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Bilateral Proliferative Retinopathy Associated With Hoyeraal-Hreidarsson Syndrome, a Severe Form of Dyskeratosis Congenita

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Abstract

Dyskeratosis congenita (DC) is the prototypical member of a family of diseases caused by defective telomere maintenance. These “telomeropathies” also include Hoyeraal-Hreidarsson syndrome (HH) and Revesz syndrome, which are severe forms of dyskeratosis congenita, as well as a subset of idiopathic pulmonary fibrosis, aplastic anemia, and Coats’ plus syndrome. Retinopathy has only rarely been reported in DC and HH, but is universally present in Coats plus and Revesz syndromes. The care of these patients is typically a multidisciplinary effort, and this should include monitoring by an ophthalmologist.

INTRODUCTION

Dyskeratosis congenita (DC) is an inherited, multisystem syndrome caused by defects in the molecular machinery responsible for telomere maintenance. Classically, the diagnosis is characterized by the triad of reticular skin pigmentation, dystrophic nails, and oral leukoplakia. Hoyeraal-Hreidarsson syndrome (HH) is a severe variant of DC that is distinguished by the presence of cerebellar hypoplasia, neurological deficits, aplastic anemia, and variable immunodeficiency.[1] Here we present a case of bilateral proliferative retinopathy in a patient with HH.

CASE REPORT

A 5-year-old Hispanic boy with history of HH presented to the pediatric ophthalmology service for ocular evaluation prior to planned bone marrow transplantation to treat chronic progressive bone marrow failure. The patient’s mother reported that she first noted leukocoria in the left eye (OS) 1 month ago. Vision was 20/30 in the right eye (OD) and 7/120 OS by Allen acuity cards. Intraocular pressure was 10 mm Hg in both eyes (OU), and there was no afferent pupillary defect. Anterior segment examination was notable for 4+ anterior vitreous cell OS. Limited dilated exam OD revealed clear vitreous, healthy optic nerve, and grossly normal posterior pole. In the left eye there was a poor view due to dense

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vitreous cell and debris. B-scan revealed vitreous opacity without retinal detachment or mass.

Vitrectomy OS with exam under anesthesia was performed. Exam OD showed sclerotic retinal vessels in the temporal periphery and preretinal heme inferotemporally (Figure 1A). Fluorescein angiography (FA) OD revealed 360° peripheral nonperfusion most prominent temporally and associated telangiectasia with late leakage, suggesting neovascularization (Figures 1B and 1C) with limited view, which suggested a similar picture in the fellow eye. Diagnostic vitrectomy OS showed chronic vitreous hemorrhage. Intraoperative examination of the retina confirmed similar findings to those seen OD. Laser photocoagulation of nonperfused retina was performed OU. Our patient did well postoperatively but unfortunately sustained blunt trauma to the left eye during postoperative week 6, resulting in recurrent vitreous hemorrhage and irreparable funnel retinal detachment with vision OS falling to no light perception.

Follow-up examination-under-anesthesia 2 months later revealed telangiectatic vessels just inside the posterior border of prior panretinal photocoagulation. Repeat FA revealed a new area of nonperfusion superotemporally and nasally, which were treated with further indirect laser (Figure 1D). Our patient was followed for 7 months after his initial presentation and vision in the right eye remained stable at 20/30 without further progression of his retinopathy.

DISCUSSION

DC was initially described in 1910 and remained primarily a clinical diagnosis until the late 1990s, when the first of several genes responsible for DC were identified. Since that time, genetic testing, including analysis of telomere length has led to the diagnosis of DC in the absence of the classic clinical findings and has served to accentuate the clinical heterogeneity of DC. Interestingly, DC is now considered the proto-typical member of a group of telomeropathies that include HH and Revesz syndrome variants, a subset of aplastic anemia; idiopathic pulmonary fibrosis; and most recently, Coats' plus.[2] Notably, retinopathy is a prominent component of both Revesz syndrome[3] and Coats' plus,[4] but has been only rarely reported in HH5 and DC.[6-9] A recent study that included 28 patients with DC found three of the patients had retinal vascular abnormalities, which included neovascularization, exudative retinopathy, and retinal detachment,[10] suggesting that retinopathy, although infrequent, is present in a significant minority of DC patients. Because retinopathy has been reported in autosomal dominant forms of DC, which can present later in life and with subtle systemic findings,[6,7] a high index of suspicion may be required to make the diagnosis.

