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**SHORT COMMUNICATION**

**Case report**

# Retinal periphlebitis resembling frosted branch angiitis with nonperfused central retinal vein occlusion

*A.M. ABU EL-ASRAR[1], S.A. AL-OBEIDAN[1], A.G.M. ABDEL GADER[2]*

[1]Department of Ophthalmology
[2]Coagulation Research Laboratory, College of Medicine, King Saud University, Riyadh - Saudi Arabia

PURPOSE. *To report the unusual association between severe retinal periphlebitis resembling frosted branch angiitis and nonperfused central retinal vein occlusion (CRVO).*
METHODS. *Observational case reports.*
RESULTS. *Patient 1 was a 28-year-old man who presented with extensive sheathing involving all retinal veins in one eye followed by nonperfused CRVO. Twenty-seven months after initial presentation, he developed perfused CRVO in the other eye followed by periphlebitis that progressed into nonperfused CRVO. Patient 2 was a 47-year-old man who presented with unilateral severe retinal periphlebitis associated with nonperfused CRVO. Despite systemic administration of corticosteroid therapy, rubeosis iridis developed in both patients and neovascular glaucoma developed in Patient 1 despite full panretinal photocoagulation. Extensive systemic workup and coagulation studies were unremarkable except for the presence of antiphospholipid antibodies in both patients and elevated plasma homocysteine level in Patient 2.*
CONCLUSIONS. *Severe retinal periphlebitis complicated by nonperfused CRVO is associated with poor visual outcome despite appropriate medical and surgical treatment. (Eur J Ophthalmol 2003; 13: 807-12)*

KEY WORDS. *Central retinal vein occlusion, Retinal vasculitis, Frosted branch angiitis, Neovascular glaucoma*

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## INTRODUCTION

Frosted branch angiitis, first described in 1976 by Ito et al (1), occurs in young, healthy individuals who typically have acute bilateral (but sometimes unilateral) visual loss, associated with anterior and posterior segment inflammation. The retinal findings include swelling of the retina and severe sheathing of the retinal venules, creating the appearance of frosted tree branches. Additional findings include intraretinal hemorrhages, hard exudates, and serous exudative detachments of the macula and periphery. Fluorescein angiography demonstrates leakage of dye from the vessels, but no evidence of decreased blood flow or occlusion. The disease usually responds rapidly to systemic corticosteroids with a rapid resolution of the vascular sheathing. The visual prognosis is usually good and there is no recurrence in most patients. The term "acute frosted retinal periphlebitis" was suggested to describe the condition by Kleiner et al (2).

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This report describes two cases of fulminant retinal periphlebitis resembling frosted branch angiitis associated with nonperfused central retinal vein occlusion (CRVO). Despite systemic corticosteroid therapy and full panretinal photocoagulation, rubeosis iridis and neovascular glaucoma developed and visual acuity worsened in both cases.

## Case reports

### *Case 1*

A 28-year-old man presented with a 1-week history of decreased vision in the right eye that was preceded by two attacks of transient visual loss, each lasting for 3 hours. Past medical history was significant for migraine. Best-corrected visual acuity was counting fingers at 2 feet in the right eye and 20/20 in the left eye. Intraocular pressure by applanation was 16 mmHg bilaterally, and pupillary reactions were normal. There were 2+ cells in the anterior chamber and trace vitreous cells in the right eye, but no cells in the left eye. Ophthalmoscopy of the right eye showed extensive, thick, white, confluent sheathing surrounding all the retinal veins from the posterior pole to the periphery with the tributary venules terminating in retinal hemorrhages. The optic disc showed swelling and hyperemia and there was macular edema. There were also widespread scattered intraretinal hemorrhages in the posterior pole and midperipheral retina, and multiple cotton-wool spots in the posterior pole (Fig. 1, a and b). The left eye was ophthalmoscopically normal. Fluorescein angiography demonstrated extensive dye leakage from veins and optic disc, and marked staining of the vein walls in the right eye. However, there was no evidence of vascular occlusion or decreased flow.

