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DYSKERATOSIS CONGENITA: CASE SERIES AND LITERATURE REVIEW

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ABSTRACT

Dyskeratosis congenita (DC) is complex, multisystem inherited disorder which classically presents as a triad of abnormal skin hyperpigmentation, nail dystrophy and oral leukoplakia. Oral physicians may be the first to see and diagnose DC and have important role in monitoring the oral malignant changes in white keratotic plaque in oral cavity. Aim of this paper is to present four rare and unique cases of DC with classic triad which are described in two females and two male patients. One of the females had squamous cell carcinoma of right buccal vestibule. Also this paper reports comparative assessment of different global DC cohorts. India has been consistently under-represented in these cohorts. This is one of the first reported cases of oral squamous cell carcinoma (SCC) in DC in Indian population. It contributes in increasing awareness that tobacco use acts as a complicating factor for oral SCC in Indian DC patients and its use should be discouraged. Its presence in DC reflects that leukoplakic lesion needs to be closely monitored for carcinoma.

KEYWORDS: Dyskeratosis congenita, Oral squamous cell carcinoma, DC cohorts.

INTRODUCTION

The term “dyskeratosis congenita” was coined by Zinsser in 1910 after noticing the classical triad of abnormal skin hyperpigmentation, nail dystrophy and oral leukoplakia. Later cases also reported of other medical and systemic complications.[1]

The minimal clinical criteria for diagnosis include the occurrence of at least 2 of the 4 major features (reticulated skin hyperpigmentation, nail dystrophy, oral leukoplakia, and bone marrow failure) and 2 or more of the other systemic features that are acknowledged to occur in dyskeratosis congenital (DC).[2]

DC is known to associate with telomerase dysfunction, ribosome deficiency, and protein synthesis dysfunction.[3] Leukoplakic regions are also more prone to malignant transformation.[4] Oral physicians may be the first to see these cases and have important role in diagnosis and monitoring the oral malignant changes in oral white keratotic plaque. The aim of this paper is to increase the awareness of DC in clinicians as described in the case series.

CASE ILLUSTRATION

Case 1

A girl aged 20 years reported with a white patch on hard palate since 6 months.
She was apparently normal till the age of 8 years, when she started developing symptoms as summarised in table 1, on the basis of which diagnosis of DC was made.

Case 2

Younger sibling of case 1, aged 16 years, male presented with a white patch on palate. His milestones were normal up to 1 year after which they slowed down. Patient has been chewing tobacco 1-2 times/day since 1 year. Patient’s clinical and lab findings are summarised in table 1, based on which the case was identified as DC.

Case 3

Female aged 15 years reported with pain and hard swelling over right buccal mucosa. She showed pallor of face with all vitals normal. She was apparently normal till the age of 5 years, but started developing symptoms, summarised in table 1.

Extraoral examination revealed pus discharging sinus located 1cm inferolateral to right angle of mouth. Right submandibular lymph nodes were non tender, hard and fixed.
Incisional biopsy of right lower gingivobuccal sulcus revealed presence of squamous cell carcinoma. TERF1

(Telomeric repeat binding factor) interacting nuclear factor 2 (TINF2) gene hot spot mutation was noted on mutation analysis**.** Diagnosis of DC was made on the basis of clinical features, lab and radiographic findings (Table 1).

Similar findings were present in the younger sibling of this case, who had history of pancytopenia and died at the age of 8 years because of excessive blood loss after a traumatic accident.

Case 4

Father of case 3, 38 years, presented with a white patch on tongue. He was asymptomatic till the age of 8 years, thereafter started developing symptoms summarised in table 1.

TINF2 gene hot spot mutation was evident by mutation analysis. Diagnosis was made on the basis of clinical and lab findings (Table 1).

Table 1: Sequelae of events in development of disease.

