Central Retinal Vein Occlusion due to retinal vasculitis

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Case
A 53 year old male presenting to us with sudden unilateral visual loss

History
Approximately two weeks prior to presentation, the patient developed sudden, persistent, painless loss of vision in the right eye, noted first on awakening. He was seen by his primary care physician and referred to us for evaluation and management.
The patient was a Type II diabetic, well controlled on diet modification and exercise. Past medical and family history were otherwise unremarkable.

Examination
The visual acuity in OD and OS were Finger counting at 4 meters and 20/20 respectively. There was a 2+ afferent papillary defect OD and the anterior segment OU was unremarkable with open angle in all four quadrants on gonioscopy and normal IOP OU. Fundus examination revealed a hyperemic disc OD, with filled cup and blurred disc margins. Blood vessels overlying the disc were dilated and tortuous with splinter hemorrhages. There was generalized dilatation and tortuosity of the veins with altered arteriolar: venular ratio of 2:4, and multiple dot and blot hemorrhages in the posterior pole and periphery of all four quadrants. Flame shaped hemorrhages and cotton wool spots were noted to be distributed along the inferotemporal quadrant. The background retina in the posterior pole appeared to be pale in comparison with the periphery OD and background retina OS.
The left eye revealed a normal optic disc with a cup-disc ratio of 0.2. The blood vessels, macula and background retina were normal.
Blood pressure recorded was 140/100 mm Hg.

