# Coronary fibromuscular dysplasia: a rare cause of familial acute coronary syndrome

## Case report and review of the literature

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## Summary

In this review we describe an unusual case report of familial fibromuscular dysplasia with involvement of coronary arteries which manifested as two distinct types of acute coronary syndrome. This case report allows us the opportunity to discuss the distinct forms of presentation of this rare disease, i.e., when there is an involvement of the coronary arteries, and highlighting pathophysiological, diagnostic and therapeutic issues. It underlines the potential role of genetic predisposition to this condition and discusses the role of vascular screening of the patients with suspected non-atherosclerotic coronary artery disease.

*Key words: Coronary fibromuscular dysplasia; acute coronary syndrome; spontaneous coronary artery dissection.*

## Case description

A 53-year-old Dominican female with a history of hypertension, dyslipidaemia and positive family history for cardiovascular diseases was admitted to our hospital due to intermittent typical chest pain associated with transient ST elevation in $V_2$–$V_5$ on ECG. Emergency coronary angiography revealed dissection of the left anterior descending artery (LAD) extending from proximal to distal segments with otherwise normal coronary arteries (fig. 1A, 1B). Due to the extent of the lesion and spontaneous regression of symptoms a conservative approach was initially chosen. The following days, however, the patient experienced further chest pain episodes with ST elevation and flow obstruction was detected at follow-up angiography (fig. 1C), so that percutaneous coronary angioplasty with positioning of the five drug-eluting stents was successfully performed (fig. 1D). Selective renal angiography showed mild left renal artery wall alterations compatible with fibromuscular dysplasia (FMD) (fig. 2). The post-procedural period remained uneventful. The standard pharmacological treatment consisted of dual antiplatelet therapy with as-pirin and clopidogrel, beta-blocker, statin and titration of the antihypertensive therapy with ACEI, and calcium antagonist. Owing to the rarity of the cause of acute coronary syndrome in our patient, we reviewed the family history, and the medical recordings of the relatives of the patient. In fact, a sister of our patient experienced non-ST elevation myocardial infarction at the age of 46 and coronary angiography demonstrated the typical aspect of "string of beads" of the LAD with normal circumflex and the right coronary artery. These findings were compatible with fibromuscular dysplasia. Selective renal angiography performed during the same procedure revealed the typical aspect of FMD in the right renal artery. The case was managed conservatively and the patient remained asymptomatic up to eight years after the index event. The clinical case of the sister of our patient has been already described by our group as the case of acute coronary syndrome associated with FMD [1]. Moreover, we discovered that the aunt of our patient died at the age of 50 following acute myocardial infarction and the cousin (daughter of the aunt) experienced sudden cardiac death at the age of 28. We hypothesised, that we are facing an unusual form of familial FMD with involvement of the coronary

**Abbreviations**

| | |
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| FMD | fibromuscular dysplasia |
| IVUS | intravascular ultrasound |
| LAD | left anterior descending artery |
| OCT | optical coherence tomography |
| SCAD | spontaneous coronary artery dissection |

