

Two Cases of Frosted Branch Angiitis with Central Retinal Vein Occlusion

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Background: Frosted branch angiitis usually occurs in children, and has a good prognosis. We report two cases of unilateral frosted branch angiitis in adults. Both had poor visual outcomes because of associated central retinal vein occlusion and neovascular glaucoma.

Cases: Case 1 was a 36-year-old woman. Almost all retinal veins and some retinal arteries showed vasculitis in her right eye, and veins were slightly dilated and sheathed. Case 2 was a 23-year-old woman. Angle hypopyon was observed in her left eye. Retinal veins were dilated, meandering, and sheathed. Retinal hemorrhages were also observed. In both cases, after systemic steroid therapy the retinal vasculitis gradually decreased, but central retinal vein occlusions gradually developed. Despite systemic administration of urokinase and panretinal photocoagulation, neovascular glaucoma developed, and visual acuity diminished in both cases.

Conclusions: Two cases of frosted branch angiitis complicated by retinal vein occlusion are reported. Careful observation of retinal blood flow is necessary in frosted branch angiitis in adults. **Jpn J Ophthalmol 2001;45:628–633** © 2001 Japanese Ophthalmological Society

Key Words: Central retinal vein occlusion, frosted branch angiitis, neovascular glaucoma, systemic corticosteroid therapy.

Introduction

Frosted branch angiitis was first reported in 1976 by Ito¹ in a 6-year-old boy with severe sheathing of all retinal vessels, resembling the frosted branches of a tree. Since then, frosted branch angiitis has been reported mainly in Japan^{2–5} but also in other countries.^{6–16} The characteristics of typical cases of frosted branch angiitis are as follows. A bilateral (but sometimes unilateral) retinal vasculitis occurs in young, otherwise healthy patients and visual acuity is usually profoundly affected, presenting as 20/200 or worse in the majority of reported cases. Inflammation is seen in the anterior chamber and the vitreous in all cases. Bilateral retinal phlebitis and arteritis are present, expanding from the posterior pole to the periphery with uninterrupted severe sheathing of all

vessels, resembling the frosted branches of a tree. The inflammation may predominantly affect the veins only, but some cases had extensive arterial involvement. Fluorescein angiography shows normal blood flow without evidence of occlusion or stasis, but there is late staining and leakage of dye from affected vessels. Additional fundus findings may include intraretinal hemorrhage, punctate hard exudate, and serous exudative retinal detachment.¹⁷ Almost all cases of this disease respond to systemic corticosteroid therapy with a rapid resolution of the vascular sheathing, retinal hemorrhages, and exudative retinal detachment. The visual prognosis is usually good and there is no recurrence in most patients.¹⁷

However, recently, Seo et al¹⁶ reported one case of recurrent unilateral frosted branch angiitis that had a poor visual outcome due to occlusion of retinal vessels. In their report, they suggested that this disease could be related to retinal vascular occlusion, and that intravenous corticosteroid therapy might actually worsen the disease prognosis. Therefore, in-

Received: August 10, 2000

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travenous corticosteroid therapy in this disease may still be controversial.

We encountered two unusual cases of frosted branch angiitis with central retinal vein occlusion (CRVO). Despite systemic administration of corticosteroids, urokinase, and panretinal photocoagulation, the complication of neovascular glaucoma developed and visual acuity worsened in both cases. These cases may indicate that intravenous corticosteroid therapy exacerbates vascular occlusion in this disease.

Case Reports

Case 1

On January 10, 1996, a 36-year-old woman visited our hospital because of sudden visual loss in her right eye 2 days earlier. Her systemic and ocular histories were unremarkable. On initial examination, visual acuity was RE 2/100 and LE 25/20. The intraocular pressure was within normal limits in both eyes. There were some cells in the anterior chamber and vitreous in the right eye, but no cells in the left eye. Fundus examination showed extensive white sheathing surrounding the retinal veins and some of

the retinal arteries from the posterior pole to the periphery in the right eye, with scattered retinal hemorrhages, exudates, and papillary edema. The retinal veins were slightly dilated (Figure 1A). The left eye was normal. Fluorescein angiography demonstrated extensive dye leakage from veins and the optic disc in the right eye. However, there was no evidence of vascular occlusions (Figure 1B). Laboratory studies including blood cell count, hemoglobin, plasma proteins, urea, and electrolytes revealed no obvious abnormalities except for slight iron deficiency anemia. Other examinations including polymerase chain reaction (PCR) assay for herpes simplex and varicella zoster virus in the aqueous humor, chest x-ray and B-mode echo tomography were conducted. Results of all these tests were negative or normal. Human leukocyte antigen typing results were A2, A24, B39, B60, Cw3, and Cw7. The patient showed no systemic manifestations of Behçet's disease, such as aphthous oral ulcers, genital ulcers, or erythema nodosum of the skin.