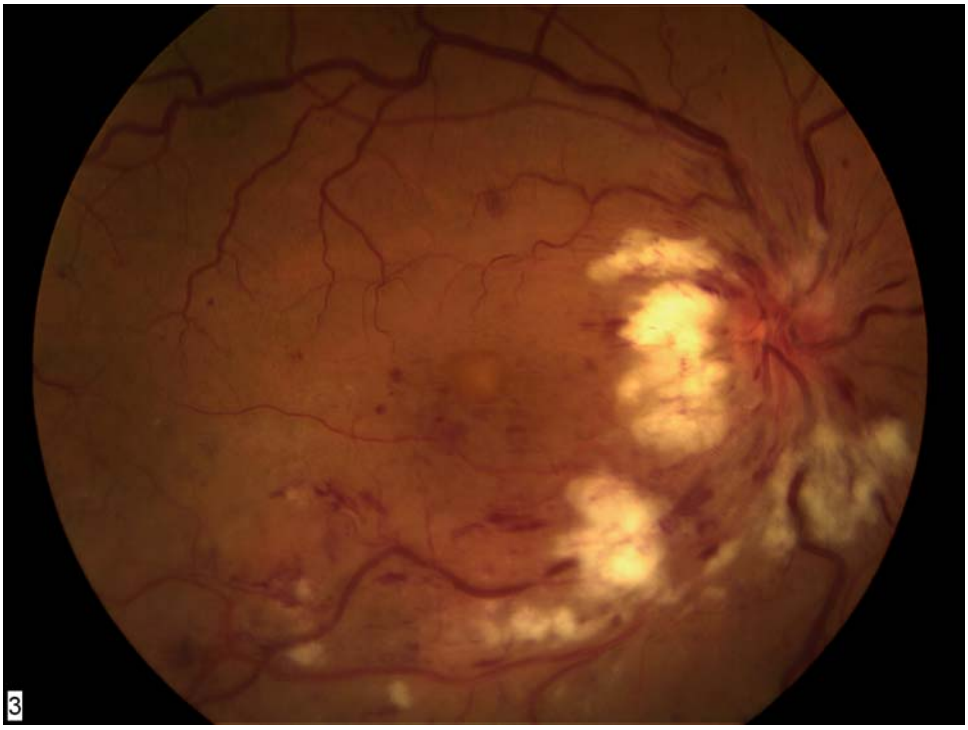

Figure 1: Fundus photograph OD

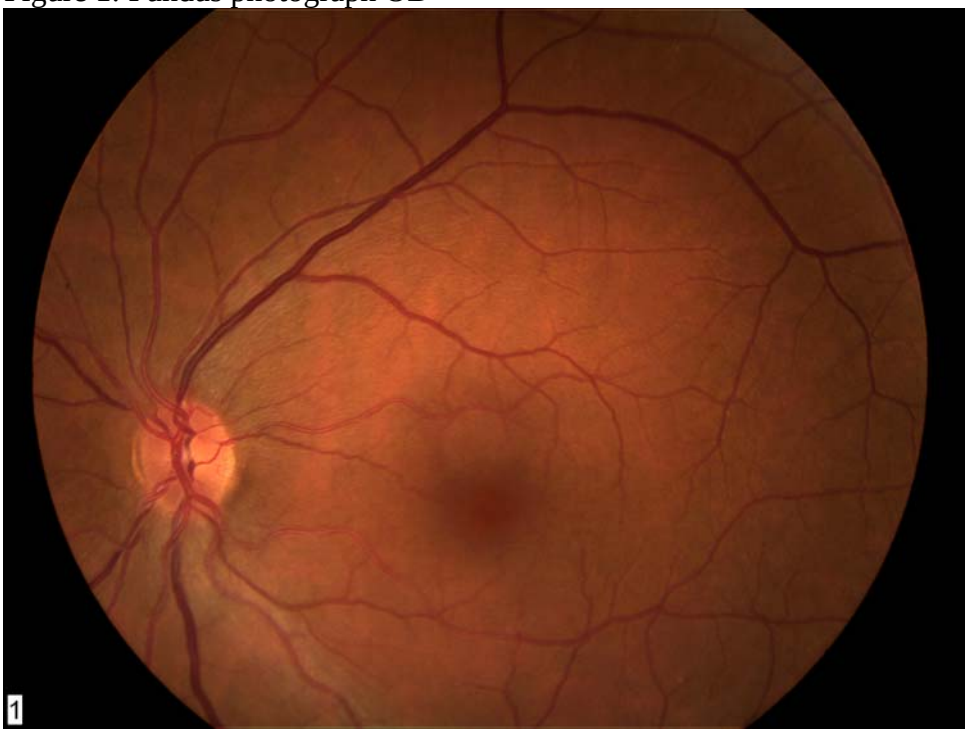

Figure 2 – Fundus photograph OS

Laboratory tests

He was noted to have a raised ANA titre (1:40, homogenous pattern) with raised protein C activity (>200). His complete blood count, total complement, c1 complement, protein S

activity, interleukin 6, TNF alpha, C3d complement, antithrombin III, ANCA, properdin factor, rheumatoid factor, FTA-ABS, C3,C4 complement, c-reactive protein, homocysteine and hematocrit were found to be within normal limits.

Fluorescein Angiography (FA)
FA was notable for delayed A-V transit time OD, moreso in the inferotemporal vasculature. Areas of blocked fluorescence were noted, corresponding to hemorrhages and cotton wool spots. Diffuse hyperfluorescence was noted in all four quadrants along the vascular arcades and in the macula. Extensive areas of capillary non-perfusion were seen in the inferior quadrants with late-staining of the venous architecture.

