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Lauren Magnani, Danilo C. Delcampo, Marian Russo

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Case Report: We hereby present a case of an eight-year-old girl with dyskeratosis congenita with leukoplakia, nail dystrophy, and skin hyperpigmentation.

Conclusion: Herein, we report a case of presumed sporadic mutation for DC in a patient with leukoplakia on lingual surface with no family history of similar condition. In such rare genetic conditions, case reports are crucial in expanding the knowledge base pertaining to DC. Multidisciplinary healthcare is paramount to treating this condition.

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CASE REPORT

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Keywords: Genetic, Inherited, Leukoplakia, Pediatric, Syndrome

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INTRODUCTION

Dyskeratosis congenita (DC) is a genetic condition with a multitude of implications in all organ systems, including bone marrow failure, lung disease, and malignancies. Dyskeratosis congenita (DC) has an annual incidence of less than one per million. It is a progressive, genetic condition that escapes prompt diagnosis due to slow onset of clinical features in early youth. The pathogenesis involves defective telomere maintenance, and can be inherited in X-linked, autosomal dominant, or autosomal recessive pattern [1]. However, case reports note sporadic mutations in unidentified genes [1]. Mutations in at least ten telomere- and telomerase-associated genes have been described, but no targeted therapies are currently available.

The syndrome is marked by a classic triad of abnormal skin pigmentation, nail dystrophy, and oral leukoplakia. Patients are at increased risk of squamous cell carcinoma and hematolymphoid neoplasms. Patients usually

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succumb to complications related to deficient renewing capability of hematopoietic stem cells. Allogeneic hematopoietic stem cell transplantation is the only curative treatment currently available, though morbidity and mortality from transplantation remains high. This condition prompts the importance for multidisciplinary management and ongoing investigation.

Herein, we report a case of presumed sporadic mutation for DC in a patient with leukoplakia on lingual surface with no family history of similar condition. In such rare genetic conditions, case reports are crucial in expanding the knowledge base pertaining to DC. We aim to highlight the importance of various laboratory testing, clinical monitoring and the multidisciplinary nature of ongoing management.

CASE REPORT

At the age of three, the patient was noted by pediatrician to have new onset fingernail changes. She was otherwise healthy without noted medical problems. By the age of 6 years old, she developed bilateral toenail onychodystrophy and notable hyperpigmentation on the bilateral anterior shins. The patient's mother stated that the above changes became more significant with each preceding year. She was then referred to dermatology for ongoing investigation.

Upon initial presentation to clinic at age seven-years-old, the patient was noted to have scattered reticulate hyperpigmented patches on the trunk and anterior lower extremities (Figure 1A). Further examination noted abnormal dentition with rudimentary conical teeth and an area of lingual leukoplakia with a white nodule on right lateral tongue (Figure 1B). Exam of extremities was notable for extensive onychodystrophy of the bilateral hands and feet (Figure 1C). Complete review of systems was otherwise negative, including no changes in eyesight, no gastrointestinal distress, and no shortness of breath. The patient has no other medical history and takes no medications. She has no family history of cancer, skin conditions, or any other contributory illnesses. Parents state they have no other children and have no similar skin changes in any known family members.

The parents agreed to a skin biopsy for histopathological confirmation. The patient tolerated a punch biopsy of anterior thigh which revealed classic histopathologic features of DC, including epidermal atrophy, telangiectasia of the superficial blood vessels, liquefaction degeneration of basal cells, and increased papillary dermal melanophages (Figure 2).

For concern with a genetic syndrome, further investigation was made into laboratory studies. To evaluate and monitor bone marrow status and cell blood lines, multiple blood tests were obtained including a complete blood count and telomere length testing. Her CBC was within normal limits. Further genetic laboratory testing reported an abnormally low telomere length,

which is consistent with DC. Genetic mutations in DC affect telomerase components or telomere-stabilizing components that alter the renewing capabilities of hematopoietic stem cells. This results in very short telomeres that are responsible for genetic instability and predisposition to malignancy [1]. Due to financial constraints, specific gene sequencing and specific inheritance pattern was not obtained. Hence, a sporadic mutation can only be assumed in light of no other affected family members. Patient and family are considering further genetic testing in the future.

DISCUSSION

Currently, dyskeratosis congenita remains a difficult genetic condition without readily accessible curative

Figure 1: (A) Reticulated hyperpigmentation on anterior legs, (B) Lingual leukoplakia, and (C) Nail dystrophy.

Figure 2: Skin biopsy of anterior thigh showing epidermal atrophy, telangiectasia of the superficial blood vessels, liquefaction degeneration of basal cells, and increased papillary dermal melanophages (H&E stain, x200).

treatment besides bone marrow transplantation. Bone marrow failure (BMF) is a major cause of morbidity and mortality in DC patients in which 80% of patients develop pancytopenia before age twenty, of which half are before age ten [2]. Patients must have coordinated care and be closely followed by different specialists and pediatrics.

