INTRODUCTION

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, non-inflammatory vascular disease that mainly affects the renal and internal carotid arteries. Involvement of other sites, including arteries of the extremities, is uncommon, and only a few histologically confirmed cases have been reported. FMD of the arteries of the extremities can result in ischemia requiring surgical or endovascular reconstruction. In the present report, two cases of FMD are described: one case of femoropopliteal artery occlusive disease, and one case of nonsymptomatic progression of external iliac artery dissection, both with histological confirmation of FMD. Clinical presentation, treatment, outcome and histological findings of previously reported cases are reviewed. FMD should be considered as a cause of occlusion, stenosis, dissection or aneurysm of the peripheral arteries: although rare, it can lead to limb-threatening ischemia or life-threatening aneurysm rupture.

Key words: fibromuscular dysplasia, femoral artery, iliac artery, dissection, aneurysm, extremity

Case Report

Fibromuscular Dysplasia of the Lower Extremities

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Fibromuscular dysplasia (FMD) is a nonatherosclerotic, non-inflammatory systemic occlusive arteriopathy of unknown etiology that mainly affects renal and carotid, and splanchnic arteries. Since it was first described in 1938, numerous reports have appeared describing the disease both in renal arteries and extra-renal vessels. Involvement of the arteries of the extremities is uncommon, and only a few histologically confirmed cases have been reported. FMD-related lesions in the extremities occasionally cause limb ischemia through luminal stenosis or peripheral thrombus. Aneurysm formation caused by FMD may also cause limb ischemia through peripheral thrombus. This ischemia can be resolved with arterial reconstruction.

Report of Cases

Case 1

Clinical findings

A 63-year-old woman presented with disabling left leg claudication, along with hypertension and hypercholesterolemia treated by oral medication. Physical examination revealed a pulsating mass in the lower abdomen, normal pulses over the femoral arteries, a bilateral pulsating mass on the popliteal arteries, and no pulsation over the left pedal artery. The left foot was cold with skin pallor. Ankle-brachial pressure indices were 0.37 on the left and 0.75 on the right. Laboratory values upon admission included serum cholesterol of 396 mg/dl and triglycerides of 674 mg/dl. Three-dimensional computed tomography (CT) revealed bilateral common iliac artery aneurysms (measuring 5.9 cm in the left and 4.0 cm in the right), and serial stenoses altering with mural aneurysms in bilateral superficial femoral and popliteal arteries (the classic “string-of-beads” appearance) (Fig. 1). Popliteal arteries presented with aneurysms (measuring 17 mm in the left and 20 mm in the right) with luminal thrombi. The left popliteal artery was occluded above the trifurcation, and only the peroneal artery was contrast enhanced through collateral vessels. On the right side,
the lumen of the right popliteal aneurysm was patent, the tibioperoneal trunk was occluded, and only the anterior tibial artery was patent. There were no abnormal findings on the renal or visceral arteries, although the “string-of-beads” appearance was observed bilaterally in the internal carotid arteries. From the characteristic “string-of-beads” appearance, FMD of bilateral femoropopliteal and internal carotid arteries, and bilateral common iliac and bilateral popliteal artery aneurysms were diagnosed.

The iliac aneurysms were successfully excised and reconstructed with a Y graft. After 1 month, left leg ischemia was treated with a femoral to peroneal artery bypass with a reversed great saphenous vein. The superficial femoral artery was ligated at its origin, and its short segment was excised for histological examination. The postoperative course was uneventful.

**Histological findings**

The medial layer of the femoral artery was thickened by marked collagen fibrosis and muscular hyperplasia. Smooth muscle fibers were focally disorganized, and internal elastic membrane was partially fragmented. Intima contained marked fibrous thickening and a focus of atheromatous gruel (Fig. 2). Findings were compatible with medial fibroplasia with associated atherosclerotic change caused by aging and hyperlipidemia.

