Progesterone receptor expression in fibromuscular dysplasia: A report of two unusual cases

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ABSTRACT

Fibromuscular dysplasia is rarely biopsied. Progesterone receptor expression in myofibroblastic cells is useful for the histopathological evaluation in difficult-to-diagnose cases. Herein, we report two unusual cases of fibromuscular dysplasia in which progesterone receptor expression was shown in vessel sections.

Keywords: Fibromuscular dysplasia, progesterone receptor, popliteal artery, coronary artery, spontaneous coronary artery dissection.

Fibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic segmental vascular disease which mostly affects renal (58%), extracranial carotid and vertebral (32%) arteries of women aged between 20 and 60 years.[1] Splanchnic, extremity, pulmonary, coronary, and intracranial arteries constitute less commonly involved sites.[1] Although being a rare disease, recent data have revealed that FMD is more common than previously reported. Hendricks et al.[2] investigated FMD prevalence in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial participants and healthy renal donor population. Although FMD was an exclusion criterion in the CORAL trial, 5.8% of the patients showed incidental FMD and 2.3% of the healthy renal donors also demonstrated FMD. Due to the non-specific clinical and histopathological findings or asymptomatic presentation, there is a limited number of data regarding the prevalence of carotid, vertebral, and intracranial disease.[2]

Etiology and pathophysiological mechanisms which cause FMD are still unknown. Interestingly, hormonal factors were proposed to have a role in the etiopathogenesis, although this theory still remains to be confirmed by further studies.[3] Clinical signs and symptoms depend on the vessels which are involved. Renal disease presents with hypertension in most cases, whereas tinnitus, transient ischemic attack, stroke, spontaneous dissection are the most common findings in the carotid/vertebral arteries.[1,3]
A significant proportion of patients (28 to 86%) have multifocal disease. Therefore, definitive diagnosis and search for the involvement of other vascular beds are critical in the management to prevent further complications.

In general, FMD affects small-to-medium-sized arteries, including renal artery in 60 to 75% of the cases. Arteries of the cervicocranial, non-renal visceral (i.e., celiac, mesenteric, hepatic, or splenic), and limb regions constitute 25 to 30%, 9%, and 5% of the FMD cases, respectively. Of note, involvement of pulmonary and coronary arteries is much less common.

The gold standard diagnostic method is catheter-based digital subtraction angiography in all vascular sites. Computed tomography (CT) angiography, magnetic resonance (MR) angiography, and ultrasound (US) can be also used in the diagnosis and surveillance of the patients as non-invasive methods. Typically, vessel segments show dilatations and constrictions in an alternating pattern which form a string-of-beads appearance on angiographic examination. Currently, there are no guidelines for specific treatment and imaging surveillance of FMD patients.

In histopathological examination, the most common alterations are medial fibroplasia (60 to 70%), perimedial fibroplasia (15 to 25%), medial hyperplasia (5 to 15%), intimal fibroplasia (<10%), and adventitial/periartherial fibroplasia (<1%).

Previously, in 1970s, FMD classification was based on the involved arterial layer (i.e., intimal, medial, and adventitial). This classification has become difficult to apply due to the advances in radiographic and endovascular methods, resulting in less need for histopathological examination. Yet, the histopathological classification system shifted to a radiographic classification which was proposed by Belgian and French Consensus and American Heart Association in 2012 and 2014, respectively.

However, due to the multiple factors such as rarity, unknown etiology, and non-specific histopathological, radiological and clinical findings, FMD is usually misdiagnosed as atherosclerosis or sporadic spontaneous vascular lesion of unknown origin, unless fatal complications occur. Biopsy material is obtained infrequently and, thus, defining and understanding the histopathological characteristics of FMD still remain limited. Also, accompanying vascular complications (i.e., dissection, intramural hematoma, aneurysm, arteriovenous fistula, thrombosis, and infarction) and involvement of uncommon sites with unusual clinical presentations make the diagnosis of FMD more complicated.