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**Figure 1**
**A** showing the dissection of LAD from proximal to distal segments (arrows). **A** and **B** showing the absence of arteriosclerotic lesions in RCx and RCA. **C** demonstrates the flow obstruction after 2 days of conservative treatment (arrows). **D** describes the final result after LAD stenting with five drug-eluting stents.
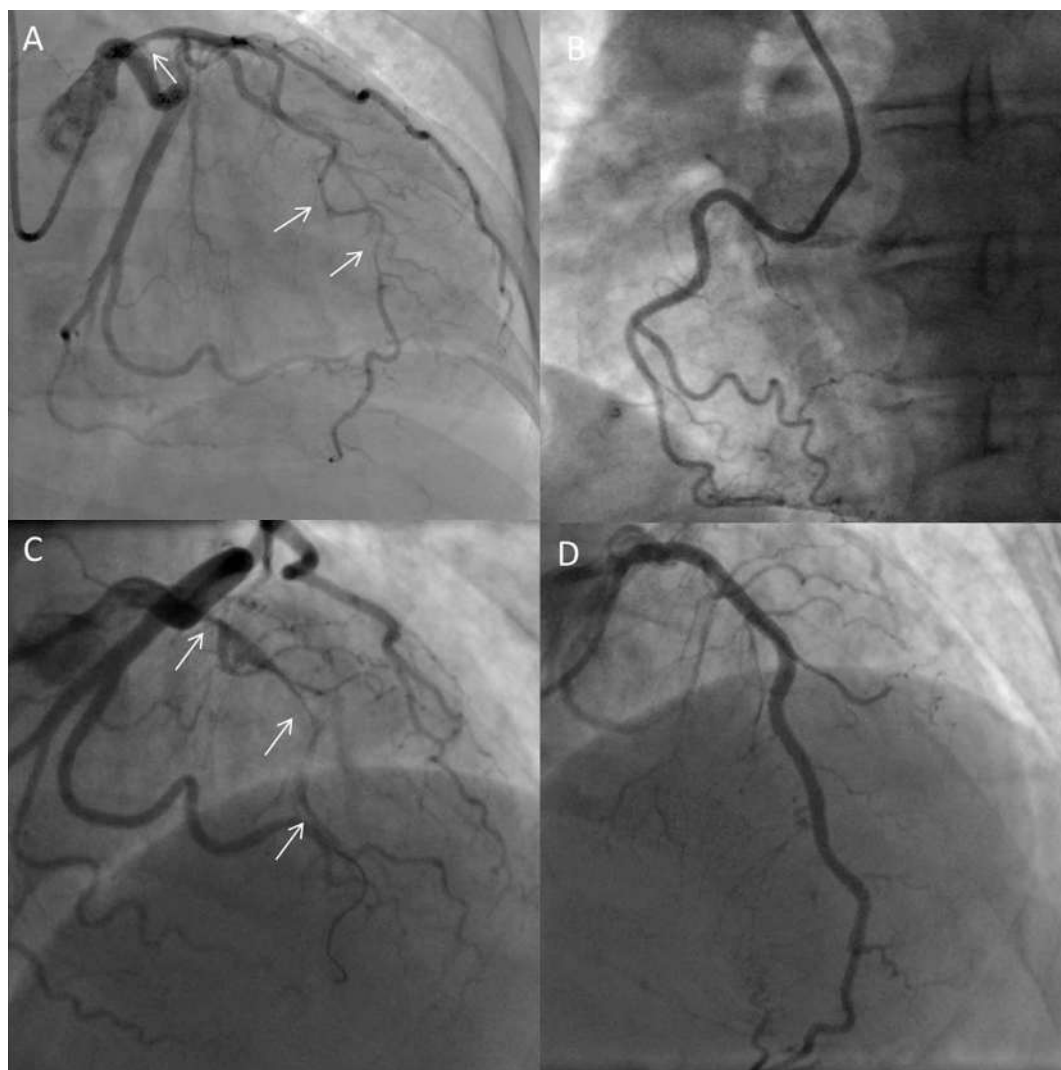


arteries and renal arteries which could predispose this family to acute coronary syndrome.

## Introduction

FMD is a non-atherosclerotic, non-inflammatory vascular disease that has been reported in different arterial beds, most commonly in renal and extracranial carotid and vertebral arteries [2–5] and may lead to stenosis, aneurysm, dissection, and/or occlusion of arteries [2]. It was first described in 1938 by Leadbetter and Burkland [6], and classified as pathological entity by Harrison and McCormick in 1971 [7]. Most epidemiological data of this pathology are based on the description of renal and cerebrovascular involvement.

