

# Nonatherosclerotic Vascular Disease in Women

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**C**oronary atherosclerosis is responsible for most cases of ischemic heart disease. However, nonatherosclerotic processes can also cause luminal narrowing. Three conditions that can lead to coronary artery disease and sudden cardiac death are fibromuscular dysplasia (FMD), spontaneous coronary artery dissection (SCAD), and Takayasu arteritis. Each is more prevalent in women than in men, and each can be underdiagnosed.

## Fibromuscular Dysplasia

Fibromuscular dysplasia occurs predominantly in women (9:1, women to men).<sup>1</sup> Its estimated prevalence in the general population is 1% to 6.6%. Although the cause is unknown, patients with FMD often have a family history, with 7% to 11% of first-degree relatives affected. Clinical presentation varies from no symptoms to sudden death. Typical symptoms are hypertension, headaches, tinnitus, dizziness, neck pain, chest pain and shortness of breath, and abdominal pain. Diagnosis is established by using computed tomography, magnetic resonance imaging, duplex ultrasound, or angiography, the last of which is considered the gold standard.

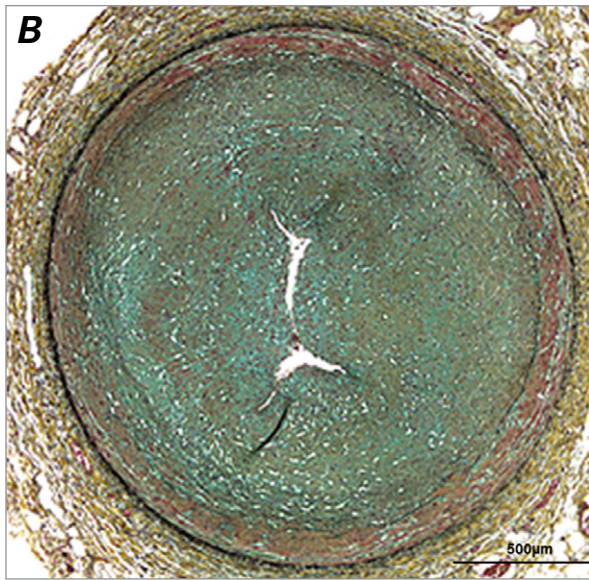
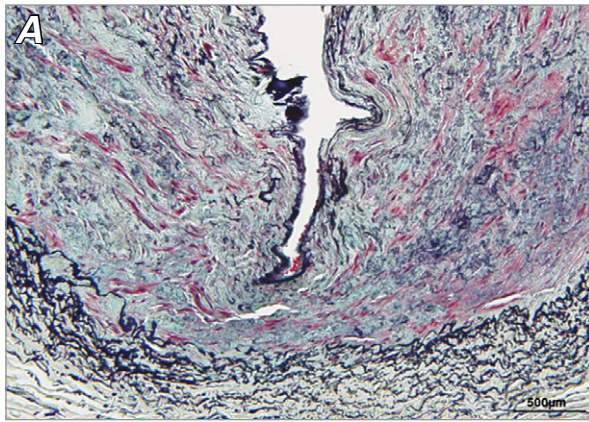
Histologic classification depends upon the arterial layer affected. Medial involvement, the most prevalent, is characterized by multifocal thickening; areas of markedly thinned arterial wall alternate with thickened fibromuscular ridges in which the arterial muscle is replaced by fibroplasia with loose collagen (Fig. 1A). Intimal involvement is characterized by circumferential fibrointimal proliferation of smooth-muscle cells in a fibrous matrix; this results in severe luminal narrowing (Fig. 1B). In adventitial involvement, marked circumferential thickening from fibroblasts and collagen is seen.

The disease is multifocal in 60% to 70% of cases. When the vascular beds in a large registry of patients were examined, various arteries were affected as follows: renal, 80%; extracranial carotid, 74%; vertebral, 37%; mesenteric, 26%; lower extremity, 60%; intracranial carotid, 17%; and upper extremity, 16%. Coronary arteries are not often affected; however, it is thought that coronary artery dissection can result from FMD (prevalence, 3.4%).<sup>1</sup> On the other hand, SCAD has been associated with FMD in 52% to 91% of cases.

## Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection is defined as nontraumatic, noniatrogenic spontaneous separation of the coronary artery wall. Contemporary usage of the term SCAD typically applies to the nonatherosclerotic variant; most modern series exclude patients whose SCAD is caused by atherosclerosis. In 92% to 95% of cases, SCAD affects women (typical age range, 44–55 yr). In young women who present with acute coronary syndrome, including those with pregnancy-related myocardial infarction, the prevalence of SCAD is 24.2% to 35%.<sup>2</sup>

Chest pain has been reported in 96% of cases, followed by pain radiating to the arm (51%), nausea and vomiting (24%), pain radiating to the neck (22%), and diaphoresis (21%); other symptoms are dyspnea, back pain, and dizziness. Angiographically, SCAD is classified into 3 types: multiple radiolucent lumina, diffuse stenosis of varying severity and length, and focal or tubular stenosis usually <20 mm in length. The mechanism of SCAD is generally thought to be intimal tearing, in which a primary disruption in the intimal luminal interface creates an entry point for hematoma to accumulate inside the false lumen. Intraluminal imaging is required to confirm the