Therefore, ancillary studies may be useful to elucidate accurate diagnosis. In a recent study of Silhol et al., nuclear PR positivity was observed in medial smooth muscle cells in all five cases. In accordance with this finding, herein, we present two unusual FMD cases in whom we performed immunohistochemical progesterone receptor (PR) staining and confirmed nuclear positivity in myofibroblasts and smooth muscle cells of the arterial wall.

**Figure 1.** (a, b) Tissue causing obstruction in popliteal artery. Nodular proliferation of disorganized fibroblasts and smooth muscle cells along with increased fibromyxoid connective tissue matrix. (H-E×40). (c, d) Masson Trichrome stain showed that proliferation is mostly composed of collagen fibers; accompanying relatively decreased and disorganized smooth muscle cells (Masson Trichrome, ×100, ×40). (e) Elastic fibers discontinued in fibroblastic intimal layer (Weigert Van Gieson, ×200). (f) Disorganization, splitting and destruction of elastic fibers through fibroblastic intima and superficial media layers (arrow) (Weigert Van Gieson, ×40). (g) There is no staining in non-pathological vascular segment as a negative control tissue (IHC, 40XPR). (h) Nuclear PR positivity in cells of the tissue obstructing the vascular lumen (IHC, 200XPR).
CASE REPORT

Case 1- A 49-year-old female patient presented with leg pain which was aggravated by physical exertion for two weeks. Her medical history revealed no smoking history ever and similar symptoms during her pregnancy 20 years ago. She was hypertensive for 26 years without any renal complications. She was gravida 2, para 2, and her gynecologic history revealed premature menopause at the age of 30. The underlying reason for menopause was unable to be identified and she was on hormone replacement therapy for about 20 years. As there was no evidence of thrombotic events or any recurrent missed miscarriage, antiphospholipid syndrome was ruled out. A few relatives of her maternal lineage had recurrent vascular disease in lower extremity which were not further specified. Computed tomography angiography and Doppler US revealed thickening of the popliteal artery wall extending through the femoral artery. Endarterectomy procedure was scheduled. A written informed consent was obtained from the patient.

Figure 2. (a) Dissection through thickened arterial vessel wall, organized hemorrhage, irregularity in elastic lamina (arrow) (H-E×100). (b) Dissected intimal layer (asterix), intimal hyperplasia with fibroblastic/myofibroblastic cells and increased connective tissue matrix (H-E×100). (c) Fibroplasia encompassing both intima and media; discontinuation of elastic lamina (arrow) (H-E×200). (d) Increased collagen fibers with relatively diminished smooth muscle cells (Masson Trichrome, ×100). (e) Destruction, splitting and partial loss of elastic fibers (Weigert Van Gieson, ×100). (f) Nuclear PR positivity in smooth muscle cells and myofibroblastic cells within fibroblastic areas in intima and media of pathological vascular segment (IHC, 200XPR). (g) Angiography: Dissection of circumflex artery.
Endarterectomy material consisted of two vessel segments which were 8.5 cm and 5.5 cm in length with 0.5 cm and 0.1 cm in thickness, respectively. The vessel walls were observed as white, fibrillary, and elastic consistency. The soft, brown, and hemorrhagic tissue fragments also accompanied the specimen.

In light microscopy, fibromuscular proliferation composed of disoriented smooth muscle cells along with abundant fibroplasia was seen in intimal and medial layers. Hypertrophic muscle cells and fibroplasia were observed to be responsible for the vascular obstruction in the popliteal artery. Disoriented hypertrophic smooth muscle cells were demonstrated by Desmin immunostaining, whereas fibroplasia was displayed by the Masson’s trichrome staining. In the Weigert Van Gieson, destruction (i.e., discontinuation, splitting and loss) of elastic fibers in the internal elastic lamina was evident. Nuclear PR positivity was detected only in smooth muscle cells and myofibroblastic cells, while adjacent non-involved segments were negative (Figure 1). Histopathological and immunohistochemical diagnosis was reported as FMD. The patient was referred to the cardiology outpatient clinic and was prescribed antihypertensive medication and no further vascular study was scheduled for the investigation of other vascular sites.

