Frosted Branch Angiitis in Pediatric Dyskeratosis Congenita

A Case Report

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Abstract: Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome, usually presented with abnormal skin pigmentation, nail dystrophy, and oral leukoplakia. The main cause of mortality in DC is immunodeficiency and vital infection. DC involves multisystem, but retinal involvements are rare.

Herein, we report an unusual case of pediatric DC suffering from frosted branch angiitis (FBA) after recovery of mycoplasma pneumonia. Cytomegalovirus infection and cytokine changes were found relevant to the onset of FBA. Despite corticosteroids, antiviral medication, and hematopoietic stem cell transplantation, the patient ended in poor vision with optic atrophy.

This case implies that pediatricians should be aware of FBA as a rare retinal manifestation in children with DC and bone marrow failure. Cytomegalovirus may be one of the common causes and cytokines could be triggering factors.

INTRODUCTION

Dyskeratosis congenita (DC) is a rare inherited disease characterized by excessively short telomeres in highly proliferative tissues and predisposition to cancer.1 X-linked recessive inheritance with mutation in DKC1 accounts for half the cases, and is thought to predominantly manifest as bone marrow failure (BMF) in childhood.2 The immune cells in BMF patients are highly vulnerable, and immunodeficiency often results in fatal infections and mortality in DC.3

Dyskeratosis congenita is a multisystem disorder. Ophthalmic manifestations of DC include blepharitis, conjunctivitis, nasolacrimal duct obstruction, ectropion, entropion, and trichiasis. Retinal abnormalities are rare,4 and have been reported in forms of hemorrhages, neovascularization, arteriosclerosis, retinal vascular sheathing, macular edema, preretinal fibrosis, nerve fiber layer infarction, and optic atrophy.5–8 However, the vascular sheathing in the previously published description were mild and peripheral.3,5 We encountered a boy who presented frosted branch angiitis (FBA) after recovery of mycoplasma pneumonia. To our knowledge, this is the first report of FBA in children with DC.

CASE REPORT

A 6-year-old Chinese boy was referred to our hospital with 5 days of fever and cough with a 1-year history of cytopenia. Physical examinations revealed reticular pigmentation of the chest, splitting nails, oral ulcer, atrophic mucosa of tongue, and bilateral lung rales. Ophthalmic findings were normal. Laboratory studies showed a leukocyte count of $1.31 \times 10^{9}$/L, an erythrocyte count of $2.61 \times 10^{12}$/L, a platelet count of $134 \times 10^{9}$/L, and C-reactive protein (CRP) level of 70 mg/L.

A molecular diagnosis was DC with mutation in DKC1 gene (T/A; p. Ala353Val), and his mother was a carrier. His immunophenotype was T+B−NK−. A bone marrow biopsy revealed BMF. CD4 T-cell count was $130 \times 10^{9}$/L. Serum immunoglobulin (Ig)G, IgA, and IgE were elevated, whereas IgM was normal. Besides positive VCA IgG and EBNA1 IgG antibodies against Epstein–Barr virus, serology tests were negative for Legionella, Chlamydia pneumoniae, Mycoplasma pneumoniae (MP), cytomegalovirus (CMV), human metapneumovirus, adenovirus, respiratory syncytial virus, influenza virus, and parainfluenza virus. Commercial real-time polymerase chain reaction (PCR) assay of spumt was positive for MP by targeting P1 gene (Da An Gene Co., Ltd., China). CMV-PP65 antigen was negative. Chest computed tomography revealed frosted branch angiitis, FFA = fundus fluorescein angiography, APTT = activated partial thromboplastin time, BCVA = best-corrected visual acuity, BMF = bone marrow failure, CMV = cytomegalovirus, CRP = C-reactive protein, CT = computed tomography, DC = dyskeratosis congenita, FBA = frosted branch angiitis, FFA = fundus fluorescein angiography, HIV = human immunodeficiency virus, HSCT = hematopoietic stem cell transplantation, Ig = immunoglobin, IL = interleukin, MP = Mycoplasma pneumoniae, OCT = optical coherence tomography, PCR = polymerase chain reaction, TNF = tumor necrosis factor, UCBT = umbilical cord blood transplantation.

