patients have a higher incidence of buccal mucosa hyperpigmentation and hypocalcified teeth.[11] Leukoplakia carries a risk of squamous cell carcinoma, with 30% of the patients progressing to squamous cell carcinoma in 10–30 years. Leukoplakia occurs in almost 90% of the patients, with first manifestation most commonly occurring between the ages of 5 and 14 years.[12] Our patient noticed leukoplakia when she was 10-years old.

In another study, a 21-year-old female was diagnosed with DC and she had infantile secondary sexual characters. This patient also had primary amenorrhoea.[13] Our patient did not complain of amenorrhoea and her gynaecological examination was normal.

In a series of 300 patients with DC, the estimated rate of cancer was found to be approximately 10%.[8]

Among DC patients, the most common type of cancers reported are head and neck malignancies and squamous cell carcinomas (SCC) followed by anorectal, gastrointestinal and pulmonary cancers.[3]

Cases of acute myeloid leukaemia and myelodysplastic syndrome in DC have been reported. The cancers in DC are diagnosed at an early age than their average mean age of presentation.[14]

Life expectancy ranges from infancy to well into the sixth decade of life. Major causes of morbidity include BMF, cancer and pulmonary complications.[15] The only curative treatment for DC is HSCT. If there is no HLA-matched donor, then androgen should be considered.

Our case report will add more information to the existing pool of knowledge of this rare disease.

The strength of this case report is the fact that it could lead to a better understanding of this rare disorder. Another strength is that it is the first ever case reported from Pakistan. The limitations of this case report is that the patient could not be followed up for a longer period of time and genetic testing could not be done.

The main take away lesson from this case report is that the clinician should always do a thorough physical examination as it would assist in proper diagnosis. Physical examination skills have been underemphasised in the current health care system and if properly done can certainly prevent unnecessary diagnostic testing.

Conclusion

Dyskeratosis Congenita is a severe multisystem disorder associated with significant morbidity and mortality. Although DC is a rare disease, diagnosis should not be missed, for which close examination of the mucocutaneous abnormalities is important, and the patient should be monitored regularly for progression to bone marrow failure and other systemic complications**.** Due to heterogeneity of the disease, it is very important for clinical experts to make a correct diagnosis. A delay or a mistake in diagnosis can lead to inappropriate and inadequate management and increased morbidity and mortality. Close surveillance and monthly self-examination is recommended to monitor progression of disease.

Informed consent of the patient was taken for the publication of this case report

Disclaimer: None to declare

Disclosures: None to declare.

Conflicts of Interest: None to declare.

Funding sources: None to declare.

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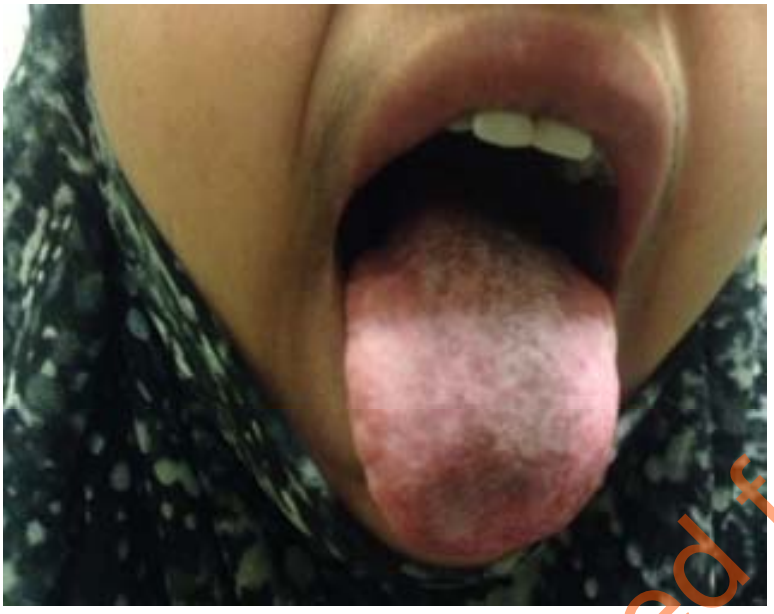

