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Case Report

A rare case report of bilateral brachial fibromuscular dysplasia and literature review

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Abstract: We present a 46-year-old woman with bilateral brachial arterial fibromuscular dysplasia (FMD) causing a systolic murmur in the antecubital fossa of the bilateral brachial. The diagnosis relied on angiography, by which "string-of-beads" sign in bilateral brachial arteries was found. The literatures on bilateral brachial arterial fibromuscular dysplasia were reviewed.

Keywords: Fibromuscular dysplasia, brachial artery

Introduction

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, nonatherosclerotic, noninflammatory vascular disease. It primarily affects women, but may also occur in infants, children, and men. We present the case of a 46-year-old woman who had FMD associated with bilateral brachial arteries.

Case report

A 46-year-old woman was referred because of a 2-week cephalalgia. The cephalalgia was localized at the occiput. Her past medical history and life history were unremarkable except cervical spondylopathy. She had a family history of hypertension and stroke. Upon physical examination, the patient was determined to have a blood pressure of 140/70 mmHg in the right arm and 135/70 mmHg in the left arm. The brachial and radial pulses were palpable and symmetric bilaterally. The patient had a systolic murmur in the antecubital fossa of the bilateral brachial. But she had no coldness, cyanosis, or skin ulceration. The basic laboratory examinations were within normal range. Immunological evaluation such as antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, did not provide any evidence of systemic disease. The "string of beads" sign in bilateral brachial arteries (**Figures 1**, **2**) were observed by DSA. No other cervical or intracranial vessels were affected and no intracranial aneurysms were found. Finally, both renal arteries and iliac arteries showed no abnormalities.

Based on the typical imaging findings, the diagnosis of fibromuscular dysplasia (FMD) was established [1]. The patient received a fortnight of flunarizine therapy (5 mg per day), and then was maintained on antiplatelet agents (asprin 100 mg per day). She had no residual cephalalgia at 24 months follow-up.

Literature review

The prevalence of FMD could not be precisely described. Since not all vascular beds were imaged in all patients and different imaging methods were used, the incidence may be underestimated in the general population. The United States registry for Fibromuscular Dysplasia shows brachial and/or radial arteries FMD occurred in 0.9% (4/447) of patients [2]. Olson et al in 1984 first reported a patient with bilateral brachial FMD [3]. Up to now, there are only *eleven* known cases of bilateral brachial FMD, including the present case, have been reported [3-11] (**Table 1**). To our knowledge, this is the first reported case of bilateral brachial arterial FMD in China.

