

Dyskeratosis Congenita: A Case Report

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Abstract:

Dyskeratosis Congenita (DC) is a rare inherited bone marrow failure disorder characterized by lacy reticulated skin pigmentation, nail dystrophy and mucosal leukoplakia. In DC bone marrow failure is the main cause of premature death with an additional predisposition to malignancy. DC results from progressive shortening of telomeres resulting in DNA replication. X-linked recessive is the main mode of inheritance. Most of the patients respond to Androgen therapy. This is a case report of a 5-year-old boy presented with features of bone marrow failure and had abnormality of skin, oral mucosa and nail. His complete blood count with peripheral blood film showed pancytopenia and no blast cell. Hypocellular marrow was present in his Bone marrow examination. Chromosomal analysis- fluorescence in situ hybridization (FISH) revealed very short telomere of chromosome. Microarray genotyping showed DKC1 gene abnormality.

Key words: *Dyskeratosis Congenita (DC), Inherited disorder, Bone Marrow failure, Dystrophic Nail, Oral Leukoplakia, skin pigmentation.*

Introduction:

Dyskeratosis Congenita (DC) is an inherited telomere disorder with an estimated annual incidence of 1 case in 1 million.¹ DC first described by Zinsser in 1906. Engman and Cole et al.² reported other cases in details. DC is also known as Cole-Engman syndrome. DC case was reported in Bangladesh 2020 in Bangladesh Journal of Child Health. DC is a rare disease but it can be diagnosed by simple inspection of mucocutaneous abnormalities. With multiple and variable clinical manifestations, classic and initial form are usually characterized by mucocutaneous triad of skin pigmentation, nail dystrophy and leukoplakia.³ Patients with DC have been shown to have disease diversity in terms of age at onset, symptoms and severity.⁴ Skin findings can be variable, ranging from patchy areas of hypo or hyperpigmentation with a reticulated or mottled pattern. Nail changes are characterized by thin, dystrophic nails that may be markedly shortened and fragile. DC is also frequently associated with oral findings included oral leukoplakia, dental caries, thin enamel structure, aggressive periodontitis and tooth loss.⁵

The Bone Marrow (BM) findings in DC are variable and range from normal to different severity of aplasia depending on the stage of disease. The BM abnormality can progress in different forms with the appearance of myelodysplasia in one or more lineages or leukemia.⁶ Mucocutaneous changes usually appear first, before the age of 10 years and then bone marrow failure develops often before the age of 20 years.⁷ Studies over the last 10 years have demonstrated that DC is principally a disease of defective telomere maintenance. DC patients have very short telomeres and the genetically characterized cases of DC have mutations in different genes which encode components of the telomerase complex.⁸ Mutations in telomerase cause excessive telomere attrition which leads to premature cell death and chromosome instability that eventually either reduces or exhausts the stem cell reverse, there by leading to clinical features such as BM failure.⁹ Another major cause of death is malignancy. It is vital to recognize the increased risk of cancers in these patients (11 fold increase compared to general population).¹⁰ Patients who meet the clinical diagnostic criteria of DC should be investigated further. Therefore, doctors should be aware that DC could be one of the causes of bone marrow failure in young patients.

Case report:

A 5-year-old boy 3rd issue of non-consanguineous parents hailing from Feni admitted into Bangladesh Shishu Hospital and Institute with progressive pallor and generalized weakness for 1 month, gum bleeding for 10 days. He had history of recurrent fever but no

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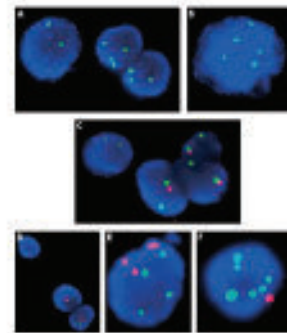
Fig.-1: Lacy reticulated



Fig.-2: Leukoplakia



Fig.-3: Nail Dystrophy



FISH-Shows short telomere

history of headache, convulsion, jaundice, exposure to radiation and taking any offending drugs. His maternal uncle died from same type of illness.

On examination he was ill looking, febrile, severely pale, vital parameters within normal limit. Anthropometry was age appropriate. Skin survey revealed multiple petechiae, purpura, ecchymosis all over the body, lacy reticulated pigmentation present over neck and upper part of trunk. (Figure-1) Active gum bleeding, oral leukoplakia (Figure-2) and nail dystrophy (Figure-3) present. Bony tenderness was absent and there was no lymphadenopathy or organomegaly. Other systemic examinations revealed normal finding.