Figure: I Patch of Leukoplakia on the anterior surface of the tongue

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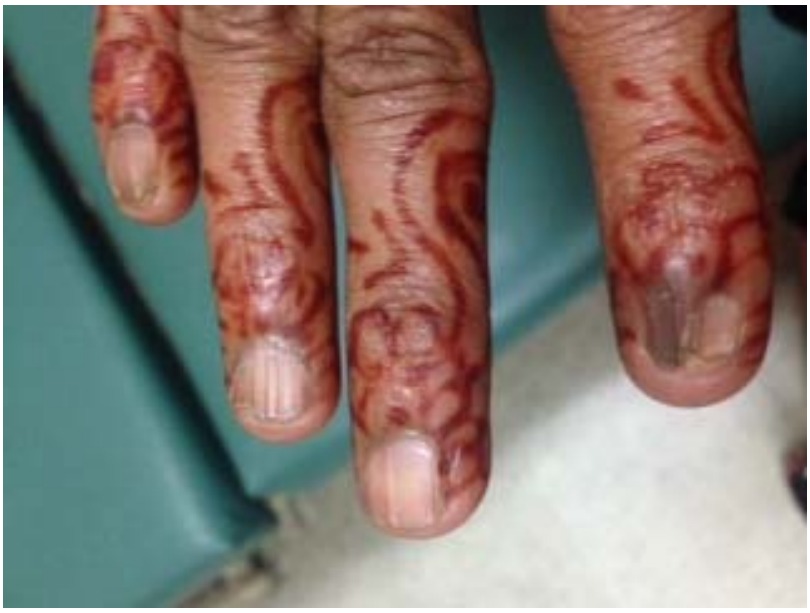

Figure II: Fingernails showing vertical ridges with dystrophic changes in index finger nail.

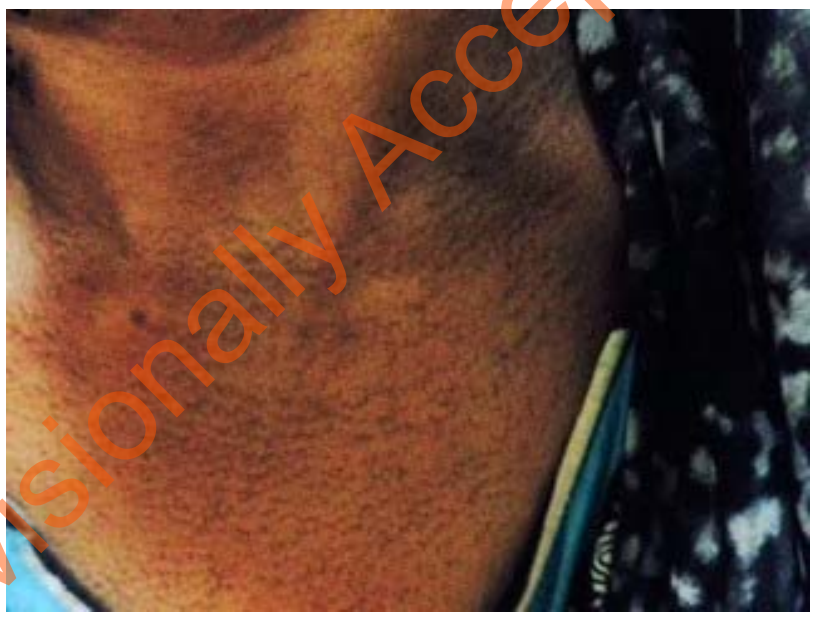

Figure III: Reticulate Hyperpigmented and a few hypopigmented areas on neck and chest