

Case Report

# A Case of Presumed Dyskeratosis Congenita Causing Severe Retinal Vascular Occlusion

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## Keywords

Dyskeratosis congenita · Retinal detachment · Retinal vascular occlusion · Vitreous surgery · Photocoagulation

## Abstract

Dyskeratosis congenita (DKC) is a rare, multisystem, bone marrow failure disease characterized by abnormalities such as in the skin, mucosa, nervous system, and lungs. Here we report a rare case of presumed DKC causing total retinal detachment in the right eye and severe peripheral retinal vascular occlusion in the left eye. A 3-year-old boy was presented with vitreous hemorrhage and total retinal detachment in the right eye and was scheduled to undergo vitreous surgery in the right eye and detailed ophthalmologic examination of the left eye under general anesthesia. Since a systemic examination revealed anemia and marked thrombocytopenia, he underwent a detailed pediatric examination. Although genetic testing revealed no significant pathologic mutations, the presence of shortened telomere length and other clinical findings suggested the possibility of DKC. His right eye had severe proliferative vitreoretinopathy, and retinal reattachment was not achieved with vitreous surgery, thus resulting in phthisis bulbi. The left eye showed a wide retinal avascular area in the temporal retina, retinal neovascularization, and hard exudates on fluorescein fundus angiography and was treated with laser photocoagulation using a binocular indirect ophthalmoscopic photocoagulator. Following laser surgery, the new blood vessels regressed, and the visual acuity was maintained at 1.0. The findings in this rare case indicate that DKC can cause severe retinal vascular occlusion, thus leading to vitreous hemorrhage and retinal detachment. Therefore, early detection with fundus examination and early treatment with photocoagulation are important.

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## Introduction

Dyskeratosis congenita (DKC) is a rare, multisystem, bone marrow failure disease characterized by abnormalities, such as in the skin, mucosa, nervous system, and lungs [1]. In an epidemiological survey conducted in the United Kingdom, the authors reported that the incidence of DKC is approximately 1 case per million people [2]. Moreover, a definitive diagnosis can be difficult due to the fact that the symptoms and severity of DKC vary from patient to patient as some patients present with typical symptoms while others may have very mild symptoms [3].

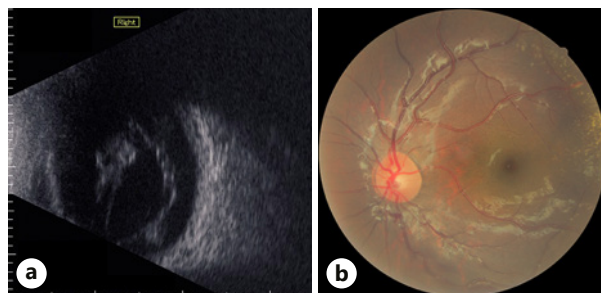
In regard to the ophthalmologic manifestations, there reportedly have been a few cases of DKC with blot hemorrhages, macular edema, retinal vasculopathy, and optic nerve atrophy [4–7]. Moreover, in a study by Vaz-Pereira et al. [8], the authors reported a case of DKC with severe vascular occlusion in the retinal periphery. Here we report a rare case of presumed DKC causing total retinal detachment in the right eye and severe peripheral retinal vascular occlusion in the left eye.

## Case Report

This study involved 3-year-old boy who was born at full term and had previously undergone examination at a local eye clinic at around the age of 2.5 years after his parents noticed exotropia of his right eye. At around 6 months after that first examination, he was subsequently referred to our hospital for a more detailed examination. At the first examination, his visual acuity measured on the decimal acuity chart was unmeasurable in the right eye and 0.6 in the left eye. The eye position was mild exotropia for both near and distant vision, with no limitation of eye movement. Hirschberg-method testing revealed that the strabismus angle was approximately 30 prisms. In the patient's right eye, the fundus was not visible and there was no reflex due to the vitreous hemorrhage, and B-mode ultrasound examination revealed total retinal detachment (Fig. 1a). In the patient's left eye, a retinal hemorrhage and hard exudates were observed in the temporal retina, as well as a small retinal hemorrhage inferior to the optic disc (Fig. 1b). Since the patient was scheduled to undergo vitreous surgery in the right eye and a detailed ophthalmologic examination of the left eye under general anesthesia, a systemic examination was performed. There was nothing of note in the parents' family history.