Features	Case 1 (Figure 1)		Case 2 (Figure 2)		Case 3 (Figure 3)		Case 4 (Figure 4)		
	+/-	Age (years)	+/-	Age (years)	+/-	Age (years)	+/-	Age (years)	Median (Mean) age in years
Hyperpigmentation	+	8	+	5	+	5	+	8	6.5(6.5)
Hyperhidrosis	-		-		+	7	-		7(7)
Nail dystrophy/ splitting/ cracking	+	10	+	11	+	5	+	10	10(9)
Pulmonary involvement/ tuberculosis (pulmonary/ abdominal)	+	16	-		+	12	+	13	13(13.6)
Oral carcinoma	-		-		+	14	-		14(14)
Aplastic anaemia	+	15	+	14	+	12	+	32	14.5 (18.25)
Aggressive periodontitis	+	18	+	14	+	12	-	16	15(15)
Leukoplakia	+	20	+	15	+	10	+	22	17(16.7)
Ocular involvement/ bulbar conjunctivitis	-		-		-		+	20	20(20)
Gastro esophageal reflux disease (GERD)	-		-		-		+	20	20(20)
Hepatic involvement/ Cirrhosis of liver/ Portal hypertension	-		-		-		+	37	37(37)
Gene mutation test (TINF 2 gene hot spot mutation)	-		-		+	11	+	35	23(23)

Table 2: Global collection of DC cases as reported by different groups.

	United Kingdom based Dyskeratosis Congenita Registry (DCR)[16]	National Cancer Institute's Inherited Bone Marrow Failure Syndrome (NCI IBMFS) Dyskeratosis Congenita cohort[17]	Cumulative record of literature reports of DC maintained by author (Alter et al) [18]	Present case series
Duration (years)	1995-1999	2002-2007 followed up to 2008	1910-2008	2011-2015
Total number of cases	148	50 (32 families)	552 (278 reports)	4 (2 families)
Total number of DC cancer cases	13 (8.78%)	7 (14%)	51 (60 cancers) (9.23%)	1 (25%)
Total number of	2	3	24 HNSCC	1

oral/HN cancer cases	(1.35%)	(6%)	(22 patients) (4.34%)	(25%)
Male: female ratio (DC cases)	6:1	2.8:1	3.1:1	1:1
Male: female ratio (DC cancer cases)	ING	ING	4.2:1	0:1
Median age of DC cancer (years)	ING	37 (25-44)	29	14

**ING= Information Not Given, **HN= Head and neck, ***HNSCC= Head and neck squamous cell carcinoma*

Figure legends

Figure 1. Clinical images. A. Leukoplakic patch on palate. B. Atrophied tongue associated with pigmentation. C. Dystrophied/absent finger nails. D. Hyperpigmentation on skin and dystrophied toe nails.

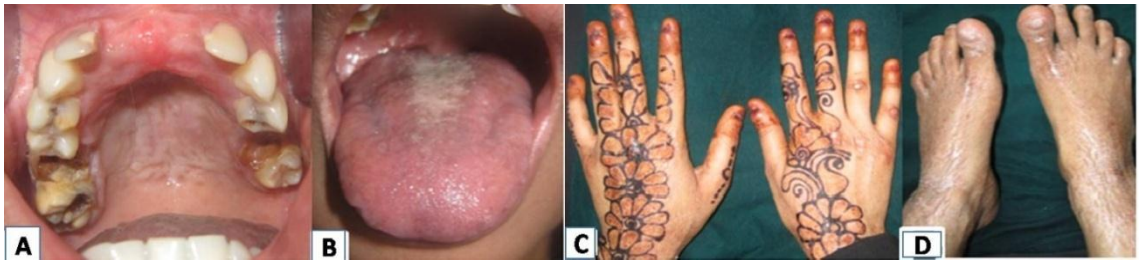

Figure 1.

Figure 2. Clinical Images. A. Leukoplakic patch on palate. B. Atrophied tongue associated with pigmentation. C and D. Hyperkeratotic skin associated with dystrophied nails.

Figure 2.

Figure 3. Clinical, radiological and histopathological Images. A. Chronic ulcer seen on buccal mucosa adjacent to 46(➞). B. Leukoplakic patches associated with pigmentation on tongue. C. Dystrophied/absent nail. D. Panoramic view showing generalised decreased root crown ratio and taurodontism of posterior teeth. E. MRI axial view showing heterogenous enhancing soft tissue involving lower right buccogingival sulcus. F. Invasive islands and chords of malignant squamous epithelial cells in the connective tissue.

