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PEG-LEG ARTERIOLES: AN ADAPTATION TO CHRONIC RETINAL HYPOPERFUSION

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Purpose: To describe a heretofore unreported retinal vascular sign related to chronic retinal hypoperfusion.

Methods: A case report of a 42-year-old woman who was found to have a novel pattern of retinal vascular remodeling in the setting of severe bilateral occlusive disease of the carotid and vertebral arteries.

Results: The patient had a childhood history of nasopharyngeal carcinoma, treated with external beam radiation. At age 35, she suffered bilateral occipital infarctions. A cerebral angiogram showed complete occlusion of both common carotid arteries and complete occlusion of the proximal segments of both vertebral arteries. Seven years after her stroke, examination of her fundus revealed a remarkable pattern of vascular remodeling that involved nearly all of the major retinal arterioles in both eyes. In each vessel, a narrowed proximal segment abruptly dilated to a larger-than-normal caliber at a distance of 1 to 2 disk diameters from the optic disk. The abnormally increased caliber extended into the retinal periphery.

Conclusion: Chronic severe retinal hypoperfusion due to profound carotid occlusive disease can lead to adaptive remodeling of the retinal vasculature in a pattern that closely resembles the iconic image of a pirate's peg leg.

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Ocular ischemic syndrome (OIS) refers to the constellation of clinical signs that typically accompany longstanding, clinically significant compromise of arterial blood flow in one or both eyes. The most common cause of OIS is occlusive disease of the carotid artery. Posterior segment signs include dilated retinal veins and mid-peripheral blot hemorrhages. Of note, nearly all large series of OIS patients have documented pathologic narrowing of the retinal arterioles in affected eyes.[1] This case report describes a patient with total occlusion of both common carotid arteries and both vertebral arteries who manifested a strikingly different and heretofore unreported pattern of retinal vascular remodeling. Nearly every major retinal arteriole exhibited a narrowed proximal segment, a markedly dilated distal segment, and an abrupt transition in caliber at a distance of 1 to 2 disk diameters from the optic disk.

Case Report

A 42-year-old woman was referred to the Department of Ophthalmology at Duke University for further evaluation of persistent bilateral visual deficits. At age 12, she developed recurrent nosebleeds and was found to have mass lesions in the posterior nasopharynx and left neck. Biopsy revealed a poorly differentiated carcinoma. She was treated with cobalt-60 external beam radiation—62.5 Gy to the left neck and lower doses to the nasopharynx and right neck. All tumors regressed, and no signs of recurrence developed over the subsequent 30 years.

At age 35, the patient experienced acute visual loss in both eyes. A magnetic resonance imaging scan of the brain performed as part

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of a neurologic evaluation revealed bilateral occipital infarctions. One year later, a carotid ultrasound was attempted but could not be completed because the examiner was unable to locate either carotid artery. A subsequent cerebral angiogram, performed at age 37, revealed a dramatic picture of compromised cerebral blood flow (Figure 1). Both the right common carotid artery and the left common carotid artery were completely occluded, as were the proximal segments of both vertebral arteries. A digital subtraction angiogram revealed that the distal portions of the vertebral arteries were reconstituted by collateral vessels and that the distal portion of the right internal carotid artery was partially reconstituted by collaterals supplied by the right vertebral artery. The left vertebral artery did not extend intracranially but did supply blood to the distal portion of the left internal carotid artery through a muscular branch.

Medical history was negative for diabetes, heart disease, or hyperlipidemia. The patient had been treated for hypertension at a time in her life when she was obese, but after she lost weight, her blood pressure normalized and she no longer required antihypertensive medication. She reported having smoked for 25 years. Her only medication was one aspirin per day.

Before referral, the patient was followed by her local ophthalmologist with acuities in the range of 20/30 to 20/60, stable visual field defects, and intraocular pressures in the range of 8 in both eyes.

