



## A Rare Genetic Disorder Dyskeratosis Congenita with Vivid Manifestations

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### ABSTRACT

*Dyskeratosis congenita (DC) is a rare disease with an estimated annual incidence of, <1 in 1 million, with multiple and variable clinical manifestations. It is also known as Zinsser-Engman-Cole syndrome, have progressive bone marrow failure syndrome characterized by the triad of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia. Telomerase dysfunction, ribosome deficiency, and protein synthesis dysfunction evidence exists in this disorder. Early mortality is often associated with bone marrow failure, infections, fatal pulmonary complications, or malignancy. We report two cases of DC one with left hip avascular necrosis and other with fatal pulmonary complications, multidrug resistant pulmonary tuberculosis. First patient had onset of symptoms at 10 years of age with lacy reticulated pigmentation over face, neck, upper chest, forearms and hands, nail dystrophy, intraoral lichenoid pigmentation and rough, sparse greyish hair and painful left hip joint. Episodes of severe anaemia managed with blood transfusions. No features suggestive of GIT, pulmonary and neurological involvement and no evidence of any malignancy were seen in first case. Avascular necrosis of hip joint is a still rare association with DC. He was managed with supportive treatment and left hip replacement surgery. Second case had skin and mucosal manifestations with total teeth loss by the age of 26 years, sensory neural deafness in left ear, drug resistance pulmonary tubercular infection as bone marrow failure resulted in immunosuppressive state in this case. Ultimately the patient succumbed to pulmonary manifestations of DC in the form of opportunistic infection.*

**Keywords:** avascular hip necrosis, dyskeratosis congenital, reticular pigmentation, bone marrow failure, drug resistant pulmonary tuberculosis.

### INTRODUCTION

Dyskeratosis congenita (DC) is a rare, hereditary disease, which was first described by Zinsser in 1906.<sup>(1)</sup> Dyskeratosis is Latin and means the irreversible degeneration of skin tissue, and

congenita means inborn. It is an inherited bone marrow failure (BMF) and cancer predisposition syndrome caused by defects in telomere biology. The consequences of DC affect all body systems; these may include the diagnostic triad of abnormal

nails, reticular skin pigmentation, and oral leukoplakia. BMF, pulmonary fibrosis, liver disease, neurologic and ophthalmic abnormalities and increased risk for cancer also occur.<sup>(2,3)</sup> The known clinical complications are listed in Table 1.<sup>(2,4)</sup>

Clinical features in DC	
Systems	Findings
Dermatologic	Lacy, reticular hyper pigmentation, primarily of the neck and chest; subtle or diffuse hyper- or hypo pigmentation, Abnormal finger and toe nails, Early gray hair or hair loss and hyperhidrosis.
Growth and Development	Short stature, Intrauterine growth retardation, Developmental delay.
Ophthalmic	Epiphora, Blepharitis, Sparse eyelashes, ectropion, entropion, trichiasis, Exudative retinopathy.
Dental	Caries, periodontal disease, decreased root/crown ratio, Taurodontism (enlarged pulp chambers of the teeth).
Ears, Nose and Throat	Oral leukoplakia, lichen planus like oral pigmentation, Deafness (rare), head and neck cancer.
Cardiovascular	Atrial or ventricular septal defects, fibrosis, dilatated cardiomyopathy.
Respiratory	Pulmonary fibrosis.
Gastrointestinal	Esophageal stenosis, Enteropathy, Liver fibrosis
Genitourinary	Urethral stenosis in males, Epithelial cancers
Musculoskeletal	Osteoporosis, Avascular necrosis of the hips and shoulders
Neurologic	Developmental delay, Microcephaly, Cerebellar hypoplasia Intracranial calcifications .
Psychiatric	Schizophrenia
Endocrine	Hypogonadism
Hematologic	Bone Marrow Failure a common presenting sign, Myelodysplastic Sydrome, Leukemia.
Immunologic	Immunodeficiency

**CASE REPORT**

A 25 year old male presented to the department of dermatology with lacy reticulated pigmentation for last 15 years distributed over face, neck, upper chest, forearms and hands. There was associated nail dystrophy for the last 13 years, intraoral pigmentation and avascular necrosis of the left hip though the patient was not on any systemic steroid therapy for the last 10 years. He also had rough and sparse hair along with premature canitis. There was past history of suffering from a single episode of

severe anaemia at 10 years of age for which three blood transfusions were given (Table 2). There was no history of associated hyperhidrosis, deafness, epiphora, respiratory complaints, developmental delay or neurological and psychiatric symptoms. He had three sibling two sisters and one brother all were normal, also there was no history of similar complaints in first or second cousins.

