A child with dyskeratosis congenita with *TINF2* mutation

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Introduction

Dyskeratosis congenita (DC) is a rare telomeropathy which manifests as bone marrow failure and predisposition to malignancies[1]. It is characterized by mutations in multiple genes which encode the components of the telomerase complex involved in the maintenance of the length of telomeres, the end parts of the chromosomes[2].

Case report

A 5-year-and-3-month-old boy presented to the outpatient department of a tertiary care hospital in Sri Lanka for further evaluation of a murmur found incidentally during treatment of an upper respiratory tract infection. He developed cough, cold and runny nose a few weeks ago for which he got medical advice. His mother had noticed that the child had exertional dyspnoea following playing and increased sleepiness during daytime for last two months for which they had not sought medical advice. There was no history of recurrent infections, bleeding manifestations. loss of weight, loss of appetite, low-grade fever, body swelling, reduced urine output, joint pain/swelling, hair loss, rashes, yellowish discolouration of sclera. There was no history of significant exposure to lead or other heavy metals.

He is the youngest child of non-consanguineous parents. His elder brother and sister appear healthy. His antenatal and immediate postnatal history were uneventful. His mother had noticed hypopigmentation in both his arms with abnormal nail growth from six months of age which were progressive and not previously evaluated. There was no family history of haematological disorders including haemoglobinopathies.

On examination, his weight was 13.2 kg and his height was 99cm which were less than the fifth centile and the body mass index was 12.93 kg/m^2, which was less than the third centile. He had marked pallor and was not icteric. There was marked leucoplakia in the tongue and dental caries (Figure 1).

Figure 1: ***Leukoplakia and dental caries***

There was no glossitis or angular stomatitis suggestive of micro-nutritional deficiency. He had hypopigmentation in the chest and both upper limbs. There was nail dystrophy involving all finger and toe nails (Figure 2).

Figure 2: ***Nail dystrophy***

There was no hypogonadism, undescended testes or phimosis. There was no alopecia, malar rash or joint swelling. There was no lymphadenopathy, periorbital or ankle swelling. His pulse rate was 108 beats per minute with low volume and blood pressure was 100/66 mmHg. There was a systolic flow murmur best heard at the lower left sternal area. Other system examination was unremarkable including absence of hepatosplenomegaly.

His full blood count revealed a haemoglobin level of 3.2g/dL, mean corpuscular volume of 96fl, mean corpuscular haemoglobin of 30pg, mean corpuscular haemoglobin concentration of 33g/dl, total white blood cell count of 2.04x10^{3}µL with absolute neutrophil count of 0.93x10^{3}µL and a platelet count of 17x10^{3}µL. Blood picture revealed severe pancytopenia with no abnormal cells. Bone marrow aspiration showed evidence of markedly hypocellular fragments and cell trails with markedly suppressed trilineage haematopoiesis with no significant dysplasia. Trephine biopsy revealed markedly hypocellular marrow spaces with 15% marrow cellularity and normal bony trabecular pattern (Figure 3).

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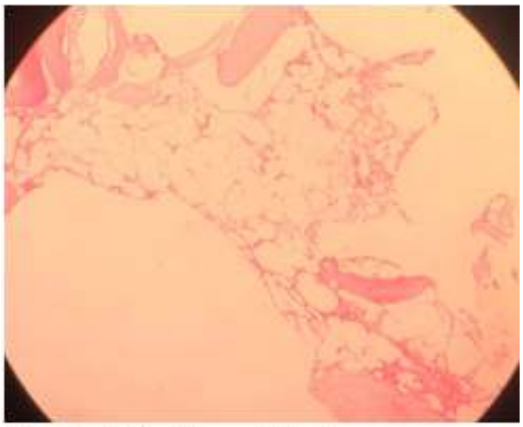

Figure 3: ***Markedly hypocellular bone marrow spaces***

Trilineage haematopoiesis was markedly suppressed with absence of abnormal infiltration, marrow fibrosis or necrosis. His lactate dehydrogenase level was 204 U/L which was within the normal range. His serum creatinine was 0.43 mg/dL, and blood urea was 8.1 mg/dL which were normal. His liver function tests were within the normal range (alanine transaminase 17 U/L, aspartate transaminase 22 U/L, total bilirubin 0.53 mg/dL and serum albumin 4.22 g/dL). His reticulocyte count was $0.18x10^3\mu L$ which was normal.