On examination at Duke, visual acuity was 20/40 in both eyes. Formal perimetry revealed a complete right homonymous hemianopia and a complete left inferior quadrantanopia. Anterior segments were normal. Intraocular pressures were nine in both eyes. The optic disk was normal in each eye, while the retinal veins exhibited moderate-to-marked dilation without tortuosity. The most striking fundus finding involved the major branch retinal arterioles (Figure 2). Each arteriole manifested segmental variation in caliber, with a narrowed proximal segment and a markedly dilated distal segment. The latter extended well into the retinal periphery. In each instance, the change in caliber was abrupt, and it occurred within an annular zone located between one and two disk diameters from the optic disk. Several of the dilated arteriolar segments were comparable in width to adjacent second-order veins, indicating that arteriolar caliber was much greater than normal, not merely increased relative to a narrowed proximal segment. The entire capillary bed was dilated as well, making it possible to easily view capillaries throughout the fundi using a direct ophthalmoscope. In each eye, a number of discrete yellow-orange subretinal dots were scattered in the temporal macula and surrounding area. The maculae were otherwise unremarkable.

The patient has been followed annually for the last 24 years. Over that interval, her visual deficits, fundus findings, and general health have not changed.

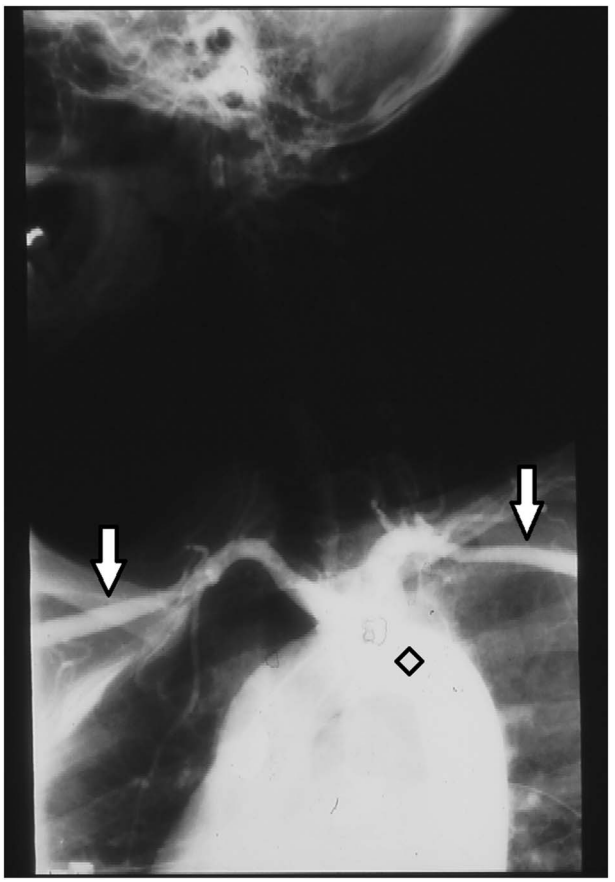

Fig. 1. Cerebral angiogram showing complete occlusion of both common carotid arteries and complete occlusion of the proximal segments of both vertebral arteries. The aortic arch is marked with a diamond. Both subclavian arteries (arrows) fill normally.

Discussion

The patient described herein manifests many of the defining clinical features of OIS, including profound carotid occlusive disease, intraocular pressures in the single digits, marked dilation of the retinal veins, and absence of retinal venous tortuosity. However, in place of uniform arteriolar narrowing, each of the major retinal arterioles exhibits segmental variation in caliber, with a narrow proximal segment and a much longer distal segment that exhibits markedly abnormal dilation. In each affected vessel, the change in caliber is abrupt, and the site of transition is located between one and two disk diameters from the optic disk. To the author's knowledge, this retinal vascular configuration has not previously been reported in the context of OIS or in association with any other retinal condition.

