A Filipino Child with Dyskeratosis Congenita with a C→T substitution on nucleotide 1058 of the DKC1 gene

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ABSTRACT

We present a 4 year old Filipino male child with leukoplakia, poor dentition, reticular hyperpigmentation, mild hyperkeratosis of both heels, nail dystrophy, and pallor/anemia. These features are consistent with Dyskeratosis Congenita (DKC) or Zinsser-Engman-Cole syndrome, a rare genodermatosis. He is the youngest in a sibship of three, born to non-consanguineous Filipino parents. The family pedigree is consistent with the X-linked recessive type of DKC. Our patient's bone marrow examination revealed erythroid hyperplasia, dysplastic changes in granulocyte and erythroid cells, and was negative for tumor cells. There was no undue proliferation of immature blast cells. Bone marrow failure in this syndrome is usually progressive but severity is known to vary. His skin biopsy results were consistent with DKC showing atrophic squamous epithelium, mild hyperkeratosis, melanophages, and telangiectatic vessels. Molecular studies revealed a C→T substitution on nucleotide 1058 of the DKC1 gene producing a commonly reported alanine to valine change at position 353 (A353V).

Key Words: dyskeratosis congenita, DKC, Zinsser-Engman-Cole syndrome, congenita dyskeratosis

Introduction

Dyskeratosis congenita (DKC), classically characterized by cutaneous reticulated hyperpigmentation, nail dystrophy, premalignant leukoplakia of the oral mucosa, and progressive pancytopenia, was first described in 1930.[1] It is a rare genodermatosis with an estimated prevalence of 1 in a million.[2] It can be confused with more familiar conditions like oral candidosis or ectodermal dysplasias with nail defects. Majority of the cases of DKC follow an X-linked recessive pattern of inheritance, but autosomal dominant and autosomal recessive forms have also been described.[3,4] Vulliamy et al in 2006, reviewed cases enrolled in the Dyskeratosis Congenita Registry. Of the 228 families, 22 showed true X-linked inheritance, 19 had at least 2 affected brothers, 123 had sporadic affected male, 35 had sporadic affected female, 11 families had an autosomal dominant pattern of inheritance and 18 families had autosomal recessive pattern .[4] The most striking finding in reviewing these families, according to the authors, was the large proportion of families (63%) where no mutation has been found in the genes known to be associated with DKC. For the X-linked recessive form of DKC, the condition is caused by mutations on the DKC1 gene located on the Xq28 region, which encodes a protein called dyskerin.[5] Majority of these mutations are missense mutations. DKC1 mutations among Asian families have been reported.[6,7] The actual role of dyskerin, whether it involves a ribosomal biogenesis problem, a telomerase defect, or a defect in internal ribosome entry site (IRES)-dependent translation which results in impaired translation of mRNAs, is still under debate.[8] Here we present a case of a Filipino patient with DKC following an X-linked pattern of inheritance.

Clinical Summary

The proband was a 4 year and 5 month old Filipino male, born to non-consanguineous parents, delivered term to a 29 year old G4P2 mother. He had a birth weight of 3 kg. His mother, who worked as a janitress, had prenatal exposure to chemical cleaners. Perinatal course was unremarkable and the developmental milestones were within normal limits.

At 8 months of age, a peanut-sized white plaque was noted on the dorsum of the patient's tongue. He developed fingernail and toenail deformities described as thinning and curling of the outer margins of the nails on the following year. Medical consultation was done and the complete blood count (CBC) showed anemia. Iron supplementation and multivitamins were prescribed. At 4 years of age, pallor was more noticeable. He was brought to a pediatric hematologist who suspected DKC based on the features of anemia, oral leukoplakia, nail dystrophy, and fine reticular markings on his eyelids. There was occasional bleeding from the leukoplakia. His CBC at this time showed anemia (Hb 10.4g/dL), leukopenia (4.7K/uL) and a platelet count of 114,000/uL, while the peripheral smear showed thrombocytopenia with toxic changes in the granulocytic cells. His bone marrow smear revealed erythroid hyperplasia, dysplastic changes in granulocytic and erythroid cells, and was negative for tumor cells. Tongue scrapings for fungal studies showed no fungal elements.