The patient was admitted to the hospital and full medical, neurologic, and rheumatologic examinations had normal results. There was no evidence of a systemic disorder, particularly Behçet's disease or sarcoidosis. The following laboratory investigations were performed: chest x-ray, complete blood count, erythrocyte sedimentation rate, routine blood chemistry, hemoglobin electrophoresis, serum protein electrophoresis and immunoelectrophoresis, urinalysis, Venereal Disease Research Laboratory test

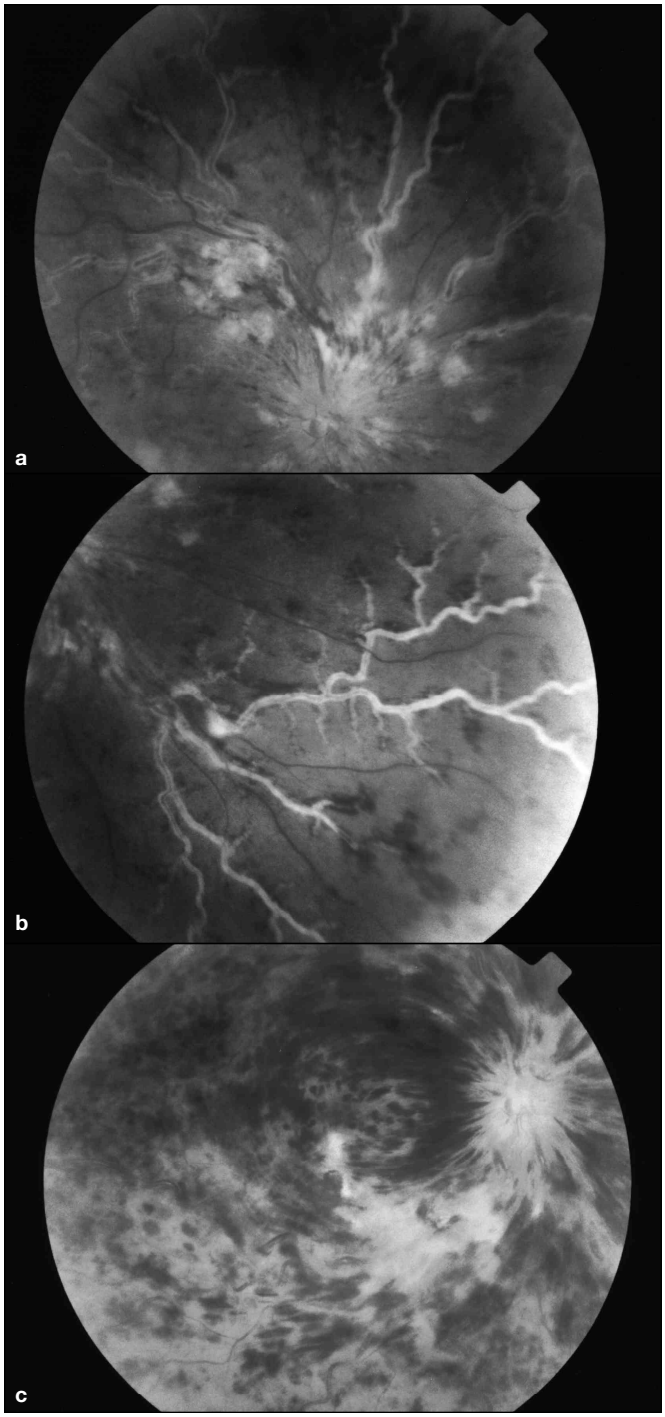


**Fig. 1 -** *Patient 1. Fundus photographs of the right eye at presentation.* **a)** *Note the prominent sheathing of the retinal veins, optic disc swelling and hyperemia, scattered intraretinal hemorrhages, and cotton-wool spots.* **b)** *The nasal retina demonstrates prominent perivenous sheathing and intraretinal hemorrhages.* **c)** *Four weeks later. Notice massive intraretinal hemorrhages, severe macular edema, optic disc swelling and hyperemia, and venous congestion and tortuosity.*

(VDRL), fluorescent treponemal antibody absorption test, human immunodeficiency virus, Mantoux test, antinuclear antibody, anti-double stranded DNA antibody, rheumatoid factor, C3 and C4 components of complement, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies including IgG and IgM anticardiolipin antibodies, and tests for lupus anticoagulant, serum calcium, angiotensin-converting enzyme, and gallium scan. His Westergren erythrocyte sedimentation rate was elevated to 74 mm/h, rheumatoid factor was positive at a titer of 256 IU/ml, and IgM anticardiolipin antibody titer was 87 mpl units (normal 6 to 12 mpl units). There were no other laboratory abnormalities.