Autoregulation of retinal blood flow—through two interrelated mechanisms—partially explains the arteriolar dilation observed in this case. First, severe carotid occlusive disease produces a significant reduction in ocular perfusion pressure, defined as mean pressure in the ophthalmic artery minus intraocular pressure. The reduction in perfusion pressure prompts an autoregulatory response whereby retinal arterioles dilate, vascular resistance decreases, and retinal blood flow is maintained in a physiologic range.[2] Release of adenosine appears to mediate the arteriolar dilation that accompanies pressure autoregulation.[3] The second mechanism by which carotid occlusive disease leads to an increase in retinal arteriolar diameter involves a reduction in the supply of oxygen (O_2). Hypoxia initially causes small arterioles and capillaries to dilate in response to tissue metabolites, including lactate,

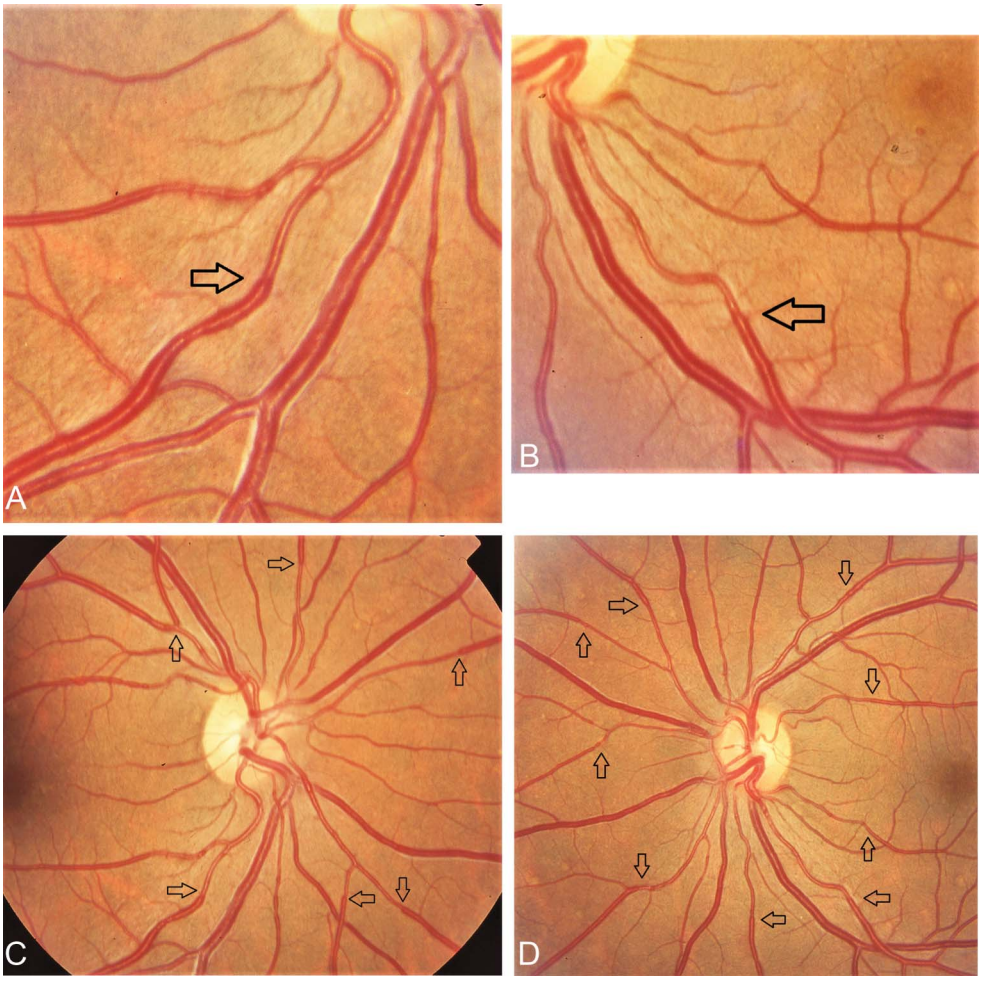

Fig. 2. **A** and **B.** Images of the inferotemporal retinal arteriole in the right and left eyes, respectively. Each vessel exhibits the peg-leg configuration, with a narrow proximal segment, a markedly dilated distal segment, and an abrupt change in vessel caliber approximately two disk diameters from the optic disk. Note that the diameter of the dilated segments equals or exceeds that of the dilated second-order veins. **C** and **D.** Fundus photographs of the right and left eyes, respectively. The peg-leg configuration involves nearly all the major branch retinal arterioles. The point at which the diameter of each vessel abruptly changes is marked with an arrow.

