

## Case report

# Branch retinal artery occlusions as the presenting feature of primary central nervous system vasculitis

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**Key words:** Primary CNS vasculitis, Susac's syndrome, branch retinal artery occlusions, MRI, brain calcification, CT.

### ABSTRACT

A 39-year-old woman presented with multiple branch retinal artery occlusions almost three years before developing a mass lesion containing calcium in the left frontal lobe. Brain biopsy revealed a small vessel vasculitis and ischemic necrosis of brain with dystrophic calcification. We believe this to be the first case of primary CNS vasculitis with branch retinal artery occlusions and brain calcification.

### Introduction

Primary vasculitis of the central nervous system has been notoriously difficult to diagnose (1-15). Confined to the central nervous system, it can affect any size vessel in the brain as well as leptomeningeal arterioles. The clinical manifestations are protean and include brain tumor presentation. The MRI changes are nonspecific and include multifocal hyperintense signal changes in both gray and white matter (9). In addition, diffuse white matter involvement has been described, mimicking a leukoencephalopathy (10) and isolated leptomeningeal enhancement has also been described (11). Calcification, however, has never been recognized. Lumbar puncture is abnormal in 80-90% and arteriography in 50% but both are nonspecific findings. The diagnosis usually requires brain biopsy.

Occasionally papilledema is seen because of increased intracranial pressure, but optic nerve involvement has not been documented until just recently. Hassan *et al.* (15) reported a 38-year-old woman with bilateral optic perineuritis with swollen discs in a setting of normal spinal fluid pressure (150 mm of mercury). Branch retinal artery occlusions have never been previously reported and were the presenting features in our patient.

### Case report

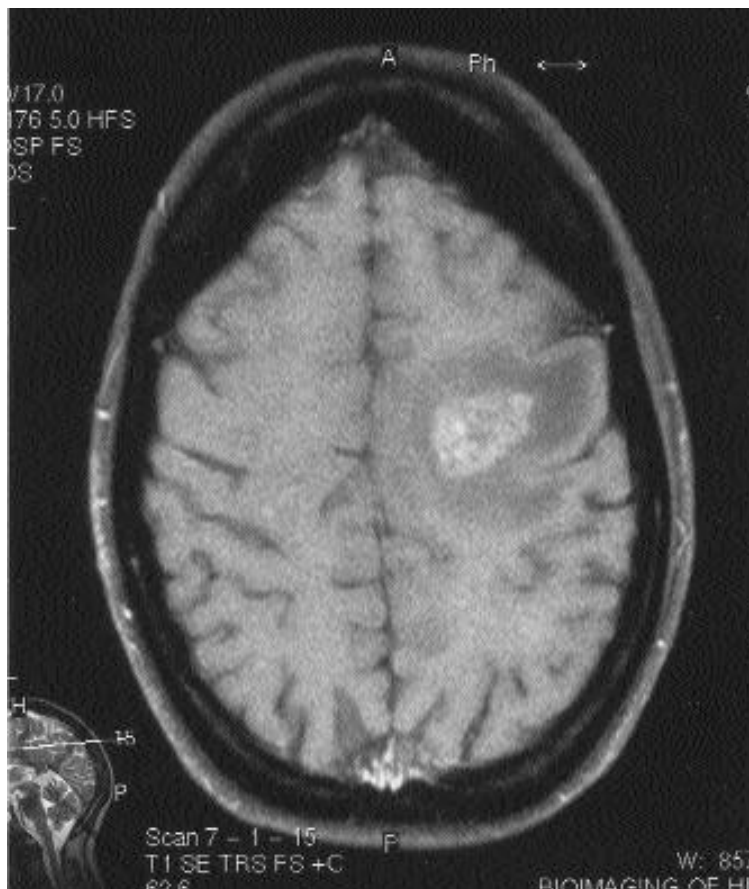
This 39-year-old right-handed woman complained of loss of vision in her left eye in February 2001. Visual acuity was 20/20 in her right eye where she had a single cotton-wool spot and 20/200 in her left eye where she had multiple cotton-wool spots and narrowing of the arterioles. The patient was in excellent health and a comprehensive evaluation for cardioembolic disorder, coagulopathy, connective tissue/infectious disease was unremarkable. Anti-platelet medication was started and oral contraceptive stopped.

Routine eye examination a year and a half later revealed two new cotton-wool spots in her right eye and further arteriolar occlusions in her left eye. When her younger sister developed a retinal disturbance in October 2002, both were referred to a retinal specialist who diagnosed the sister with choroidopathy; he felt that our patient had Susac's syndrome.