**Case 2**

**Clinical findings**

A 37-year-old man presented with sudden-onset back pain. No clinical features suggestive of Marfan or Ehlers-Danlos syndrome were present. Although the patient reported no history of vascular events, he had a family history of maternal death at 60 years of age by rupture of an aneurysm. Because CT revealed the presence of a retroperitoneal hematoma surrounding the body of the pancreas, acute pancreatitis was diagnosed and the treatment with intravenous administration of protease inhibitor was initiated. Thereafter, detailed CT findings suggested dissection and rupture and spontaneous thrombus of the celiac artery (Fig. 3). Percutaneous transluminal coil embolization of the partially thrombosed celiac trunk was successfully conducted. Systemic vascular investigation revealed a short segment of dissection in the right external iliac artery. The renal, cerebral, and peripheral arteries appeared normal. No symptoms of lower leg ischemia were present initially. After follow-up by three-dimensional CT for 17 months, the right iliac dissected lumen was enlarged, and a new dissection appeared in the left external iliac artery (Fig. 4). Resection and interposition of bilateral external iliac arteries with ePTFE prosthetic grafts were performed.

**Fig. 1** Computed tomographic angiography of case 1. “String-of-beads” appearance on bilateral the femoral and popliteal arteries.

**Fig. 2** Femoral artery of case 1 in cross-section. Medial layer is focally thickened with marked collagen fibrosis and disorganized muscular hyperplasia. Internal elastic membrane is partially fragmented. Intima also shows a marked fibrous thickening and focus of atheromatous gruel. (elastic van Gieson stain, original magnification × 40)
Luminal visualization of the resected external iliac arteries revealed dissection and unusual corrugations by serial wall thickening and an intervening crease (Fig. 5). The postoperative course was uneventful.

**Histological findings**

External iliac artery cross-section revealed both intimal and medial thickening and medial dissection. Intimal layer had irregularly arranged mesenchymal cells present in a loose matrix of fibrous connective tissue. No lipid or inflammatory components were present. The inner media was thickened with disoriented smooth muscle fibers, and the internal elastic membrane was partially fragmented. A dissected channel was present at the outer third of the media, dividing the medial layer into a fibroplastic inner layer and an almost intact paramedial layer. External elastic membrane and adventitia were almost intact (Fig. 6). Findings were compatible with medial dissection with concomitant secondary intimal fibroplasia.

**DISCUSSION**

Fibromuscular dysplasia is a group of nonatherosclerotic, non-inflammatory arteriopathy that most commonly involve renal and carotid arteries, though it has been described in almost every arterial bed in the body. The clinical presentation may vary from an asymptomatic condition to a limb-threatening ischemia or life-threatening hemorrhage, depending on the involvement of the arterial bed, degree of stenosis, and pathological
types of FMD.

A pathological classification of FMD was proposed by Harrison and McCormack according to the vessel layer involved; i.e., medial, intimal, and adventitial. Medial fibromuscular dysplasia is most common (85%) and has been defined further into four subgroups: medial fibroplasia, perimedial fibroplasia, medial hyperplasia, and medial dissection.

Medial fibroplasia occurs most frequently and is well known because of the “string-of-beads” appearance on angiography. This appearance is the result of focal areas of stenosis with intervening areas of aneurysmal dilatation. Stenotic areas are due to thickened fibromuscular ridges, in which the arterial muscle is completely replaced by fibroplasia with loose collagen. The mural aneurysm results from thinning or complete loss of smooth muscle. The internal elastic membrane is deficient in the aneurysms.

In medial hyperplasia, the stenosis is produced primarily by hyperplasia of arterial smooth muscle cells.

In medial dissection, a channel is located on the outer third of the media. The media displays zones of fibroplasia replacing degenerated elastic fibrils, particularly around the channel.

Perimedial fibroplasia is characterized by marked, intense fibroplasia in the outer half of the media which usually replace the external elastic membrane. The fibroplastic layer varies in thickness, so considerable irregularity of the lumen is produced.

