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Case Report

Dyskeratosis congenita: a rare case report

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Abstract

Dyskeratosis congenita (DKC) is a rare genetic disorder characterized by lacy reticular skin hyperpigmentation, bone marrow failure, nail dystrophy, and oral leukoplakia. To the best of our knowledge, only around 200 cases were reported in the medical literature, and in this report, we present another distinctive case from Syria. This case report describes a male patient with generalized reticular pigmentation and abnormal nails since childhood. The patient reported a history of recurrent urethral stenosis and corneal density. Dermoscopic examination revealed pigmented lines arranged in a netlike pattern. Histopathological findings were nonspecific. Hematological values were unremarkable. A contrast CT scan revealed changes in the bladder wall. The final diagnosis of Dyskeratosis Congenita was made based on the clinical criteria. This disorder can present with additional cutaneous manifestations and systemic complications. Treatment are generally prescribed to maintain bone marrow function, based on the fact that it is the major cause of death. Regular monitoring and screening for associated conditions are recommended.

Keywords: dyskeratosis congenita, hyperpigmentation, nail dystrophy, telomerase, incontinent melanin, bone marrow failure, leukoplakia

INTRODUCTION

Dyskeratosis congenital (DKC) is a rare condition classified under a broad spectrum of genetic disorders known as telomerase diseases. First described in the medical literature in 1906 by Zinssar, DKC was originally thought to be a skin disease that also affected the nails and the mouth. Only later in the sixties was it realized that patients with these skin changes almost always developed bone marrow failure, lung disease, and other systemic features. Only around 200 cases were reported worldwide [1], and in this report, we present another distinctive case from Syria.

CASE PRESENTATION

A male in his 30s presented with a complex medical history, characterized by generalized reticular pigmentations and abnormal nails since childhood, starting at the age of 7 months. Noteworthy clinical aspects include recurrent urethral stenosis treated surgically three times, corneal density resulting in visual impairment, and a familial association with his brother exhibiting a similar presentation. His parents and four sisters, however, remain healthy. Upon physical examination, diffuse reticular hyperpigmentation on the trunk and extremities was noted (Fig. 1A–D). Additionally, longitudinal ridging and dystrophy of fingernails and toenails were observed (Fig. 2A–D). Oral and genital mucosa showed no significant lesions. Dermoscopic examination revealed pigmented lines composed of brown dots and globules arranged in a net-like pattern (Fig. 3).

The initial presentation prompted consideration of two main differential diagnoses:

1) Gougerot-Carteaud Syndrome (GCS).
2) Dyskeratosis Congenita.

A skin biopsy was performed, yielding histological features including a thin epidermis, hyperkeratosis, a superficial peri-vascular lymphocytic infiltrate, and incontinent melanin (melanophages in the dermis) (Fig. 4). Despite the biopsy being inconclusive, clinical criteria played a pivotal role in reaching a final diagnosis.

Histological analysis excluded GCS due to the absence of hyperkeratosis, papillomatosis, focal acanthosis, or increased melanin pigmentation. Notably, the presence of nail abnormalities, absent in GCS, further supported the differential diagnosis.

Comprehensive systemic evaluation revealed abnormalities in various systems:

Urinary: Recurrent urethral stenosis treated surgically three times.

Ophthalmic: Visual impairment (5/10), blepharitis, corneal vascularization.

Pulmonary: Normal chest X-ray.

Others: Hyperhidrosis, alopecia.

Hematologic: Normal lab values with a blood film showing atypical lymphocytes at 8%. (Table 1).

A contrast CT scan revealed a thickened bladder wall, attributed to urethral stenosis. Synthesizing all findings, the final diagnosis was Dyskeratosis Congenita. Given the absence of

