Dyskeratosis congenita: report of two cases with distinct clinical presentations

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Dyskeratosis congenita (DC) is a rare, inheritable disorder characterized by a triad of abnormal skin pigmentation, nail dystrophy and mucosal leukoplakia. Inheritance is mainly X-linked recessive; however, autosomal dominant and recessive forms have also been reported. Here, we report two cases of DC with distinct clinical presentations together with different genetic screening results, which emphasize the quite heterogeneous clinical as well as genetic nature of DC.

Key words: dyskeratosis congenita, leukoplakia, nail disease, hyperpigmentation.

Dyskeratosis congenita (DC) was first described by Zinsser in 1906. It was subsequently described by Engman in 1926 and Cole in 1930. DC, which is also designated as Zinsser-Engman-Cole syndrome, is a triad consisting of nail dystrophy, mucosal leukoplakia and abnormal skin pigmentation. In addition to this clinical triad that defines DC, a severe pancytopenia, a predisposition to malignancy and a poorly defined immunodeficiency may accompany the syndrome. Bone marrow failure or aplastic anemia is the principal cause of premature mortality in patients with DC[1-4]. Squamous cell carcinoma is the most common malignancy, found in areas of leukoplakia such as the mouth, tongue, nasopharynx, esophagus, anus, cervix and rectum[4]. In addition to its clinical variability, the inheritance of the condition is also variable. The most common form is X-linked, but there are also families showing autosomal dominant and autosomal recessive inheritance. The major X-linked form of the disease is due to DKC1 gene mutation. DKC1 is encoding the protein dyskerin, which is a component of ribosomal RNA and telomerase complex. Recently, TERC gene mutations were identified in the rarer autosomal dominant subtype of DC. TERC is one of the two core components of telomerase and is essential for telomere maintenance. The genetic basis for the autosomal recessive form of the disease remains unknown[5].

Herein, we describe two cases of DC, with distinct clinical presenting features as well as different genetic screening results, underlining the wide spectrum of the genotype and the phenotype.

Case Reports

Case 1

A five-year-old boy who had a four-year history of ulcerated white plaque on his tongue, which disturbed eating, and a six-month history of easy splitting of the nails, was referred to our department for further evaluation. He was born at term (2250 g) to a marriage with third- degree of consanguinity. His mother and father were 26 and 31 years old, respectively. A detailed family history indicated that his uncle had suffered from severe anemia and had died due to infection. His brother and sister had no signs of systemic infection or mucocutaneous abnormality.

Physical examination revealed reticulate hyperpigmentation predominantly on the neck and the inguinal areas, accompanied by dystrophic toe- and fingernails. The dystrophic fingernails are shown in Figure 1. As shown in Figures 2 and 3, evident leukokeratosis on the dorsum and sides of the tongue and prominent dental caries were noted. The patient had thin and sparse hair.

Laboratory tests were as follows: Complete blood count with a white blood cell count of 8900/mm³, with 80% neutrophils and 6%

Fig. 1. Dystrophic fingernails observed in Case 1.
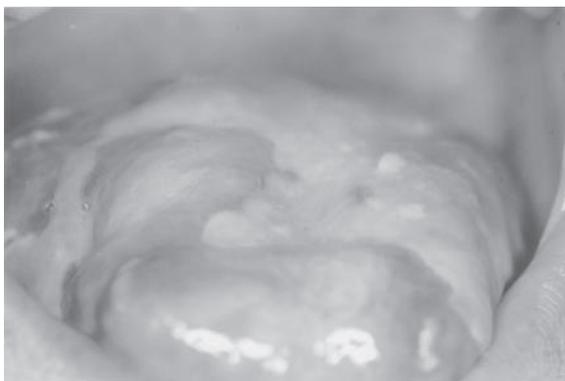
Fig. 2. Evident leukokeratosis on the dorsum and sides of the tongue.
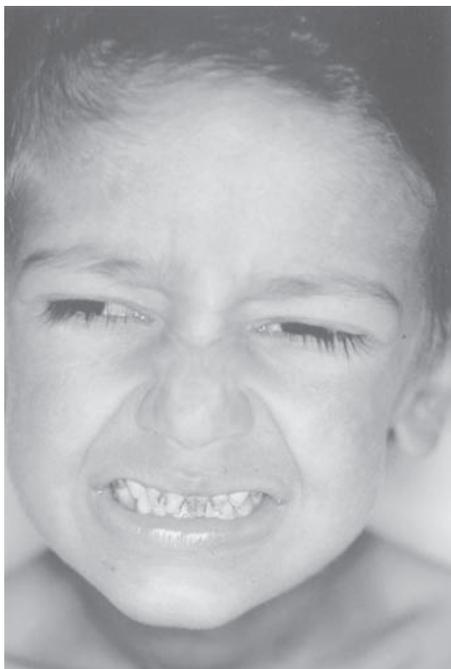
Fig. 3. Prominent dental caries.

lymphocytes; red blood cell count 2950x103/μl; hemoglobin 7.8 mg/dl; hematocrit 24%; and platelet count 144x103/μl. Mild anisocytosis, polychromasia and spherocytosis were noted in the peripheral blood smear. Direct Coombs test was negative and osmotic fragility test result was normal.