Laboratory finding revealed Hb-6.3 gm/dl, WBC-2800/mm³, neutropenia present, platelet-30000/mm³. Peripheral Blood Film showed normocytic normochromic anemia but atypical cell was absent. Bone marrow examination showed hypocellular marrow and devoid of hemopoietic cells. We confirmed the case as DC by automated multicolor fluorescence in situ Hybridization (FISH) which revealed very short telomere of chromosome. Microarray genotyping showed DKC1 gene abnormalities. The patient was treated with Danazol (Androgen). Within couple of weeks, with this treatment trilineage blood counts became normal.

Discussion:

DC is an inherited multisystemic disorder characterized by mucocutaneous abnormalities along with predisposition to cancer and MDS. The clinical features of classical DC revealed the presence of 2 of the 4 major features—abnormal skin pigmentation, nail dystrophy, leukoplakia and bone marrow failure. Individuals develop criteria of DC at variable rates and ages. Lacy reticulated skin pigmentation involving the

face, neck, upper part of chest, arms is common finding (89%). Nail dystrophy is next common finding (88%). Leukoplakia usually involves the oral mucosa specially the tongue (78%). Our patient presented with features of bone marrow failure along with skin pigmentation, nail dystrophy and oral leukoplakia.

Excessive tearing due to nasolacrimal duct obstruction is common and is observed 30% of individuals. Approximately 25% of individual have learning and/ or developmental delay. Hyperhidrosis, hair loss, dental caries, esophageal stricture, pulmonary disease, short stature are seen approximately (15-20)% of individuals. Ocular, skeletal, genitourinary and gastrointestinal abnormalities are seen in (10%) of cases.⁴ Our patient had no such finding.

Hemopoietic change in DC is usually thrombocytopenia, anemia or both followed by pancytopenia and aplastic anemia. Bone marrow specimens may be normocellular with time markedly hypocellular with devoid of hemopoietic cells. Our Patient showed pancytopenia in CBC and hypocellular marrow was present in bone marrow examination specimen. Some patients have decreased B/T lymphocyte counts, reduced or elevated immunoglobulin value.

DC is genetically heterogenous, patients have mutations in genes that encode components of telomerase complex. X-linked recessive DC maps to X q28, many mutations identified in the DKC1 gene. Autosomal dominant inheritance DC is caused by mutations occur in (TINF2, TERC, TERT). Autosomal Recessive DC is linked to mutations in (NOP10, NHP2, PARN). Impaired telomere maintenance in all 3 inherited forms of DC. Extremely short telomeres (<1st percentile for age) are demonstrated in the

peripheral blood cell by FISH.⁴ We confirmed our case DC by chromosomal analysis FISH and microarray genotyping. Microarray genotyping showed DKC1 gene abnormality. Cancer develops in approximately 10-15% patients with DC usually in 3rd and 4th decades of life. Patients with DC are predisposed to AML, MDS and solid tumor. Androgens can induce improvement of bone marrow function in approximately 70% patients, and in some this treatment can result in normal trilineage blood counts for a number of years. Our patient responded to Androgen therapy. There is little published information on the use of immunosuppressive therapy for DC patients. Allogeneic Hemopoietic Stem Cell Transplantation is only curative option for severe bone marrow failure, MDS, and AML.⁴

Patients with genetic abnormalities (TERC, TERT) may develop aplastic anemia or fibrosis of lungs and liver. But these complications may develop on in life. Patients with certain genetic groups (DKC1, TINF2, PARN) have a higher incidence and earlier onset of aplastic anemia and cancer. The mean age of death for DC patients who are diagnosed in childhood is approximately 30 years. The main cause of death are bone marrow failure, fatal pulmonary problems and GI bleeding.⁴

Conclusion:

Our Dyskeratosis Congenita patient presented with history and clinical features of Bone marrow failure along with muco-cutaneous triad of DC. By evaluating muco-cutaneous triad we differentiated DC from

Acquired Aplastic Anemia. FISH and Microarray genotyping can confirm DC as in our case and treatment protocol was changed. So if physician finds history and clinical features of Bone marrow failure, he must search for other clinical manifestations to exclude Inherited Aplastic Anemia.

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