The systemic examination findings revealed that the patient's blood test results were as follows: RBC  $317 \times 10^4/\mu\text{L}$ , Hb 10.0 g/dL, Ht 31.1%, MCV 97.9 fL, MCH 31.5 pg, MCHC 32.2%, WBC 5,910/ $\mu\text{L}$ , Plt  $4.5 \times 10^4/\mu\text{L}$ , Fe 74  $\mu\text{g/dL}$ , TIBC 379  $\mu\text{g/dL}$ , and UIBC 305  $\mu\text{g/dL}$ . Since the patient had anemia and thrombocytopenia, a detailed pediatric examination was performed. His height was 89.0 cm, indicating a short stature (2.0 standard deviation below the mean), weight was 12.5 kg, vital signs were normal, skin was slightly anemic, and there

**Fig. 1.** Ocular findings at the initial presentation. **a** B-mode ultrasound image of the patient's right eye showing vitreous hemorrhage and total retinal detachment. **b** Fundus photograph of the patient's left eye showing hard exudates at the temporal area to the macula and a small retinal hemorrhage inferior to the optic disc.



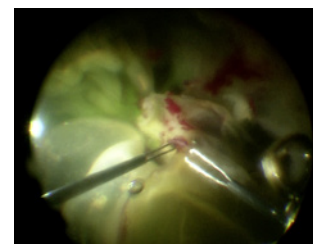
was a deformity in the nail of the first toe. He was also found to have a mild developmental disability. MRI findings showed cerebellar atrophy (Fig. 2). The findings of a bone marrow examination performed at the Department of Pediatrics of our University Hospital were as follows: nucleated cell count:  $2.9 \times 10^4/\mu\text{L}$ , megakaryocyte percentage: 0%, and myeloid/erythroid ratio (i.e., the ration of maturing myeloid cells to erythroid cells in the bone marrow): 6.15.

Those findings revealed mild bone marrow hypoplasia with almost no megakaryocytes, and there were mild megaloblastic changes and pseudo-Pelger-Huët anomaly cells. Refractory cytopenia of childhood, among other possibilities, was suspected, and a bone marrow biopsy was performed. The cellularity of the bone marrow was 60%, showing almost normocellular bone marrow; the myeloid/erythroid ratio was 2, and no mature megakaryocytes were present in the sample. Immunohistologically, there were no p53-positive cells. The possibility of congenital hematopoietic failure was suspected and genetic testing (i.e., DKC1 and TERC) was performed, yet no clinically significant mutations were observed. However, a telomere length test showed a shorter telomere length compared to that of healthy controls (i.e.,  $-4.45$  standard deviation below the mean). Thus, the presence of the shortened telomere length, as well as the other clinical symptoms, was suggestive of DKC. In regard to the familial history, it should be noted that the patient's great-grandmother on the father's side had been diagnosed with myelodysplastic syndrome that progressed into acute myeloid leukemia.