Topical betamethasone sodium phosphate (0.1%) six times/day resulted in no change in the retina of the right eye. Then, 6 mg/day of betamethasone was administered intravenously for 6 days. The vascular

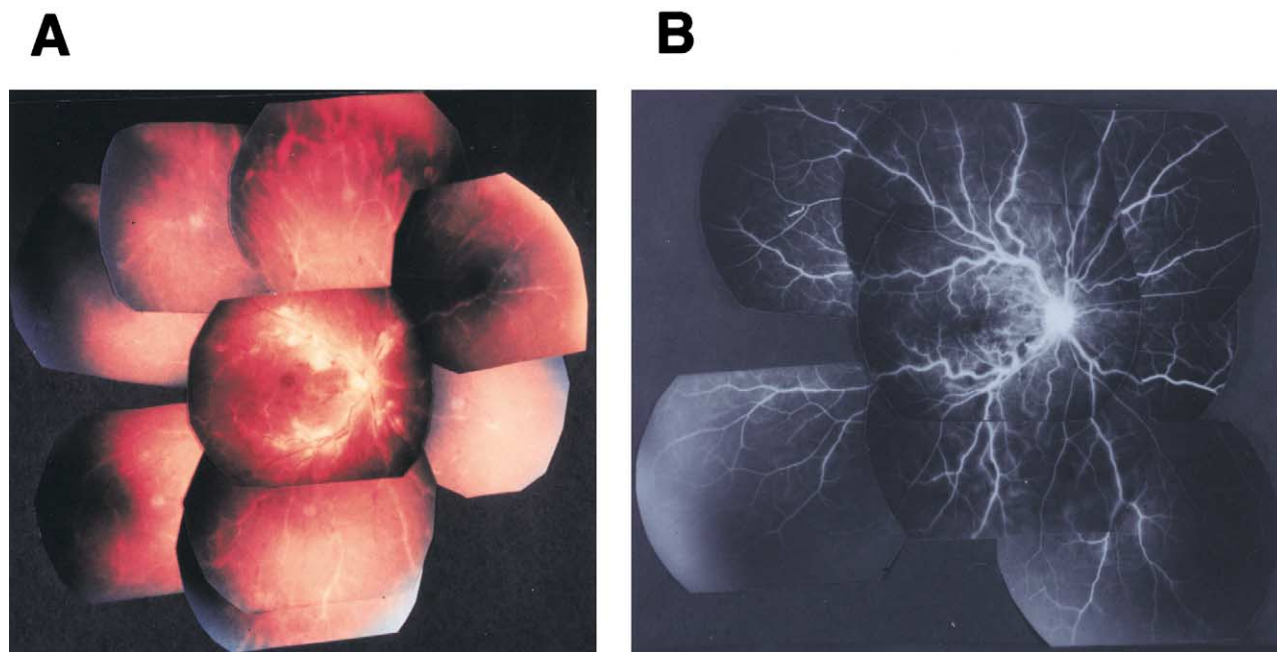


Figure 1. (A) Patient 1. Right eye of 36-year-old woman at initial examination. Retinal veins showed slight meandering and dilation. There was extensive white sheathing surrounding retinal veins and some retinal arteries from posterior pole to periphery, with scattered retinal hemorrhages, exudates and papillary edema. (B) Right eye of patient 1 at initial examination. Fluorescein angiography showed leakage of dye from retinal veins and optic disc. There was no evidence of vascular occlusions.

