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Case Report

Dyskeratosis congenita: a case report

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ABSTRACT

Dyskeratosis congenita is a rare hereditary disorder characterized by skin pigmentation, nail dystrophy and leukoplakia along with bone marrow failure and increased predisposition to malignant tumours. Here we describe a 7-year-old child who presented with classic triad of pigmentation, nail changes, leukoplakia along with manifestations of bone marrow failure. He was initially put on androgen therapy with plan for a possible matched related allogenic HSCT. A haematologist should be aware of the complications of therapy, bronchopulmonary complications, futility of IST and dangers of using myeloablative transplant in such a patient.

Keywords: Dyskeratosis congenita, Hereditary, Bone marrow failure

INTRODUCTION

Dyskeratosis congenita (DC) is a rare hereditary disorder characterized by skin pigmentation, nail dystrophy and leukoplakia of mucosal surfaces along with bone marrow failure and increased predisposition to malignant tumours.[1] This entity was first described by Zinsser in 1906 and later by Cole and Engmann and is also named as Zinsser- Engmann-Cole syndrome.[2]

The vast majority of patients in literature are males (73%) in accordance to X linked recessive pattern being the most common mode of inheritance. But as more autosomal cases were identified the proportion of males were seen to be lower.[3] Skin and nail changes appear early in life usually in the first decade followed by leukoplakia and bone marrow changes in second decade.[4]

The average life expectancy of these patients with severe disease is around 20 years, and infection and bleeding are the commonest causes of death.[1,5]

However, there is paucity of literature from India on this rare and fatal disorder. Here we describe a case of 7-year-old male child along with detailed investigations and brief review of literature.

CASE REPORT

A 7-year-old child a resident of South 24 Parganas adjoining Kolkata came to our OPD with complaints of intermittent fever and weakness and pallor of 2 months duration. There was no history of bleeding from any site. There was history of jaundice 1 and half years back which was treated with ayurvedic medicine. The patient had received 4 units of transfusion in a local hospital.

He had an elder sister 11 years old who was apparently normal.

He had moderate pallor and prominent (beaked nose), reticulated pigmentation of the upper torso (neck and trunk) and upper extremities, (Figure 1) ridged and atrophic nails on both fingers and toes (Figure 3) and a white patch of 1 cm diameter on the dorsal surface of the tongue (Figure 2). This whitish patch could not be scraped. There was no organomegaly or lymphadenopathy.

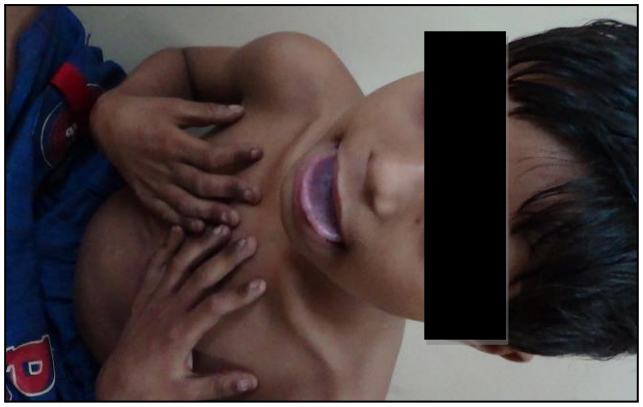

Figure 1: Pigmentation of trunk and upper extremity.

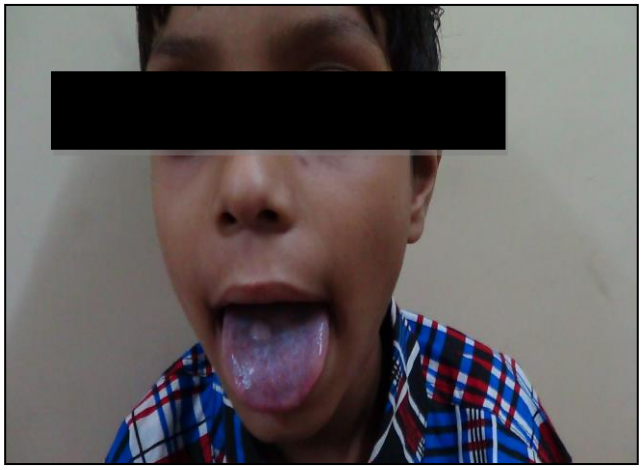

Figure 2: Leukoplakia.