For treatment, the patient underwent vitreous surgery in the right eye and detailed ophthalmologic examination of the left eye under general anesthesia. His right eye had vitreous hemorrhage and severe proliferative membrane formation, and the condition was considered to be proliferative vitreoretinopathy (grade D-3) (Fig. 3). The retinal detachment was longstanding and the retina was no longer extensible. The pre- and subretinal membranes were removed as much as possible, and liquid perfluorocarbon was injected. However, the extension was insufficient. Considering that the prognosis was poor, no further treatment was performed. For the patient's left eye, fluorescein fundus angiography was performed under general anesthesia. A wide retinal avascular area was observed in the temporal retina, and retinal neovascularization, exudative changes, such as hard exudates, and preretinal

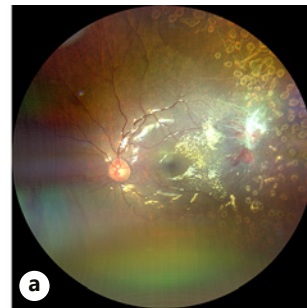
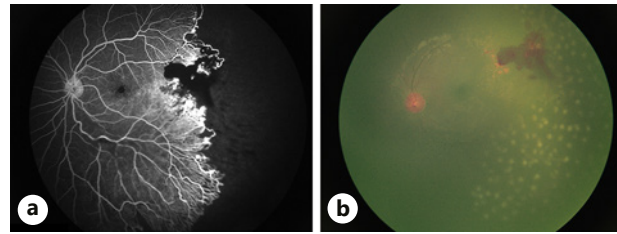


**Fig. 2.** MRI of the patient's brain showing cerebellar atrophy (area circled with a dashed line).

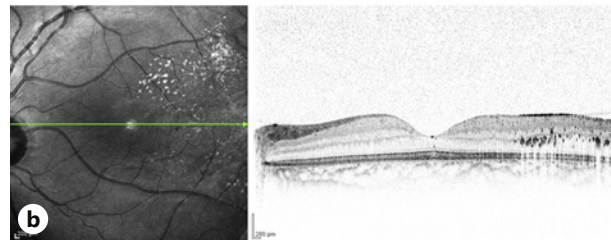


**Fig. 3.** Intraoperative findings of the patient's right eye. Image showing total retinal detachment with severe proliferative membrane formation in the patient's right eye.

**Fig. 4.** Intraoperative findings of the patient's left eye. **a** Fluorescein fundus angiography image showing wide retinal avascular area in the temporal retina and retinal neovascularization and hard exudates in the marginal region of the left eye. **b** Transpupillary photocoagulation was performed in the retinal avascular area using a binocular indirect ophthalmoscopic photocoagulator.



**Fig. 5.** Ocular findings at 6 months postoperatively in the left eye. **a** Image showing that the retinal neovascularization had regressed and the preretinal hemorrhage had diminished by laser treatment. **b** Optical coherence tomography imaging of the patient's left eye showing residual hard exudates at the temporal area to the macula.



hemorrhage were observed in the marginal region (Fig. 4a). Transpupillary photocoagulation was performed in the retinal avascular area using a binocular indirect ophthalmoscopic photocoagulator (Fig. 4b). Following surgery, there were no remarkable complications, and the patient was discharged at 1 week postoperatively. However, it should be noted that after surgery, phthisis bulbi occurred in the patient's right eye, while the retinal neovascularization in the patient's left eye had regressed and the preretinal hemorrhage had diminished by laser treatment (Fig. 5a). Optical coherence tomography imaging of the left eye revealed residual hard exudates at the temporal area to the macula (Fig. 5b), and the corrected visual acuity in that eye at 6 months and 1 year postoperatively was 0.8 and 1.0, respectively, thus illustrating a favorable course.

## Discussion

Reportedly, DKC is caused by impaired telomere maintenance [9, 10], and in cell division, telomeres are involved in the maintenance of chromosomes, etc. Thus, DKC is a disease of telomere shortening and dysfunction, and it affects the skin and bone marrow, which both have a high rate of cell proliferation. DKC is an inherited bone marrow syndrome characterized by the triad of nail dystrophy, oral leukoplakia, and skin pigmentation. In addition to the symptoms described above, patients with DKC can present with a variety of other symptoms, including bone marrow failure, eye disorders, and skeletal abnormalities [11].