Intimal fibroplasia occurs in less than 10% of patients with FMD and is characterized by an accumulation of loose, moderately cellular fibrous tissue without atherosclerotic or inflammatory components. Blunt trauma, catheter-induced intraluminal injury, or luminal stenosis of the vessel may cause “secondary” intimal fibroplasia.

Adventitial fibroplasia is the least common in the renal FMD and, to our knowledge, has never been reported in extremity arteries.

Using the Harrison and McCormack classification, case 1 was diagnosed as medial fibroplasia with added atherosclerotic change; case 2 was diagnosed as medial dissection with secondary intimal fibroplasia. Without a histological diagnosis, we are not certain if the celiac arterial dissection in case 2 was caused by FMD, although FMD could occasionally occur in visceral arteries, and there are some reports describing celiac artery dissection caused by FMD, with a histological diagnosis.

The etiology of FMD has been the subject of much speculation. Cigarette smoking is associated with an increased risk of this disease; however, the mechanisms by which smoking contributes to the development of FMD have not been elucidated. The predominance of the disease in middle-aged women has led to the suggestion that it is caused by a hormonal influence on smooth muscle. Mechanical vessel wall stress is another classical hypothesis, as FMD of the renal arteries often co-presents with ptosis of the right kidney. Sang et al. analyzed these environmental factors in a case-control study of 33 patients with FMD. The number of pregnancies, oral contraceptives, gynecological disorders, and incidence of abnormal renal mobility did not differ between patients with FMD and matched controls. Genetic factors may also play a role in FMD, and since the disease is more common among first-degree relatives, an autosomal dominant transmission of the disease has been suggested. Some inheritable connective tissue disorders, such as Ehlers-Danlos syndrome (type IV) and Marfan syndrome, are associated with multiple aneurysms and arterial dissection and have been associated with FMD. Bofinger et al. reported a significantly higher frequency of angiotensin-converting enzyme I allele in FMD patients than in controls and suggested that a polymorphism of the renin-angiotensin system may cause defective remodeling in the muscular layer of arteries and subsequent development of FMD. Autoimmunity associated with HLA Drw6 was also suggested in a limited study.

Because of the lack of large cohorts, these studies on the possible causes of FMD have not been confirmed.

Numerous reports have described FMD occurring in
renal arteries and extrarenal vessels. In 1982, Mettinger and Ericson reviewed reports concerning 1 197 patients with FMD. Renal arteries were involved in 58%, cervico-cranial arteries in 32%, visceral arteries in 25%, and iliac arteries in 25% of cases. Of these nearly 1200 cases, only one was located in an infrainguinal artery of the lower extremity.

To the best of our knowledge, only 13 cases of FMD of the femoral or popliteal artery have been reported in the literature, including case 1 in the present report (Table 1). Of these 13 cases, seven were female and six were male, the mean age was 33 years, and the age range was 1-69 years. Angiographically, six cases appeared beaded, four were single aneurysms, and three were total occlusions. Eight cases of FMD of the femoral or popliteal artery had histological FMD diagnoses: seven were medial and one intimal.

Although FMD of the iliac artery (the third most common arterial site) with a beaded appearance or with aneurysm formation has been well documented, iliac artery dissection caused by FMD has been rarely reported. To our knowledge, only 12 cases of iliac artery dissection associated with FMD have been reported, including case 2 in this report (Table 2). Of these cases, seven were male and five were female. The mean age was 42 years, and the age range was 21-56 years. Most patients presented with leg ischemia or local pain, underwent bypass or resection and interposition, and had good outcomes. Two patients involved rupture and hypovolemic shock; and, in both cases, the patients died post-operatively. Seven reported cases of FMD of the iliac artery had histological diagnoses; all were medial FMD. Although our case was asymptomatic, an operative indication was decided from the progressive enlargement of the dissected pseudolumen, newly developed contralateral iliac dissection, and possible disastrous consequences of ruptured dissecting aneurysm.