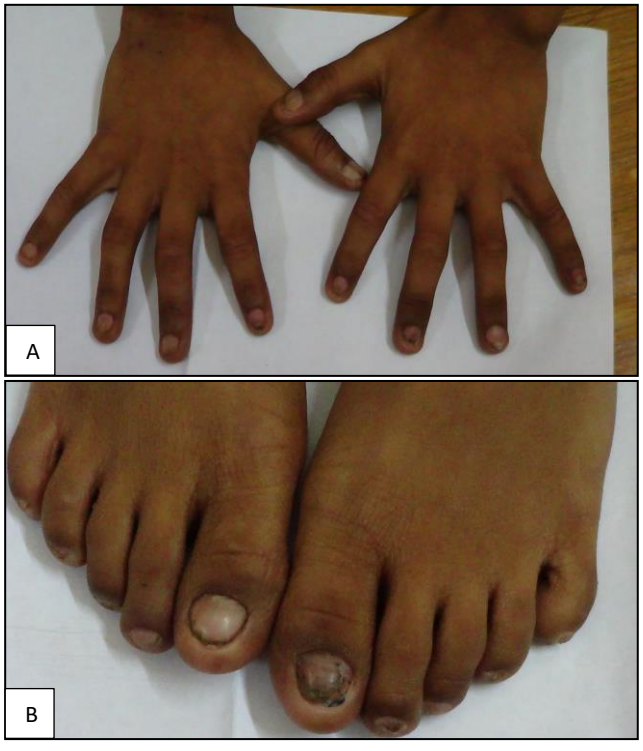

Figure 3 (A and B): Nail dystrophy.

His CBC showed Hb-8.6 gm%, TLC-4.2×10^3 (N-09%, Ly-87%, M-04%) and platelet<10,000. RBCs were macrocytic and there were no abnormal cells in the peripheral smear. His corrected reticulocyte count was 0.6%. His serum ferritin value was 187.4 ng/ml and serum LDH, LFT and urea, Cr values were within normal limit (Table 1).

His bone marrow examination was done and was suggestive of hypoplastic marrow. Predominant cells were lymphocytes and normoblastic erythroid precursors with relative paucity of granulocytic precursors. Megakaryocytes were not seen. Trephine biopsy showed around 30% cellularity. Biopsy of the tongue showed hyperkeratosis and flattened rete ridges.

USG of whole abdomen didn't reveal any abnormality.

A panel-based sequencing for known TBD associated genes were done and was positive for DKC1 mutation.

Table 1: Laboratory findings.

Tests	Results
CBC	Hb-8.6 gm%, TLC-4.2×10^3 (N-09%, Ly-87%, M-04%) and platelet<10,000
Reticulocyte count	0.6%
Bone marrow aspiration	Hypoplastic marrow changes
Trephine biopsy	Hypoplastic marrow changes
Biopsy from tongue lesion	Hyperkeratosis and flattened rete ridges
Serum LDH	209U/l
Serum ferritin	187.4 ng/ml
Urea, creatinine	18, 0.6
LFT	WNL
USG of whole abdomen	WNL
HbF level	3%
Pulmonary function test	Within normal limit
DKC1 gene study	Positive

Differential diagnosis

Diagnosing a case of DC is relatively easy when classical mucocutaneous features are present as in this case. However, we still need to differentiate it from Fanconi anaemia and acquired aplastic anaemia. A chromosomal breakage study with DEB/MMC can be helpful in this aspect. In our case stress cytogenetics came out to be negative. Other differentials are Pachyonychia congenita and GVHD. Pachyonychia congenita is an autosomal dominant condition characterized by nail abnormalities, hyperkeratosis or hyperhidrosis of the palms and the sole and mucosal leukoplakia. However hematological abnormalities are absent in pachynochia congenita. GVHD may be considered in the differential since they

may manifest with similar skin and nail changes. In GVHD lichenoid lesion rather than leukoplakia occurs.