FMD is characterised by a fibrous or fibromuscular thickening of the vessel wall affecting, medial, intimal, and adventitial layers at varying degrees [7]. Kincaid et al. described angiographic features in 125 patients with renal FMD, including 60 patients from whom also a histological specimen was obtained [8]. They pro-

posed an angiographic classification of FMD into four types. The multifocal type, with multiple stenoses and the 'string-of-beads' appearance, was present in 62% of cases; the tubular type, with a long concentric stenosis was present in 14% of cases. The appearance of beading is due to alternating areas of stenosis and poststenotic dilatation. The focal type, with solitary stenosis less than 1 cm in length, was present in 9 cases 7%; and 17% of patients had mixed-type stenoses. Thus, according to this and other studies the most common type of FMD is medial fibroplasia, which corresponds to the angiographic type of string of beads [2, 9].

The cause of FMD is unknown. A number of theories have been proposed, including environmental factors, such as smoking, estrogens, mechanical factors such as micro-traumata due to renal mobility, as well as genetic factors [10, 11]. The predominance of female sex among patients with FMD suggests that exposure to endogenous or exogenous oestrogens may predispose to the condition [10, 11]. Approximately 11% of patients with FMD have an affected family member according

**Figure 2**
Demonstrates mild abnormalities of left renal artery on selective renal angiogram compatible with FMD (arrows).

to the analysis of Pannier-Moreau et al. [12], and the occurrence of renal FMD in identical twins further suggests the possibility of inheritability in the subgroup of patients [13].

The prevalence of FMD in the general population is not well known. The studies that documented the FMD of renal arteries in kidney donors reported the prevalence of 3.8% to 6.6% [14–16]. The number of reported cases of carotid artery FMD is about half that of renal artery [17]. It is either diagnosed accidentally during the imaging for other causes or based on the specific symptoms. In the largest to date registry for FMD involving 447 patients, carotid or vertebral artery dissection was a presenting manifestation in 12.1% of patients, and other cerebrovascular events, including hemispheric transient ischaemic attack (8.7%), stroke (6.9%), or amaurosis fugax (5.2%), were initial clinical manifestations of FMD in a significant percentage of patients. Chest pain or shortness of breath was reported as a presenting symptom in 16.1% of patients, and myocardial infarction was reported as a presenting clinical syndrome in 1.8% [18].

The commonly accepted gold standard for diagnosing FMD is intra-arterial angiogram with digital subtraction. Stenosis quantification is, however, frequently difficult in medial FMD with the "string of beads" appearance because multiple web-like defects are often present in patients with FMD, contributing to clinically significant stenosis that may not be apparent on angiography. Other imaging modalities such as

computed tomographic angiography and gadolinium-enhanced magnetic resonance angiography have the advantages of being non-invasive techniques and demonstrate good specificity. However, due to the lower spatial resolution comparing with standard angiography the mild abnormalities of the arteries could often be missed. In fact, the sensitivity results are quite disappointing according to Vasbinger et al. [19].

Histopathologic confirmation of the diagnosis of FMD is usually rarely available. In the majority of patients, diagnosis is based on angiographic or noninvasive imaging and classification of disease according to previously published histopathologic-angiographic correlates [7, 8]. In the absence of tissue diagnosis, imaging of other vascular beds by other diagnostic means is frequently instructive.

## Coronary FMD

The coronary artery FMD has been rarely reported in the literature. Lüscher et al. in a series of 92 patients affected with fibromuscular hyperplasia described the coronary involvement in two patients [20]. It was first described ante-mortem by angiography in 2005 by Pate et al. [21]. He proposed that the typical appearance of well-demarcated abrupt transition to diffuse obliterative disease in the middle or distal segment of LAD in seven peri-menopausal women represent the clinical entity of coronary FMD [21]. Before that several post-mortem case reports described the sudden cardiac death case related to coronary FMD [22–25]. A retrospective postmortem study reviewing a 30 year experience in a single pathology laboratory found nine cases of essential hypertension with FMD of small coronary arteries in 1000 cases of sudden cardiac death [26]. All nine cases had focal FMD involving small arteries, either the atrioventricular nodal artery or the sinoatrial artery. Focal FMD in these arteries was typically less than a few millimetres in length and was not likely to be visible on angiography.