The patient was treated with oral prednisone 1 mg/kg/day. Two weeks after the start of treatment, visual acuity in the right eye improved to 20/200, and the vascular sheathing markedly decreased. However, there was prominent venous congestion and tortuosity associated with scattered flame-shaped intraretinal hemorrhages involving both the peripheral retina and posterior pole, and optic disc edema and hyperemia. Fluorescein angiography of the right eye demonstrated good capillary perfusion. The diagnosis of perfused CRVO was made and oral prednisone was tapered. Additional testing, including blood lipids, plasma fibrinogen, plasma homocysteine, antithrombin III, protein C and protein S activities, activated protein C resistance, tissue plasminogen activator activity, and plasminogen activator inhibitor activity, revealed normal findings. An additional 80 mg/day of oral aspirin was given for anticoagulation.

Two weeks later, visual acuity in the right eye had deteriorated to counting fingers at 1 foot with a right afferent papillary defect. Ophthalmoscopy of the right eye revealed massive intraretinal hemorrhages, severe macular edema, and optic disc swelling and hyperemia (Fig. 1c). Fluorescein angiography demonstrated widespread areas of nonperfusion. The diagnosis of nonperfused CRVO was made. Six weeks later, the vision had decreased to hand motions, and iris rubeosis had developed. He received extensive panretinal photocoagulation (total 2630 shots) that was complicated by exudative macular detachment. Two weeks later, neovascular glaucoma developed and intraocular pressure was elevated to 56 mmHg. Cyclocryotherapy was performed, and intraocular pressure subsequently decreased. Visual acuity in the right eye finally decreased to light perception. Repeated serologic studies showed that anticardiolipin antibody titers had returned to normal, and oral aspirin (80 mg/day) was continued.

Twenty-seven months after initial presentation, the patient presented to the emergency room with a 1-day history of blurring of vision in the left eye. One day before presentation he had had a transient attack of loss of vision that had lasted for 30 minutes. Visual acuity was no light perception in the right eye and 20/30 in the left eye. The right eye was phthisical. Funduscopic examination of the left eye disclosed venous congestion and tortuosity, few scattered intraretinal hemorrhages, few cotton-wool spots, and optic disc edema and hyperemia. There was no macular edema (Fig. 2a). The diagnosis of CRVO was made. Fundus fluorescein angiography showed a prolonged arteriovenous transit time at 16 seconds (normal ≤ 11 seconds), extensive dye leakage from veins and optic disc, marked staining of the vein walls, and good capillary perfusion. Laboratory studies similar to those undertaken during previous admission revealed normal findings except for positive rheumatoid factor at a titer of 128 IU/ml. Duplex scan of carotid arteries revealed atheromatous plaques in both common carotid arteries, origin of right internal carotid artery, and in left internal carotid artery. Magnetic resonance imaging of the brain showed normal findings. Full assessment was performed by a hematologist and the patient was started on anticoagulant therapy with heparin followed by warfarin. In addition, the patient received oral aspirin 80 mg/day, and oral pentoxifylline 400 mg three times daily. However, 10 days later, ophthalmoscopy of the left eye showed thick, white sheathing of the retinal veins, many large cotton-wool spots around the optic disc, and severe macular edema (Fig. 2b). Fluorescein angiography demonstrated a prolonged arteriovenous transit time at 18 seconds, extensive dye leakage from veins and optic disc, marked staining of the vein walls, and good capillary perfusion. The patient was treated with intravenous 1 g methylprednisolone repeated each day for 3 days, followed by a regimen of oral prednisone 1 mg/kg/day. In addition, azathioprine (100 mg/day) was added, and plasmapheresis was performed. The sheathing had disappeared by 2 weeks and the prednisone dose was gradually tapered thereafter. In view of the poor outcome of the right eye, extensive pan-