Chest x-ray and 2D echocardiography were normal. Ultrasound scan of abdomen was normal, with no evidence of hepatosplenomegaly or intra-abdominal lymphadenopathy or structural renal abnormalities. Hepatitis B and C, Epstein-Barr virus, cytomegalovirus and parvovirus B19 serology were negative. Serum B_{12} and red cell folate levels were within normal range. His karyotype was 46, XY and the chromosomal breakage was normal, which excluded the possibility of Fanconi anaemia. Next generation sequencing revealed a heterozygous missense variant in exon 6 of the *TINF2* gene

In the presence of characteristic mucocutaneous manifestations, bone marrow failure with the presence of *TINF2* gene mutation, a diagnosis of dyskeratosis congenita was made. A trial of danazol was initiated for the bone marrow failure and supportive therapy with red cell transfusion was given.

Discussion

DC is an inherited bone marrow failure syndrome with an incidence of 1 per million[1,2]. It is estimated to constitute 2-5% of cases of bone marrow failure. DC is characterized by the bone marrow failure, mucocutaneous and somatic manifestations with a predisposition to malignancies[3]. The first case of DC in a Sri Lankan child was reported by Amerasena TSD, *et al* in 2005[4].

Clinical criteria for diagnosis of DC are: presence of two of four major features viz. bone marrow failure, abnormal skin pigmentation, nail dystrophy and leucoplakia with the presence of 2 or more somatic features. Somatic manifestations known to occur in DC include short stature, dental caries or loss, microcephaly, pulmonary or hepatic disease, enteropathy, hypogonadism, undescended testes and deafness[3,5].

This rare telomere disorder is genetically heterogenous in inheritance. X-linked recessive inheritance accounts for 20-25% of cases; it occurs due to the mutation in *DKC1* gene which encodes dyskerin protein, a component of telomerase[3,5]. Autosomal dominant cases (12-20% of reported cases) occur due to mutation in *TERC, TERT TINF2* and *NAF1*[5]. *TINF2* mutation is the second most common[5]. The rare autosomal recessive form is associated with mutation in *NOP10, NHP2, CTC1* and *RTEL1* genes[5].

Androgens are effective in the improvement of haemopoietic function in DC[3,5]. Granulocyte colony stimulating factor, alone or in combination with erythropoietin, is documented to have beneficial effect in some cases[4,5]. The only curative option for bone marrow failure is haemopoietic stem cell transplantation. Prognosis is poor compared to other inherited bone marrow failure syndromes even following bone marrow transplantation due to the high risk of pulmonary vascular complications in these patients[3].

Our patient with DC had the rare *TINF2* mutation and presented with early bone marrow failure with incidental finding of severe anaemia. This case highlights the importance of searching for evidence of bone marrow failure in children who are having classical mucocutaneous manifestations of DC.

References

1. Agarwalla SK, Raj AB. A case of dyskeratosis congenita with early onset bone marrow failure: A rare case report. *Journal of Medical Science and Clinical Research* 2019; **7**(10). https://doi.org/10.18535/jmscr/v7i10.124
2. Hussein F, Omar Z. Dyskeratosis congenita: Rare case report of Syria. *Oxford Medical Case Reports* 2021; **2021**(11): omab041. https://doi.org/10.18535/jmscr/v7i10.124
3. Dokal IS. Inherited aplastic anaemia/bone marrow failure syndromes. In: Post graduate Haematology. 7th ed. Chichester, West Sussex: John Wiley and Sons Ltd; 2016. p. 156–73. https://doi.org/10.1002/9781118853771.ch10
4. Amarasena T, Hapaurachchi G, De Silva M. A female with dyskeratosis congenita. *Sri Lanka Journal of Child Health* 2009; **34**(4):130. https://doi.org/10.4038/sljch.v34i4.395
5. Kliegman RM, Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM. Dyskeratosis congenita. In: Nelson Textbook of Pediatrics 21st ed. Elsevier; 2020. p. 10123–9.