The classical triad associated with DC includes abnormal skin pigmentation, nail dystrophy and oral leukoplakia. However, this triad is not observed in every clinical setting and the time of onset for these medical problems varies among individuals. Therefore, the manifestations of DC do not progress in a predictable pattern [3]. Clinical manifestations often first appear in childhood. In general, abnormal skin and nail changes appear before age 10-years-old and BMF often occurs before age 20, with 90% of patients showing signs of failure before age 30-years-old. BMF is the principal cause of premature mortality [3].

Dyskeratosis congenita (DC) is inherited either by X-linked, autosomal dominant, or autosomal recessive pattern. Ten genes have been identified X-linked DKC1 is the most frequent mutation, occurring in approximately 40% of patients [1]. It encodes the nucleolar protein dyskerin, which is involved in telomere maintenance and ribosomal biogenesis. All mutations affect telomerase components or telomere-stabilizing components that result in very short telomeres. This alters the enzyme's normal function, and results in defective renewing capabilities of hematopoietic stem cells.

Multidisciplinary management is critical for these patients for both screening and treatment of associated medical conditions (Table 1). Ophthalmology consultation is important as per DC patients are at risk for conjunctivitis, retinopathy, blepharitis, pterygium, and epiphora due to lacrimal duct stenosis. Ophthalmologic complications occur in half of DC patients, with epiphora being the most common [1]. Our patient was seen by ophthalmology and thus far has normal eye examinations.

Oral maxillary facial surgery consultation needs to be pursued since DC patients have an increased prevalence and severity of periodontal disease, as evidenced by our patient who has several abnormal teeth at the age of eight.

In addition to the classic oral leukoplakia, DC patients have a higher incidence of buccal mucosa hyperpigmentation, hypocalcified teeth, and taurodontism [2]. Early childhood caries and other dental abnormalities are thought to be due to anomalies within structures of ectodermal origin, resulting in defects of the enamel organ or its epithelial attachment [4]. Leukoplakia carries risk of degeneration into squamous cell carcinoma, with 30% progressing to squamous cell carcinoma in 10–30 years [1]. Leukoplakia occurs in almost 90% of patients, most commonly first manifesting between ages 5 and 14 years old. Recurrent ulceration and erythroplakia occurs between ages 14 and 20-years-old. Erosive leukoplakia leading to carcinoma later develops in patients ages 20–30 [5]. This patient was evaluated by oral surgery within two months of initial presentation to dermatology. Parents declined immediate biopsy of lesion and patient will be closely monitored with oral surgeon for any changes into potential malignant transformation.

Pulmonary consultation is another multidisciplinary management for DC patients. Pulmonary fibrosis is one of the potential complications of DC that develops in up to 20% of patients [1]. It is thought to be due to cell apoptosis resulting from critically short telomeres in rapidly dividing lung cells [1]. Therefore, patients require routine close pulmonary follow-up with pulmonary function testing and chest X-rays to monitor for lung disease development. Pulmonary function testing was performed on this patient and the results were normal at that time, with no indication of restrictive lung disease.

Surveillance should include annual CBC if normal, and more frequent CBC if abnormalities are detected. One can also consider annual bone marrow aspirate and biopsy. Monthly self-examination for oral, head, and neck cancers are advised. Annual cancer screening by an otolaryngologist and dermatologist should be performed, as should annual gynecologic examination. Additionally, annual pulmonary function tests starting either at diagnosis or when the patient can perform the test (often around age eight years old). Routine dental screening every six months to yearly and good oral hygiene are recommended [3].

Table 1: Summary of multidisciplinary management and monitoring

Medical Specialist to consider	Conditions to monitor	Labs/Procedures with frequency
Ophthalmology Clinic	Conjunctivitis, retinopathy, blepharitis, pterygium, epiphora from lacrimal duct stenosis	Yearly exam
Ear/Nose/Throat and Oral Maxillary Facial Surgery Clinic	Oral leukoplakia, oral squamous cell carcinoma, buccal hyperpigmentation, hypocalcified dentition, taurodontism	Every six months to yearly exam
Pulmonary Clinic	Pulmonary fibrosis	Pulmonary function test (PFT), yearly.
Hematology Clinic	Bone marrow failure	Complete blood count (CBC), yearly
Dermatology Clinic	Skin hyperpigmentation, nail dystrophy, oral leukoplakia	Full Body Skin Examination, yearly.

Early diagnosis of DC is advantageous in that it enables harvesting and storage of bone marrow before the onset of the BMF [3]. Hematology consultation is recommended for treatment of BMF if the hemoglobin is consistently below 8 g/dL, platelets below 30,000/mm³, and neutrophils below 1000/mm³. If a matched-related donor is available, HSCT should be the first treatment for hematologic complications regardless of age, such as BMF or leukemia [3].

CONCLUSION

Dyskeratosis congenita is a rare condition with a predisposition for malignant progression. This case report describes a young girl with progressive changes of leukoplakia concerning for malignant transformation. Patients must have coordinated care and be closely followed by different specialists and primary care providers.

Author Contributions

Lauren Magnani – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Danilo C. Delcampo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Marian Russo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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