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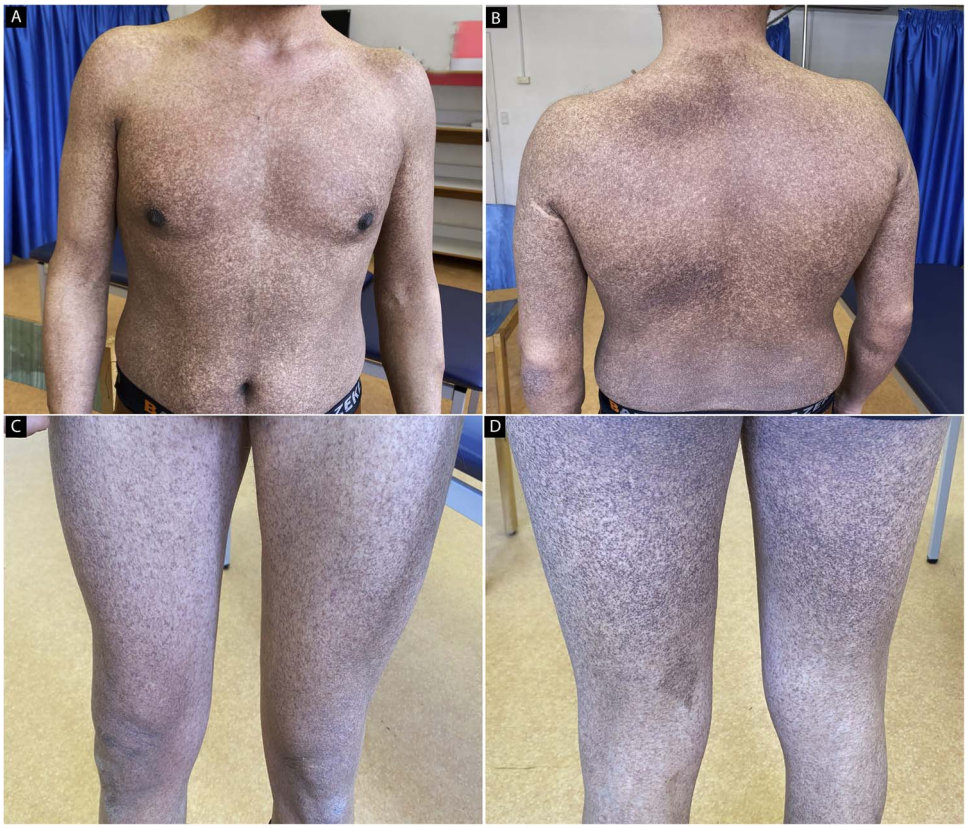

Figure 1. (**A**–**D**) Clinical images of the patient show diffuse reticular hyperpigmentation on the trunk (**A** and **B**) and on the extremities (**C** and **D**).

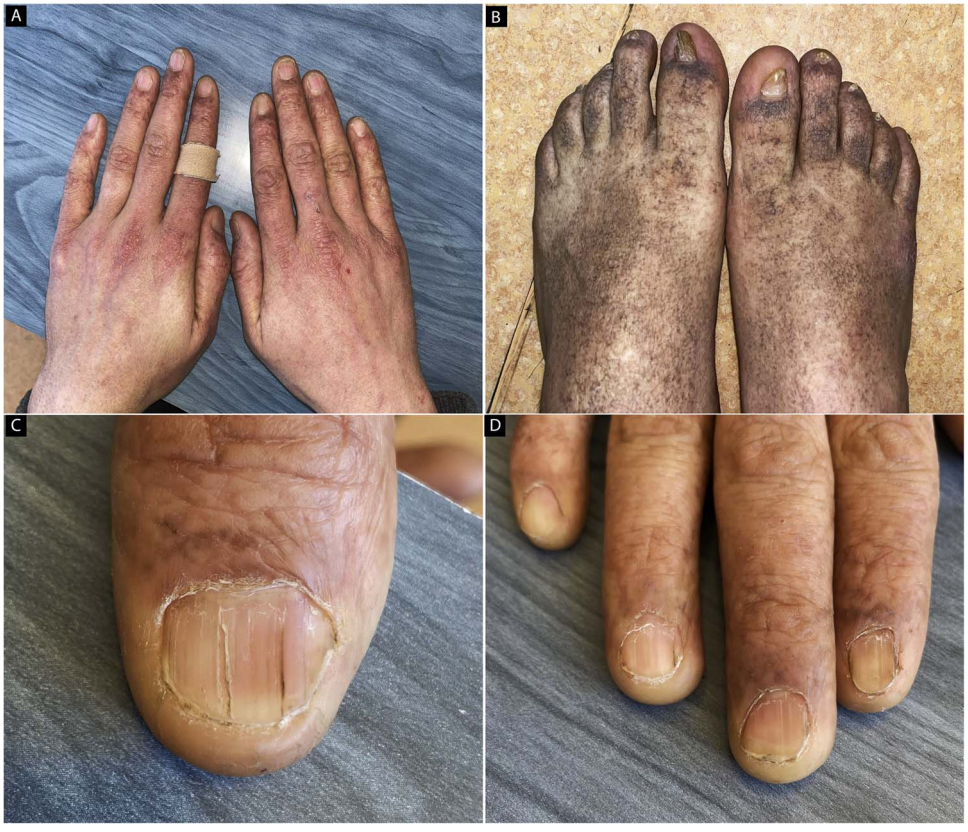

Figure 2. (**A**–**D**) Clinical images of fingers. Longitudinal ridging and dystrophy of finger- and toenails are seen.