It is generally not considered difficult to differentiate

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age</th>
<th>Sex</th>
<th>Site of disease</th>
<th>Appearance</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prince and Vawter (1971)</td>
<td>16</td>
<td>M</td>
<td>Bilateral femoral arteries</td>
<td>Beaded</td>
<td>Ischemia</td>
<td>Amputation</td>
<td>Amputation</td>
<td>Medial</td>
</tr>
<tr>
<td>Tisnado et al. (1982)</td>
<td>69</td>
<td>F</td>
<td>Bilateral femoral to popliteal arteries</td>
<td>Beaded</td>
<td>Microemboli of toes</td>
<td>Conservative</td>
<td>Good</td>
<td>N/A</td>
</tr>
<tr>
<td>Iwai et al. (1985)</td>
<td>25</td>
<td>F</td>
<td>Right popliteal artery</td>
<td>Beaded</td>
<td>Claudication</td>
<td>Angioplasty</td>
<td>Good</td>
<td>Medial</td>
</tr>
<tr>
<td>48</td>
<td>M</td>
<td>Right deep femoral artery</td>
<td>Beaded</td>
<td>Raynauds syndrome</td>
<td>Sympathectomy</td>
<td>Good</td>
<td>N/A</td>
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<tr>
<td>Stinnet et al. (1987)</td>
<td>10</td>
<td>F</td>
<td>Bilateral popliteal arteries</td>
<td>Aneurysm</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>Medial hyperplasia</td>
</tr>
<tr>
<td>Dungen et al. (1990)</td>
<td>15</td>
<td>F</td>
<td>Right superficial femoral artery</td>
<td>Occlusion</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>Perimedial fibroplasia</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>Left superficial femoral artery</td>
<td>Occlusion</td>
<td>Claudication</td>
<td>Sympathectomy and bypass</td>
<td>Amputation</td>
<td>Medial dissection</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>Left popliteal artery</td>
<td>Occlusion</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>Intimal</td>
<td></td>
</tr>
<tr>
<td>Fiche et al. (1991)</td>
<td>20</td>
<td>M</td>
<td>Right popliteal artery</td>
<td>Aneurysm</td>
<td>Knee effusion</td>
<td>Interposition</td>
<td>Good</td>
<td>Medial</td>
</tr>
<tr>
<td>Neukirch et al. (1996)</td>
<td>39</td>
<td>F</td>
<td>Left popliteal artery</td>
<td>Aneurysm</td>
<td>None</td>
<td>Resection and anastomosis</td>
<td>Good</td>
<td>Media</td>
</tr>
<tr>
<td>present case (2009)</td>
<td>63</td>
<td>F</td>
<td>Bilateral femoral to popliteal arteries</td>
<td>Beaded</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>Medial</td>
</tr>
</tbody>
</table>

FMD, fibromuscular dysplasia
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Atherosclerosis typically occurs in older patients with typical cardiovascular risk factors. On the other hand, FMD usually occurs in younger patients who have few cardiovascular risk factors. Lacking specific markers or effective non-invasive tests, angiographic imaging is almost essential for the diagnosis of FMD. Recently, computed tomographic angiography or gadolinium-enhanced magnetic resonance angiography have emerged as less invasive diagnostic imaging compared to contrast-enhanced digital subtraction angiography. Although the “string of beads” appearance is well known as a specific angiographic feature of FMD, FMD subtypes other than medial fibroplasia can present with a wide variety of angiographic appearances. For example, intimal fibroplasia and medial hyperplasia may present as a smooth or focal stenosis. Perimedial fibroplasias also may present with “string-of-beads” appearance. However, the beads in perimedial fibroplasia do not exceed the original arterial lumen. Kincaid et al. reported that “string-of beads” appearances were observed in 78 (62%) of 125 patients with renal FMD.27) In cervicocranial vessels, Mettinger et al. reported that 26 (62%) of 37 patients had a “string-of-beads” appearance.28) In cases of infrainguinal femoral and popliteal arteries, 6 (46%) of 13 had a “string-of-beads” appearance (Table 1). Therefore, the “string-of-beads” appearance can be specific to medial fibroplasia, but is not sensitive enough to diagnose all cases of FMD. Moreover, these angiographic signatures are only visible at the early stage of disease. Once an occluded vessel takes on atherosclerotic and/or inflammatory features, it can be difficult to distinguish FMD from atherosclerosis or arteritis without histological confirmation. The collection of tissue for histological analysis may not be possible from occluded peripheral arteries treated with bypass surgery. Therefore, a fair amount of peripheral arterial occlusion caused by fibrodysplastic disease may be misdiagnosed as a common atherosclerotic disease.