In November 2003, she began having difficulty with her handwriting and word-finding difficulties. Her symptoms slowly worsened and in December 2003 she developed a right hemiparesis and aphasia. She was admitted to hospital where again her general physical examination was normal. She had no systemic signs or symptoms. Her hearing was normal. Ophthalmoscopic examination revealed new cotton-wool spots in her right eye and progression of the occlusions in her left eye where ghost vessels now outlined the macula. The retina now had a "bald appearance" due to the absence of the nerve fiber layer (Fig. 1). MRI showed several abnormalities. Most impressive was a 3 cm subcortical white matter lesion that enhanced with gadolinium and was positive on diffusion weighted images (Fig. 2). There were also small-



**Fig. 1.** Left eye. Notice the cotton-wool spots primarily in the inferior temporal arcade and nasal to the disc. Striking arteriolar narrowing (ghost vessels) is present in the superior temporal arcade, associated with loss of nerve fiber layer (bald retina). Notice the "bald" retina above the macula as compared to the still preserved nerve fiber layer in the inferior portion of the retina (inferior to the macula). Also notice the marked arteriolar narrowing and tortuosity in the inferior temporal arcade where the cotton-wool spots are and the marked tortuosity – these corkscrew vessels – reflecting severe ischemia. The left optic nerve is pale reflecting the severity of the retinal process.



**Fig. 2.** Axial T1 weighted image with gadolinium showing enhancement within the central portion of the lesion.

er enhancing lesions in the right parieto-occipital white matter as well as the left temporal region, as well as numerous small white matter hyperintensity foci in the subcortical and periventricular white matter. There was diffuse involvement of the genu of the corpus callosum. Both MR and CT angiography were normal but the CT surprisingly showed numerous calcifications (Fig. 3). Repeat spinal fluid examination, including IgG synthesis and a search for oligoclonal bands, was normal.

Prior to any treatment the patient's right hemiparesis largely disappeared, but the aphasia persisted and she was treated with prednisone 60 mg a day. In late December 2003, she underwent yet a third extensive diagnostic evaluation that showed no evidence of systemic illness, infectious disease, coagulopathy or connective tissue disorder. Lumbar puncture again was normal.

In late January 2004, stereotactic biopsy of the left frontal lesion showed lymphocytic infiltration of the small arterioles (Fig. 4) with ischemic necrosis that was associated with dystrophic calcification. The infiltrating lymphocytes appeared benign and there was no evidence of any micro-organism. Perivascular rimming of lymphocytes around the small arterioles was also noted, but there was no evidence of fibrinoid necrosis, eosinophilia, or granulomata. Following the biopsy, cyclophosphamide 2 mg/kg/day orally was added to the prednisone 60 mg a day.

The patient's aphasia improved on this regimen and a repeat MRI showed a decrease in size of the left hemisphere lesion without any other changes. Her eye findings showed that the cotton-wool spots were resolving in the right eye and her left eye was stable, although peripheral hemorrhages were noted, reflecting the severe ischemia. The patient was tapered off the prednisone and cyclophosphamide was discontinued after 3 months. She is now on mycophenolate mofetil 1 gram twice a day and seems to be slowly improving.