**Table 2.** Sequelae of events in the development of disease.

AGE	SIGNS & SYMPTOMS	TREATMENT
10 years	Severe anaemia	Blood transfusions
10 years	Hyper and hypopigmented areas all over the body.	Vitamin supplements, topical cream
12years	Nail atrophy of toes,diffuse skin pigmentation	Supportive treatment
15 years	Pain left hip joint radiating to knee joint	Hip replacement surgery but postponed due to severe anemia.

**CUTANEOUS EXAMINATION:** Lacy reticulated pigmentation with interspersed areas of hypopigmented macules distributed over face, neck, upper chest, back, forearms and hands[Figure – 1.1, 1.2 & 1.3]. Premature canities and dystrophic finger and toe nails. [Figure1.3&1.4]. Diffuse lichenoid intraoral pigmentation [Figure1.5]. trichiasis and lid margin pigmentation [Figure 1.6] .



FIG 1.1: Lacy reticulate pigmentation



FIG 1.2: Hyperkeratosis of palms.



FIG 1.5: Lichenoid intraoral pigmentation



FIG 1.3: Nail dystrophy of hands

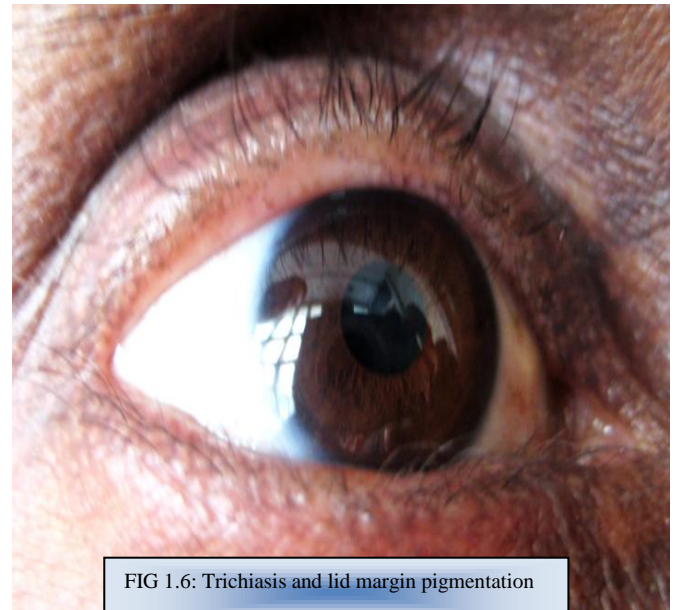


FIG 1.6: Trichiasis and lid margin pigmentation

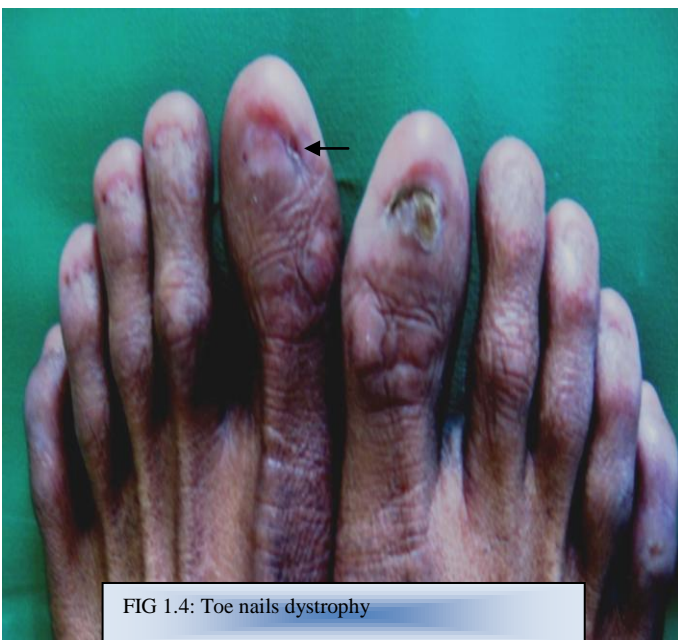
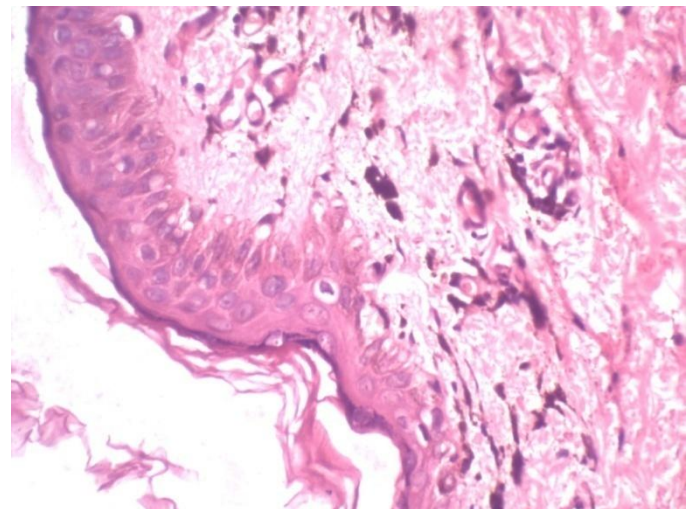
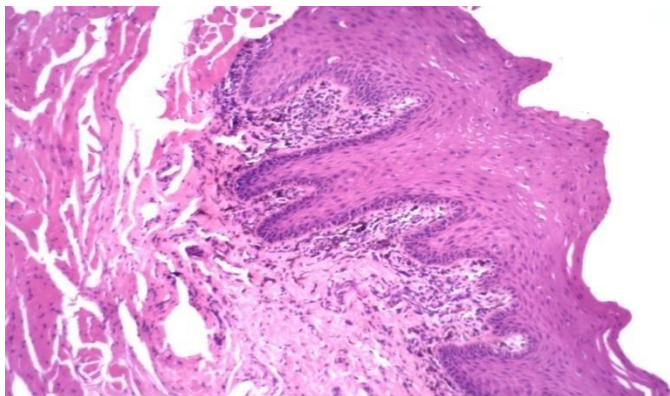