Our patient had initially been referred to pediatric hematology/oncology at 20 months of age when complete blood count revealed macrocytic anemia and thrombocytopenia. His medical history was also significant for developmental delay. Additionally, neurological evaluation, including MRI of the brain, revealed hypoplasia of the cerebellar vermis, prominent foramen Magendie, and foramen magnum. Karyotype was normal and an extensive genetics workup was also negative. Although, the classic mucocutaneous signs were not present, the diagnosis of HH was made at age 4 when his telomeres were found to be extremely short in

all cell lines. Sequencing of genes known to be associated with HH revealed a novel mutation in the DKC1 gene. This mutation is also present in the patient's brother, who is 2 years older. Although the brother's telomeres are shortening more quickly than normal, he has not manifested any signs of HH to date. This is not entirely surprising, as DC is known to be clinically heterogeneous, displaying variability in age of onset and clinical manifestations even in individuals that share a common genetic etiology.[1,6] Moreover, DC exists in X-linked, autosomal recessive, and autosomal dominant forms, with eight causative genes identified to date with known mutations found in only 60% of cases.[1] It is possible that the DKC1 mutation in our patient represents a novel pathological mutation. Alternately, he may have an as-yet-unidentified mutation.

This case serves to illustrate the clinical heterogeneity of DC. Proliferative retinopathy is variably present in DC depending on subtype and has been reported in other telomeropathies. We recommend that all patients diagnosed with this family of conditions undergo complete ophthalmic examination to ensure early identification and treatment of any associated ocular pathology.

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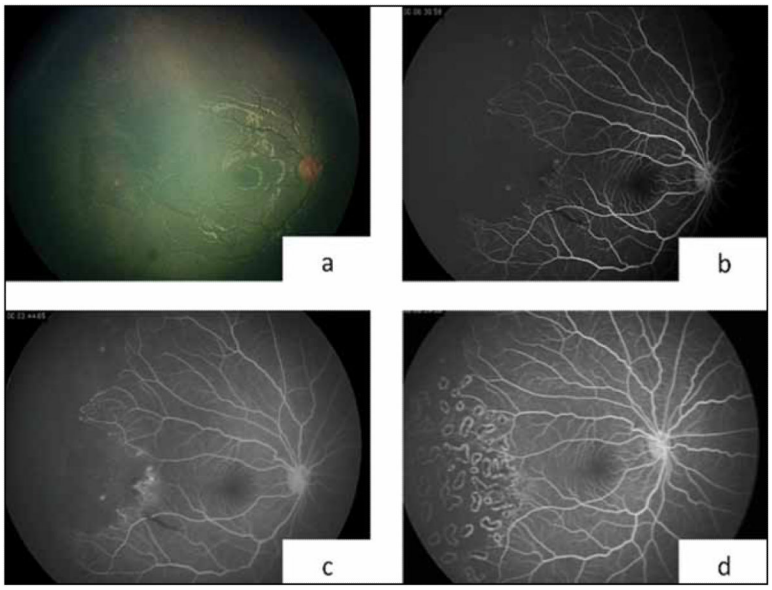

Figure 1.

Fundus photo demonstrates temporal vascular attenuation with telangiectasia and inferior preretinal heme (A). Concurrent fluorescein angiography (FA) demonstrates temporal nonperfusion and blockage due to preretinal heme (B) with vascular telangiectasia and late leakage (C). Follow-up FA shows new, untreated areas of nonperfusion superotemporally (D).