Huizar et al. described three cases of myocardial infarction in middle age women due to the significant mid-to-distal diffuse stenosis of the LAD related to FMD [27]. Remarkably, all three patients had nearly identical anterior ST-elevation myocardial infarction, despite the fact that none of the lesions were totally occlusive at the time of cardiac catheterisation. The authors speculate, that that these lesions were possibly spontaneous dissections without an intimal flap, and could have been diagnosed if intravascular ultrasound had been performed. As FMD is well known to cause dissection of the carotid, visceral and renal arteries, probably due to changes in the underlying structure of the arteries, it seems reasonable that coronary dissection without intimal flap or intramural haematoma, despite the absence of the typical angiographic evidence, is the most likely pathophysiologic mechanism

underlying the acute myocardial infarction in these patients.

## Spontaneous coronary artery dissection as the complication of coronary FMD

Recent studies indicate spontaneous coronary artery dissection (SCAD) as a possible complication of coronary FMD in a subgroup of patients. SCAD accounts for 0.2% of all acute coronary syndromes according to the registry reported by Mortensen et al. [28]. Toggweiler et al. report the prevalence of 0.7% of all acute coronary syndromes at their institution [29]. It occurs typically in younger women with otherwise low cardiovascular risk [30, 31]. Normally, the definition of SCAD excludes the patients with atherosclerotic coronary artery disease as in this case the dissection may be the manifestation of plaque rupture. Coronary FMD is a newly recognised risk factor which could predispose to coronary dissection together with previously described triggers such as intense physical stress in men, post-partum period for women and connective tissue disorders [32].

According to Saw et al. with the largest described series of patients affected by SCAD screened for FMD, the co-existence of these two clinical entities is too prevalent to be coincidental. Formerly, this group elegantly described the series of six patients with SCAD in whom concomitant FMD in other vascular beds was diagnosed [33]. Recently, the authors published a study where they reported, that out of 50 patients with SCAD 86% had FMD in ≥1 noncoronary territory, such as renal (58.1%), iliac (48.8%) and cerebrovascular (14%) [30]. Another study by Toggweiler et al. in a small series involving 12 patients revealed renal artery abnormalities in 25% of patients with SCAD [29]. The lower prevalence of FMD in this series could be explained by difference in the diagnostic imaging modality employed to rule out the pathology. In fact, in the study of Toggweiler et al. the MR angiography was used as a diagnostic tool whereas in the study by Saw et al. most patients underwent angiography which has higher spatial resolution and capability to detect even mild wall abnormalities. The study by Tweet et al. reported the prevalence of iliac artery FMD of 50% out of 16 femoral angiograms performed before device closure in subgroup of patients with SCAD [32]. Even though, in these studies none of the patients presented the typical angiographical pattern of "string of beads" which is associated with advanced FMD in peripheral arteries, it is well recognised that angiographic findings can be subtle or even absent [34, 35]. The data described above suggest that vascular screening for FMD in all young female patients with SCAD should be strongly considered and that SCAD should be considered in the differential diagnosis of chest pain occurring in patients with known FMD.