retinal photocoagulation (total 3700 shots) was performed in the left eye. Photocoagulation was followed by large exudative macular detachment with turbid, shifting subretinal fluid and extensive intraretinal hemorrhages in the macular area. Three months later, exudative retinal detachment had resolved but visual acuity decreased to counting fingers at 1 foot due to severe macular ischemia (Fig. 2c). Two months later, he developed neovascular glaucoma and intraocular pressure was elevated to 45 mmHg. Glaucoma tube surgery was performed. One year later, visual acuity in the left eye was only hand motions and intraocular pressure was 8 mmHg. There was no rubeosis. Ophthalmoscopy showed traction retinal detachment involving the macula due to extensive preretinal fibrovascular tissue. One year later, visual acuity in the left eye was no light perception.

## *Case 2*

A 47-year-old man presented with a 1-week history of decreased vision in his left eye. Past medical history was significant for hypertension. Best-corrected visual acuity was 20/20 in the right eye and hand motions in the left eye. Intraocular pressure by applanation was 14 mmHg, bilaterally. There was an afferent papillary defect in the left eye. The right fundus appeared normal. Ophthalmoscopy of the left eye revealed extensive thick, confluent, white sheathing surrounding the retinal veins from the posterior pole to the periphery, venous congestion and tortuosity, severe macular edema, optic disc swelling and hyperemia, and massive intraretinal hemorrhages (Fig. 3). Fluorescein angiography demonstrated a prolonged arteriovenous transit time at 21 seconds, widespread areas of nonperfusion, extensive dye leakage from veins and optic disc, and marked staining of the vein walls. The patient was admitted. Full medical, hematologic, and rheumatologic examinations had normal results. Laboratory studies similar to those undertaken in Case 1 revealed the presence of antiphospholipid antibodies (tests for lupus anticoagulant were positive), and plasma homocysteine level was 30.9 µmol/L (the 95th percentile in the control group was 13.6 µmol/L). He was started on oral prednisone 1 mg/kg/day, folic acid 5 mg/day, and aspirin 80 mg/day. Retinal vasculitis decreased in response to the systemic corticosteroid therapy, and the sheathing disappeared by