Bone marrow aspirate was hypocellular and revealed increased fat droplets, compatible with aplastic anemia. A barium swallow esophagography demonstrated a narrowed proximal esophagus and web formation. A biopsy specimen obtained from the tongue revealed ulcerative inflammation and no evidence of squamous cell carcinoma. He had no respiratory symptoms and a chest X-ray was within normal limits.

A diagnosis of DC was made with typical skin lesions (reticulate hyperpigmentation), leukoplakia of the tongue, dystrophic toe- and fingernails, thin sparse hair, dental caries, and esophageal web formation. Seven years after his first admission, the X-linked nature of the disease was confirmed by genetic screening, which revealed DKC1 gene mutation. Denaturing high performance liquid chromatography and direct DNA sequence analysis of the DKC1 gene showed he was hemizygous for DKC1 gene mutation (a nucleotide transition of C to T (1150 C--> T). In Figures 4 and 5, dystrophic fingernails and leukokeratosis on the dorsum and sides of the tongue are shown seven years after his first admission.

Treatment with 30 mg/kg prednisolone orally was considered for his anemia, which had been gradually tapered and was discontinued

Fig. 4. Dystrophic fingernails 7 years after the first admission of Case 1.
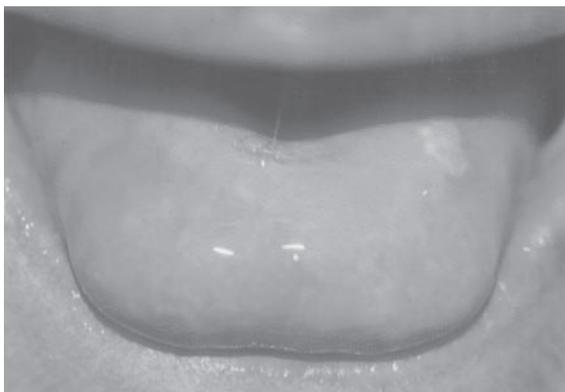
Fig. 5. Leukokeratosis on the dorsum and sides of the tongue 7 years after the first admission of Case 1.

Fig. 6. Reticulated hyperpigmentation and atrophy on the neck and V area of the chest.

after the follow-up visit one month later when his hemoglobin was found to have reached 12.2 mg/dl.

Case 2

A 12-year-old boy presented with a two-year history of easy bruising with trauma. A detailed history revealed skin lesions that were first noticed at the age of 8, nail abnormalities of three-years' duration and a white plaque on the tongue that had appeared two months before.

The patient was the product of a full-term pregnancy with cesarian section delivery due to neonatal distress. His mother and father were 32 and 41 years old, respectively, and there was no consanguinity. There was no remarkable medical problem in his family and no history of significant infections, skin pigmentation, or bone marrow failure in his parents or other relatives.

On physical examination, reticulated hyper-pigmentation and atrophy on the neck, V area of the chest and the posterior auricular sites were noted, as shown in Figure 6. The longitudinal ridging accompanied by distal dystrophy of the nails is shown in Figure 7. Examination of the mucosal sites revealed a white plaque on the side of the tongue and hypoplastic conic teeth. Figure 8 shows the white plaque on the side of the tongue.

Laboratory tests were as follows: white blood cell count of 4000/mm³ with 34% neutrophils, 54% lymphocytes; red blood cell count $3170 \times 10^3/\mu l$; hemoglobin 10.4 g/dl; hematocrit 34%; mean corpuscular volume 98.2 fl; platelet count $72 \times 10^3/\mu l$; vitamin B_1: 254 g/ml; and folic

Fig. 7. Longitudinal ridging accompanied by distal dystrophy of the nails.

Fig. 8. White plaque on the side of the tongue.

acid: 6.9 ng/ml. There was a mild polyclonal gammopathy: IgA: 366.5 mg/dl (45-250 mg/dl) and IgG: 1870 mg/dl (650-1600 mg/dl).

Ultrasound examination of the abdomen was normal. The bone marrow aspirate revealed hypocellularity and increased fat droplets and was found compatible with aplastic anemia.

