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Case Report

Fibromuscular Dysplasia: An Important Vasculitic Mimic

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Abstract

Fibromuscular Dysplasia (FMD) is uncommon and can often be misdiagnosed for vasculitis. We present 7 FMD patients who presented to our centre between 2016-2018. The mean age was 49-years and the majority were female but were atypical for FMD given that they did not smoke nor did they have hypertension. Vasculitis was the initial diagnosis in 75% of non-cardiac related cases, and was diagnosed later on average 5.3months after initial symptom-onset compared with 8.6days where vasculitis was not considered. This article emphasises the need to consider FMD as a potential diagnosis particularly in patients suspected of having medium or large vessel vasculitis.

INTRODUCTION

Fibromuscular Dysplasia (FMD) is an uncommon vascular condition with the potential to affect any arterial bed. It has a prevalence of up to 7% in the general population, and typically presents in females (90%) at an average age of 52 years [1]. FMD can have wide variety of vascular manifestations including stenosis, aneurysm, dissection, occlusions and arterial tortuosity and thus has often been termed a *pseudovasculitis* [1]. Unsurprisingly, diagnosing FMD can be difficult given that it requires a high index of suspicion. The aim of this report is to describe the potential manifestations of FMD and compare this with alternative diagnoses in seven patients that attended our tertiary hospital.

CASE REPORT

This was a retrospective audit of patients who attended the Princess Alexandra Hospital in Brisbane, Australia between 2016-2018. FMD was diagnosed based on the presence of at least 1 dysplastic stenosis. Seven patients were identified, the majority of whom were female (86%), did not previously smoke (71%) and did not have a history of hypertension (57%). The mean patient age was 49 +/- 9.69 years. The most common initial presentation was chest pain (43%), however, there were a wide variety of other clinical presentations.

The most common radiological feature that suggested FMD was an irregularity of the affected arteries (Figure 1). All our patients had FMD manifesting in multiple vessels and 86% in multiple arterial beds on diagnosis. 57% of patients had arterial dissections, but none had detectable aneurysms. Renal involvement was the most common site accounting for over 70% of cases. Renal FMD was also the most common cause of bilateral arterial disease, followed by extracranial internal carotid (eICA) and vertebral involvement respectively.

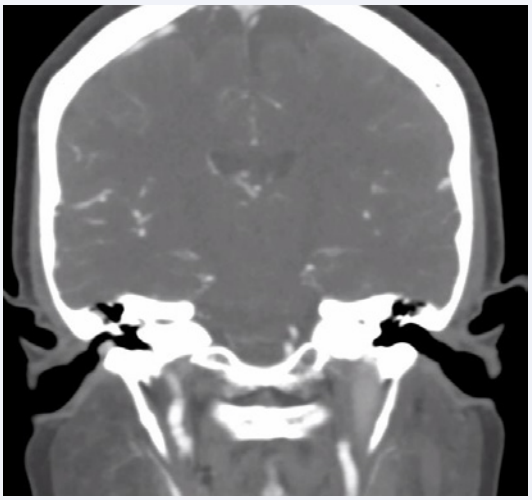

Figure 1 Right common carotid arterial irregularity on CTA (arrow).

Of note, vasculitis was suspected as the underlying cause in 75% (3 cases) of the 4 non-cardiac related cases. This resulted in longer diagnostic delays with a mean of 5.3 months in patients initially suspected of having vasculitis compared with a mean of 8.6 days in those who were not. Of the three cases suspected of vasculitis, a CT/PET was performed in 67% cases, in which one patient demonstrated a non-specific low-grade avidity involving the descending aorta and common iliac arteries.

DISCUSSION

Despite our small series size, our experience highlights the importance of considering alternative differentials of large vessel vasculitis, particularly given the marked delay in diagnosing FMD in patients presenting with features suggestive of vasculitis.

FMD is an idiopathic non-atherosclerotic and non-inflammatory vascular disorder and is typically diagnosed based upon radiological findings [2]. The gold standard for identification of FMD is catheter-based angiography, however this has been replaced by non-invasive imaging due to its wider availability and lower radiation risk. At present CTA is recommended to be the imaging modality of choice by the European expert consensus because of high spatial resolutions, ability to distinguish between atherosclerotic plaques versus FMD lesions and shorter scan times [3]. The characteristic CTA findings include arterial irregularities or a "beading" appearance, focal stenosis, dissections and aneurysms. FMD can present in any vessel, however it most commonly involves the renal, eICA and vertebral arteries in a corresponding descending order of frequency [4]. FMD has a high prevalence of multi-vessel involvement in up to 66% patients in literature and was present in all of our patients [2]. Meanwhile, bilateral disease is common in FMD patients, with 41% having at least bilateral renal artery stenosis and 37% having either bilateral carotid or vertebral artery involvement [2]. Our series confirmed a considerable proportion of FMD patients had bilateral involvement and supports the recommendation to strongly consider FMD as a potential diagnosis in these patients.

Despite our small series size, several parallels can be drawn between our patients and the larger known registries. Our patients had a similar mean age and rates of female predisposition compared with the US FMD Registry at 52 years and 91% respectively [4]. However, our study reported lower rates of smoking history and hypertension in contrast with the registry at 37% and 64% respectively [4]. There were similar rates of renal arterial involvement but higher rates of cervico-cephalic arterial manifestations in our study in relation to those in the ARCADIA Registry (70% *vs* 76.6%) and (42% *vs* 23.4%) respectively [5]. Nevertheless, our results highlight the marked delay in diagnosing FMD in patients presenting with features suggestive of vasculitis. In this discussion, we will therefore explore the clinical and radiological features that suggest the possibility of FMD, as well as discuss the key features of the main differential diagnoses of FMD.