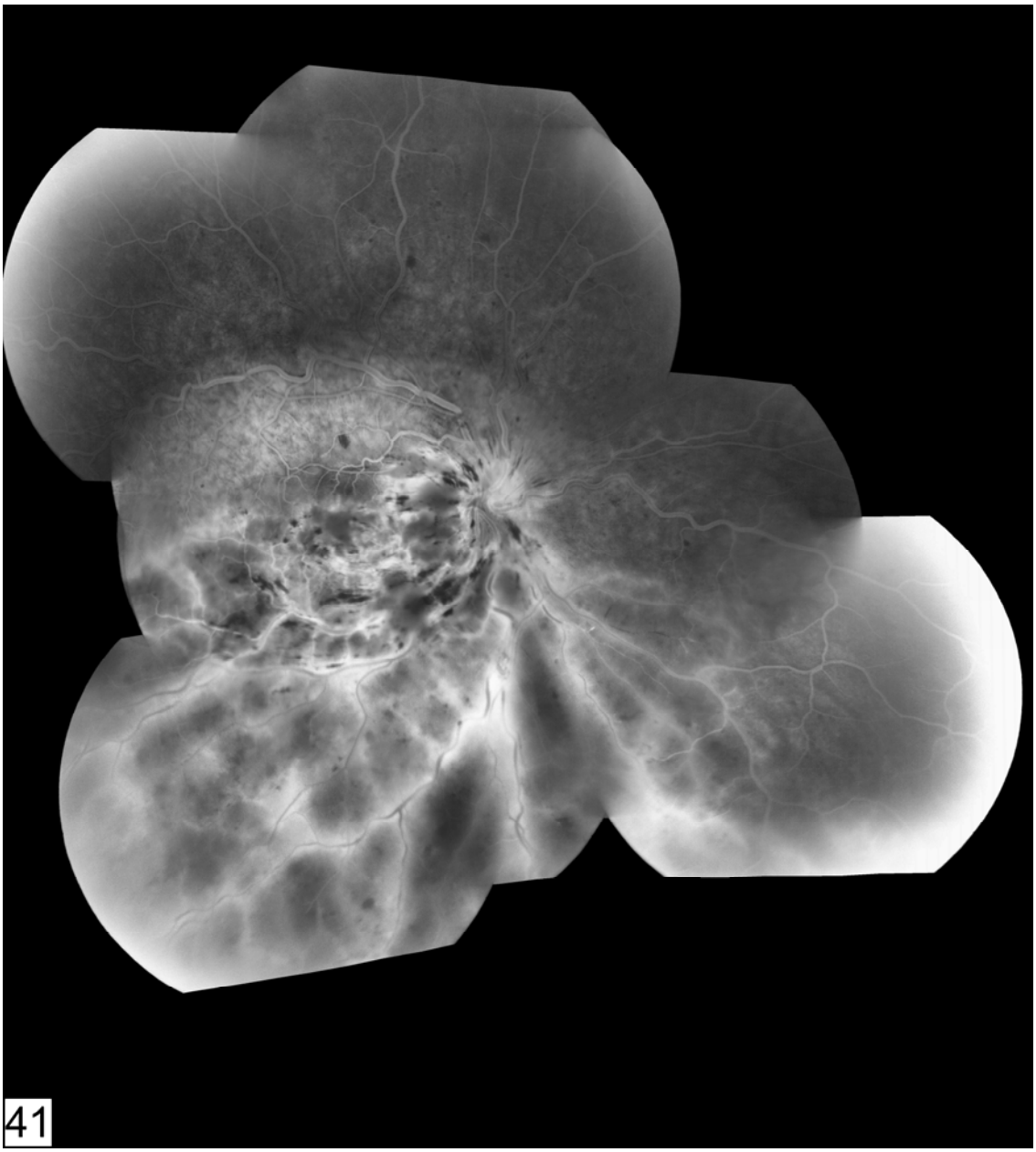

Figure 3: Fluorescein angiogram OD

Clinical Course

In view of his clinical presentation, we made a diagnosis of OD Central Retinal Vein Occlusion. In view of the age of the patient, atypical findings of increased involvement of a particular quadrant in a case of CRVO, late staining of vessels on FA and paucity of identifiable risk factors, vasculitis was being considered as an etiology of vascular occlusion in this case.

After initial treatment with Hydrochlorthiazide 25mg and Aspirin, he came in for review after 1 week with a marginally improved visual acuity of finger counting at 6 meters, but with increased hemorrhages and cotton wool spots in the inferotemporal quadrant OD. We then treated him with 3 daily infusions of 1000mg Solumedrol, to which he responded well with BCVA OD 20/300 after 2 weeks and started a regime to 2 weekly Solumedrol with 25mg Methotrexate infusions.

3 weeks later, he came in with OD Vitreous hemorrhage reportedly after sneezing violently. This was treated with intravitreal Avastin and 2 weekly infusions of Solumedrol with 50mg Methotrexate. FA at subsequent visits revealed markedly improved perfusion with resolution of vascular staining OD. He is currently asymptomatic on a regime of monthly infusions of Solumedrol(1000mg) with 50mg Methotrexate with a BCVA OD of 20/60, resolution of hemorrhages on fundus examination and normal FA.

Central Retinal Vein Occlusion

Central Retinal Vein Occlusion (CRVO) is one of the most common causes of visual loss. Population-based studies have reported a prevalence of CRVO of between 0.1% and 0.4% in individuals >=40 years of age. [1,2] Visual morbidity in CRVO is primarily due to the development of macular ischemia and neovascular glaucoma.

Pathogenesis

Klein and Olwin [3] postulated the following three occlusive mechanisms in CRVO:

(a) occlusion of the vein by external compression by sclerotic adjacent structures (i.e. central retinal artery and fibrous tissue envelope) and secondary endothelial proliferation;
(b) occlusion by primary venous wall disease (degenerative or inflammatory in nature); and
(c) hemodynamic disturbances produced by a variety of factors (e.g. subendothelial atheromatous lesions in the central retinal artery, arterial spasm, sudden reduction of blood pressure, blood dyscrasias etc.). These produce stagnation of blood flow and result in thrombus formation. In patients with these predisposing changes, a fall in systemic blood pressure during sleep would finally complete the thrombotic process. This is suggested by numerous reports of patients discovering marked visual loss on waking up in the morning.

The site of occlusion determines the type of CRVO.[4] In Ischemic CRVO, the site of occlusion is most probably in the region of the lamina cribrosa or immediately posterior to that as demonstrated in histopathological studies. In contra-distinction, an occlusion

that is further posterior has the availability of more collateral channels, leading, therefore to milder retinopathy and the non-ischemic type of CRVO.