Table 1. Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP) Results

WBCs/μl	LYM %	GRAN %	RBCs million/μl	HGB g/dl	HCT %	PLTs $\times$ $10^3/\mu$l
5400	25.3%	69.7%	5.1	15.7	45.9	176
GLU mg/dl	UREA	CREA	CRP	ALT	CHOL	TG
	mg/dl	mg/dl	mg/dl	U/L	mg/dl	mg/dl
94	23.5	1.2	29.7	31	134	101

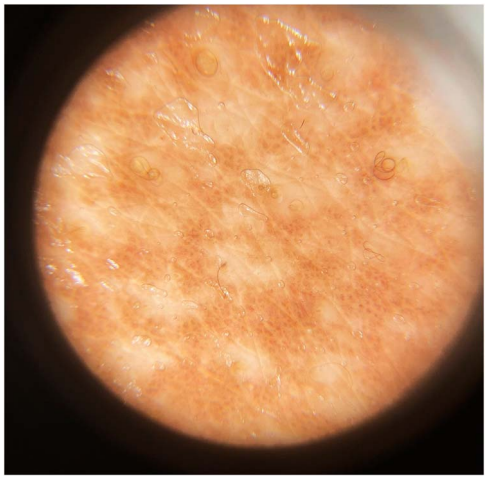

Figure 3. Dermoscopy image shows pigmented lines made up of dots and globules arranged in a netlike pattern.

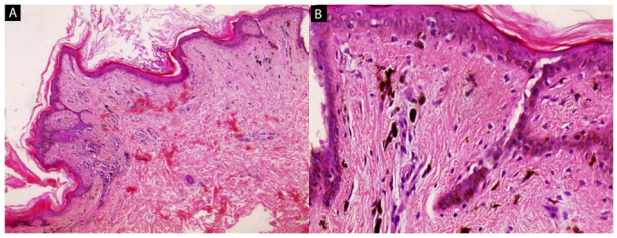

Figure 4. (**A** and **B**) Histopathologic findings of the biopsy showing nonspecific features. (**A**) The thin epidermis, hyperkeratosis, and superficial peri-vascular lymphocytic infiltrate are identified (H&E 40×). (**B**) Incontinent melanin (melanophages in the dermis) is present (H&E 100×).

hematological disorders, specific treatments were not prescribed. Instead, the patient was advised to minimize sun exposure, use sunscreens, avoid extreme temperatures, reduce alcohol intake, and abstain from smoking. The patient has been regularly followed up since the initial presentation, allowing for the ongoing evaluation of both cutaneous and systemic manifestations associated with DKC. Monitoring has been conducted at regular intervals, typically every six months, to assess the response to recommended lifestyle modifications and to identify any emerging complications.

DISCUSSION

DKC is a rare genetically heterogeneous disorder with an incidence of (1/million). It is characterized by two of the major criteria:

1) Bone marrow failure (aplastic anemia).
2) Lacy reticular skin hyperpigmentation.
3) Nail dystrophy.
4) Oral leukoplakia.

And 2 of the systemic symptoms (pulmonary fibrosis, liver cirrhosis, neurological and ophthalmic abnormalities, genitourinary system abnormalities, as well as increased risk of malignancies including squamous cell carcinoma (especially in the mucosa, head, and neck) and Acute Myeloplastic Leukemia) [2]. In our case, the patient met four of the criteria: the skin and nail manifestations, in addition to the ophthalmic and genitourinary abnormalities. Epidemiologically, X-linked recessive is the most common type of inheritance, but autosomal dominant and autosomal recessive forms were also mentioned in the literature, and there is considerable variation between patients concerning the age of onset and severity of disease, even within affected individuals of the same family. This causes difficulty in making a diagnosis. Equally, it is not uncommon for BM failure, immune deficiency, or another abnormality to present before the more classic mucocutaneous abnormalities [3]. The overall male-to-female ratio is 3:1, and it usually presents during the first decade. The lacy reticular hyperpigmented rash is sometimes mixed with macules of hypopigmentation. It is noted that telangiectasis and epidermal atrophy may also be seen. Additional cutaneous manifestations may include wrinkled skin on the extremities as well as the genitalia, palmoplantar hyperhidrosis and loss of dermatoglyphics, frictional bullae, acrocyanosis, and premature graying of the hair, none of which was present in our patient. Nail involvement is seen in the vast majority of patients, typically appearing during early childhood. Initial changes include longitudinal ridges and splitting, and that's something our patient had, followed by pterygia formation, and occasionally complete nail loss. Premalignant leukoplakia, unfortunately, occurs in most patients, usually during early adolescence, but luckily nothing was found on examination of the oral mucosa in this case. White plaques on the oral mucosa are observed most commonly, with a predilection for the lateral portions of the tongue. Involvement of the urethra, vagina, and anus is also possible but was absent in our case. The teeth may be malformed, missing, or have aberrant spacing or extensive caries. Epiphora (continuous lacrimation) due to lacrimal duct atresia is also common. BMF develops by the age of 30 in 50-90% of cases following the mucocutaneous triad [4]. Evidence exists for telomerase dysfunction because most patients show severe shortening of telomerase, ribosome deficiency, and protein synthesis dysfunction. The most common cause of DKC is a mutation in the DKC1 gene, which encodes dyskerin, a small nucleolar protein that is responsible for the stabilization of telomerase [5]. Other complications can include developmental delay, short stature, lung cancer, stomach cancer, pulmonary fibrosis, avascular necrosis of the femoral head, cryptorchidism, male hypogonadism, and immunologic dysfunctions leading to opportunistic infections [1–4]. That's why we strongly recommend our patient perform a regular systemic check-up to detect any early signs or malfunctions and manage them properly.