FIG 1.4: Toe nails dystrophy



Cutaneous biopsy revealed epidermal atrophy and melanophages in dermis.



Mucosal biopsy revealed histopathological changes consistent with lichen planus.

**INVESTIGATIONS:** Routine biochemical investigations were normal. Hemoglobin (Hb) was 8.4 g/dL, total leucocyte count 12,450/cmm with a differential count of N64,L36,M0 and platelet count of 119,000/ $\mu$ L. Peripheral blood smear and bone marrow aspirate examination revealed hypoplastic anemia. Pulmonary Function Test, E.C.G. and Echocardiography were normal. Skiagram of chest and skull were normal, C.T. head was normal. USG abdomen, kidney and urinary bladder revealed no abnormality. Eye examination revealed bilateral lid margin pigmentation and trichiasis, slit lamp and fundus examination was normal. Ear, nose and throat examination was within normal limits. Genetic mutational analysis could not be done because of non affordability of the patient.

MRI of left hip joint: confirmed avascular necrosis.

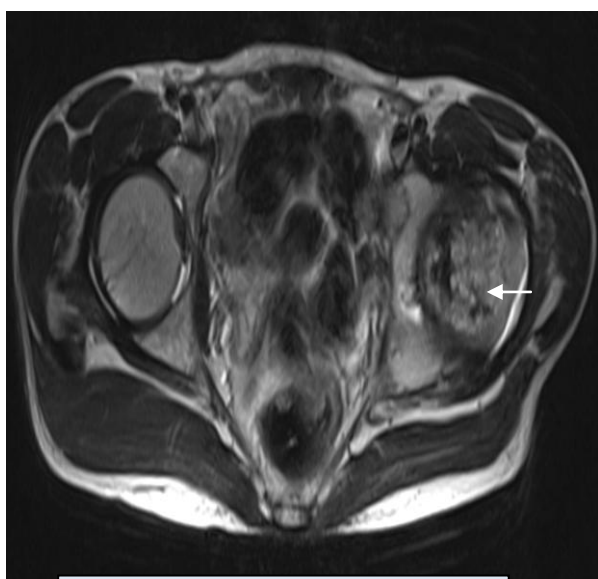


FIG 1.7: Transverse T<sub>2</sub>W image of hip joints

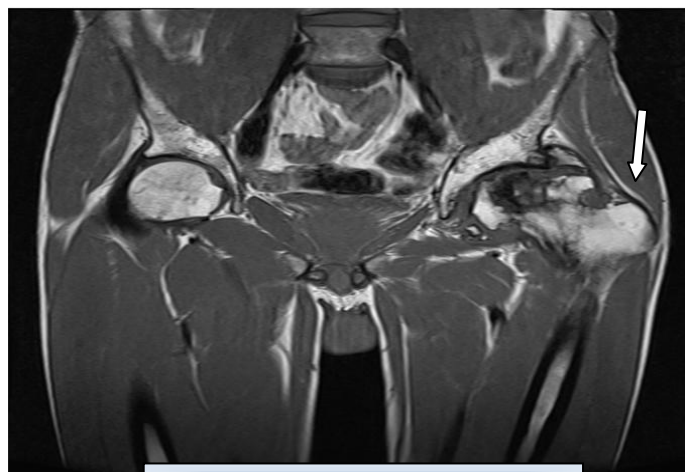


FIG 1.8: T<sub>1</sub>W image of hip joints

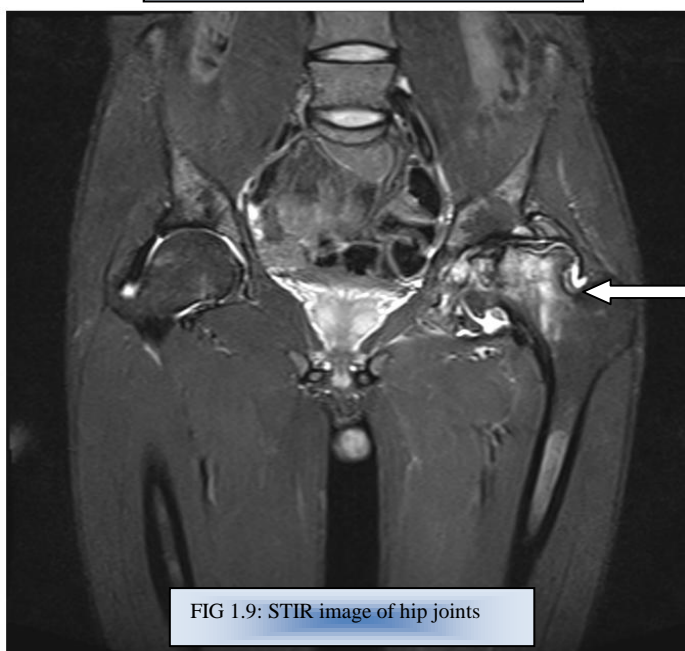


FIG 1.9: STIR image of hip joints

**MANAGEMENT:** Supportive therapy. Orthopaedic treatment, hip replacement surgery was done.

### Case 2

A 47 years male presented to the department of pulmonary medicine with a diagnosis of Koch's chest, with asymptomatic skin lesions, since early childhood as brownish discolouration with interspersed whitish lesions over nape of neck which progressively spread to involve the trunk and lower limbs. At the age of 26 years he lost all his teeth with in a period of 2 years. He noticed asymptomatic pigmentation over tongue and buccal mucosa. For few years he developed hearing loss in

