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CASE REPORT

Dyskeratosis congenita: oral hyperkeratosis in association with lichenoid reaction

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Dyskeratosis congenita is an inherited disorder that usually presents in males, consisting of a triad of leukoplakia of the mucous membranes, nail dystrophy and skin pigmentation. Whilst most cases are X-linked, autosomal dominant and recessive forms have also been reported. The significance of the condition lies in premature mortality arising from either bone marrow failure or malignant change within the areas of mucosal leukoplakia. We present a case (X-linked recessive form) where the classic triad of signs were present, along with the development of lichenoid reaction in the buccal and labial mucosa. This is believed to be the first case in which such a reaction has been noted together with the oral hyperkeratosis. The identification of a white patch within the mouth of a child, in the absence of any other obvious cause must arouse suspicion of this rare condition. All clinicians should be aware of this rare genetic disorder so that early referral can be made and appropriate management instigated.
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Introduction

Dyskeratosis congenita (DC) was first described nearly a century ago in 1906. It is a rare, inherited, multisystem disorder, which is also known as Zinsser-Engman-Cole syndrome, after its original descriptors (1–3). It usually presents in males and in its classical form is characterized by the triad of reticulate skin hyperpigmentation; nail dystrophy and mucosal hyperkeratosis (1–3). Whilst most cases are X-linked, autosomal dominant and recessive forms have been reported. The significance of the condition lies in premature mortality arising from bone marrow failure or malignant change within the areas of hyperkeratosis. Various mucocutaneous and non-mucocutanious manifestations have been reported, however progressive bone marrow failure is by far the most frequently encountered cause of premature mortality. The identification of a white patch within the mouth of a child in the absence of any other obvious cause should arouse suspicion of this rare condition. Dental surgeons may be the first health professional to come across this condition, and thus recognition of this disorder will enable early referral and appropriate treatment. The initial presentation of this case was reported in 1988 (4). We now present a detailed report of how his condition evolved, culminating with his eventual death at the age of 24. The development of lichenoid reaction/lichen planus in the buccal mucosa and lower lip is a previously unreported finding in association with the oral hyperkeratosis seen in DC.

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Case presentation

A 10-year-old Caucasian male was referred by his general dental practitioner for an opinion regarding a symptomless white patch on the dorsum of his tongue (Fig. 1). This lesion had been present for approximately 1 year before the patient had sought medical attention. He was seen initially by both ENT and Dermatology, who were unable to make a diagnosis. He was thus referred to the Dundee Dental Hospital for a further opinion. There had been no preceding history of bullae formation, ulceration, discomfort or bleeding and there was no obvious preceding factor or habitus that could be attributed to the formation of the lesion.

Past medical history revealed a history of dysphagia 1 year previously that had required an oesophagoscopy, which demonstrated a post-cricoid web and was subsequently removed. Otherwise the patient was fit and well, with no known drug allergies and no current medication.

On examination the patient appeared generally well, there was apparent increased reticular pigmentation around the anterior neck and upper chest, and slight dystrophy of the fingernails were noted. There was no regional lymphadenopathy associated with the patient's oral manifestation. Intraorally, white lesions were