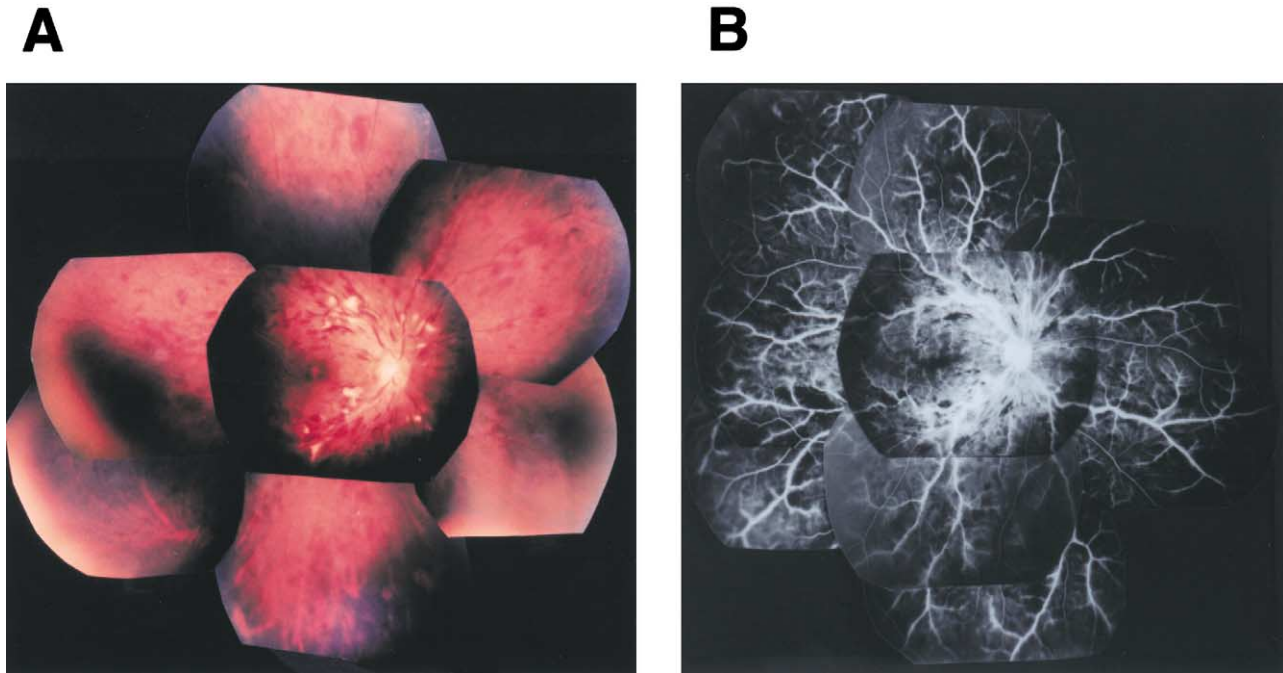


Figure 2. (A) Right eye of patient 1 one month after initial examination. Despite systemic steroids and anti-coagulant therapy, retinal hemorrhages continued to increase. (B) Right eye of patient 1 one month after initial examination. Fluorescein angiography demonstrated extensive leakage of dye from all veins and widespread area of nonperfusion on nasal side of retina.

sheathing decreased in response to the systemic corticosteroid, and visual acuity improved to RE 2/20. Subsequently, we switched the intravenous injection to 40 mg/day of oral prednisolone and gradually tapered the dose thereafter. On January 30, the sheathing of the retinal vessels had disappeared and visual acuity had improved to RE 20/40. However, retinal flame-shaped hemorrhages increased around the optic disc and gradually spread to the periphery. The diagnosis of CRVO was made. An additional 80 mg/day of oral aspirin was given for anti-coagulation and 120,000 IU/day of intravenous urokinase was also administered for 7 days. However, the retinal hemorrhages continued to increase (Figure 2A). On February 8, fluorescein angiography demonstrated a widespread area of nonperfusion on the nasal side of the retina (Figure 2B). Panretinal photocoagulation (total 1,300 shots) in the right eye was done from February 15 to June 6. Photocoagulation reduced the hemorrhages in the peripheral retina, but macular edema increased and visual acuity decreased to RE 4/100 on July 4. Rubeotic glaucoma developed and intraocular pressure was elevated to 50 mm Hg on August 26. Trabeculectomy was done twice, and intraocular pressure subsequently decreased to the normal range. However, thereafter several vitreous

hemorrhages occurred and visual acuity decreased to light perception only in the right eye.

