A 44-Year-Old Woman With Intracranial Hemorrhage

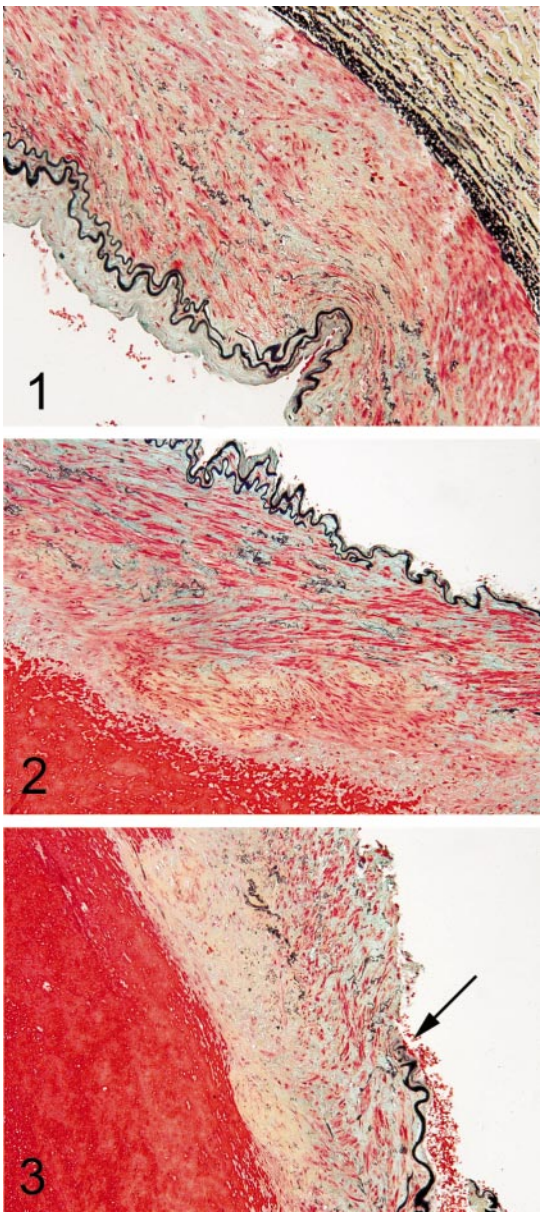
Cynthia Ann Allen, MD; Kim Adams Ely, MD

A 44-year-old woman with a past medical history significant for migraine headaches, hyperlipidemia, and hypertension initially presented after experiencing a tonic-clonic seizure. She had no history of head trauma. Cranial computed tomographic scan and arteriogram revealed a subarachnoid hemorrhage secondary to a ruptured left anterior communicating artery aneurysm. A left pterional craniotomy with aneurysm repair was performed; however, postoperatively, the patient remained comatose. Subsequent computed tomographic scan confirmed a left anterior cerebral infarct. After several weeks of hospitalization, she developed a left-sided pulsatile exophthalmos due to a carotid cavernous fistula. At this point, a hospital transfer was initiated in order to evaluate and potentially treat the fistula. On transfer, pertinent laboratory studies included prothrombin time, 13.6 seconds (reference range, 13.0–15.0 seconds); prothrombin time international normalized ratio, 1.0; partial thromboplastin time, 25.9 seconds (reference range, 25.0–36.0 seconds); platelet count, 382 $\times$ $10^3/\mu L$ (reference range, 150–400 $\times$ $10^3/\mu L$); and bleeding time, 4 minutes (reference range, 2–9 minutes). Clinical examination revealed an unresponsive, intubated woman with gross proptosis of the left eye greater than 2 cm beyond her lateral orbital rim.

The decision to proceed with cerebral angiography and endovascular balloon occlusion of the fistula was made after careful consideration. However, the procedure was terminated because of the development of left carotid and right external iliac dissections. Extensive intra-abdominal bleeding leading to hypotension and disseminated intravascular coagulation ensued, and the patient expired soon after termination of the procedure.

Because of the multifocal nature of arterial disease in the patient, an underlying connective tissue disorder was suspected, which prompted an autopsy limited to the abdomen and pelvis. Significant postmortem findings included a dissection of the right external iliac artery extending just proximal to the femoral artery, a right-sided rectus sheath hematoma, and 3.5 L of serosanguinous fluid within the peritoneal cavity. The splenic artery appeared calcified, with a tortuous configuration. Multiple hematoxylin-eosin– and Movat pentachrome–stained histologic sections of the splenic and right external iliac arteries showed decreased smooth muscle and a deposition of collagen and proteoglycans within the outer media (Figures 1 through 3, Movat). A right external iliac arterial dissection characterized by an accumulation of blood within the arterial media is shown in Figures 2 and 3 (Movat). Fragmentation of the internal elastic lamina (Figure 3, arrow, Movat) and transmural extension of fibrosis were focally present. The vessels did not contain atheromatous lesions or evidence of a vasculitis. No additional significant gross or microscopic findings were identified in the liver, spleen, or kidneys.

What is your diagnosis?



Accepted for publication February 1, 2005.

From the Department of Pathology, Vanderbilt University Medical Center, Nashville, Tenn.

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Cynthia Allen, MD, 125 Carriage Dr, Nashville, TN 37221 (e-mail: cindy.allen@vanderbilt.edu).