Editor: Yi Shu.
Received: November 18, 2015; revised: February 21, 2016; accepted: February 24, 2016.

This research is financially supported by grants from the Health Department of Zhejiang Province (No. LQ13H120001), and the National Natural Science Foundation of China (No. 81202021). It is supported by the Key Laboratory of Diagnosis and Treatment of Neonatal Diseases of Zhejiang Province.

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The authors report no conflicts of interest.

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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003106
(CT) showed diffused patchy shadows. The patient was diagnosed with DC and mycoplasma pneumonia. Intravenous azithromycin 175 mg once daily was given for 5 days, and his general conditions improved.

However, on day 19, the patient complained of a sudden decrease in visual acuity, dry eyes, and relapsed fever. Ophthalmic examination showed best corrected visual acuity (BCVA) of 6/60 in the right eye and 6/7.5 in the left eye. External and anterior segment examinations were unremarkable except for shortened tear break-up time of 5 seconds and relative afferent pupillary defect. Funduscopy revealed mild vitreous haze, marked discontinuous sheathing of veins, and arteries in all 4 quadrants, with clouds of exudates surrounding the vessels and severe papilledema. Fundus fluorescein angiography (FFA) showed tortuous and dilated retinal veins, arteriolar-venular anastomoses, arterial occlusion, capillary nonperfusion, and vascular leakage. Optical coherence tomography (OCT) revealed macular edema and retinal detachment. A diagnosis of FBA was made (Figure 1A–D, G, and H).

Several hematological changes were found concomitant with the ocular disorder (Figure 2). Serum levels of interleukin (IL)-6, IL-10, and tumor necrosis factor-α (TNF-α) started to increase when MP was detected, and reached a high level 19 days later. Elevated leukocyte count, decreased platelet count, increased CRP, shortened activated partial thromboplastin time (APTT), and increased fibrinogen were also noticed. Serum and bone marrow specimens were found to be positive in real-time PCR, targeting the IE2 gene of CMV (Da An Gene Co., Ltd., China), and the DNA amounts were $1.9 \times 10^4$ and $4.7 \times 10^4$ copies/mL, respectively. CD4 T-cell count dropped to $80 \times 10^6/L$. Diagnostic workup to rule out other causes of retinal vasculitis was done. Serology analyses were negative for CMV, human immunodeficiency virus (HIV), herpes simplex virus, rubella virus, hepatitis B virus, hepatitis C virus, parvovirus B19, Treponema pallidum, and Toxoplasma gondii. Fasting glucose level, antistreptolysin O, rheumatoid factor, tuberculin test, antineutrophil cytoplasmatic antibody, and antinuclear antibody were normal. He was treated with intravenous methylprednisolone 20 mg twice daily and intravenous acyclovir 175 mg 4 times daily for 10 days, and then oral methylprednisolone 16 mg twice daily and valaciclovir 150 mg twice daily. Corticosteroid was tapered off over 1.5 months.

After 2 weeks, his BCVA improved to 6/30 in the right eye and 6/15 in the left eye. Pupillary reactions were sluggish in both eyes. Funduscopy revealed scattered hard exudates and vascular sheathing was resolved (Figure 1E and F). OCT showed relieved retinal edema (Figure 1K and L). One month later, the vision dropped to counting fingers (at 30 cm) in the right eye and 6/30 in the left one. The vitreous humors were clear. Attenuate retinal vessels, especially the arteries, with scattered shining crystalline deposits, were seen in the fundus. To treat his BMF, the patient received unrelated umbilical cord

![Figure 1](https://example.com/fig1.jpg)