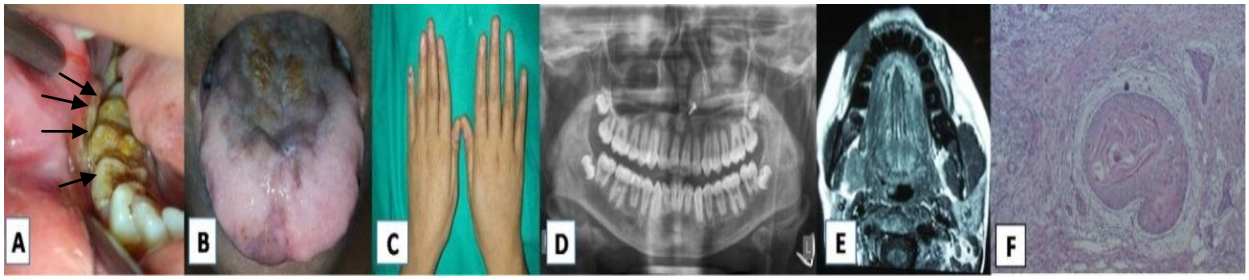

Figure 3.

Figure 4. Clinical Images. A. Leukoplakic patches associated with pigmentation on tongue. B. Leukoplakic patch on palate. C and D. Hyperpigmented skin associated with dystrophied nails. E. Hyperpigmented skin of neck, chest and trunk.

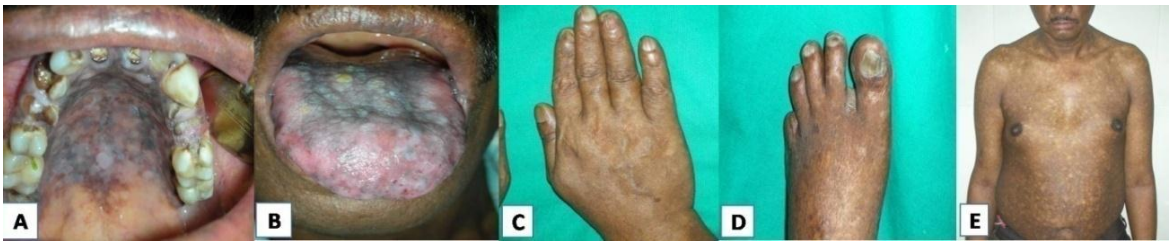

Figure 4.

DISCUSSION

DC is a fatal disease involving multiple systems of the body**.** It continues to be of interest to the clinicians and researchers because its inadequately known pathogenesis. Although rare, its ramifications can be devastating for patients and their family members. [5] It is a complex inherited syndrome which occurs approximately in 1 in 1 million people and is mostly X linked inherited with male predilection and male: female ratio of 13:1.[5] Rarely, it occurs in females which show its inheritance as autosomal dominant trait in some subsets.[6] Interestingly this series presents an equal gender distribution.

DC patients show involvement of both the hard and soft tissues of the oral cavity, with 80% of them demonstrating oral leukoplakia,[7] which was seen in all the reported cases. Common sites for white patch in oral cavity are buccal mucosa, tongue or palate, with tongue most commonly affected[8] as also seen in three of our patients. Additionally palate and alveolar ridge was affected in case 1. In DC patients, associated white patch is mostly leukoplakia,[4] as seen in our cases, but lichen planus or lichenoid lesions are also reported.[4]

Prevalence of mucous malignant changes is usually increased, mainly squamous cell carcinoma of mouth, nasopharynx, oesophagus, rectum, vagina and cervix, manifesting mostly in third decade of life as reported in previous cases.[9] Contrastingly in our third case, oral squamous cell carcinoma was diagnosed in second decade of life.

Periodontal disease may also have increased prevalence and manifestations are severe.[10] Gingival inflammation, bleeding, recession and bone loss are the usual manifestations.[11] All of our patients demonstrated similar findings.