Case 2

On February 10, 1997, a 23-year-old woman visited our hospital because of sudden visual loss in her left eye a week earlier. Her systemic and ocular histories were unremarkable. Visual acuity was RE 25/20 and LE 6/100 at the initial examination. The intraocular pressure was normal in both eyes. A moderate number of cells and flare were present in the anterior chamber and the vitreous of the left eye, but there were no cells in the right eye. Angle hypopyon was observed in the left eye. Extensive white sheathing of the retinal veins and some of the retinal arteries was seen in the left eye, with many scattered retinal hemorrhages, some exudates and papillary edema (Figure 3A). Retinal veins were dilated, meandering, and sheathed. The right eye was normal. Fluorescein angiography of the left eye demonstrated extensive dye leakage from veins and the optic disc without occlusions in the retinal vessels (Figure 3B). Results of laboratory examinations were normal except for slight elevation of rheumatoid factor. As for herpes simplex virus and varicella zoster

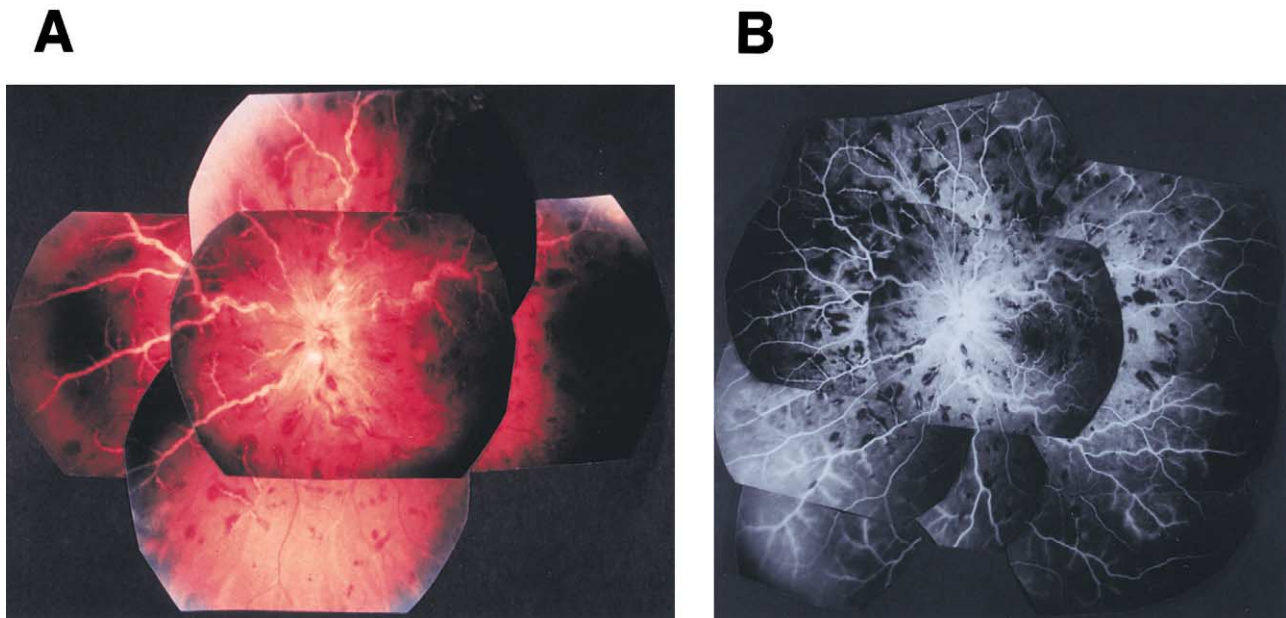


Figure 3. (A) Patient 2. Left eye of 23-year-old woman at initial examination. Extensive white sheathing of retinal veins and some retinal arteries is seen, with many scattered retinal hemorrhages, some exudates, and papillary edema. Retinal veins are dilated and meandering. (B) Left eye of patient 2 at initial examination. Fluorescein angiography demonstrated extensive dye leakage from veins and optic disc without retinal vessel occlusion.

virus, serum antibody titers and PCR assay of the aqueous humor were examined, but the results were negative. The serum anti-cardiolipin antibody titer was within normal limits. Results of other examinations, including chest x-ray and computed tomography of the brain, were normal. In human leukocyte antigen typing, results were A24, A26, B35, B61, Cw3, DR8, and DR11. The patient had no systemic manifestations of Behçet's disease, such as aphthous oral ulcers, genital ulcers, or erythema nodosum of the skin.