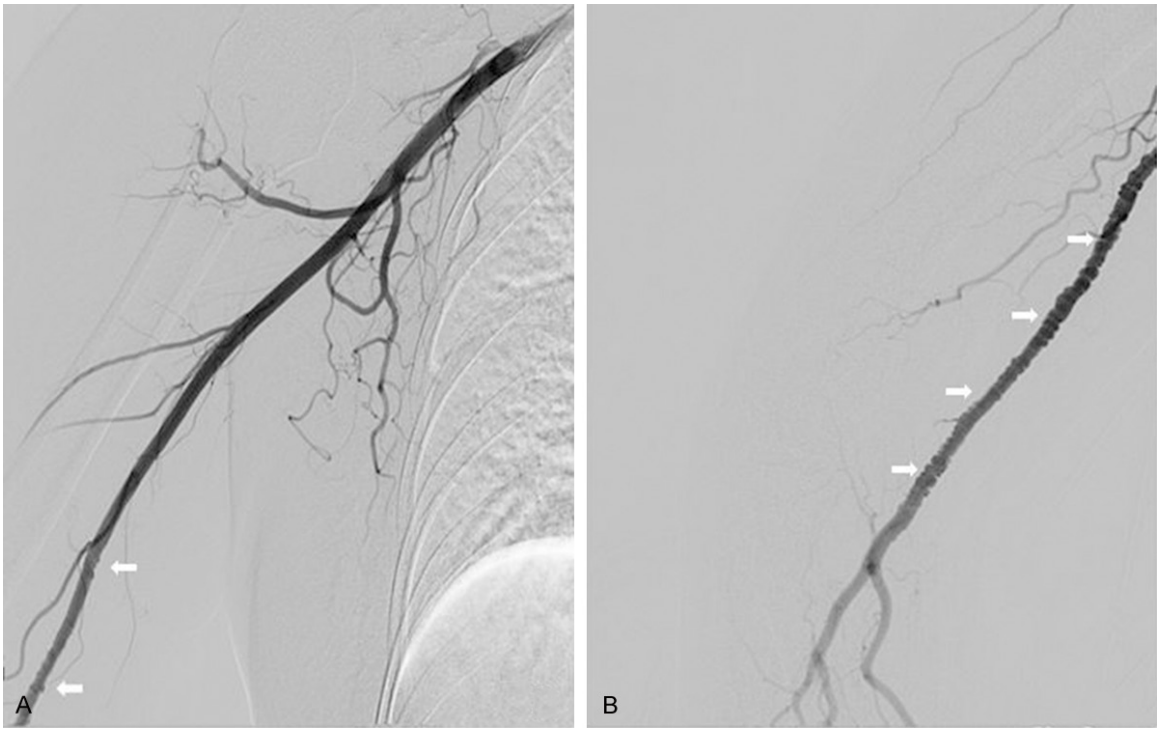

Figure 1. Typical "string of beads" appearance of right brachial artery.

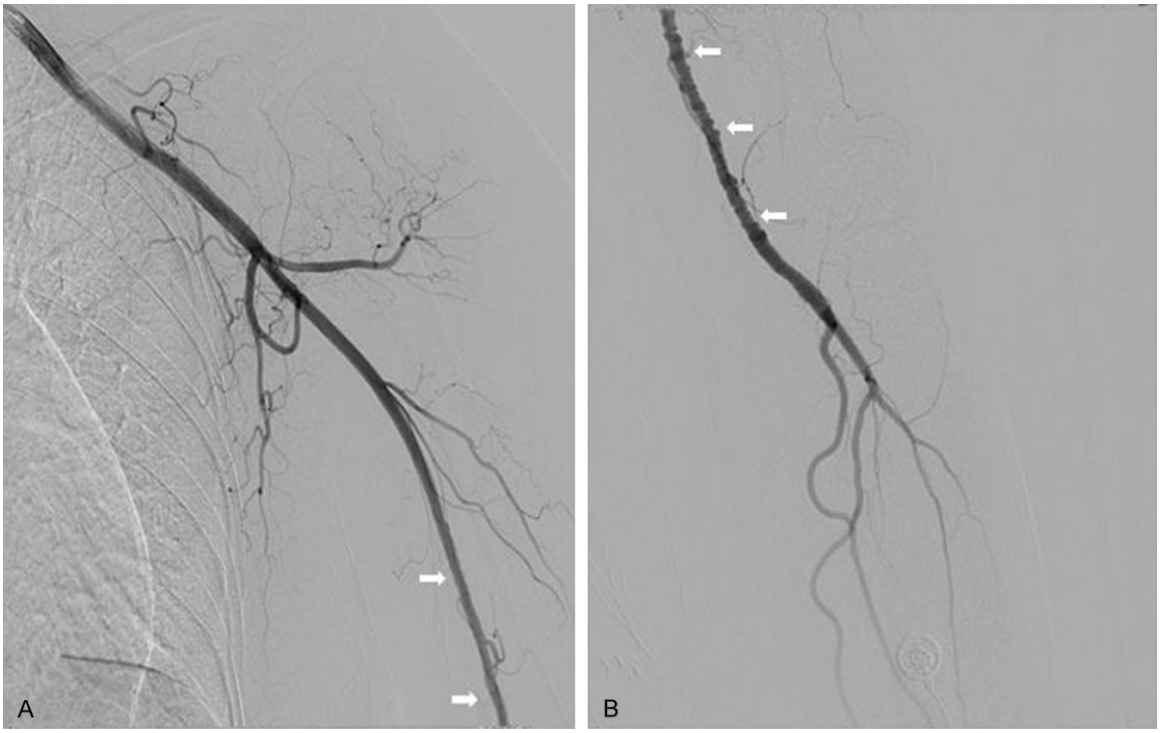

Figure 2. Typical "string of beads" appearance of left brachial artery.

Mean patient age was 62.5 years (range 42-89 years, SD 12.9), and 100% of patients were female. Case 4 and case 5 were a mother and a daughter. The affected sits were the bilateral brachial arteries in all patients. Among them two patients had coexistent bilateral renal