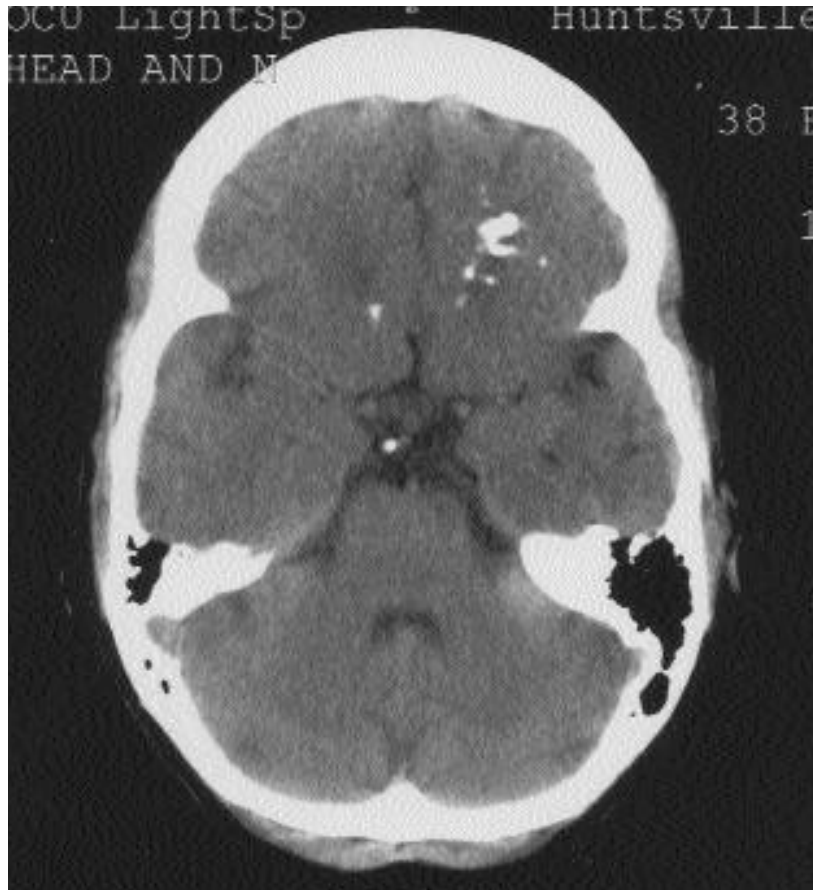
#### Discussion

This 39-year-old woman presented with multiple branch retinal artery occlusions without any other systemic

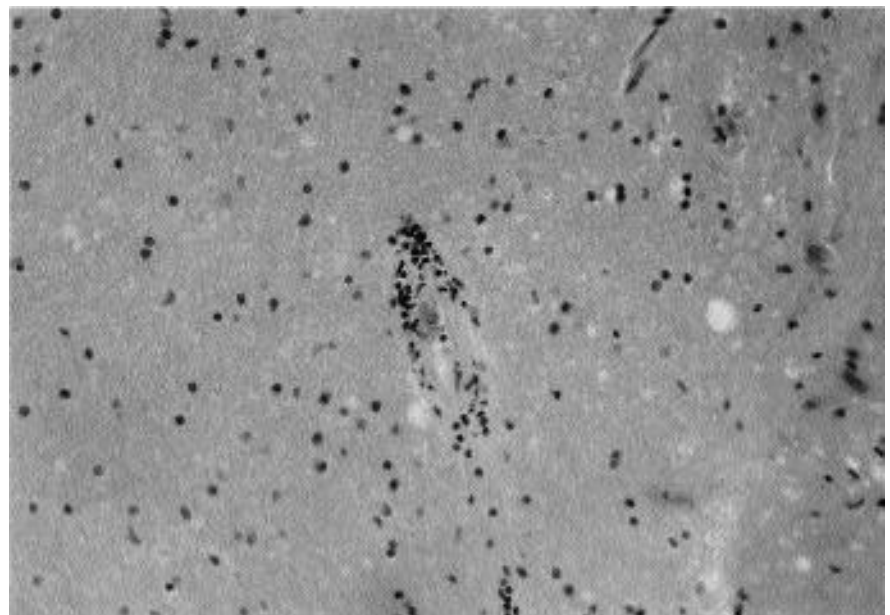
features or laboratory abnormalities. Three different extensive investigations for cardioembolic disorder, coagulopathy, connective tissue and infectious disease were unremarkable.

The differential diagnosis of this type of retinal vascular presentation is complex. But in a young patient, when the evaluation for the cause of branch retinal artery occlusions is negative, Susac's syndrome (16-26) is the most common cause of idiopathic recurrent branch retinal artery occlusions. It consists of the clinical triad of encephalopathy, hearing loss, and branch retinal artery occlusions. It can present, however, with any of the three features and the triad does not necessarily have to be present at the onset. It usually affects young women between the ages of 21 and 41, and there is a strong female predominance of 3:1; the age range extends from 16 to 58 years. When the nervous system is involved (encephalopathy), there is headache, cognitive changes, confusion, memory or psychiatric disturbances, as well as multifocal neurological signs. At times focal signs can predominate the encephalopathic picture.