nitrous oxide (NO), and adenosine. Reduced downstream vascular resistance results in an increase in flow velocity within larger (>100 μm) upstream arterioles. The endothelium of large arterioles responds to the associated increase in wall sheer stress by releasing NO, a potent vasodilator. Accordingly, the autoregulatory response stimulated by hypoxia involves both metabolic and flow-induced mechanisms.[4]

For two reasons, the autoregulatory responses outlined above are insufficient to fully account for the vascular alterations reported herein:

1. Autoregulation is an inherently reversible process, whereas the retinal arteriolar abnormalities in the present case are clearly permanent, that is, a product of vascular remodeling.
2. The magnitude of arteriolar dilation in this case exceeds that which can be attributed solely to autoregulation. In the study reported by Cheng et al,[5] retinal arteriolar diameter increased only 8.53% in human subjects whose arterial partial pressure of O_2 was reduced to approximately 40 mmHg. Although greater percentage increases in arteriolar diameter have been documented in subjects exposed to severe hypobaric hypoxia during high-altitude ascents,[6] these changes too were completely reversible.

It seems reasonable to assume that the transition from reversible physiologic dilation to permanent vascular remodeling must have occurred over an extensive period. The documented occlusion of both common carotid arteries and both vertebral arteries lends support to a timeframe spanning years or even decades, since acute four-vessel occlusion is simply not compatible with survival. The existence of a well-developed system of cerebral collateral vessels also strongly suggests a chronic process. Furthermore, given that the patient became symptomatic in her thirties, a lengthy evolution of large vessel disease would imply that her retina was first exposed to reduced perfusion pressure and reduced arterial O_2 tension when she was in her teens or early twenties. One can plausibly hypothesize that vascular plasticity

is greater in young retinae, lowering the threshold for morphologic adaptations.

The patient's carotid and vertebral occlusive disease is almost certainly due to the radiation therapy she received for nasopharyngeal carcinoma at age 12. Large vessel disease as a late complication of radiation for head and neck cancer is extensively documented in the radiotherapy, otolaryngology, oncology, vascular disease, and stroke literature.[7] Furthermore, complete occlusion of both common carotid arteries is a recognized complication of previous radiation therapy but almost never occurs on the basis of typical atheromatous disease. Finally, the fact that the patient became symptomatic at a very young age (35) despite having relatively few vascular risk factors strongly implicates radiation in the pathogenesis of her large vessel occlusions.

In 2010, Tang et al[8] reported a case of OIS and carotid artery occlusion resulting from previous radiotherapy of nasopharyngeal carcinoma. Their patient's clinical presentation bore striking similarities to the patient described herein:

1. A relatively young age at onset of symptoms (39 years old);
2. A lengthy interval between treatment and presentation (14 years);
3. Four-vessel involvement, including 100% occlusion of both common carotid arteries.

However, unlike the present case, both ophthalmoscopy and fluorescein angiography revealed narrowed retinal arterioles throughout the fundi. Peg-leg arterioles were not present.

The present case leaves unanswered three key questions:

1. Why do the retinal arterioles exhibit bimodal variance in caliber? Stated differently, what physiologic advantage derives from coexistent narrowed and dilated segments?
2. Given that the anatomic, histologic, and ultrastructural characteristics of retinal arterioles change in gradual fashion along the course of each vessel,[9,10] what accounts for the abrupt transition in arteriolar diameter?
3. Why is that abrupt change in diameter consistently situated between one and two disk diameters from the optic disk?

The answers to these questions will likely depend on future observations in patients with OIS secondary to profound carotid occlusive disease.

Key words: ocular ischemic syndrome, radiotherapy, radiation-induced carotid occlusive disease, retinal arterioles, retinal vascular remodeling, stroke.

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