Table 1. Reported cases of bilateral brachial arteries fibromuscluar dysplaisa

Author, year	Age (yr)	Sex	Symptoms	Atery affected	Treatment
Olson, 1984	42	F	B arm intermittent paresthesia, paralysis	L brachial, R axillary-brachial	Nifedipine (failure); Resection, L brachial RSVG
Reilly, 1993	77	F	R hand coolness, intermittent pain	B brachial; R renal	Resection, R brachial RSVG
Dorman, 1994	64	F	R index finger pain, discoloration	B brachial	Resection, R brachial RSVG; Coumadin
Suzuki, 1999	65	F	L chest pains	B brachial, iliac, carotid and vertebral	Not mentioned
Suzuki, 1999	89	F	Fingers and toes coldness	B brachial	Not mentioned
Cutts, 2000	62	F	L hand paresthesia, pain, weakness	B brachial	Resection, R brachial RSVG and L brachial RSVG; Asprin (75 mg per day)
Kolluri, 2004	61	F	B hand blue, painful	B brachial	Percutaneous balloon angioplasty (B)
Shin, 2007	61	F	R hand paresthesia, pain, weakness, pale	B brachial; B renal	Resection, R brachial RSVG; Thrombolysis and asprin
Yoshimuta, 2008	56	F	Chest discomfort	B brachial	Not mentioned
Lewis, 2011	65	F	B upper limb pain during activities	B brachial	Percutaneous balloon angioplasty
Present case	46	F	Cephalalgia	B brachial	Flunarizine therapy (5 mg per day); Aspirin (100 mg per day)

B = bilateral; R = right; L = Left; RSVG = reversed saphenous vein graft.

arteries FMD, and one patient had coexistent iliac, carotid and vertebral artery FMD. Sensory disturbance was the most common symptom, eight patients had paresthesia, pain, coolness, etc. Two patients had weakness, and three patients had discoloration. Two patients were found by accident because of chest discomfort. Only the present patient experienced a headache. Bruits were detected over the brachial arteries in five patients. Only one patient had a positive history of smoking. All cases were diagnosed FMD by angiography, among which five cases were confirmed by pathology. All patients were diagnosed as medial FMD, one of which complicated with intimal damage. Five patients underwent surgical bypass of saphenous vein grafting, two of them combining with asprin and one combining with Coumadin. Two patients underwent percutaneous transluminal angioplasty (PTA). The present patient received oral flunarizine (5 mg per day) and aspirin therapy (100 mg per day). Treatments were not mentioned in three patients. There was no death reported in all cases.

Discussion

Previous studies showed that FMD most seriously affected the renal arteries (70%) and less frequently the cerebrovascular arteries (25-30%) [12-16]. Mettiger KL et al. reported that the cases of carotid artery FMD is about half that of renal artery FMD [17]. However, FMD is more common than previously suggested. It was reported in a literature that the prevalence of carotid and vertebral arterial FMD, as assessed by an examined consecutive angiograms study, ranges from 0.3% to 3.2% [16]. Data from the the CORAL trial showed that among 997 patients, 58 patients (5.8%; mean age, 71.8 years; 75.9% female) were incidentally found to have FMD, again illustrating that FMD was underdiagnosis [18]. The United States Registry for Fibromuscular Dysplasia showed that extracranial carotid and vertebral FMD occurred as frequently as renal FMD (renal 79.7% and extracranial cartotid 74.3%, respectively). In the first 200 patients entered into the Registry study, nearly 70% had extracranial cerebrovascular FMD. This finding clarified a common misunderstanding that the renal artery was the most commonly affected vascular bed in FMD patients. It reaffirmed that the most frequent types were renal and cervicocephalic FMD [2, 19, 20]. Actually, FMD could be found throughout every artery of the body. Multivessel involvement in the same patient

was also common. However, cerebrovascular FMD may be asymptomatic or nonspecific (ie, syncope) and serendipitously discovered by physical examination or when imaging was performed for unrelated reasons [14, 17, 21]. Therefore, the prevalence of carotid, vertebral FMD in general population was almost impossible to be determined.

Cerebrovascular FMD has been reported not only in the internal carotid arteries but also in the vertebral arteries. The external carotid artery and intracranial artery (especially the middle cerebral artery) were relatively less affected [2, 22]. The middle and distal portion of the internal carotid arteries were most frequently involved rather than bifurcation in carotid FMD [13, 14, 17]. The majority of internal carotid FMD cases were often bilaterally (60-85%) [16]. Meanwhile, vertebral arteries were less common (7% to 19%) and frequently coexisted with carotid disease [17, 23, 24]. The brachial arteries were the most common involvement of the upper extremity FMD, but the incidence is relatively rare. As with cerebrovascular FMD, the brachial FMD was most commonly an asymptomatic imaging or physical examination finding [6]. The symptoms (ie, paralysis, paresthesia, pain, weakness, or claudication) of brachial FMD were most commonly due to thromboembolic events [25-27]. Sensory disturbance was the most common symptom in these 8 of 11 cases. In the United States Registry study, the main four symptoms of FMD were hypertension, headaches, pulsatile tinnitus, and dizziness. However, dissection, aneurysm, transient ischemic attack, and stroke also occurred with a high frequency of FMD involving the carotid or vertebral arteries.