**Figure 1.** Imaging characterization of FBA. A, B, Bilateral funduscropy showed FBA, retinal edema, hemorrhages, and papilledema. C, D, FFA showed tortuous and dilated retinal veins, arteriolar-venular anastomoses (white arrow), arterial occlusion (white arrow head), capillary nonperfusion and vascular leakage. G, H, OCT showed macular edema and retinal detachment (red arrow). E, F, After 2 weeks, vascular sheathing resolved, leaving hard exudates. K, L, OCT images also improved. J, After 3 months, pale optic nerve heads, retinal vessels with a “silver wire” appearance, crystalline deposits, and peripheral atrophic depigmentation were observed. FBA = frosted branch angiitis, FFA = fundus fluorescein angiography, OCT = optical coherence tomography.
blood transplantation (UCBT) and haploidentical hematopoietic stem cell transplantation (HSCT) consecutively, and leukocytes engrafted on day +9. Unfortunately, the patient got an intracranial CMV infection 1 month later and was transferred to the intensive care unit. Three months after the onset of FBA, ocular examination showed dilated pupils, diminished pupillary light reflex, optic atrophy, retinal vessels with a “silver wire” appearance, crystalline deposits, and peripheral atrophic depigmentation (Figure 1I and J). The patient’s condition was exacerbated and he received mechanical ventilation after an episode of cardiac arrest. He was discharged automatically half a year later.

**DISCUSSION**

Frosted branch angiitis was first described in 1976 in Japan, and the young and fit are most susceptible. It is characterized by heavy vascular sheathing producing the appearance of frosted branches of a tree. The pathogenesis of FBA remains unknown and is possibly related to immune-complex deposition.
along the vessel walls after various prodromal infection. Kleiner considered CMV the most commonly concurrent infective agent with FBA.9

Cytomegalovirus-associated FBA has been mainly reported in HIV patients.10–12 Few literatures have been documented about CMV-related retinal impairments in DC; only 1 case of peripheral CMV retinitis in a 23-year-old woman with DC was described.13 Herein we reported a case of FBA in DC. Intravascular high copies of CMV were supposed to be responsible for the ocular complications. In addition, the changes of leukocytes, CRP, and platelets indicated that the mechanism of FBA was associated with not only immune hypersensitivity to infection, but also inflammation reaction and coagulation disorder. Why did the patient develop FBA on the basis of an apparent improved condition? The following reasons should be taken into account. First, CMV easily proliferates and affects organs when CD4 T-cell count decreases. Second, cytokines play an important role of a triggering factor.

Few studies have been reported about the circulating cytokine induction in DC.14 In this patient, an increasing production of IL-6, IL-10, and TNF-α was noticed after MP infection. Especially for IL-6, the rate of rise was steeper, whereas the amount of MP DNA was lower. These observations are in accordance with that of Matsui et al15 who implemented a series of cytokines analyses in bone marrow cells in vitro. Cytokines have been reported to take part in some ocular vasculitic diseases.16–18 IL-6 is a multifunctional proinflammatory cytokine; it does not drive severe immune response by contributing to both B-cell differentiation and T-cell proliferation, but also increases vascular permeability and causes retinal exudates.18 TNF-α participates in local vasculitic and/or thrombotic vascular occlusion.19 On the contrary, IL-10 is classically described as an anti-inflammatory and immunoregulatory factor by inhibiting T-cell immunity and TNF-α production.17 However, it seemed not strong enough to counteract the effects of IL-6 and TNF-α in this patient. Overall, certain cytokines can contribute to the inflammation and immunomodulation of the retinal vessels, and may play a part of triggering factors in the development of FBA.

It is noteworthy that MP could cause ophthalmic manifestations as extrapulmonary involvement. Papilledema, retinal exudates, and hemorrhages have been described in patients with MP.20 MP can stimulate B and T lymphocytes and induce formation of autoantibodies that react with vessels.21 However, we could not get positive results of the vasculitis-associated autoantibodies such as ANA or ANCA. Type III hypersensitivity reaction is another common mechanism to cause microvasculitis via immune complexes deposition.20 Immune complex formation is based on a relatively overload of antigen, but for our case, MP antigen was eliminated before the ocular event. In this case, MP was not likely to be the etiologic agent of FBA.

Cytokine regulatory medication might be useful, but it needs further study.

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