DISCUSSION

The estimated prevalence of dyskeratosis congenita in childhood is 4 in 1 million.[3] DC is a genetically heterogenous disorder. The modes of inheritance are X-linked recessive, AD and AR.[3] Studies have shown that the genes mutated in XLR and AD forms of DC encode core components of the telomerase complex. The DKC1 gene mutated in XLR subtype of DC has been mapped to Xq28. Autosomal dominant DC is due to the mutation in the TERC gene located on chromosome 3q.[6] TERC is a 451 nucleotide RNA. Recently TERC mutation has been detected in some aplastic anaemia and MDS patients.

In the year 1995 a dyskeratosis congenita registry was established at the Hammersmith hospital, U. K. In the 46 families recruited 76/83 patients were male. Besides the classic triad, a variety of non-cutaneous (dental, gastrointestinal, genitourinary, neurological, ophthalmic and skeletal) abnormalities have also been reported. The majority (93%) had bone marrow failure which was the principal cause of early mortality. Pulmonary abnormalities were present in 19% of patients.[7]

The disease manifestations in the usual order of presentation are skin pigmentation, nail dystrophy, leukoplakia, epiphora and bone marrow failure.[4] In our case the child presented because of anaemia and later bleeding manifestations as a consequence of bone marrow failure and at presentation he was already having skin pigmentation, nail dystrophy and leukoplakia. Since his earlier records are not available, so it was not possible to determine the correct sequence of disease manifestations. His skin showed fine reticulated hyperpigmented areas in the upper extremity, neck and trunk. No bullous changes were seen. Both the finger and toe nails showed dystrophic changes, though severity was more in the finger nails. Hyperhydrosis of palms and soles described in literature as a frequent finding was not present in our case. Leukoplakia of oral mucosa most commonly involving the tongue is the most frequent finding.[8] The other sites of leukoplakia described in literature are urethra, glans penis, vagina and recto-anal region. In our case leukoplakia was present in the tongue. The biopsy showed hyperkeratosis and flattened rete pegs. There was no evidence of malignant transformation.

Dental abnormalities like malformation of teeth were not present in our case, though caries teeth were present. The child didn't have graying of eyebrows or eyelashes. Epiphora resulting from obstruction/obliteration of the nasolacrimal duct was not seen in our patient.

Though IQ testing was not done in our case, the level of mental development appeared to be low and the child was a poor performer in the class.

Our patient had normal height for age but had a hyposthenic built.

The CBC showed pancytopenia and bone marrow aspiration and biopsy revealed hypoplastic marrow changes. Though initially anaemia and later bleeding manifestations in the form of purpuric spots and occasional gum bleeding was present, secondary infections which are important causes of morbidity and mortality were not seen in our case.

Pulmonary fibrosis and pulmonary vascular abnormalities are frequently seen (20%) and are important cause of morbidity in these patients.[7] A pulmonary function test was performed in our patient which showed FEV1/FVC ratio and total lung capacity were within normal limits.

The DC patients (10-15%) are predisposed to develop MDS as well as solid tumours, but to a lesser extent as compared to Fanconi anaemia. Squamous cell carcinoma and adenocarcinoma of oropharynx or gastrointestinal tract are most common solid malignancies.[9]

Androgens combined with low dose corticosteroids are effective in around 50% patients. However, the response may be lost as the disease progresses. Immunosuppressive therapy is usually ineffective in these patients. Minority of patients show response to GCSF with increase in neutrophil count. However concomitant use of GCSF and androgen is not recommended as it may precipitate splenic rupture.[2]

Allogenic HSCT is the only curative option, however experience is limited.[2] High mortality rate was seen in these patients when myeloablative conditioning regimen was used as these patients are predisposed to endothelial injury and bronchopulmonary disease.

Avoiding busulphan and TBI and using fludarabine based regimens may be appropriate in these patients.

CONCLUSION

Our patient presented with classic triad of skin pigmentation, nail changes, leukoplakia along with manifestations of bone marrow failure. His pulmonary function test was within normal limit. There was no other affected family member and the only sister was apparently normal. Her bone marrow examination showed normal cellularity. The patient was put on androgen therapy. Samples for HLA matching of the patient and her sister had been sent and reports are awaited.

A haematologist should be aware of the complications of therapy, bronchopulmonary complications, futility of using IST and dangers of using myeloablative conditioning regimens in patients of DKC though allo HSCT is a curative option getting a matched related

donor from unaffected family members and high-rate post-transplant complications limits its usefulness.

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