Case 2- A 31-year-old female patient was admitted to the emergency department with acute-onset chest pain. She was nulliparous with no known hormone dysfunction and/or intake. Also, she did not have a history of other vascular or hypertension-related renal diseases. Her family history revealed myocardial infarction in her mother at the age of 44; however, the underlying condition was not further searched. Clinical findings of the patient were consistent with acute coronary syndrome. Coronary angiography revealed dissection of the circumflex artery, and coronary artery bypass grafting was indicated. A written informed consent was obtained from the patient.

Dissecting segment of the vessel was explored. The circumflex artery was so fibrotic to be grafted and by pass grafting was performed with the left mammary artery to the left anterior descending coronary artery. Macroscopic materials were composed of irregular, white, and hemorrhagic vessel fragments measuring 1.6x1.4x0.7 cm in size. Histopathological examination demonstrated hemorrhage and granulation tissue formation secondary to the intimal rupture. Dissection through both intima and media layers was remarkable. In addition, some parts of the media were found to be hypertrophic with an accompanying interstitial fibrosis and fibromyxoid matrix deposition. Internal elastic lamina was also disrupted and discontinuous using the Weigert-van Gieson’s stain. Nuclear PR positivity was demonstrable in the lesion. Histopathological and immunohistochemical diagnosis was reported as FMD (Figure 2). The patient was consulted to the cardiology outpatient clinic and was given anticoagulant therapy. A systemic angiographic study of the other vascular sites was not conducted.

DISCUSSION

Fibromuscular dysplasia is a rare non-atherosclerotic arterial disease, particularly affecting women with renal artery involvement. It is an idiopathic event caused by the hypertrophy of fibrous and muscular elements of the arterial media and adventitia, leading to stenosis. It is thought to be related to aneurysms, as well as spontaneous arterial dissection. Although cases were reported in the early literature which can be attributed to FMD, it was 1960s that arteriographic and clinical manifestations were well-recognized. A few years later, pathological and radiographic correlation was also described. However, despite all the efforts to identify the prevalence, etiology, pathological mechanism, and histopathological findings and to establish a uniform classification system, there are still so many obscurities about this entity, including its management and surveillance.

Histopathological alterations of FMD are the aberrations of the normal histological structures which may easily be obscured by its various complications, such as dissection, rupture, aneurysm, intramural hematoma, thrombosis, and infarction. Furthermore, similar histopathological changes may be seen secondary to underlying conditions, such as hypertension and genetic collagen disorders to some extent. Therefore, objective ancillary tests besides well-known histopathological features would be very useful in the differential diagnosis.