## Diagnosis

In case of acute coronary syndrome related to coronary FMD additional vascular imaging modalities on top of coronary angiography could be helpful to establish the correct diagnosis and guide the therapy. Coronary FMD appearance is often subtle and could be underdiagnosed or misdiagnosed with atherosclerotic lesions in case of less typical angiographic presentation. Even in case of the typical "string of beads" angiographic aspect, the intramural haematoma or dissection without intimal flap could be missed. In the series of Saw et al. three patients out of six with SCAD had an angiographic appearance readily mistaken for atherosclerotic coronary artery disease [33]. This underscores the need to maintain the high index of suspicion in relevant clinical situations and, when appropriate, consider adjunctive imaging modalities such as intracoronary imaging with optical coherence tomography (OCT) and intravascular ultrasound (IVUS). These advanced imaging techniques could help both to determine the extent of vessel wall abnormalities (which may be underappreciated at angiography), to provide real-time guidance of interventional strategy and detect the complications [32, 36, 37]. Indeed, the first prospective study by Alfonso et al. has demonstrated the role of OCT in diagnosing/ruling out SCAD in patients with angiographically/clinically suspected pattern [38]. Moreover, it helped to define the typical double lumen morphology, the extension of the disease and to guide the revascularisation intervention, when necessary. However, one should be aware of the potential complications of this invasive technique related to propagation of dissection due to the vessel injury, that limit its routine use in suspected cases. Modernisation of the current OCT systems could help to overcome these limitations in the future.

## Treatment strategies

The optimal treatment strategy in the setting of acute coronary syndrome related to coronary FMD remains undetermined. In case of SCAD the conservative strategy is a good option for the patients without recurrent chest pain, with the dissection of the distal segments and with normal flow in the affected artery. Spontaneous resolution of SCAD during the follow-up angiography has been documented [32]. Revascularisation therapy is usually reserved for the patients with ongoing chest pain, proximal dissection with impaired blood flow as in our patient or in case of haemodynamic instability [39]. Canulation of the false lumen and coronary perforation/occlusion are described as the potential complications of the attempted intervention [39]. In the study of Tweet et al. PCI strategy was associated with elevated rates of failure due to technical aspects of the procedure and propagation of the dissection [32].

Moreover, in this series of patients, 7 of 87 patients underwent coronary bypass grafting as an initial strategy. Even taking into the account the small sample size, however, it should be emphasised that the high rate of late bypass graft occlusion demonstrated in this study suggests that bypass surgery may not provide long-term protection against the effects of recurrent native coronary artery dissection [32]. There is poor literature regarding the management in case of stenotic lesions related to coronary FMD.

## Prognosis

Long term outcome of coronary FMD, is generally good, however, recurrent dissection may occur [31]. The study by Tweet et al. reports the occurrence of repeat SCAD in 17% of the study population during long-term follow-up [32]. Thus, because FMD is a progressive disease, the close monitoring by cardiovascular specialists is strongly recommended [31].

## Screening strategies

Although it is quite obvious that not all SCAD patients have coronary FMD, it is however important to exclude FMD, last but not least, since involvement of other vascular territories may have long-term consequences. There are no accepted screening strategies for detection of FMD in the patients with suspected coronary involvement. The group of Saw et al. from the tertiary referral care centre for SCAD from the Vancouver General Hospital, however, routinely perform nonselective abdominal angiogram on digital subtraction (for renal and iliac) and head computed tomographic angiography in patients with suspected coronary FMD [33].

## Conclusions

We have described for the first time to the best of our knowledge the familial case of acute coronary syndrome related to coronary FMD with two distinct presentations: one due to the spontaneous dissection of LAD and another probably due to local dissection without flap or intramural haematoma in an affected LAD with typical angiographic aspect of FMD. This underlies the importance of family history and probable genetic predisposition to this pathology at least in a subgroup of patients. It strengthens even more the hypothesis that genetically determined FMD predisposes to the coronary pathology with increased risk of acute coronary syndrome. Additional coronary imaging such as IVUS and OCT should be considered in the setting of atypical angiographical presentation of acute coronary syndrome in order to clarify the nature of the lesion, increase the awareness of the problem as well as optimise the treatment strategies. Moreover, vascular screening for FMD in other vascular beds should be considered in highly suspicious cases as it is already routinely performed in referral centres with expertise in SCAD. Further studies are needed to fill the gaps in treatment strategies, prognosis and eventual need of family screening in case of this non-classical manifestation of acute coronary syndrome.

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