left ear and dystrophy in toe nails in childhood. He had history of cough and sputum for last 20 years with severe dyspnoea from last 2 years. No urinary and bowel complaints, No complaints of vomiting, diarrhoea, haemoptysis and melena. He noticed significant weight loss over last 2 years. He was treated for Koch's chest 12 years back. Now his sputum examination by concentration method revealed acid fast bacilli (AFB) and was started on anti tubercular medication.

In family no similar illness in the sibling, but one of his two sons, who is 6 years old had oral pigmentation, mongolian spots and nail dystrophy with anaemia and one 13 year old daughter has only nail dystrophy.

On general physical examination he had thin built with poor nutrition, pale, emaciated look, pedal oedema, with cervical and axillary lymphadenopathy.

#### MUCO-CUTANEOUS EXAMINATION

Over neck, chest, trunk, and extensors of the extremities revealed reticulate brownish hyperpigmentation interspersed hypopigmentation. Oral and tongue mucosa showed lichenoid reticulated pigmentation. All the teeth were lost. Nail dystrophy in left foot toe nails and mild changes in finger nails.

**On investigations** Complete haemogram:- Hb 7.1gm%, TLC 5.65m/mm<sup>3</sup>, platelets 1.5m/mm<sup>3</sup> ESR 110mm/1<sup>st</sup> hr with peripheral smear showing picture consistent with diamorphic anemia.

**Bone marrow examination:-** Revealed diamorphic anemia predominantly megaloblastic with no evidence of malignancy and no parasites or granuloma.