In elderly persons, sclerotic changes in the central retinal artery which shares a common adventitial sheath with the central retinal vein, leading to secondary endothelial proliferation. [3,5] In younger patients, hematological factors and phlebitis of the central retinal vein may be responsible for thrombosis. [6]

Risk factors

Systemic vascular disease is associated in 74% of patients with CRVO greater than 50 years of age. Hypertension and hyperlipidemia are seen in 32-60% and diabetes in 15-34% of patients. Hemostasis-related factors include antiphospholipid antibodies, elevated levels of PAI-1, activated protein-C resistance, factor V Leiden, hyperhomocysteinemia, elevated levels of lipoprotein(a), plasminogen deficiency, factor XII deficiency and deficiency of physiological clotting inhibitors. Mitral valve prolapse has been postulated to contribute to platelet hyperactivity. Migraine has been noted with increased prevalence in cases of CRVO, as have collagen vascular disoders and AIDS. Carotid artery disease may lead to venous stasis as a result of decreased central retinal artery perfusion pressure. Raised sedimentation rate reflects changes in shear forces and increased plasma viscosity. Medications responsible include oral contraceptive pills, sympathomimetics and diuretics. [7]

23% of cases of CRVO are found to be associated with ocular disease. These include primary open angle glaucoma in 25-66%, optic nerve disease, retinal artery occlusion, retinal vascular malformations which may lead to mural changes or cause a mass effect and uveitides including tuberculous, syphilitic and AMPPE.

Trauma, either by sudden eyeball compression or change in intraocular pressure, may cause damage to the vessel wall by shearing or compressing the central retinal vein against the lamina cribrosa. [7]

Retinal vasculitis as a cause of CRVO

Retinal vasculitis may lead to vascular occlusion by a thrombotic or obliterative mechanism. Thrombosis may occur as a result of local endothelial injury / dysfunction or more generalized prothrombotic tendencies, both of which have been found to occur in retinal vasculitis. An obliterative process may result from mural inflammatory infiltration. [8]

Retinal vasculitis

Retinal vasculitis is defined as vascular leakage and staining of vessel walls on fluorescein angiography, with or without the clinical appearance of fluffy, white perivascular infiltrates in the eye, usually with evidence of inflammatory cells in the vitreous body or aqueous humor. [9,10]

Clinical findings

It often manifests as gradual painless loss of vision associated with floaters, though isolated peripheral vasculitis may be asymptomatic.

Retinal vasculitis represents small vessel inflammation involving the arterioles, capillaries and/or post-capillary venules. Arteriolar attenuation, sheathing and cotton

wool spots are suggestive of arteriolar involvement. Terminal arteriolar occlusion may lead to the superficial retina becoming opaque. Vasculitis involving the venous side of the circulation produces retinal hemorrhages, edema, telangiectasia and microaneurysms. Active retinal disease is typified by fluffy white perivascular infiltrates which transform into perivascular fibrosis on quiescence. Macular edema and papillitis may be observed.[11]

Etiology and Pathogenesis

Vasculitis may be:

(a) Infective vasculitis – either by direct invasion of microbes such as *Mycobacterium tuberculae*, *Treponema pallidum* or several viruses. It may also occur as a result of immune complex deposition as a result of antigenic microbial components.
(b) Immune vasculitis is usually T-cell mediated and may also involve immune complex deposition
(c) Idiopathic – These cases are usually associated with lymphopenia, serum immune complexes, anticardiolipin antibodies, reduced retinal S-antigen affinity and Interleukin-2.

Several putative autoantigens have been described, including Myelin basic protein, myelin-associated glycoprotein, s100 beta and glial fibrillary acid protein. T-cell specificity for s-100 beta has been shown to lead to retinal involvement.
Concerning immunogenetics, HLA-DR15 and HLA B27 are most noteworthy as concerns retinal vasculitis. Interestingly HLAB51 and B27 share sequence homology to uveitogenic retinal s-Antigen, which may explain the association. [8]