Topical betamethasone sodium phosphate (0.1%) and oral indomethacin (50 mg/day) were administered for 1 week. However, the retina of the left eye was unchanged. Therefore, 6 mg/day of betamethasone was administered intravenously for 3 days, followed by oral prednisolone (40 mg/day for 4 days). The prednisolone dose was gradually tapered thereafter. Retinal vasculitis decreased in response to the systemic corticosteroid therapy. On February 25, sheathing of the retinal vessels had disappeared, but CRVO had developed and retinal hemorrhages increased (Figure 4A). On February 27, fluorescein angiography demonstrated a widespread area of nonperfusion in the peripheral retina (Figure 4B). Panretinal photocoagulation (total 2,900 shots) was performed in the left eye, divided into eight sessions, from March 1 to May 2. Oral beraprost sodium (60

µg/day) was also administered to increase the blood flow in the retinal vessels. Photocoagulation reduced the retinal hemorrhages in the periphery, but macular edema increased and visual acuity had decreased to 1/100 by May 2. Iris rubeosis was seen in the left eye on May 23, and retinocryopexy was performed in the peripheral retina. However, intraocular pressure was elevated to 40 mm Hg on July 3 due to the development of rubeotic glaucoma. Cyclophotocoagulation was performed three times, and intraocular pressure decreased to the normal range. Visual acuity in the left eye finally decreased to light perception only because of retinal hemorrhages and macular degeneration.

Discussion

Both our cases had unilateral retinal angiitis, mainly periphlebitis, and both were young adults. Retinal periphlebitis has been reported in association with tuberculosis,¹⁸ syphilis,¹⁹ sarcoidosis,²⁰ Behçet's disease,²¹ multiple sclerosis,²² Eales disease,²³ cytomegalovirus retinitis with HIV infection,⁹⁻¹² and collagen diseases.²⁴ These diseases had to be ruled out to make the diagnosis of frosted branch angiitis in our cases. Behçet's disease was denied because neither patient had any history of systemic manifes-

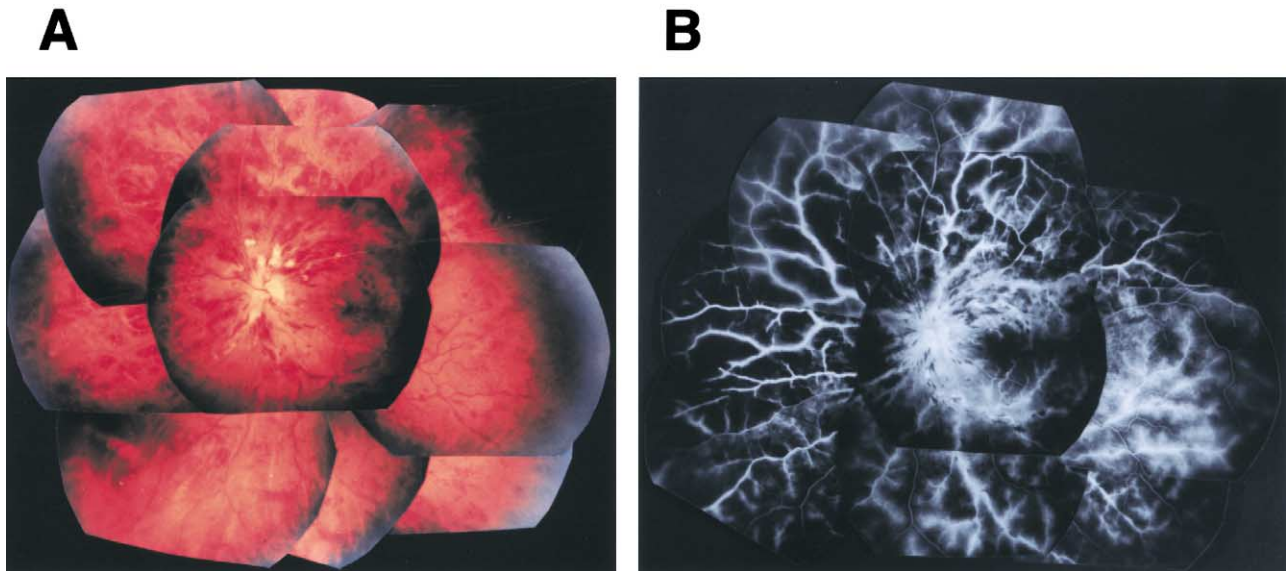


Figure 4. (A) Patient 2. Right eye 17 days after initial examination. In response to systemic corticosteroid therapy, sheathing of retinal vessels disappeared. However, retinal hemorrhages increased and complication of central retinal vein occlusion developed. (B) Patient 2. Right eye 17 days after initial examination. Fluorescein angiography demonstrated widespread area of non-perfusion in peripheral retina.