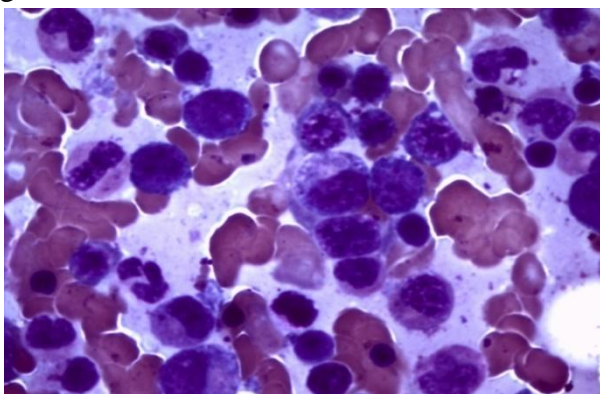
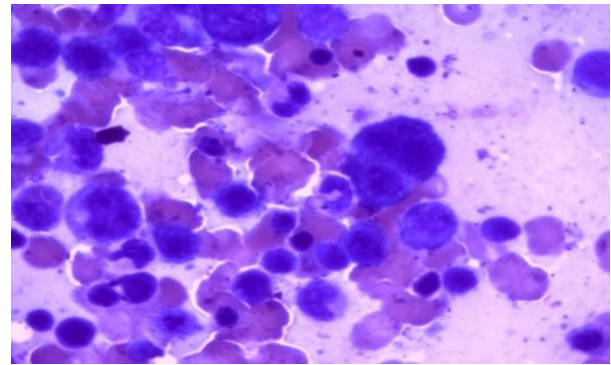
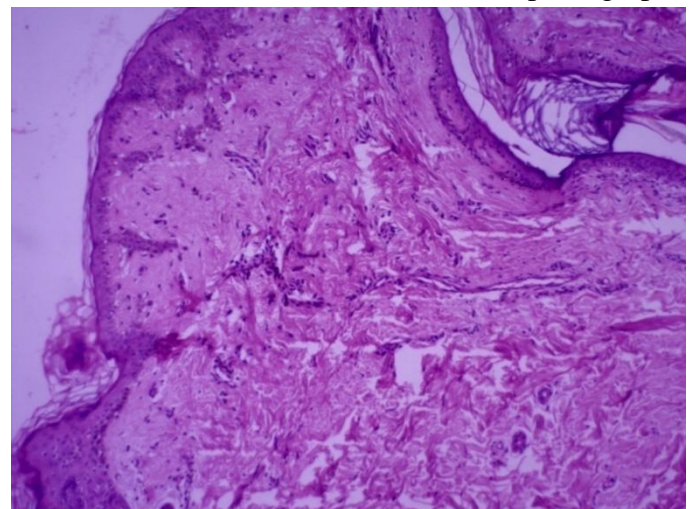


Figure a and b

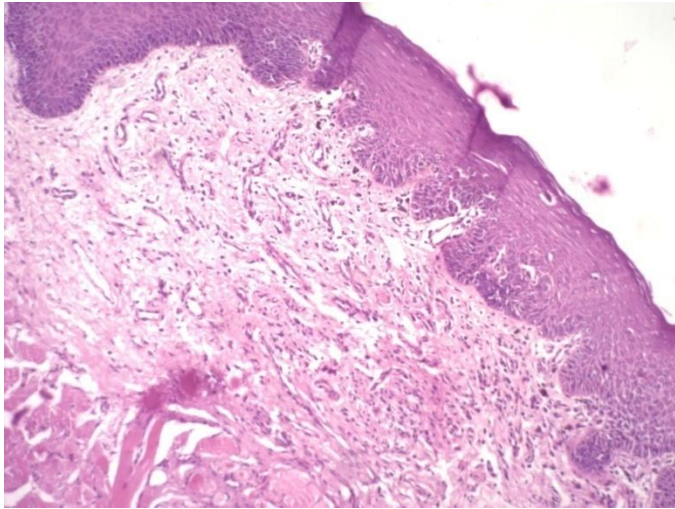


Bone marrow revealed dimorphic Anemia (predominantly megaloblastic picture, no evidence of any granuloma or malignancy) in figure a and b.

HIV serology was non reactive. Bio-chemistry was normal, Fasting blood sugar 68mg%. Skin biopsy revealed keratinising stratified squamous epithelium with focal basal layer vacuolization. Upper dermis reveals numerous scattered melanophages along with mild mononuclear inflammatory cell infiltrate and was consistent with dyskeratosis congenita as shown below in this histomicrophotograph.



Mucosal biopsy revealed stratified squamous epithelium with acanthosis mild parakeratosis with focal spongiosis. Upper dermis reveals numerous scattered melanophages along with lymphocytic infiltrate as seen in the following microhisto-photograph.