Associations

Ocular associations	
Idiopathic	Affects young adults Vasculitis with associated vitritis Over half of these patients develop a major cerebrovascular event
Eales' disease	Common in the Indian subcontinent, males in their 30s to 50s. Vasculitis beginning in the periphery. Diagnosis of exclusion.
Idiopathic retinal vasculitis , aneurysms, neuroretinitis (IRVAN) syndrome	Bilateral retinal arteritis, multiple microaneurysms, neuroretinitis and uveitis
Bilateral iridocyclitis with retinal capillaritis	Bilateral granulomatous uveitis, retinal capillaritis. Associated with HLA DR6, HLA Cw7
Acute multifocal hemorrhagic retinal vasculitis	Occlusive phlebitis, retinal hemorrhages, infiltrates
Frosted branch angiitis	Extensive sheathing of blood vessels
Idiopathic recurrent branch retinal artery occlusion	Healthy middle-aged patients. Recurrent branch retinal artery occlusions. Focal periarterial sheathing, arteritis
Neurological associations	

Multiple sclerosis	Peripheral, subtle, transient periphlebitis.
Microangiopathic syndrome of encephalopathy, hearing loss, and retinal arteriolar occlusions	Occlusive arterial disease affecting brain, inner ear and retina
Isolated central nervous system angiitis	Granulomatous inflammation of intracerebral and leptomeningeal vessels, occlusive retinal vasculitis
Systemic associations	
Systemic Lupus Erythematosus	Cotton wool spots, intraretinal hemorrhages, arteriolar dilation. Large vessel occlusion
Wegener's granulomatosus	Granulomatous necrotizing vasculitis of upper, lower respiratory tract, kidneys. Sclerokeratitis. Retinal vasculitis rare. cANCA specificity.
Polyarteritis Nodosa	Inflammatory lesions of medium- and small-sized vessels, involving heart, kidneys, liver, gastrointestinal tract, CNS. Rarely retinal arteritis.
Relapsing Polychondritis	Recurrent chondritis, both auricles, non-erosive, inflammatory polyarthritis, sasal chondritis, ocular inflammation, respiratory tract chondritis, cochlear and/or vestibular dysfunction

Management of CRVO

The aim of management of retinal vein occlusions include the identification of modifiable risk factors and their medical management, and the recognition and management of sight-threatening complications.

Ischemic CRVO should be differentiated from non-ischemic CRVO and is associated with poor visual acuity at presentation (<20/200), relative afferent papillary defect, presence of multiple intraretinal hemorrhages, cotton wool spots, >10 disc diameters of retinal ischemia and a reduced b wave amplitude, reduced b:a ratio and prolonged b-wave implicit time on ERG.

Evidence supports the use of pan-retinal photocoagulation when iris new vessels or angle neovascularization is visible.

Vitrectomy may be employed for non-clearing vitreous hemorrhage. Chorioretinal anastomosis and radial optic neurotomy have been described but are associated with complications. Hemodilution, ticlodipine, troxerutin, and streptokinase have been tried with questionable benefit.

Intravitreal triamcinolone acetonide (4mg in 0.1ml) for cystoid macular edema in retinal vein occlusions and intravitreal bevacizumab have proven to be of benefit, though large randomized controlled trials have yet to be carried out to support their efficacy.

Management of vasculitis[12]

Corticosteroids remain the mainstay of treatment of retinal vasculitis. When anterior segment inflammation is associated with posterior segment pathology, topical corticosteroids may be employed. Periocular corticosteroids may be considered if the patient has asymmetric involvement requiring the treatment of only one eye or if systemic corticosteroids are contraindicated. Triamcinolone acetonide 40mg/ml is typically the drug employed. Potential side-effects include steroid-induced glaucoma and cataract and the risk of iatrogenic trauma. The steroid may either be placed deep in the sub-tenon's space or anteriorly by a transseptal approach. Oral corticosteroids may be employed in cases with bilateral involvement or in cases unresponsive to periocular injections. Taper of corticosteroids must be gradual and based on clinical findings at follow-up examinations. Pulse intravenous corticosteroids can be used in severe cases. One gram of methylprednisolone is administered each day for a total of three days, followed by oral corticosteroids.

Immunosuppressive steroid-sparing agents may be used to either reduce or eliminate the use of corticosteroids. The available immunosuppressive drugs are either alkylating agents (cyclophosphamide, chlorambucil), antimetabolites (methotrexate, azathioprine) of cyclosporine A.
Methotrexate is a folate analogue administered as a starting dose of 7.5mg/week which may be increased to a maximum of 20mg/week. Azathioprine can be administered in a single or divided (twice daily) dose of 1 to 2.5mg/kg/day. Cyclophosphamide, an alkylating agent, can have an effect on both the cellular and humoral immune responses. It is administered at a dose of 1-2mg/kg/day either orally or intravenously. Cyclosporine inhibits T cell activation and recruitment. The starting dose is 2.5 – 5mg/kg/day usually given as a twice daily regimen.

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