tations of Behçet's disease and did not have HLA-B51. In previous reports of frosted branch angiitis, high herpes virus titers were noted.^{5,6} However, the possibility of herpes virus infection was also ruled out because of negative serum titers of antibodies to these viruses and negative PCR results in the aqueous humor in both cases. Neither of our patients had any other clinical or laboratory findings supporting other diagnoses. CRVO also had to be ruled out in our cases at presentation, because the two patients had retinal hemorrhages at their initial visits. However, at the first visit cells and flare were seen in the anterior chamber and the vitreous. Therefore, our cases did not have CRVO at the beginning, but rather, showed the complications of uveitis, particularly retinal angiitis.

Recently, Kleiner classified the patients with frosted branch angiitis into three subgroups.²⁵ The first group consists of patients with lymphoma¹³ or leukemia¹⁴ whose disease is due to infiltration of malignant cells. The second group includes patients with associated viral infections^{9–12} or autoimmune disease.²⁴ The third group is composed of otherwise healthy young patients, as initially described by Ito et al.¹ Given the lack of systemic complications, Kleiner proposed that the third group be referred to as having "acute idiopathic frosted branch angiitis." Our two cases meet the criteria for this group.

On the other hand, the most important characteristic of our cases was the complication of CRVO. The complication of retinal vein occlusion with neovascularization has been reported in adult cases,^{4,6,16} but not in pediatric cases. Unfortunately, the outcome of our cases may be the worst reported to date. Systemic corticosteroid therapy appeared to be effective in both cases, because the sheathing of the vessels was reduced and then disappeared in response to corticosteroids. However, CRVO progressed and rubeotic glaucoma ultimately developed. One possible reason for the development of retinal vein occlusion would be thrombosis due to vasculitis of the optic disc. However, when CRVO developed, the vascular sheathing had already disappeared. Therefore, factors other than vasculitis might also have played a role in worsening the retinal vein occlusion in these two cases. CRVO developed after the reduction in the doses of systemic steroid administration in our two cases, as well as in Seo's case. Therefore, there is a possibility that the cause of the CRVO might have been the recurrence of retinal vasculitis as the result of reducing the dose of the drug. However, CRVO could not be prevented even when the systemic steroid administration was resumed after CRVO developed in Seo's case. Moreover, the sheathing of the vessels was not observed after tapering the dose of the systemic steroid in our cases. Therefore, we speculate that the reduction of the systemic steroid did not affect the onset of CRVO.

It is widely known that the administration of a large amount of systemic steroid can enhance platelet coagulation and cause vessel occlusion complications, such as myocardial infarction and thrombosis. Therefore, there is a possibility that large systemic corticosteroid doses might have worsened the retinal vein occlusion in our cases. Seo et al¹⁶ also pointed out this possibility in their report. At first, they used 1 g/day of intravenous methylprednisolone for 3 days and then switched to oral prednisolone (1 mg/kg per day) for 11 days. One month after discontinuing the systemic steroid therapy, retinal hemorrhages and macular edema had recurred, and additional oral prednisolone (40 mg/day) was administered. However, ultimately, arteriovenous anastomoses developed as well as neovascular glaucoma. They recommended that patients with frosted branch angiitis be treated with moderate doses of systemic corticosteroids to achieve early recovery. There have been five reported cases of adult frosted branch angiitis with retinal vascular occlusion including our two cases.^{4,6,16} The doses of systemic steroid administration were quite different in each case, ranging from 20 mg/day to 1000 mg/day. There might not be any correlation between the dose of systemic corticosteroid and the complication of CRVO in frosted branch angiitis. More cases should be accumulated and the most appropriate systemic steroid dose for adult cases of this disease should be determined to prevent the complication of CRVO.

Our cases suggested that frosted branch angiitis in adults could be related to vascular occlusion, and systemic corticosteroid therapy appeared to have an effect on the course of the disease. Therefore, the systemic steroid doses must be carefully considered in frosted branch angiitis with retinal hemorrhages. Careful observation of retinal blood flow is necessary in frosted branch angiitis in adults because the serious complication of neovascularization may develop.

This paper was published in part in Japanese in the *Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc)* 1999;103:617–25. It appears here in a modified form after peer review and editing for the *Japanese Journal of Ophthalmology*.

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