On chest X ray examination left hemi-thorax shows in-homogenous opacity with plural effusion and pleural thickening, Rt. upper zone shows in-homogenous opacity with fibrotic bands. Eye examination on slit lamp revealed maculopathy. ENT examination showed wax in Rt. ear with sensory neural hearing loss on PTA examination. He was diagnosed a case of multidrug resistant (MDR) pulmonary tuberculosis. After streptomycin injection he developed acute urticaria and angioedema so streptomycin was stopped and maintained on etheonamide 250mg bd, pyraznamide 1000mg od, ethambutol 800mg od, levofloxacin 750mg od, ciloserine granules 1tsf tds with lemon juice, and tricox 250mg bd. Along with iron & multivitamin supplementation.

Subsequently he developed depressive symptoms and was started on duloxetine 20mgbd and clonazepam 0.5mg hs. He was again admitted after 4 months with complaints of pain abdomen with ascitis, anasarca, for 2 months, hypothyroidism, malnutrition, hypotension, prolapsed haemroids and severe anemia.

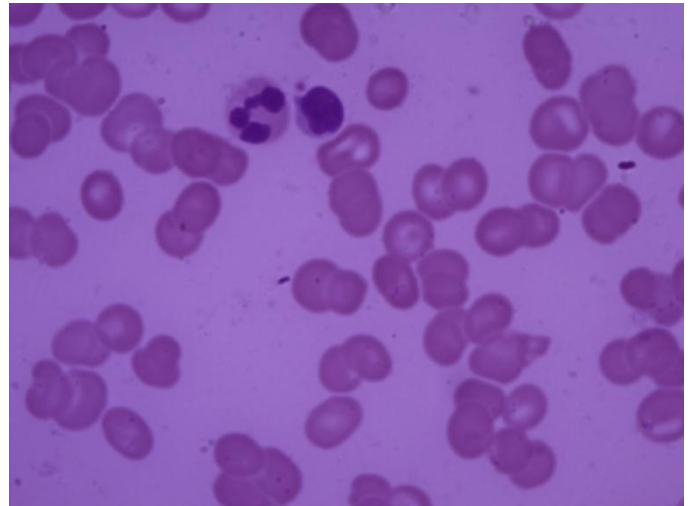
**On investigations** Severe anemia--- Hb 5.5gm, TLC 2.94million/cmm, ESR-80mm,

**Peripheral smear** revealed anisocytosis with predominant macrocytes, schistocytes, with moderate hypochromasia and reduced platelets with overall picture of diamorphic anemia.

Blood sugar-80mg%, proteins 6gm, Alb-2.2gm, Bil.-0.4mg, SGOT/SGPT—27/15, Urea 11mg%, creatinine—0.4mg%, with normal electrolytes.

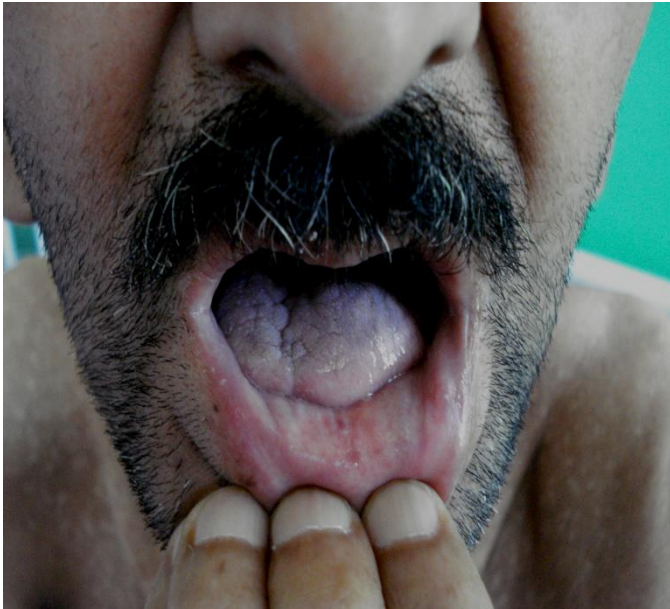
**Urine examination** ---albumin traces, no sugar, puscells—10-20/hpf, RBC--15-16/hpf, 24hrs urine—260mg/L proteins. Urine culture---sterile.

**Sputum** examination became negative for AFB even with conc. method. **Plural fluid** Proteins 1gm%, ADA --12U/L. **Peritoneal fluid**---WBC—160/cmm, Lymphocytes—25/cmm, PMNC—15/cmm, ADA -16U/L. **Ascitic fluid** revealed occasional macrophages, degenerated mesothelial cells with neutrophils, and occasional lymphocytes with no malignant cells.