In the present case, vitreous hemorrhage and retinal detachment were both observed in the right eye at the initial examination, and the blood test findings revealed anemia and marked thrombocytopenia. Therefore, bone marrow and telomere length tests were performed at the Department of Pediatrics of our university hospital. The presence of the shortened telomere length, as well as the other clinical findings (i.e., short stature, cerebellar atrophy, and ophthalmologic findings, etc.) was strongly suggestive of DKC. Hoyeraal-Hreidarsson syndrome and Revesz syndrome, which have been considered as independent disease concepts due to recent advancements in genetic diagnosis, have both been classified as clinical variants of DKC [12]. Genetic testing performed for a definitive diagnosis revealed no significant pathological mutations. Reportedly, the modes of inheritance in this disease include X-linked recessive, autosomal dominant, and autosomal recessive patterns [13]. *DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *TCAB1*, and *RTEL1* have been identified as responsible genes; However, it is important to note that in several cases, the responsible gene has not been identified [14]. Thus, as the clinical symptoms and severity of DKC are known to vary from patient to patient, genetic testing plays an important role in a definitive diagnosis. Moreover, it is reported that skin pigmentation and nail changes often appear in early childhood and that bone marrow failure develops by the age of 20 years, with 90% of the patients showing signs of bone marrow failure by the age of 30 years [9]. However, the symptoms and time of onset vary among patients. In our present case, the symptoms were not typical. Hence, ongoing assessment in collaboration with other departments, such as the Department of Pediatrics, is required, due to the fact that new symptoms may arise and that the disease may worsen.

Upon ophthalmological examination, our patient was suspected of having familial exudative vitreoretinopathy or Coats disease and fluorescein fundus angiography revealed a wide retinal avascular area. However, it was difficult to determine whether it was due to abnormal retinal vascular growth, such as familial exudative vitreoretinopathy, or disruption of the capillary network resulting from a hematopoietic abnormality or a telomere abnormality. In addition to the abnormalities detected in both eyes, systemic symptoms such as bone marrow failure and cerebellar atrophy were observed in the present case. Thus, we presumed that the eye symptoms were caused by DKC. The reported changes in the fundus in DKC cases include retinal neovascularization, retinal detachment, exudative change, hemorrhage, and optic atrophy [4–7]. In our patient, there was also a possibility of traction retinal detachment due to a pathologic fibrovascular proliferative membrane following hemorrhage caused by marked thrombocytopenia and retinal ischemia; however, we were unable to fully elucidate the pathological mechanism. Since vitreous hemorrhage and retinal detachment in children may lead to irreversible eye damage, early diagnosis and treatment is vital. In our case, phthisis bulbi ultimately occurred in the right eye, while the exudative lesion, fundus hemorrhage, and retinal avascular area in the patient's left eye was successfully treated with laser photocoagulation. The condition did not progress to vitreous hemorrhage or retinal detachment, and visual function was preserved. Of note, exotropia was the initial symptom that led to the diagnosis in the present case. Thus, when seeing children with exotropia, clinicians should be aware of the possibility of fundus-related diseases. When hematopoietic dysfunction such as DKC is presumed from blood test results, fundus examination should be performed for early diagnosis, and photocoagulation should be performed if needed.

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### Statement of Ethics

The protocols of this study were approved by the Ethics Committee of Osaka Medical College, Takatsuki-City, Osaka, Japan. In accordance with the tenets set forth in the Declaration of Helsinki, prior written informed consent was obtained from the parent for publication of this case report and any accompanying images.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors did not receive any funding.

### Author Contributions

T.H., S.O., M.T., H.M., and A.I.: equal contribution of patient management, conception of the paper, data analysis and interpretation, manuscript drafting, and literature search. T.H., T.K., and A.I.: co-writing of the manuscript and literature search. A.A. and T.I.: design of the paper, co-writing of the manuscript, literature search, manuscript editing and revision as well as final approval. All authors read and approved the final manuscript.

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