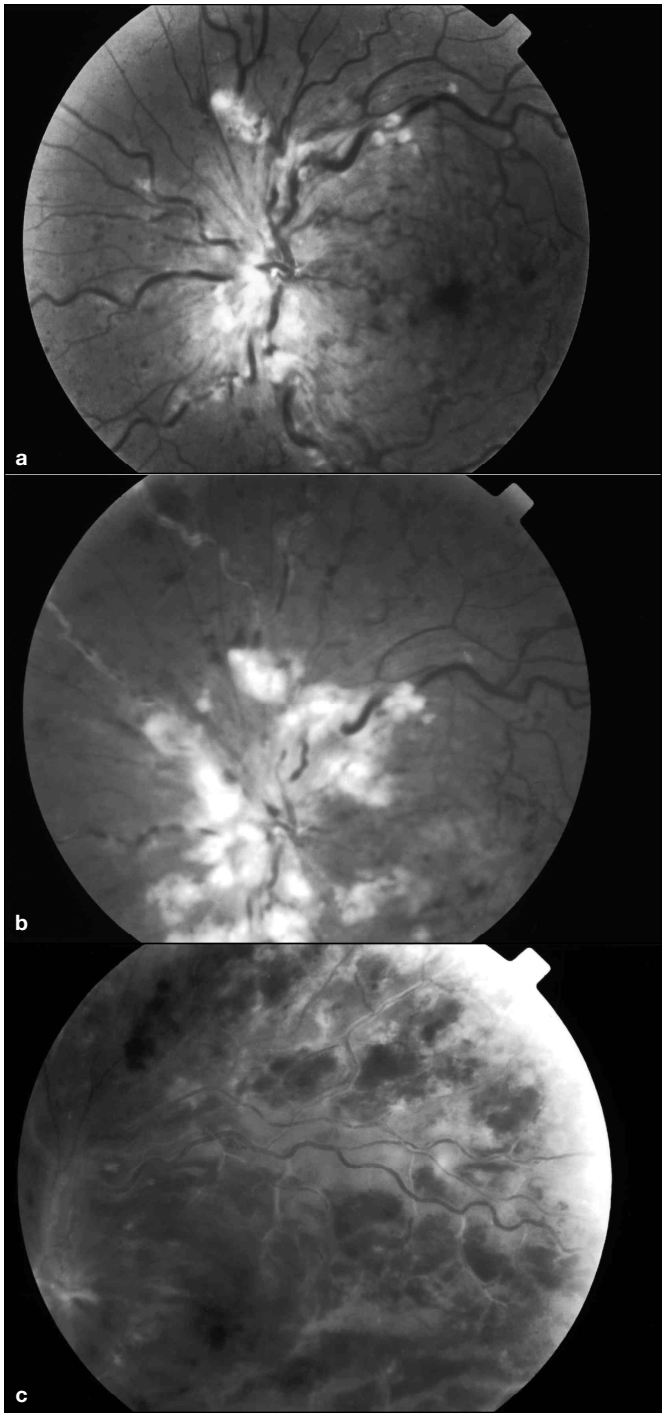


**Fig. 2 -** *Patient 1.* **a)** *Fundus photograph of the left eye at presentation. Note venous congestion and tortuosity, intraretinal hemorrhages, cotton-wool spots, and optic disc edema and hyperemia.* **b)** *Ten days later. Note the prominent sheathing of the retinal veins, many large cotton-wool spots, and intraretinal hemorrhages.* **c)** *Three months later. Note the massive intraretinal hemorrhages in the macular area, sclerosed vessels in the macular area, and scars of panretinal photocoagulation.*

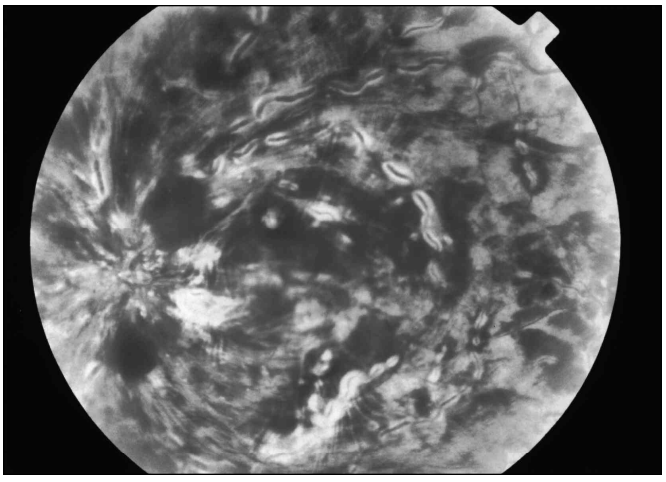

**Fig. 3 -** *Patient 2. Fundus photograph of the left eye at presentation. Note extensive white sheathing of the retinal veins, massive intraretinal hemorrhages, venous congestion and tortuosity, and optic disc edema and hyperemia.*

2 weeks. The prednisone dose was gradually tapered thereafter. One month later, iris rubeosis had developed and panretinal photocoagulation was performed; however, the patient was lost to ophthalmic observation.

## DISCUSSION

Retinal periphlebitis (vasculitis affecting predominantly the veins) has been reported in association with tuberculosis, Eales disease, syphilis, sarcoidosis, multiple sclerosis, cytomegalovirus retinitis, human immunodeficiency virus infection, and acquired disease of connective tissue. Neither of our patients had any clinical or laboratory findings to support these diagnoses. Recently, Kleiner et al (3) classified patients who have the appearance of frosted branch angiitis into three subgroups. First are patients with lymphoma or leukemia whose disease is due to infiltration with malignant cells (frosted branch-like appearance). Second is the group of patients who have associated viral infections or autoimmune disease. In these patients frosted branch angiitis is a clinical sign, possibly of immune complex deposition (secondary frosted branch angiitis). Finally, there is a group of otherwise healthy young patients described initially (acute idiopathic branch angiitis). It is likely that the frosted branch angiitis that developed in these patients represents an immune reaction to a number of different stimuli (4).