**On USG Abdomen** shows ascitis with no lymphadenopathy, or mass.

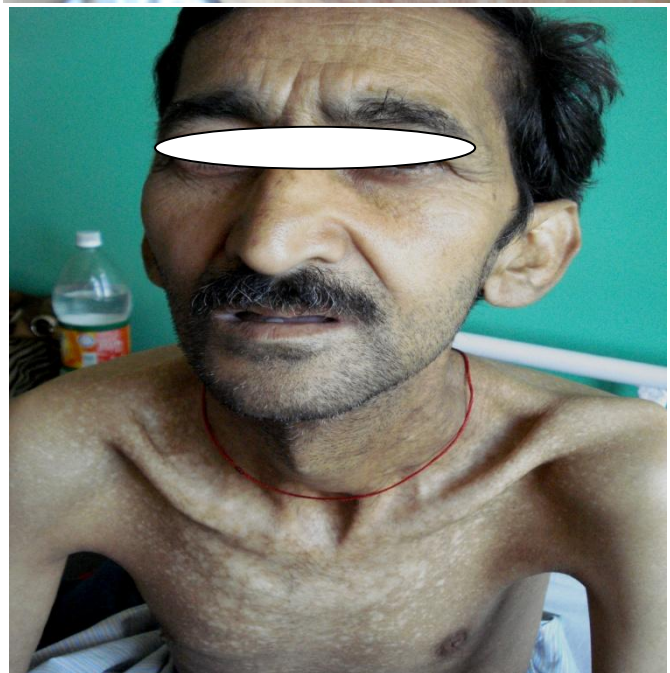
**Echocardiography** revealed pulmonary arterial hypertension with TR with pericardial effusion with normal LV/RV systolic function. He was managed on mycopas granules 1tsf with fruit juices modified ATT (pyrizinamide 1500mg, ethambutol 800mg and tricox 250mg tds). Thyronine 50ug daily, along with multiple blood transfusions and albumin transfusions with high protein diet. Dopamine drip was started to treat fluctuating BP with vital monitoring, frequent ascetic taps were done. Sclerotherapy was done for prolapsed haemorrhoids (grade 2). He developed oral thrush for which started on fluconazole 150mg daily. But he succumbed to the illness and died due to sudden cardiopulmonary arrest.



Total teeth loss with lichenoid pigmentation over tongue.



Lacy reticulate pigmentation of back and trunk.



Lacy reticulate pigmentation over face, neck, chest.



Nail dystrophy and pigmentation of hands



Normal teeth in the child.



Nail dystrophy in the child

## DISCUSSION

Dyskeratosis congenita (DC) is an inherited disorder of the mucocutaneous and hematopoietic systems in association with somatic abnormalities. DC can be a fatal condition with multisystem manifestations. The clinical diagnosis of classical DC requires at least two features of the triad of dysplastic nails, lacy reticular pigmentation of the upper chest or neck, and oral leukoplakia. <sup>(2,4)</sup>

Skin and nail findings usually become apparent in the 1st 10 year of life, whereas oral leukoplakia is seen later. <sup>(5)</sup>

The pattern of inheritance may be X-linked (Zinsser-Cole-Engleman syndrome), autosomal dominant (dyskeratosis congenita, Scoggins type) or

autosomal recessive. However, in a large proportion of patients dyskeratosis congenita occurs sporadically.

Approximately 85% of patients are male, compatible with X-linked recessive inheritance. Approximately 15% of patients appear to have either autosomal dominant or autosomal recessive modes of inheritance. The X-linked recessive form of DC maps to Xq28, and many mutations have been identified in the *DKCI* gene, which codes for the nuclear protein dyskerin. Dyskerin may be involved in ribosomal assembly and RNA production. The autosomal dominant form is due to mutations in the *TERC* gene that encodes the RNA component of telomerase that is responsible for telomere maintenance. Lack of the protein telomerase contributes to the aging process and stem cell death.

In our patient systemic involvement was in the form of bone involvement as his left hip joint showed avascular necrosis without any systemic steroid therapy and episodes of severe anemia (bone marrow failure). Only few reports of hip joint aseptic/avascular necrosis are there in literature. Osteoporosis and the associated risk of fracture are major clinical challenges.