FMD was increasingly considered to be a systemic vasculopathy with clinical manifestations that extend beyond arterial pathology to include low bone density, joint laxity, and degenerative disease in the spine. Although several of the hypotheses have been proposed, the exact cause of FMD remained unclear. Estrogen was considered associated with FMD. Research has suggested FMD occurred more commonly in women (sex ratio 9:1) might be linked to elastin ratio of the collagen [28-30]. Some argued that tobacco use played an important role in development of FMD [30, 31]. It was known that smoking induced vascular damage, inhibited vascular healing, and suppressed collagen production. Hypertension was presumed as another possible etiology causing, which could make blood vessels tortuous and increase pulsation-induced movement. Some people suggested that FMD had a certain degree of genetic predisposition. Stacey L Poloskey et. al. identified two distinct variants in the TGFβR1 gene in two separate patients (c.611 C>T, p.Thr204Ile and c.1285 T>C, p.Tyr429His), but no pathogenic mutations were identified (TGFβR2, COL3A1, FBN1, ACTA2, or SMAD3) [32]. Recent data have found elevated plasma TGF-1 (P=0.009), TGF-2 (P=0.004) and additional inflammatory markers, and increased TGF-1 (P=0.0009) and TGF-2 (P=0.0001) secretion in dermal fibroblast cell lines from subjects with FMD compared to age- and gender-matched controls [33]. Even so, none of the above factors (genes and circumstances) have been proven.

Based on the predominant site of dysplasia in the arterial wall (intima, media, or adventitia), a pathologic classification of FMD was proposed by Harrison and McCormack in 1971 and modified by Stanley et al. in 1975 [34]. Three typical categories of FMD based on pathological and angiographic characteristics of the renal arteries were identified: intimal, medial, and adventitial fibroplasia [35, 36]. Although the original classification system was made in accordance with the renal artery, it was also used in extrarenal arteries [37]. Medial FMD is the most common type and is further divided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia [35]. However, the diagnosis of Fibromuscular dysplasia almost exclusively depended on image appearance because surgical specimens were rarely available, even though FMD was a pathologic diagnosis. The common noninvasive screening and diagnostic imaging tools included ultrasonography, magnetic resonance angiography and computed tomography angiography. Catheter-based angiography remained the gold standard for diagnosing FMD. Based on the histopathological-angiographic correlation researches, an angiographic classification was proposed: the multifocal type, with multiple stenoses and the 'string-of-beads' appearance; the tubular type, with a long concentric stenosis (≥1 cm); the focal type, with solitary stenosis (<1 cm in length); and the mixed-type stenoses [1, 36, 38, 39]. The multifocal stenoses were com-

monly associated with medial FMD, which behaved as typical "string-of-beads" in imaging. The focal and tubular stenoses were not clearly related to specific pathologic type. In an effort to avoid confusion and awkward phrasing, Savard et al. proposed a binary angiographic classification to discriminate two different clinical phenotypes. In this classification, unifocal FMD included focal or tubular FMD, and multifocal FMD was defined by the presence of multiple stenoses with or without the "string-of-beads" appearance [40]. The contemporary angiographic classification has progressively replaced the traditional histological classification.

For lack of randomized or prospective trials, most of the evidences for FMD treatment still come from case reports, retrospective case series and expert opinions. The most frequent indications for therapy were hypertension, aneurysm, and dissection. There were generally three treatment strategies: medical therapy, endovascular therapy and surgery. In terms of medical therapy, antiplatelet therapy was the mainstay of management of the patients with carotid artery FMD and without associated aneurysms (Class IIa indication) [41]. Although no dosage regimen was recommended, it was acceptable to take asprin from 75 to 325 mg per day in renal, cerebral, or peripheral artery FMD. FMD with stenotic lesions could be treated with graduated intraluminal dilatation, surgical bypass/resection, or PTA [42]. PTA has became the first choice of treatment in patients with operation indication [42-44]. Overall, FMD was usually a benign disease with a good prognosis.

Conclusion

FMD affecting the bilateral brachial artery is an exceedingly rare vasculopathy, whit only 10 reported cases prior to our report. The prevalence of bilateral brachial artery FMD was almost impossible to be determined. We reported the first case of bilateral brachial arterial FMD in China. We reviewed and analyzed all 11 patients' clinical data. Sensory disturbance was the most common symptom (73%) and bruit was the most common physical sign (45%). Our patient was treated successfully with a short-term flunarizine (5 mg per day) and asprin 100 mg per day with no symptoms at 24 months follow-up. It's suggested that asprin was probably an effective drug for preventing ischemic events in brachial arterial FMD patient.

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Disclosure of conflict of interest

None.

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