A cytogenic profile showed a 46 XY karyotype. Genetic screening excluded both TERC and DKC1 gene mutations.

Discussion

Dyskeratosis congenita is a very heterogeneous disorder with respect to clinical and hematological features and pattern of inheritance. The age of onset, degree of bone marrow failure and range of congenital abnormalities may vary[6]. Three distinct patterns of inheritance leading to the general DC phenotype have been observed. X-linked recessive inheritance appears to account for over three-quarters of cases, and the trait has been mapped to chromosome Xq28 by linkage analysis[7]. Since its inheritance is predominantly X-linked recessive, DC is a disease that occurs predominantly in males. Both of our patients were male. However, females can also be affected because many of the remaining cases show evidence of autosomal recessive or autosomal dominant transmission[8-10]. By November 1999, 92 DC families, comprising 148 (127 male, 21 female) patients from 20 countries, had been recruited to the DC registry. As well as confirming previous observations, the DC registry has recently identified new features of the DKC1 gene, which is mutated in X-linked DC[11]. Additionally, in autosomal dominant DC patients, mutations in the RNA telomerase component (TERC) have been identified. TERC and DKC1 encoded protein dyskerin are closely associated in the telomerase complex, showing that DC may be a disease due to defective telomerase activity. Although the gene or genes involved in the recessive form of the disease are not yet shown, they are very likely the genes encoding proteins for telomere maintenance[5]. Genetic screening in the first case revealed a DKC1 gene mutation confirming the diagnosis of X-linked DC; the second case was found to have a normal DKC1 and TERC screen. The negative genetic findings and the healthy status of the parents make autosomal recessive inheritance likely in the second patient.

Although similar to the genotype, the DC phenotype is quite variable; the occurrence of the clinical picture in DC seems to follow an order. Cutaneous findings such as lacy reticulate skin pigmentation, diffuse nail dystrophy and mucosal leukoplakia, which were found in both of our patients, are the most characteristic features of the syndrome. These cutaneous features are not usually present at birth; rather they develop progressively between the ages of 5 and 10 years[2]. The oral leukoplakia in Case 1 and reticulate hyperpigmentation in Case 2 were the first signs of the syndrome, which appeared at 1.5 and 8 years of age, respectively.

Generally the nail dystrophy, which is present in 83% of patients, is the first sign of the disease and characterized by atrophy, shedding, and ridging, and may progress to complete nail loss[4]. Although leukoplakia predominantly involves the oral mucosa, it can involve any mucosal site[11].

Other cutaneous features include hyperhidrosis, hyperkeratosis of the palms and soles, loss of dermatoglyphics and occasionally bullae within sun-exposed poikilodermatous areas.

Many other somatic abnormalities might be seen in DC; thus, DC could be regarded as a multisystem disorder[2]. Esophageal stricture, short stature, developmental delay, and thin and sparse hair in Case 1 and extensive dental caries found in both of our patients were some of these somatic abnormalities.

Bone marrow failure is much more frequent than previously suggested. By the age of 40 years, its incidence approaches 94% of all patients[2]. Since the bone marrow failure is the main cause of death, early diagnosis is important. Both of our patients had mild aplastic anemia, which was confirmed by bone marrow aspiration. Aplastic anemia presented itself as anemia in Case 1 and as mild thrombocytopenia in Case 2.

Squamous cell carcinoma is the most common malignancy observed in patients with DC, which is almost always found in areas of leukoplakia. However, gastrointestinal tract malignancies, such as signet ring carcinoma of the rectum[12], adenocarcinoma of the rectum[13], gastric adenocarcinoma[14,15], and malignancies of other systems, such as primary bronchial adenocarcinoma[16], adenocarcinoma of the pancreas[17], and Hodgkin's disease have also been reported[18].

In light of these two cases, we would like to emphasize that the clinical presentation as well as genetic nature of DC might be heterogeneous. We believe it is reasonable to consider DC in the differential diagnosis of a patient with any features of the syndrome, regardless of gender. In order to make early diagnosis, we should keep

in mind that noncutaneous abnormalities may precede characteristic classical mucocutaneous features. Furthermore, DC should be considered in any patient with aplastic anemia at any age. Although diagnosis based on clinical criteria alone is difficult, especially when noncutaneous abnormalities precede classical mucocutaneous features, identification of mutations in the DKC1 or TERC genes may help early diagnosis as well as carrier detection.

We would also like to point out that all DC patients require long-term follow-up for the detection of associated malignancies. Since UV irradiation accelerates telomere shortening[20], a strict sun protection should be advised to all DC patients.

Acknowledgement

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