The marrow failure may be due to progressive attrition and depletion of hematopoietic stem cells, which manifests as pancytopenia. Alternatively, marrow dysfunction may represent a failure of replication and/or maturation of stem cells. Constitutional pancytopenia; aplastic anemia occurs in approximately 50% of cases, usually in the 2nd decade of life. Patients also have a predisposition to cancer and MDS.

Bronchopulmonary manifestations of DC can be divided into three groups; 1] opportunistic infections such as pneumocystis carinii pneumonia <sup>(6)</sup>, 2] allergic lung diseases like asthma and 3] interstitial pneumonitis. In DC patients, immunological abnormalities such as T-cell immunodeficiency, decreased natural killer cell activity and a deficit of cell-mediated immunity have also been reported. Opportunistic infections are thought to ensue as a result of these



immunodeficiency and frequently complicated by haematological abnormalities.<sup>(7)</sup> Our second patient had severe pulmonary involvement in the form of opportunistic infection (MDR pulmonary tuberculosis). Interstitial lung fibrosis is common presentation in patients of DC.

BMF is the most frequent complication of DC in children, whereas adults suffer from pulmonary fibrosis which may be the cause of mortality. Pulmonary fibrosis, characterized by loss of lung epithelium, prominent fibrosis, and impaired gas exchange and abnormalities of pulmonary vasculature are seen in about 80% of cases.<sup>(8)</sup>

There is no effective and curative treatment for DC. The most serious aspect of dyskeratosis congenita, bone marrow failure, is treated with Erythropoietin, that stimulates the production of red blood cells, and Neupogen, which stimulates the production of white blood cells.<sup>(9)</sup> Androgen therapy may improve but not cure aplastic anemia. Colony-stimulating factors used to stimulate bone marrow in patients with cytopenia of one or more cell lineage. Stem cell transplantation is recommended if there is an HLA matched sibling donor. Chemotherapy with bleomycin or cyclophosphamide is effective for treating leukoplakia associated with DC.<sup>(1)</sup>

Vitamin A derivative, etretinate is effective for treating leukoplakia in DC.<sup>(10)</sup> In future gene therapy can provide an alternative therapy for management of this fatal condition.

## CONCLUSION

This rare disease of vivid manifestations can be easily suspected or diagnosed if asymptomatic cutaneous features are noted early and taken seriously and further the patient should be kept under surveillance to manage the risks of BMF and consequences of systemic involvements, including early onset of malignancy in dyskeratosis congenita. High index of suspicion and multispecialty consultation approach is required for correct diagnosis and management of this rare disease.

## REFERENCES

1. Tanaka A, Kumagai S, Nakagawa K, Yamamoto E. Cole-Engman syndrome associated with leukoplakia of the tongue: a case report. *J Oral Maxillofac Surg* 1999; 57:1138-41.
2. Drachtman RA, Alter BP. Dyskeratosis congenita: clinical and genetic heterogeneity. Report of a new case and review of the literature. *Am J Pediatr Hematol Oncol* 1992; 14(4):297-304.
3. Walne AJ, Dokal I. Dyskeratosis congenita: a historical perspective. *Mech Ageing Dev* 2008; 129(1-2):48-59.
4. Dokal I. Dyskeratosis congenita in all its forms. *Br J Haematol* 2000; 110(4): 768-79.
5. Melvin H. Freedman. Kliegman: Nelson Textbook of Pediatrics, 18th ed. The Pancytopenias ch 468.
6. Wiedemann HP, McGuire J, Dwyer JM, et al. Progressive immune failure in dyskeratosis congenita. Report of an adult in whom pneumocystis carinii and fatal disseminated candidiasis developed. *Arch Intern Med* 1984; 144: 397
7. Imokawa S, Sato A, Toyoshima M, Yoshitomi A, Tamura R, Suda T, Suganuma H, Yagi T, Iwata M, Hayakawa H, et al. Dyskeratosis congenita showing usual interstitial pneumonia. *Intern Med*.1994; 33(4):226-30
8. Fernández García MS, Teruya-Feldstein J. The diagnosis and treatment of dyskeratosis congenita: a review. *J Blood Med*. 2014; 5:157-67.
9. Erduran E, Hacisalihoglu S, Ozoran Y. Treatment of dyskeratosis congenita with granulocyte-macrophage colony-stimulating factor and erythropoietin. *J Pediatr Hematol Oncol*. Apr 2003; 25(4):333-5.
10. Tomita K, Ishii M. A case of Cole-Engman syndrome: Effect of etretinate on the oral leukoplakia. *Acta Dermatol Kyoto* 1992; 87:567.