FMD of lower extremities may cause both acute and chronic leg ischemia by luminal stenosis, thrombosis and distal embolism. It may present with cold legs, intermittent claudication, ischemic ulcer or limb gangrene and may require arterial reconstruction.

Table 2 Iliac artery dissection associated with FMD

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age</th>
<th>Sex</th>
<th>Site of dissection</th>
<th>Symptom</th>
<th>treatment</th>
<th>Outcome</th>
<th>histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burri et al. (1983)</td>
<td>45</td>
<td>F</td>
<td>Left external iliac artery</td>
<td>Inguinal pain</td>
<td>Bypass</td>
<td>Good</td>
<td>medial</td>
</tr>
<tr>
<td>Sauer et al. (1990)</td>
<td>56</td>
<td>F</td>
<td>Right common iliac artery</td>
<td>Claudication</td>
<td>Conservative</td>
<td>Good</td>
<td>N/A</td>
</tr>
<tr>
<td>Patel et al. (1990)</td>
<td>39</td>
<td>M</td>
<td>Left external iliac artery</td>
<td>Inguinal pain</td>
<td>Bypass</td>
<td>Good</td>
<td>medial</td>
</tr>
<tr>
<td>Thevernet et al. (1992)</td>
<td>45</td>
<td>F</td>
<td>Right external iliac artery</td>
<td>Leg ischemia</td>
<td>Bypass</td>
<td>Good</td>
<td>medial</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>Bilateral external iliac arteries</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>Right external iliac artery</td>
<td>Abdominal pain</td>
<td>Bypass</td>
<td>Good</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>Left external iliac artery</td>
<td>Abdominal pain</td>
<td>Interposition with vein</td>
<td>Good</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>Right external iliac artery</td>
<td>Claudication</td>
<td>Bypass</td>
<td>Good</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Luck et al. (2002)</td>
<td>45</td>
<td>M</td>
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<td>Endatherectomy</td>
<td>Good</td>
<td>medial</td>
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<tr>
<td>Honjo et al. (2004)</td>
<td>30</td>
<td>M</td>
<td>Left common iliac artery</td>
<td>Shock, rupture</td>
<td>Bypass</td>
<td>Dead</td>
<td>medial</td>
</tr>
<tr>
<td>Yoshioka et al. (2005)</td>
<td>21</td>
<td>M</td>
<td>Left common iliac artery</td>
<td>Abdominal pain, rupture</td>
<td>Bypass</td>
<td>Dead</td>
<td>medial</td>
</tr>
<tr>
<td>present case (2009)</td>
<td>37</td>
<td>M</td>
<td>Bilateral external iliac arteries</td>
<td>none</td>
<td>Interposition with ePTFE</td>
<td>Good</td>
<td>medial</td>
</tr>
</tbody>
</table>

FMD, fibromuscular dysplasia

In conclusion, fibromuscular dysplasia should be considered as a potential cause of arterial occlusion, stenosis, dissection or aneurysm in the peripheral arteries. Although it is a rare cause of such pathologies, FMD may lead to life-threatening hemorrhage or limb-threat-
ening ischemia.

REFERENCES