A 49-year-old Hispanic female was admitted to the hospital with sepsis and an infected upper extremity arteriovenous fistula dialysis port. Her medical history was significant for dialysis-dependent, endstage renal disease for the previous six years. Additional history was limited due to language barriers but included hypertension and hyperlipidemia. Blood cultures from admission grew *Staphylococcus aureus* for which intravenous vancomycin therapy was initiated. Despite aggressive therapy including fistula debridement and excision and additional broad spectrum antimicrobial coverage, she clinically deteriorated and died on hospital day 13. Full, unrestricted autopsy permission was granted under coroner authorization.

Pertinent findings at autopsy included bilateral renal atrophy (Table 1) and bilateral, grossly evident stenosis of the renal arteries (Figure 1). Luminal narrowing was estimated at 90%-95% in the mid and distal segments of both arteries. No atheromatous plaques were present; no mural thrombi were noted. The ostia at the aortic origin were patent. Additional related findings were fibrinous pericarditis, bilateral pleural effusions with pleural adhesions, hypertensive cardiovascular disease, a remote infarct of the right insular cortex, and remote myocardial infarct by histology. Microscopic sections of the renal arteries showed marked wall thickening with collagenous deposition in the vascular intima associated with fragmentation and duplication of the internal elastic lamina. There was slight medial thickening and adventitial fibrosis (Figure 2A-B). The intimal thickening extended into the renal arterioles but without significant luminal narrowing. Section from the left anterior descending coronary artery also showed similar findings, but the vascular lumen was not critically stenotic.

What is the underlying cause of death in this case?

Explication is on p. 296
DIAGNOSIS: Bilateral renal artery stenosis due to fibromuscular dysplasia – intimal type.

DISCUSSION

In roughly 90% of cases of renal artery stenosis (RAS), the primary cause is atherosclerotic cardiovascular disease. In the remaining 10% of cases, the cause is fibromuscular dysplasia (FMD). FMD is a non-inflammatory, non-atherosclerotic, idiopathic disorder that most frequently involves the renal arteries but has been described in virtually every arterial bed in the body. Multi-vessel FMD occurs in the majority of cases (65%), most often involving the renal arteries, the extracranial carotid, and the vertebral arteries. Other notably involved vascular beds include the coronary circulation, pulmonary arteries, and the aorta. Rarely, FMD affects visceral vessels and the lower extremity vascular beds. Bilateral involvement of the renal arteries is seen in just 35% of cases.

Symptomatology in FMD ranges from asymptomatic and incidental to a multisystem disease that can mimic necrotizing vasculitis, depending on the extent of the arterial segment involved, the severity of the luminal compromise, and the pathologic subtype of FMD. The most common presenting clinical signs and symptoms include hypertension, headache, tinnitus, and dizziness. With such an array of presentations, the true incidence of FMD is not precisely defined; the prevalence of symptomatic renovascular FMD (RFMD) is estimated at 4/1000. Of note, however, is that some large-scale studies cite a 3.8%-6.6% incidence of FMD in angiographic screening of potential kidney donors, concluding that RFMD may actually be underdiagnosed and/or underrecognized. RFMD in adults affects females nine times more often than males and, though once traditionally thought of as a disease of young females, FMD is now known to affect middle-aged and older women just as often as those in their teens and twenties. In children affected by FMD, however, there is no female predominance.

Numerous etiologies have been postulated for FMD, including a genetic component, tobacco, hormonal influences, and ischemia to the arterial wall caused by fibrotic occlusion of the vasa vasorum. Familial cases of FMD have been reported, and inheritance appears most compatible with an autosomal dominant pattern, with incomplete penetrance and variable expressivity.

The gross and histopathologic lesions seen in RFMD are both characteristic. Compromise of the lumina of the renal arteries will be visible to the naked eye on serial cross section in a segmental, skip-lesion-like pattern that is more notable in the distal two-thirds of the vessel. Unlike that which is seen in atherosclerotic cardiovascular disease, there is no atheromatous plaque, typically no significant calcification and no surface ulceration with overlying thrombotic material. Instead, the lumina usually appear concentrically stenosed by a thickened and hypertrophic appearing wall. In the vascular segments that intervene between the stenotic regions, the vessel diameter may be ectatic or aneurysmal. It is this alternating and repeating pattern of stenosis, followed by post-stenotic dilatation that represents itself as the hallmark “beads on a string” appearance on renovascular angiography. Moreover, and again unlike renal arteries affected by atherosclerotic plaque, RFMD lesions rarely affect the ostia or origin of the arteries as they branch from the abdominal aorta.

The predominant histologic pattern of the involved arteries ultimately sub-classifies the type of FMD. The original classification schema for RFMD was devised by McCormack et al in 1966 and was subsequently revised by Stanley three decades later. The schema is based mainly upon in which arterial layer (intima, media, or adventitia) the lesions predominate (Table 2). The three main types are not mutually exclusive and are said to coexist in the same arterial segment in the majority of cases. With many individuals not ever undergoing tissue analysis and with an obvious need for non-invasive diagnostics, pathologic-angiographic correlation analyses have aimed at classification schemas that align the imaging features with the histopathologic subtypes of FMD. These features are also listed in Table

| Table 1: Observed versus expected combined kidney weight at autopsy |
|---------------------------------|------------------|
| Observed Combined Kidney Weight (gm) | Expected Combined Kidney Weight (gm) |
| 90 | 270±76 |

Figure 2A (left): Histologic sections from the same segment of the renal artery demonstrating the classic features of FMD, including luminal narrowing primarily due to a widened intimal region but also due to medial thickening and adventitial fibrosis (2x, Hematoxylin and Eosin stain). Figure 2B (right): Fragmentation and duplication of the internal elastic lamina is documented by an elastin stain (2x, elastin stain).
2. Of particular importance from these correlative analyses is that the most common subtype, FMD-medial, is the main pathologic pattern that contributes to the prototypical angiographic pattern known as “a string of beads.”

The prognosis in RFMD, mainly in the less common subtypes such as the intimal and adventitial types, may be progressive and ultimately lead to severe vascular stenosis and even total occlusion. In the usual RFMD-medial type, the natural disease course is widely unknown but said to be stable in most cases. Those FMD cases involving multiple vascular beds, however, would undoubtedly have a more complex course that would logically be related to the arterial segments involved. In the US FMD Registry, the largest published series of FMD patients, the main significant complications attributed to FMD were reported to be vascular wall dissection and aneurysm in nearly 20% of patients, along with cerebrovascular events including transient ischemic attack and stroke. The case presented herein shows the pathologic features of one of the two rare subtypes of RFMD, the intimal predominant type. Similar to most cases, there was histologic evidence of vascular dysplasia involving the vascular media as well; and other arterial beds (coronary circulation) were proven to be involved. Involvement of the cerebrovasculature was suspected given the right-sided insular infarct; though microscopic confirmation could not be established. At autopsy, there was critical stenosis of up to 90%-95% in both renal arteries, resulting in marked renal atrophy, rendering the patient dialysis-dependent and consequently vulnerable to dialysis-related complications and sequelae. With bilateral RFMD being reported to occur in only one-third of cases, the current case contributes to those unfortunate cases associated with significant risks for morbidity and mortality and adds further evidence to the notion about the multisystem impact and systemic nature of the FMD arteriopathy.

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REFERENCES