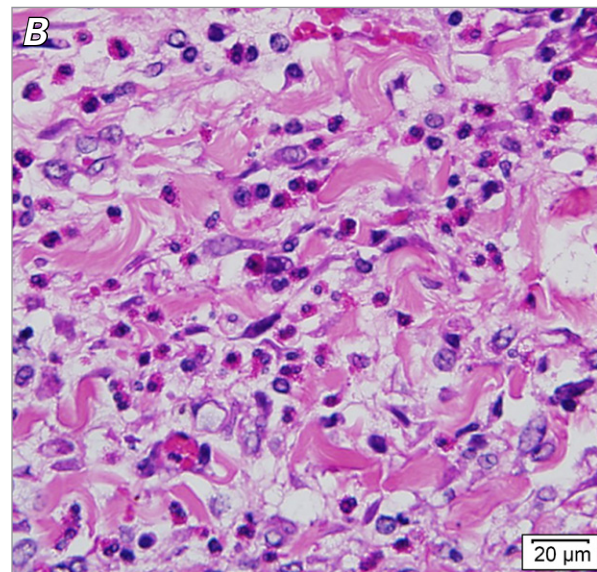
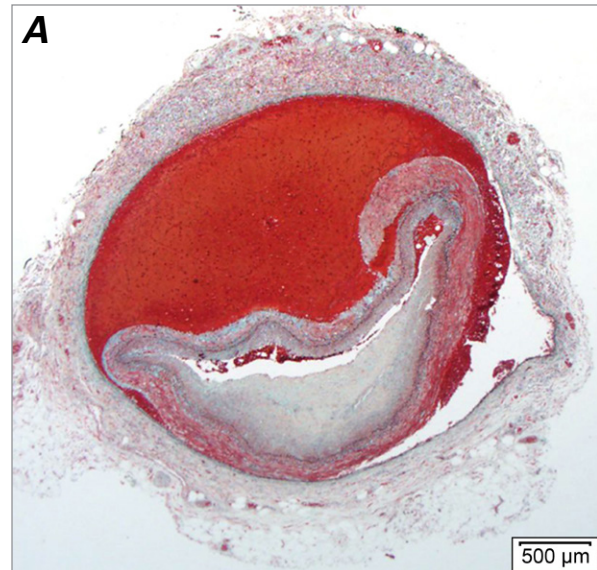


**Fig. 1** Photomicrographs show **A)** medial fibroplasia in a renal artery (Russell-Movat pentachrome stain, orig.  $\times 20$ ), and **B)** intimal fibroplasia of the left circumflex coronary artery, with concentric thickening of the intima and relatively normal media and adventitia (Russell-Movat pentachrome stain, orig.  $\times 4$ ).

presence of intramural hematoma. At autopsy, SCAD is most often observed in the proximal segments (Fig. 2A). The dissection site is usually the external elastic lamina or between the outer third and the inner two thirds of the media, usually with adaptive intimal thickening. Adventitial inflammation, including eosinophils, is frequently seen in SCAD. The eosinophils are thought to be secondary to the dissection (Fig. 2B) and do not indicate underlying vasculitis.

### Takayasu Arteritis

Vasculitis is characterized by inflammation of the arterial wall. Diagnosis can be challenging, because the nonspecific signs and symptoms can mimic infection, malignancy, thrombotic disorders, and connective-tissue disease. Clinical symptoms are associated with the affected vessel. Limb claudication, absent pulses, and unequal blood pressures are typical symptoms of



**Fig. 2** Photomicrographs show spontaneous dissection of a proximal left anterior ascending coronary artery. **A)** A blood clot in the dissection plane compromises the lumen. The dissection is at the level of the external elastic lamina and the medial wall, which is rich with smooth-muscle cells; adaptive intimal thickening is also seen (Russell-Movat pentachrome stain, orig.  $\times 4$ ). **B)** Inflammatory cells with a moderate number of eosinophils are present in the adventitia (H & E, orig.  $\times 40$ ).

large-vessel vasculitis. Medium-sized vessels are defined as main visceral arteries and their initial branches, so symptoms occur according to the organ involved.<sup>3</sup>

Takayasu arteritis is categorized as a large-vessel vasculitis. It has an incidence rate of 2.6 cases per million individuals per year in the United States and predominantly affects women of childbearing age. The *HLA-B5* genetic locus is linked with susceptibility.

Takayasu arteritis often involves the coronary arteries and the aorta<sup>4,5</sup>; coronary involvement has been reported in ostial regions (frequency, 7.2%) and in non-

ostial regions (frequency, 10.8%).<sup>4</sup> Acute-phase pathologic findings include edema, focal necrosis, chronic inflammation, and scattered giant cells in the outer two thirds of the aortic wall, including the adventitia and vasa vasorum.<sup>6</sup> Intimal proliferation and obliteration of the vasa vasorum have also been reported.<sup>6</sup> In contrast, typical findings in the late phase include notable intimal and adventitial thickening, and narrowed ostia of the aortic arch vessels. A “tree bark” appearance occurs after scarring and revascularization. Aortic involvement is focal; there are intervening areas of normal aortic wall. Complications include aneurysm and, rarely, dissection.

### Conclusion

The causes of FMD, SCAD, and Takayasu arteritis are not fully characterized. All 3 predominantly affect women and have typically been underdiagnosed. To ensure appropriate treatment with new therapies, diagnosis is crucial. Compiling detailed registries of these diseases would help to further our understanding.

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