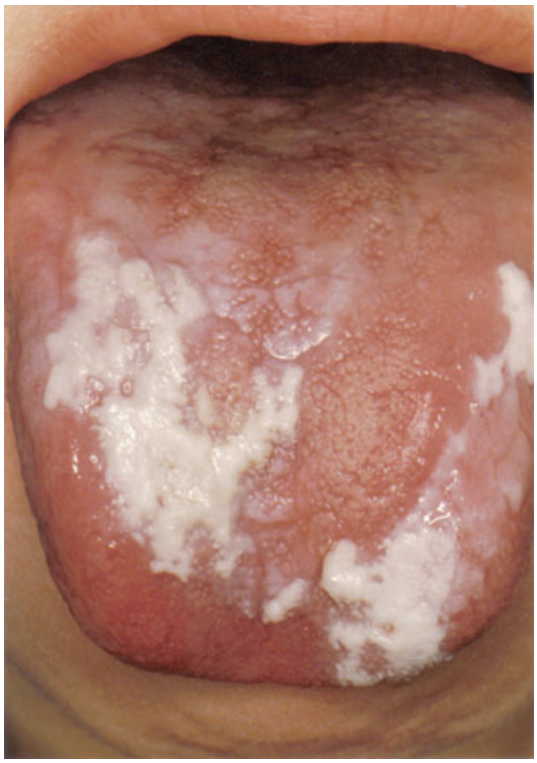

Figure 1 Oral leukoplakia of the dorsal tongue in a 10-year-old male Caucasian.

observed on the dorsum of the tongue bilaterally, encroaching the lateral borders. The lesions were of variable thickness and contour and could not be wiped away. The margins of the lesions were at certain points ill defined and there was evidence of some papillary atrophy. The tongue was soft, mobile and fully functional.

The differential diagnosis at the time consisted of candidal leukoplakia, white sponge naevus, lichen planus and DC. An incisional biopsy of the lesion on the dorsum of the tongue was performed under a general anaesthetic. The result obtained showed grossly hyperorthokeratinized epithelium of the dorsal tongue surface, a mild inflammatory reaction in the lamina propria, but no evidence of epithelial dysplasia. A bacterial plaque was present in the keratin surface, but there was no evidence of candidal infection. It was felt that in an adult patient this picture would be consistent with a benign hyperkeratotic lesion associated with chronic friction. But in a 10-year-old boy this was doubted. As there was no family history or systemic disturbance affecting keratinization no specific diagnosis could be made, however candidal infection was eliminated.

A diagnosis of DC was proposed, because of the history of oesophageal stricture, skin hyperpigmentation, oral mucosal leukoplakia and nail dystrophy. The patient was therefore kept under close review by both the oral and maxillofacial surgeons and the dermatologists. It was unfortunate to note that the patient began smoking 10–15 cigarettes per day between the years of 13 and 17.

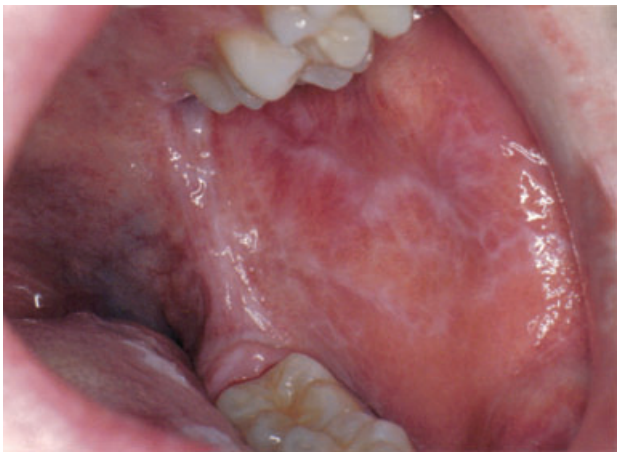

Figure 2 Lichen planus of the buccal mucosa in our patient with DC.

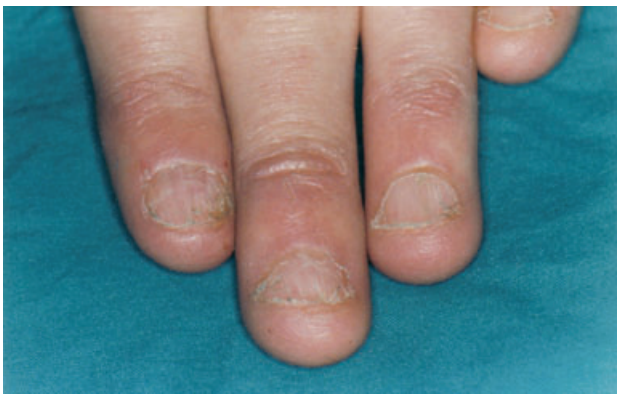

Figure 3 Dystrophic fingernails in our patient with DC.