The MRI findings are distinctive and always show corpus callosum involvement (22, 23). Although any part of the corpus callosum may be involved, the callosal lesions typically involve the central fibers with relative sparing of the periphery. Central callosal holes ensue as the active lesions resolve. There is a predilection for the white matter of both the supratentorial and the infra-tentorial compartments and the lesions are typically small (3-7 mm in size), multifocal and frequently enhance during the acute/subacute stage. Leptomeningeal enhancement is seen in 30% and deep gray matter involvement in 70%. Cerebrospinal fluid examination almost always shows an elevated protein and usually a mild, lymphocytic pleocytosis. On occasion, an elevated IGG index or synthesis rate and oligoclonal bands will be present. Cerebral arteriography is almost always normal because the involved pre-capillary arterioles (less than 100  $\mu\text{m}$ ) are beyond the resolution of angiography. Brain biopsy has shown perivas-



**Fig. 3.** CT scan non-contrast showing a globular deposit of calcification within the left frontal white matter that was independent of the active lesion. Also notice fine punctate calcification in the surrounding area.



**Fig. 4.** Arteriole and perivascular lymphocytic inflammation showing focal infiltration of the vessel wall (hematoxylin and eosin, original magnification 200x).

cular rimming of the pre-capillary arterioles, with resultant microinfarction. Calcification, however, has never been described.

The etiology of Susac's syndrome is unknown. The clinical course ranges from 6 months to 5 years with an average of 2 to 4 years. There is a natural tendency for the disorder to improve spontaneously, making it difficult to assess the effects of treatment. Patients do seem to do better, however, with immunosuppressant therapy, including steroids, cyclophosphamide, intravenous immunoglobulin and plasmapheresis, either singly or in combination.

When our patient developed right hemiparesis and aphasia, there were several features that were not consistent with Susac's syndrome. The large "brain tumor" symptomatic lesion is unheard of in Susac's syndrome; the typical lesions are small (3-7 mm). Also the diffuse callosal changes of the body and the genu that were present in our patient are unlike the central callosal involvement seen in Susac's syndrome.

Our patient's branch retinal artery occlusions had a somewhat different ophthalmoscopic appearance from the typical branch retinal artery occlusions seen in Susac's syndrome. She had progressive cotton-wool spots throughout her retina as opposed to the typical wedge-shaped infarcts that one sees with Susac's syndrome. Although cotton-wool spots are seen in Susac's syndrome, they are almost invariably associated with the typical wedge-shaped infarcts and are associated with Gass plaques (19) and a distinctive multifocal fluorescence on fluorescein angiography (20). Neither of these findings were present in our patient.

The present case displays two features not previously reported in patients with primary central system vasculitis or, as we prefer to refer to it, primary angiitis of the central nervous system (PACNS) (1-5). These include the retinal vascular lesions and the presence of extensive calcification within the lesions. Although branch retinal artery occlusions may rarely occur with other vasculitides (27-33), laboratory data and other systemic features generally help make the correct diagnosis. In our patient,

who had multiple normal laboratory data, brain biopsy was required to make the diagnosis. The biopsy showed a small vessel vasculitis with lymphocytic infiltration of the pre-capillary arterioles and ischemic necrosis of the brain associated with dystrophic calcification. There was no evidence of vascular inflammatory disease outside of the central nervous system or retina and thus the diagnosis was consistent with PACNS (1). Ocular manifestations of PACNS are rare and have largely been confined to accompanying uveitis (34). In addition Scolding *et al.* have described microvascular abnormalities in the retina by fluorescein angiography combined with slit lamp video microscopy but similar findings to ours of frank retinal vascular occlusions were not observed (35). Given the facts that patients presenting with CNS vasculitis may have altered mental status and not complain or be aware of visual and or auditory changes or may have subclinical involvement of the retinal vasculature such as in our case, we believe it is important to screen all patients with suspected PACNS with careful ophthalmoscopic as well as audiometric examinations.

The other unique finding was the presence of calcifications as detected by neuro-imaging and pathologic examination. One explanation for the deposition of calcification may relate to the slow progressive nature of the vasculitis. The ophthalmoscopic picture showed that the occlusions were slowly progressive and associated with cotton-wool spots that progressively denuded the retina of the nerve fiber layer. The calcification suggests a chronic, smoldering process. Had an MR or CT been done when the patient initially presented with branch retinal artery occlusions, one might have anticipated that asymptomatic lesions of the brain would have been present. Thus, we would recommend neuroimaging patients who present with isolated branch retinal artery occlusions even though there may be no neurological signs or symptoms. We feel that our patient represents a unique case of primary central nervous system vasculitis because it presented with branch retinal artery occlusions

and because of the brain calcification. We would recommend careful ophthalmoscopic examination of patients with the presumed diagnosis of primary central nervous system vasculitis and also recommend obtaining not only MRI but also CT to detect calcification.

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