Pertinent physical examination findings included a height of 102 cm (75% percentile, FNRI-PPS 1992) and a weight of

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13.4 kg (25% percentile, FNRI-PPS 1992). He had dry skin with hyperpigmented reticular to macular areas on the face, trunk, and upper extremities; pale palpebral conjunctivae; prominent thin blood vessels on the skin of the eyelids with violaceous discoloration; a 1.5 cm x 3 cm whitish plaque on the dorsum of the tongue, and severe dental caries. Cardiovascular, pulmonary, and abdominal findings were normal. He had palmar erythema and hyperkeratosis of the soles of his feet. The fingernails on the 2nd and 3rd digit of the left hand and 2nd digit of the right hand, and the toenails on the 1st digit of the left foot and 4th toe of the right foot were hyperconvex with atrophy of the outer margins (Figure 1). The neurological examination was normal.

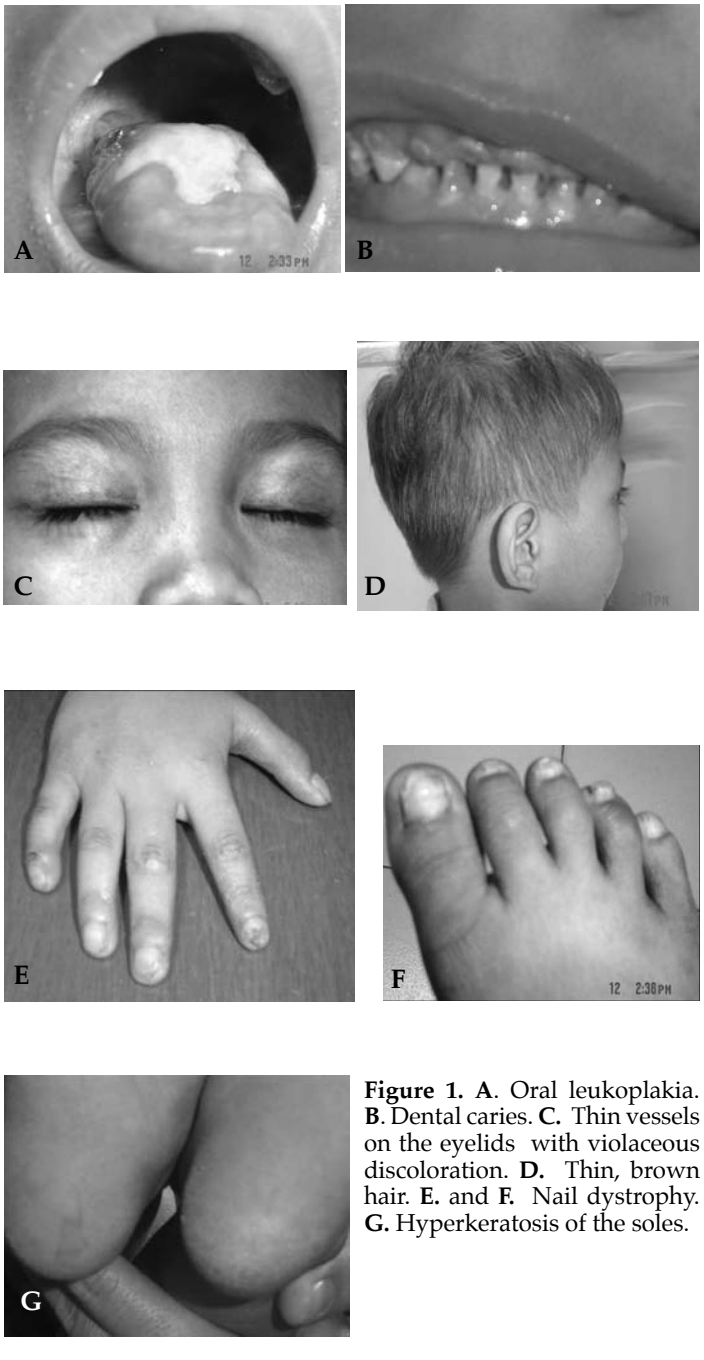

Figure 1. A. Oral leukoplakia. **B**. Dental caries. **C.** Thin vessels on the eyelids with violaceous discoloration. **D.** Thin, brown hair. **E.** and **F.** Nail dystrophy. **G.** Hyperkeratosis of the soles.

His laboratory results showed thrombocytopenia (134000/uL), a reticulocyte index of 0.2 and reticulocyte count of 0.6%. His creatinine and SGPT were normal. A skin punch biopsy showed the following: mildly hyperkeratotic stratified squamous epithelium with basal vacuolation in some areas; a focus of edema and lymphocytic infiltration of the immediate underlying stroma associated with the presence of several melanophages in adjacent areas; and a fragment showed recent hemorrhage and early organizing thrombus within portions of telangiectatic vessels lined by flattened endothelial cells. These findings were consistent with DKC. Genomic DNA sent to the California State University for molecular studies on the DKC1 gene revealed a C→ T transition on exon 11, causing an alanine to valine change at position 353 of the DKC1 gene (A353V).