Some 4 years later at the age of 14, despite no change in symptoms, the oral lesion were noted to be extending to involve the ventral surface of the tongue and new white lesions had developed, affecting the buccal mucosa bilaterally and the lower lip with a reticular pattern, consistent with a clinical diagnosis of lichen planus (Fig. 2).

At the age of 16 years, the patient had developed symptoms in his oral cavity of discomfort affecting the dorsum of the tongue, especially associated with the consumption of hot and spicy foods. It was also noted at this time that the patient's fingernail dystrophy had now considerably worsened (Fig. 3) and appeared to also be affecting the toenails.

A year later at the age of 17, a biopsy of the tongue lesions revealed the development of moderate epithelial dysplasia and laser excision of the lesion was organized. The patient had also at this time shown the first signs of haematological disturbance, with a mild thrombocytopenia although this had not resulted in clinical symptoms. Because of these early haematological changes and the risk of developing an aplastic anaemia at a later date, bone marrow was harvested for future autologous bone marrow transplantation. At the same time the dermatologists requested a urethroscopy and

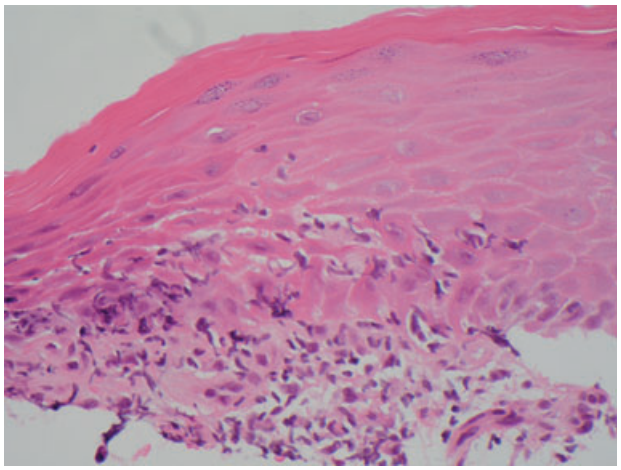

Figure 4 Biopsy of glans penis showing signs of supportive of a diagnosis of lichen planus. See text for further detail.

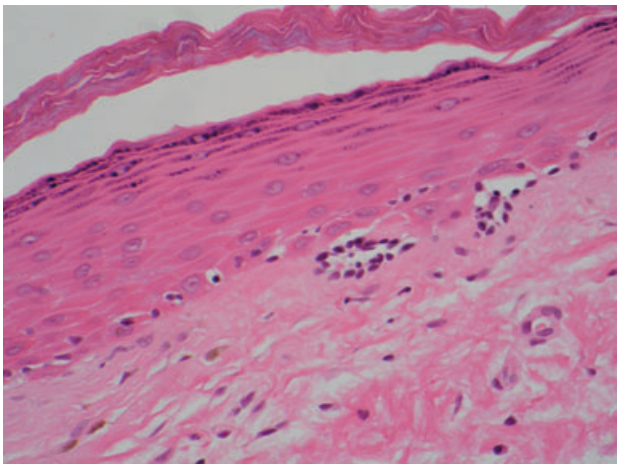

Figure 5 Area adjacent to main lesion taken from base of tongue supportive of a diagnosis of lichen planus. See main text for details.

cystoscopy, which was performed, but no abnormalities were found. It was noted however that there were changes to his glans penis, which was biopsied at the same time. The histological examination revealed features of lichen planus. A focal area of epithelial-stromal interface damage by lymphocytes and some incontinence of melanin pigment into a few macrophages were seen. The squamous epithelium shows moderate orthokeratotic hyperkeratosis with a prominent granular layer (stratum granulosum). Whilst the biopsy result could not be considered diagnostic it was felt to be supportive of lichen planus (Fig. 4).

At the age of 20, further biopsy results from the dorsum of the tongue revealed an early invasive squamous carcinoma. The patient then underwent further carbon dioxide laser therapy to remove the tongue lesion. The tumour was removed in its entirety with a good margin of healthy tissue.