Pathologic Diagnosis: Fibromuscular Dysplasia, Medial Type, Perimedial Hyperplasia

Fibromuscular dysplasia (FMD) is an unusual, noninflammatory, nonatheromatous arteriopathy that typically affects the small to medium-sized arteries of young to middle-aged white women. In Rushton's[1] formal pedigree analysis of 20 families containing at least 1 member with documented FMD, the inheritance pattern was most consistent with an autosomal dominant trait with variable expression. No precise etiology of FMD has been elucidated, but multiple factors have been associated with the disease. The increased prevalence in women suggests that hormonal factors may contribute to its genesis, particularly the influence of estrogen stimulation on smooth muscle cells.[2] Associations with α_1-antitrypsin deficiency,[3] Alport syndrome, pheochromocytoma, Marfan syndrome, and Takayasu arteritis[4] have been reported.

Originally described by Leadbetter and Burkland[5] in 1938, FMD has been demonstrated in nearly every arterial bed, and multivessel disease frequently occurs.[2] The renal artery is chiefly involved (60%–75% of cases), and renovascular hypertension may result. The cervicocranial arteries (25%–30% of cases) are the second most common location,[4] and the majority of these cases arise within the internal carotid artery (95%), often bilaterally (60%–85%).[6] Nonspecific findings associated with cervicocranial FMD include headache, altered mentation, tinnitus, vertigo, neck pain, and seizure. Transient ischemic attack and cerebral infarction are more specific manifestations.[7] Cervicocranial FMD may be complicated by arterial dissection, carotid arteriovenous fistula, and intracranial aneurysm, and, as illustrated in the current case, cervicocranial FMD should be considered in young women who present with intracranial hemorrhage. Less often, lesions that may lead to aneurysm can be encountered in the extremities (5%), particularly the external iliac arteries, and the viscera (9%).[4,8] Such involvement usually occurs in patients having fibromuscular dysplasia elsewhere and should prompt a thorough evaluation of the carotid arteries.

Microscopically, FMD has been divided into 3 subsets based on the arterial wall layer involved: intimal, medial, and adventitial. These histologic types may produce various angiographic patterns. The medial form is most prevalent and is further classified into medial fibroplasia, perimedial hyperplasia, and pure medial hyperplasia. Medial fibroplasia contains multiple foci of fragmentation of the internal and external elastic lamina with loss of smooth muscle cells, causing segmental stenosis and dilatation. This correlates with the ''string of beads'' sign on angiography. Perimedial hyperplasia results from extensive fibrous tissue deposition in the outer media. In pure medial hyperplasia, the medial wall contains circumferential smooth muscle hyperplasia with little to no fibrosis. Intimal fibroplasia represents less than 5% of lesions and is characterized by thickening of the intima by collagen without a lipid or inflammatory component. Focal stenosis or a long smooth (tubular) stenosis on angiogram is usually seen; however, other forms of fibromuscular dysplasia may produce this image as well. In adventitial (periarterial) FMD, the adventitia and surrounding adipose tissue are replaced by dense collagen with normal media and intima.[7,9]

Treatment modalities for FMD vary with symptomatology and location of the lesion. Pharmacologic therapy is initially attempted to treat renovascular hypertension, followed by surgery if this approach is unsuccessful. In asymptomatic individuals with cervicocranial involvement, administration of antiplatelet and anticoagulation agents is recommended. Percutaneous transluminal angioplasty is effective in patients who are symptomatic, and this has emerged as the surgical procedure of choice in most involved vascular beds.[10]

In conclusion, FMD is an infrequently recognized vascular abnormality that can lead to intracranial hemorrhage in young women. Lesions may compromise almost any vascular bed, with preferential involvement of the small- to medium-sized arteries. When symptomatic, patients may present with hypertension, transient ischemic attack, and cerebral ischemia. Histologically, the medial type of FMD is the most common and is responsible for the ''string of beads'' appearance on angiogram. Although radiologic findings may be characteristic, our case required a postmortem examination to determine the underlying cause of death.

References

1. Rushton AR. The genetics of fibromuscular dysplasia. *Arch Intern Med.* 1980;140:233–236.
2. Luscher TF, Lie JT, Stanson AW, et al. Arterial fibromuscular dysplasia. *Mayo Clin Proc.* 1987;62:931–952.
3. Schievink WI, Meyer FB, Parisi JE, et al. Fibromuscular dysplasia of the internal carotid artery associated with alpha 1-antitrypsin deficiency. *Neurosurgery.* 1998;43:229–233.
4. Gray BH, Young JR, Olin JW. Miscellaneous arterial diseases. In: Young JR, Olin JW, Bartholomew JR, eds. *Peripheral Vascular Diseases.* 2nd ed. St Louis, Mo: Mosby-Yearbook; 1996:425–440.
5. Leadbetter WF, Burkland CF. Hypertension in unilateral renal disease. *J Urol.* 1938;39:611–626.
6. Healton EB. Fibromuscular dysplasia. In: Barnett HJM, ed. *Stroke: Pathophysiology, Diagnosis and Management.* New York, NY: Churchill Livingstone; 1992:749–760.
7. Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol.* 2001;12:41–47.
8. Kojima A, Shindo S, Kubota K, et al. Successful surgical treatment of a patient with multiple visceral artery aneurysms due to fibromuscular dysplasia. *Cardiovasc Surg.* 2002;10:157–160.
9. Virmani R, Burke A, Farb A. *Atlas of Cardiovascular Pathology.* Philadelphia, Pa: WB Saunders; 1996.
10. Nomura S, Yamashita K, Shoichi K, et al. Childhood subarachnoid hemorrhage associated with fibromuscular dysplasia. *Childs Nerv Syst.* 2001;17:419–422.