In the past 2 years, the patient has had 4 episodes of pneumonia and a Hepatitis A infection. His oral leukoplakia has increased in size and he had two episodes of minimal bleeding from the mass. The nail dystrophy has progressed to affect the rest of the fingernails and toenails. His hematologic picture showed WBC counts ranging from 3.04K – 8.21K/uL, hemoglobin levels of 9.1-11.8 g/dL, and platelet counts of 54000-149000/uL.

The family pedigree revealed a maternal uncle who had leukoplakia (a white bleeding rectal mass), nail deformities, and epiphora (Figure 2, IIF). He died of leukemia at the age of 12 years. The other members who were noted to have skin and nail abnormalities were not well documented (Figure 2, IIJ and IIK).

Discussion

DKC has three cardinal dermatologic features namely reticulate hyperpigmentation on the neck, chest, arms, and axilla; nail abnormalities (initial longitudinal ridging and splitting eventually leading to nail loss); and leukoplakia (primarily affecting the mucous membranes of the mouth, and occasionally in the esophagus, anus, or genital area).[3] These features occur in about 89%, 88%, and 78% of male patients, respectively.[8] Our patient presented with all these features, and has severe dental caries, a less commonly reported feature (16.9%), hyperkeratosis, and thin, light-colored hair.[8] His maternal uncle on the other hand, had the classical features and epiphora, developed bone marrow failure and eventually was diagnosed with leukemia. The hematologist who first saw our patient was correct in her initial impression. General clinicians must then realize that this condition can be suspected on clinical grounds already.

The mutation found in our patient was the commonly reported, recurring mutation of A353V.[4,7] This mutation was seen in 30 out of the 72 DKC families in the DCR who had DKC1 mutations.[4] In 12 of these cases, the event occurred de novo. It is also the mutation seen in the Thai family in Viprakasit's article[7] and in two of the 5 Japanese families of Kanegane.[6] Thus, there seems to be no ethnic preference for this mutation. As for any genotypic-phenotypic correlation,