Although genetic, hormonal, environmental, mechanical, and ischemic factors have been hypothesized in the etiopathogenesis, none of them has been clearly proven yet. It has long been known that estrogen alpha-beta, progesterone and androgen receptors are expressed by vascular smooth muscle cells and intimal myofibroblasts. Furthermore, it has been well-documented that abdominal aortic aneurysms and atherosclerosis affect males much more frequently than females, as estrogen alpha and beta receptors, and their messenger ribonucleic acid (mRNA) are upregulated.
in female arterial myocytes and myofibroblasts in contrary to male arterial myocytes and myofibroblasts in which androgen receptors and mRNA are upregulated. Apart from the investigations related to the etiopathogenesis of atherosclerosis and aortic aneurysms, concerning the role of sex hormone receptors in vascular diseases, recently nuclear PR positivity, has been shown in smooth muscle cells of media layer in five patients with renal FMD. Except for this pivotal study conducted by Silhol et al., there are no studies investigating hormonal receptor status in the affected vessels of FMD cases in the literature. In our report, we present two cases in which the histopathological diagnosis was drastic due to the involvement of relatively uncommon vascular sites and the lack of the typical strings-of-bead pattern on angiography. We further searched for the presence of nuclear PR positivity and able to make a comparison between the involved and non-involved segments of the vessel walls. Case 1 presented with symptoms of lower extremity vascular obstruction. She had no history of thrombosis and/or loss of pregnancy, which are the hallmarks of antiphospholipid syndrome. Lower extremity arterial obstructions are known to be mainly caused by intrinsic vascular factors such as atherosclerosis, cystic adventitial disease, fibromuscular dysplasia, Buerger’s disease, vasculitis, and idiopathic mid-aortic syndrome. The presented case did not show any histopathological feature which can be attributed to atherosclerosis, such as intimal thickening with lipid pools and smooth muscle cells or fibroatheroma plaque. Also, there was no vascular inflammation suggesting vasculitis. Similarly, Buerger’s disease presents with thrombus formation in different stages which are not relevant with the current findings. In contrast to the histopathological findings in our case, cystic medial necrosis is characterized by the accumulation of basophilic material in the medial layer of the vessel wall and can be associated with connective tissue disorders. Mid-aortic syndrome is reported to affect pediatric population, particularly, and is frequently accompanied by ostial stenosis of its branches.

Besides intrinsic factors, non-vascular causes such as popliteal artery entrapment syndrome and endofibrosis of iliac artery which are mainly seen in healthy young men, are reported to cause obstruction in the lower extremity vessels. Our case which contained medial and adventitial histopathological changes, however, was not consistent with neither of these entities.

To the best of our knowledge, only eight cases have been reported as popliteal artery obstruction caused by FMD, to date. In addition to the popliteal involvement, overall 25 FMD cases were reported through case reports or small case series involving iliac, femoral, tibial, and peroneal arteries in the lower extremity. In this report, the presented case (Case 1) is the first FMD case of popliteal artery obstruction in which nuclear PR positivity was demonstrated in myocytes and myofibroblasts of the hypertrophic segment. According to her medical history, the patient first experienced lower extremity vascular obstruction symptoms, when she was pregnant and she had a history of hormone intake for 20 years which are consistent with the studies suggesting the relationship between FMD and hormonal alterations.

The patient was also hypertensive for 26 years without any history of renal disease. However, due to the lack of advanced radiological studies such as CT or MR angiography, we cannot exclude an undetected renal involvement of FMD. The patient also described a vascular disease history in her relatives of her maternal lineage. All these findings may suggest genetic and hormonal factors as a possible etiopathogenetic mechanism in this particular FMD case.

Recent data have demonstrated that there is a potential causal relationship between FMD and spontaneous coronary artery dissection. Spontaneous coronary artery dissection in young women is not common in the literature with only less than 800 cases to date. In the reported cases, coronary FMD was mostly detected in three major sites: 1-major epicardial and subepicardial coronary arteries, 2-cardiac conduction system vascular supply and their branches, and 3-intramural small vessel arteries. Major branches or ostia of coronary artery with chest pain has been rarely reported in the literature. In this report, Case 2 is unique due to her clinical presentation, involvement of the circumflex artery, and additional PR positivity demonstrated in the dissecting part of the vessel wall with negative adjacent normal arterial segment. The patient had none of the predisposing factors for FMD including exogenous hormonal intake or any other hormonal dysfunction. Of note, as described in the first case, histopathological findings were not consistent with atherosclerosis.

In conclusion, since fibromuscular dysplasia involves coronary and popliteal arteries very rarely and basic histopathological changes are often non-specific and frequently obscured by complications, progesterone receptor positivity may
be helpful for the accurate diagnosis of this rare entity in such complicated cases. However, there are no sufficient data to suggest that negative progesterone staining would exclude fibromuscular dysplasia. Instead, its positivity may support diagnosis in these conflicting and complicated cases. Nonetheless, we believe that further researches would shed light in the diagnostic significance of progesterone receptor status in fibromuscular dysplasia cases.

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