Interestingly an area adjacent to the main lesion with no overt clinical sign of lichen planus did show evidence supportive of lichen planus. There was moderate hyperkeratosis with traces of a granular layer and lymphocytic infiltration at the epithelial-stromal interface with extension of lymphocytes into the squamous epithelium and occasional apoptotic bodies (civatte bodies; Fig. 5).

One year later at the age of 21, genetic analysis was performed on the patient and his immediate family in order to determine the genetic basis for his condition. The results revealed an X-linked recessive form of the DC gene, which he was likely to have inherited from his maternal grandfather, despite the fact that he showed no clinical signs of the condition. The results strongly suggested that the mutation causing the patients condition arose for the first time either *de novo* in the patient or in his mother, who subsequently passed it on to him.

Unfortunately 3 years later at the age of 23, having been lost to follow-up for some time, the patient developed a squamous cell carcinoma in the base of the tongue on the left side, measuring 3 by 2.5 cm, which extended beyond the midline and to the vallecula. It was felt at the time that the tumour was too extensive for surgical resection and thus primary radical radiotherapy was proposed. Treatment was carried out and a good initial response to the treatment was achieved. However some 9 months later the patient developed pulmonary and regional left neck node metastases. The patient then underwent systemic chemotherapy, however unfortunately succumbed to his disease 6 months later at the age of 24.

Discussion

There are both mucocutaneous and non-mucocutaneous features associated with the disorder of DC. The most consistent and common mucocutaneous feature of DC is that of a reticular skin hyperpigmentation, which affects the neck, face, chest and arms, it occurs in either a localized or florid form and is reported to occur in approximately 90% of patients (5). It has been observed to increase with age, and a variety of other skin changes, which have been reported include cracking, cutaneous atrophy, telangiectasia, fissuring, bullae formation, hyperhidrosis of the palms and soles and loss of dermal ridges (6), hair tufts with keratotic plugs on the limbs and keratinized basal cell papillomas (7). Dystrophic changes in the nails appear to be the next most common finding, occurring in approximately 90% of patients (5). It has been observed to be more severe in the fingers than in the toes and can vary quite considerably in severity between digits (6). Dystrophic changes as in lichen planus usually begin with longitudinal ridging and distal splitting, thinning, subungual hyperkeratosis, pterygum formation and may even progress to complete nail loss (8–10). Leukoplakia (hyperkeratosis), which is the third feature of the classic clinical triad, has been reported in approximately 80% of cases (5), it can occur anywhere, but is most frequently found in the oral mucosa. The intraoral sites previously published include, the lingual mucosa (11–14), buccal mucosa (15) and the palate (16), with the tongue being the most frequently affected site (17). The other sites reported

include the urethra, glans penis as possibly in our patient, vagina and recto anal region (6). DC patients have a recognized increased risk of malignancy from pre-existing mucosal leukoplakia(hyperkeratosis) (18), and the incidence of this transformation is in the order of approximately 35% (11). Mortality because of malignant disease in these patients has been reported as 5–10% of cases (5), and when DC is complicated by malignant disease the prognosis is generally considered poor.

There is a wide age variation in the occurrence of clinical signs of DC, however the nail dystrophy, skin hyperpigmentation and hyperkeratosis tend to appear first of all in childhood, which emphasizes the importance of early recognition. The median ages of onset for these clinical features are 6, 8 and 7 years of age, respectively (5).

The non-mucocutaneous features of this disorder are numerous however; one of the most common and important features of this disease is bone marrow failure resulting in peripheral cytopenias. It has been shown that 85% of DC patients have a peripheral cytopenia of one or more lineages, with approximately 75% of these patients developing pancytopenia (5), a finding not noted in our patient. In 80% of these patients the age of onset for the development of pancytopenia is < 20 years of age, with half of them developing pancytopenia before 10 years. It has estimated that 80–90% of patients will have developed bone marrow failure by the age of 30 (5) and approaching 94% by the age of 40 years (5).