The two patients described herein were young adults and both developed characteristics resembling frosted branch angiitis characterized by thick, inflammatory infiltrate surrounding all of the retinal veins. The periphlebitis was followed by (Patient 1) or associated with (Patient 2) nonperfused CRVO that was complicated by rubeosis iridis in both cases and neovascular glaucoma despite full panretinal photocoagulation in Patient 1. Systemic corticosteroid therapy appeared to be effective, because the perivenous infiltrates were reduced and then disappeared in response to corticosteroids. However, CRVO progressed and rubeosis iridis and neovascular glaucoma ultimately developed. Five previous cases of retinal periphlebitis resembling frosted branch angiitis associated with nonperfused CRVO have been documented (5-7) (Tab. I). In four cases, the retinal periphlebitis was followed by nonperfused CRVO (5-7), whereas Foss et al (5) reported a 54-year-old man in whom the CRVO was associated with prominent sheathing of the retinal veins at presentation.

In the present cases, the venous occlusion may be the result of vasculitis involving the veins. However, Patient 1 developed a fundal appearance of a classic CRVO in the other eye that was followed by a scenario resembling frosted branch angiitis. Therefore, factors other than vasculitis might also have played a role in worsening the retinal vein occlusion in these two cases. At presentation, Patient 1 had raised levels of IgM anticardiolipin antibodies, and Patient 2 had positive tests for lupus anticoagulant indicating the involvement of antiphospholipid antibodies, which are known to be associated with arterial and venous thrombosis and recurrent fetal loss. Antiphospholipid antibodies may be found in patients with systemic lupus erythematosus and other autoimmune disorders. They are also described in otherwise normal individuals and this association has been termed primary antiphospholipid syndrome (8). The association between antiphospholipid antibodies and retinal venous occlusion was previously reported (9, 10). Patient 2 had in addition an elevated plasma homocysteine level, which is a risk factor for retinal vascular occlusive disease (11).

**TABLE I -** PREVIOUSLY REPORTED CASES OF RETINAL PERIPHLEBITIS ASSOCIATED WITH CENTRAL RETINAL VEIN OCCLUSION

| Author | Age, yr/sex | Treatment | Complications | Final visual outcome |
|---|---|---|---|---|
| Foss et al[5] | 23/M | Systemic corticosteroids, PRP | Rubeosis iridis, neovascular glaucoma | LP |
| | 54/M | PRP | Cystoid macular edema | Poor |
| Seo et al[6] | 27/M | Systemic corticosteroids, PRP | Neovascular glaucoma, vitreous hemorrhage | HM |
| Taburaki et al[7] | 36/F | Systemic corticosteroids, PRP | Rubeosis iridis, neovascular glaucoma, vitreous hemorrhage | LP |
| | 23/F | Systemic corticosteroids, PRP | Rubeosis iridis, neovascular glaucoma | LP |

PRP = Panretinal photocoagulation; LP = Light perception; HM = Hand movements

In conclusion, this report describes the unusual association between severe retinal periphlebitis resembling frosted branch angiitis and CRVO. Despite administration of systemic corticosteroids and maximum panretinal photocoagulation, the complications of rubeosis iridis and neovascular glaucoma developed and visual acuity worsened. With awareness of the existence of this condition, more cases are likely to be collected, and the cause of this condition and the most appropriate treatment should be determined to prevent the poor visual outcome.

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Reprint requests to:
Prof. Ahmed M. Abu El-Asrar
Department of Ophthalmology
King Abdulaziz University Hospital
Airport Road
P.O. Box 245
Riyadh 11411, Saudi Arabia
abuasrar@ksu.edu.sa

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