Hoyeraal Hreidarsson syndrome is an X-linked syndromic intellectual disability considered to be a severe variant of dyskeratosis congenital characterized by intrauterine growth

retardation, microcephaly, cerebellar hypoplasia, progressive combined immune deficiency, and aplastic anemia [6]. *Revesz syndrome* is a rare, severe phenotypic variant of dyskeratosis congenital with an onset in early childhood, characterized by features of DC (e.g. skin hyper/hypopigmentation, nail dystrophy, oral leukoplakia, high risk of bone marrow failure (BMF) and cancer, developmental delay, sparse and fine hair) in conjunction with bilateral exudative retinopathy and intracranial calcifications [7]. The main causes of death are bone marrow failure in 75–80%, lung fibrosis in 10–15%, or cancer in 10% [2].

In addition to the diagnoses that were suggested earlier in our case, it's worth mentioning that Fanconi anemia is also associated with pigmentary abnormalities, pancytopenia, and an increased risk of neoplasia (e.g. leukemia); Other diseases like Naegeli–Franceschetti–Jadassohn (NFJ) syndrome and dermatopathia pigmentosa reticularis (DPR) differ by their lack of leukoplakia and bone marrow involvement. Patients with chronic GVHD may develop poikilodermatous skin changes and lacy white patches of the oral mucosa. However, GVHD is usually easily distinguished by the history of a hematopoietic stem cell transplant (or, rarely, a solid organ transplant) [4].

Pachyonychia congenital is an autosomal dominant condition characterized by nail abnormalities, hyperkeratosis, or hyperhidrosis of the palms and soles, along with mucosal leukoplakia. In pachonychia congenita, the nails become thick and shed at an early age, and the mucosal leukoplakias do not undergo malignant transformation. Hematological abnormalities do not occur in Pachyonychia congenita [8].

Due to the etiology of DCK, patients show signs of premature aging and are more susceptible to developing cancer. There is the presence of excessive telomere shortening in this patient population, which, in the absence of a deoxyribonucleic acid (DNA) damage response, may lead to genomic instability and a predisposition for malignant transformation.

Electron microscopy studies revealed that cells in DKC have an embryonic, immature nucleus and a predisposition to undergo malignant transformation. Moreover, the barrier zone of the epithelium is less effective in DKC than in the normal epithelium, so there is an increased permeability of noxious substances and carcinogens to the germinal layers. Therefore, an increased malignant transformation rate is seen in leukoplakic areas, so they need to be monitored periodically.

Furthermore, individuals with DKC have a 40–50% cumulative incidence of malignancy by age 50. For example, squamous cell carcinoma of the tongue, Hodgkin's lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma can develop. The skeletal, gastrointestinal, and genitourinary systems may also be affected [9].

There is no cure at this time for DKC. Recommendations included reducing sun exposure through consistent sunscreen use and avoiding extreme temperatures due to the heightened fragility of the skin compared to the general population. Additionally, minimizing alcohol intake and refraining from smoking were advised [3]. Treatment in general is aimed at maintaining bone marrow function, as this is the major cause of death. Use of the anabolic steroid oxymetholone and haematopoietic growth factors (such as erythropoietin, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor) can produce improvements in the haematopoietic function. The only long-term cure for haemopoietic abnormalities is allogeneic haematopoietic stem cell transplantation, but this is not without risk. There is still significant mortality associated with bone marrow transplants for DC patients when compared with other bone marrow failure syndromes [10]. As our patient does not have any hematological disorders, no specific treatments were prescribed. The following are recommended at least twice a year: complete blood counts, annual bone marrow aspirates, biopsies, liver ultrasounds, and pulmonary function tests; gynecologic exams; and skin cancer screening [2–4].

CONCLUSION

Dyskeratosis congenita is a rare and complex disorder that presents a multitude of symptoms and diagnostic challenges. This case report sheds light on the importance of a thorough clinical evaluation, and extensive laboratory investigations to reach an accurate diagnosis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING

None.

CONSENT

Written consent for the publication of patient photographs and medical information was obtained.

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