In some patients, the development of bone marrow abnormalities may appear before the classical cutaneous manifestations, resulting in the initial diagnosis of idiopathic aplastic anaemia (5, 19). Other non-mucocutaneous abnormalities associated with DC that have been reported, include ophthalmic, genitourinary and skeletal anomalies (20). Manifestations in the oral cavity other than leukoplakia include hyperpigmentation of the buccal mucosa, severe periodontal disease (21), hypocalcified teeth (6), taurodontism (22, 23) and an increased rate of dental caries and subsequent early tooth loss (5). Lichen planus in association with DC has previously been reported as the only oral manifestation in a case of two Singoporean Chinese cousins, where leukoplakia was not observed (24). However, it appears never to have been reported before in combination with leukoplakia/hyperkeratosis of the oral mucosa.

Gastrointestinal abnormalities reported in the literature include, developmental oesophageal webs in the post-cricoid region resulting in dysphagia (6, 16, 21) and was present in our case. These changes have been associated with malignant transformation (25). The precise incidence of DC is as yet unknown, however the prevalence has been estimated to be approximately 1 in 1 000 000 (26).

The diagnosis of dyskeratosis congenita

When all the classical mucocutaneous features of DC are present then the diagnosis is a relatively straightforward one. In some cases diagnosis may not be so easy, for example with the presentation of aplastic anaemia without any mucocutaneous features. Recent advances in genetic testing have now become available enabling more accurate diagnosis of the condition.

The last 10 years have seen significant improvements in our understanding of the condition and identification of the gene responsible offers the potential for improving diagnosis of the condition, monitoring progression of the disease once diagnosed and developing novel forms of therapy for this rare inherited disorder.

The management of dyskeratosis congenita

Patients with confirmed DC should be advised regarding excessive exposure to UV light and regarding the use of barrier sun creams. The avoidance of smoking and alcohol should be emphasized as both the lungs and liver of these patients have a greater susceptibility to damage. These patients also have a greater incidence of gastrointestinal cancer, in particular oral cancer and thus the avoidance of smoking and alcohol bear's even greater importance, as these are primary, synergistic aetiological agents in the development of oral malignancy. DC patients should also undergo regular dental/hygienist review to prevent early tooth loss.

Treatment of this condition resolves around the main causes of premature mortality such as malignancy and bone marrow failure. Early diagnosis of DC patients will enable their bone marrow to be harvested and stored before the onset of marrow failure in susceptible individuals. The main, current treatment for bone marrow failure at present is allogenic haemopoietic stem cell transplantation. In the future gene therapy may provide success where other treatment methods have failed.

It is extremely important to screen for malignancies, especially of the gastrointestinal system. The management of malignancy may be complicated by a number of factors; the diagnosis may be delayed in some cases because of malignant change occurring within an area of persistent leukoplakia, thus resulting in a delay in treatment. There is also a high potential for local recurrence and multiple cancers in these patients. In addition the presence of bone marrow failure makes chemotherapy very difficult and can limit the indications for surgery. The mucosa also has a high sensitivity to radiation, which can result in severe mucosal damage and thus may result in termination of radiotherapy early.

The management of oral malignancy has centred on regular review and biopsy of the pre-malignant hyperkeratotic lesion and surgical laser excision of any suspicious areas. Neoadjuvant radiotherapy or surgical resection of confirmed malignancies, with ipsilateral node clearance, with or without adjuvant radiotherapy, in accordance with the staging of the disease is the mainstay of treatment, provided there are no medical contraindications to this. One paper has advocated the additional clearance of contra lateral neck nodes in patients with an advanced stage of oral malignancy (27).

As DC is a telomerase deficiency disorder, with an increase incidence of malignancy then it might indicate that telomerase based therapies for cancer might have a pro-carcinogenic effect. However this concern is only likely to be important for long-term treatment with telomerase inhibitors, because any pro-carcinogenic effect is likely to take years to result in the development of cancer in DC. However this does require further evaluation.

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