Dental caries may be present due to the defect in structure of the enamel like hypocalcification in DC patients.[12] Hypocalcified teeth were noted in the male patients only and one female showed high caries index. Other oral manifestations are reduced root/crown ratio and mild taurodontism.[1] Taurodontism was seen in case 3. Panoramic view of other three patients had no significant radiographic finding.

DC patients usually show dermatologic involvement as reticular hyperpigmentation of skin. Such pigmentation was observed in our patients over the skin of limbs, chest, trunk and back.[7] Nearly 90% of the patients show dystrophy of nails and may manifest along with commencement of skin pigmentation. Longitudinal splitting and furrowing of nails can be observed as nail defects.[7] In Case 3, skin and nail changes started simultaneously.

About 90% DC patients have peripheral cytopenia of one or more lineages,[13] this is supported with the haematologic picture of all four cases. In few cases, this is the early finding, with a median age of onset of 10 years.[13] In our cases median age of onset was 14.5 years.

In about 20% of DC patients pulmonary complications like pulmonary fibrosis and abnormalities of pulmonary vasculature have been reported.[7] Case 1 and 4 had pulmonary tuberculosis while case 3 had abdominal tuberculosis. This brings forth the recent upsurge of extrapulmonary tuberculosis cases reported in the literature.[14] Clinicians working with DC cases should therefore be aware of existence of extrapulmonary form of TB. Besides non specific interstitial pneumonia with fibrosis pattern and pulmonary hypertension is seen in case 4.

Gastrointestinal system abnormalities may also manifest as oesophageal webs, hepatosplenomegaly and cirrhosis.[7] In case 4, gastro esophageal reflux disease (GERD) and portal hypertension with cirrhosis of liver were present.

Ophthalmic abnormalities may also manifest in DC patients.[7] In present series, case 4 had bulbar conjunctivitis.Effective treatment for DC is still elusive. Interceptive and preventive methods can be used for which an early diagnosis is required.[15] All the above mentioned cases underwent episodes of platelet transfusion for recovery of thrombocytopenia. Case 1, 2 and 4 underwent Anti-Koch's Treatment (AKT) therapy for the treatment of tuberculosis. For squamous cell carcinoma, case 3 underwent right buccal mucosa

composite resection and marginal mandibulectomy. Patients are being closely monitored and recalled for periodic follow up.

It has been reported that multiple groups have been studying the global characteristics of DC. These groups include the UK DC registry, the NCI (National Cancer Institute) registry and the Alter et al cohort. There could be a possibility that an overlap of cases may exist within these groups. This reflects ambiguity in reporting DC cases. It is suggested that individual national registries or single global DC registry could exist globally for DC cases. We nevertheless attempted to–report comparative assessment of different DC cohorts (Table 2). India has been consistently under-represented in these cohorts.

The total DC cancer cases (DCCC) are less than 15% (Table 2) that is consistent in all the three groups and the total number of DC oral/HN cancer cases (DCOCC) are less than 7% in all the three groups. Total DC cases shows overall higher male proportion in all the three groups, the UK DC registry shows comparatively higher male predominance than other groups. The statistics for the present study (Table2) should be interpreted with caution because of relatively lesser DC cases reported. The high propensity of total % of DC, DC oral/HN cancer, the equal distribution of male to female DC cases, higher female DC cases and a lower median age for DC oral cancer needs to be reconsidered in future studies.

This is one of the first reported cases of oral squamous cell carcinoma (SCC) in DC in Indian population. This reflects that leukoplakic lesion needs to be closely monitored for carcinoma, especially given the culturally accepted tobacco consumption.

Ironically the third case in this series which presented with SCC was not associated with a tobacco habit. It will still be advisable to consider tobacco use as a complicating factor in Indian DC patients and its use should be discouraged.

CONCLUSION

We have presented four rare cases exhibiting the classical triad of DC along with various related manifestations that occurred over wide age of range. From a clinical outlook a diagnosis of DC should be considered if a patient manifests with leukoplakia, particularly in those with no history of tobacco use.

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