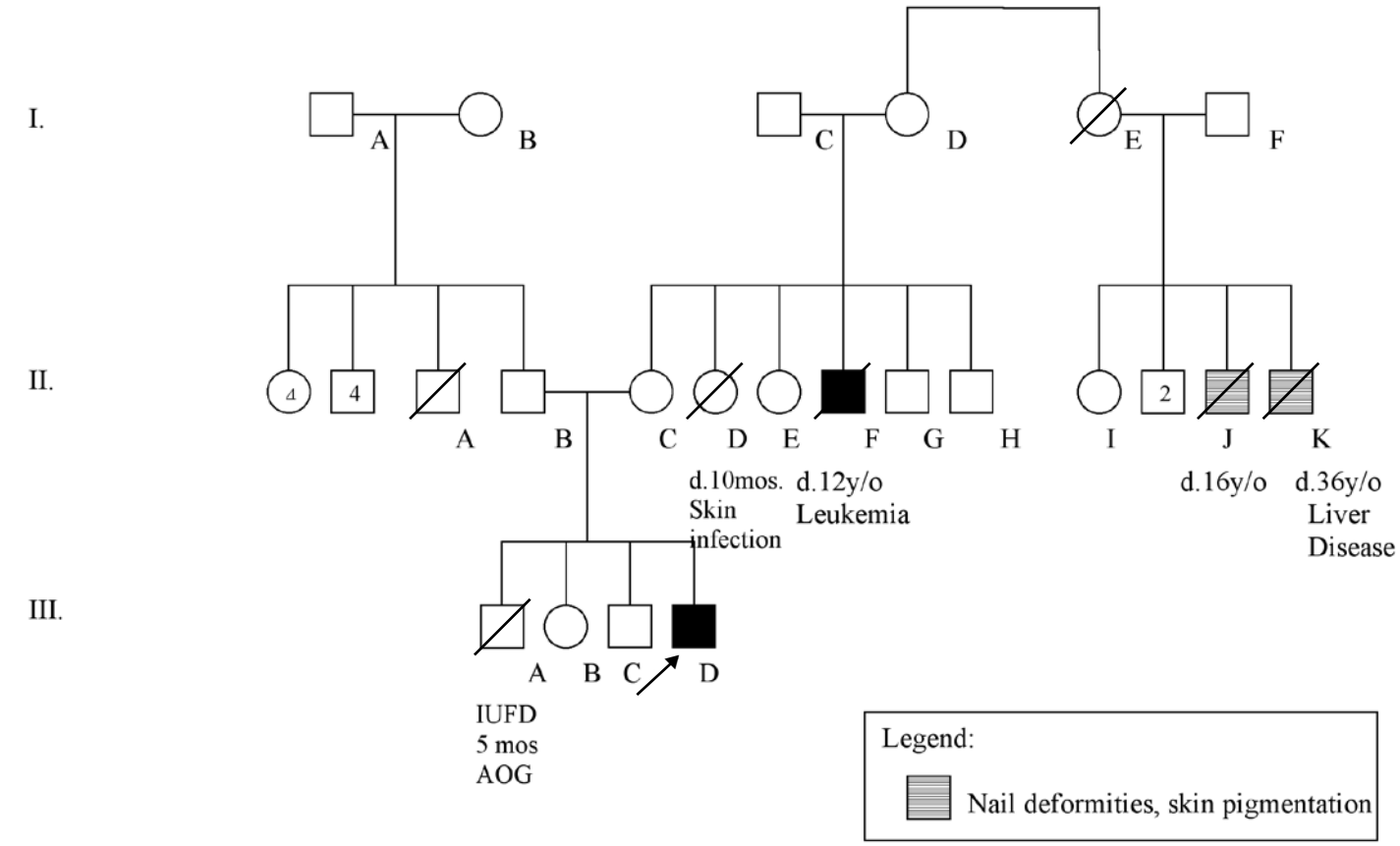

Figure 2. Family Pedigree.

Vulliamy et al reported the clinical picture to be variable for A353V after studying the records of 28 patients.[4] It has been seen not only in classical DKC patients but also in an allelic (but more severe) condition known as Hoyeraal-Hreidarsson syndrome (HH) where there is aplastic anemia, immunodeficiency, microcephaly, cerebellar hypoplasia and growth retardation. Other genetic and environmental factors are then thought to affect the disease phenotype. Dyskerin is one of many enzymes important for post-transcriptional modification of uridine to pseudouridine in non-coding RNA and for accumulation of telomerase RNA (TER).[10] The resulting short telomeres from deficient dyskerin is believed to cause cell cycle arrest, genomic instability, and cell death especially of progenitor cells who are rapidly dividing.[2,9] In the latest discovery where DKC impairs translation from IRES-containing genes, which affect a lot of anti-apoptotic and tumor-suppressor genes, it is thought that this may explain the high risk for malignancy in these patients.

Bone marrow failure occurs in 85.5-93%, usually starting at the teen years.[8] Because of this bone marrow complication, it is no longer seen as a dermatologic condition, but more as a hematologic disease. Our patient does not yet have the full picture of marrow failure. Other complications include malignancies like pharyngeal and esophageal cancer, opportunistic infections, chronic blepharitis and excessive tearing as the lacrimal punctata becomes affected, and pulmonary complications. These are not yet present in the index case. The mean age of death from complications has been reported to be around 24 years.[1] Genetic counseling for the family emphasized good compliance to monitoring for complications, family support, and the importance of testing other family members.

Treatment has been primarily symptomatic and palliative, covering supportive measures like the use of antibiotics, blood products, and procoagulant therapy.[3] Bone marrow failure can be treated with hematopoeitic stem cell transplant but pulmonary and vascular complications have led to variable results in treated DKC cases.[8] Moreover, the transplantation does not alter other features of the disease. The conditioning regimen now being advised for those undergoing transplant has been towards less myeloablative drugs and less radiotherapy.[3,8] However, financial constraints and local expertise here in Cebu limit the treatment choices of our patient to supportive ones. Researchers though are hopeful for gene therapy in the future, especially since the condition is a single gene disorder and the target cells are easily accessible.[8]

Conclusion

DKC can be diagnosed clinically with the dermatologic triad of reticulate hyperpigmentation (neck, chest, arms, and axilla), nail abnormalities and leukoplakia. Close monitoring of hematologic parameters must be integral to the care of these patients in anticipation of the associated bone marrow complications. The family pedigree must be done to identify the pattern of inheritance in the family. Diagnosis of DKC can be strengthened by mutation analysis. The pattern of inheritance and the knowledge of the mutation will be critical in the counseling of the patient and the family.

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