FMD is an idiopathic non-atherosclerotic and non-inflammatory vascular disorder with a broad degree of vascular manifestations [4]. FMD occurs due to either medial wall hyperplasia or fibroplasia of any of the three arterial wall layers. There are many proposed pathogenic factors for FMD, including genetics, oestrogen, smoking, mechanical stress and coagulation disorders [4]. FMD can present in any vessel, however it most commonly involves the renal, eICA and vertebral arteries in a corresponding descending order of frequency [6].

FMD commonly presents as a dysplastic arterial stenosis, but dissections and aneurysms are frequently present in 25.7% and 21.7% of patients respectively [7]. Dissections in FMD are most commonly found in the eICA followed by the vertebral and renal arteries [8]. Patients with dissections tend to be younger and are more likely to be male - in our series, the youngest patient was a 40 year-old male (patient 3), whereas the 3 females were aged 44, 54 and 65 (patients 1,2 and 7) [6]. Our results reflect a general recommendation that FMD should always be considered in the presence of either a spontaneous arterial dissection or stroke in young/middle-aged women; or mesenteric or renal artery dissection in men of any age.

FMD has a high prevalence of multi-vessel involvement in up to 66% patients in literature and was present in all of our patients [5]. Meanwhile, bilateral disease is common in FMD patients, with 41% having at least bilateral renal artery stenosis and 37% having either bilateral carotid or vertebral artery involvement [5]. Bilateral FMD disease is so common that it has been suggested to be the cause in up to 50% patients with bilateral carotid artery dissections [5]. However, the exact prevalence of different arterial territories amongst FMD patients with dissections is unclear. Our series confirmed a considerable proportion of FMD patients had bilateral involvement and supports the recommendation to strongly consider FMD as a potential diagnosis in these patients.

The most frequently reported symptoms in FMD include hypertension (63.8% of cases), headache (52.4%) and pulsatile tinnitus (27.5%). However, as demonstrated in this case series symptoms such as chest and abdominal pain strongly suggest dissections [1]. Given the non-specific nature of presentation, FMD can be difficult to diagnose with a mean delay time between the initial onset of hypertension and FMD diagnosis of up to 9 years [9]. However as seen in this series, hypertension is not always present, which may lead to a diagnostic delay when clinicians exclude FMD based on normotension.

FMD is typically diagnosed based upon radiological findings. The gold standard for identification of FMD is catheter-based angiography, however this has been replaced by non-invasive imaging due to its wider availability and lower radiation risk. DUS is often the most convenient scan to perform and can typically reveal increased peak systolic velocities in the mid to distal portions of the affected arteries despite an absence of atherosclerosis [2]. The PPV of DUS for diagnosing FMD in the carotid and renal arteries are high at 87.7% and 94.2% respectively [10]. Given the low NPV of 62%, routine DUS would not be an appropriate test for screening for FMD [11].

Therefore, at present CTA is recommended to be the imaging modality of choice by the European expert consensus because of high spatial resolutions, ability to distinguish between atherosclerotic plaques versus FMD lesions and shorter scan times [12]. The characteristic CTA findings include arterial irregularities or a "beading" appearance, focal stenosis, dissections and aneurysms. However, it can be less sensitive than catheter-based angiography for detecting subtle changes [10].

MRA with gadolinium is an alternative imaging modality which also has a high sensitivity of 97% and specificity of 93% compared with catheter-based angiography for diagnosing renal FMD [13]. However, whilst MRA with gadolinium can identify dissection or aneurysms, it may lead to "false-positive" results because of motion artefact. In contrast, the sensitivity and specificity of MRA in detecting extra-renal FMD manifestations is unknown due to limited studies.

The main differential diagnoses for large and medium-vessel pathology include vasculitis. Some cases of FMD have been previously been misdiagnosed as large and medium-vessel vasculitis (including Takayasu Arteritis (TA), giant cell arteritis (GCA), and Polyarteritis Nodosa (PAN).

Large-vessel vasculitis is traditionally considered to have 2 major variants, TA and GCA. TA is a granulomatous panarteritis, which typically affects younger women between 20-30 years. TA can occur anywhere along the aorta but differs from FMD by typically occurring close to the origin of the aortic branches such as the common carotid, subclavian and renal arteries [14]. Whilst the majority of lesions are stenotic, 33% patients can develop aneurysms [15]. The typical finding on non-invasive imaging is arterial wall thickening, which can be seen on DUS as an increased intima-media wall thickness and on CTA as a smooth, homogenous, circumferential and hypoechogenic lesion. MRI demonstrates vessel wall oedema on T2 and fat-suppressed sequences and mural contrast enhancement on T1 sequences [16].

GCA is an alternative differential to FMD which presents in patients with a mean age of 70 years [17]. The majority of patients present with either a temporal headache, visual loss or jaw claudication. GCA typically affects cervico-cephalic arteries proximal to the entry point of the cranial dura. Only 10-15% of patients have isolated extracranial involvement, with the most common locations being the aorta and the upper limb arteries (subclavian and axillary artery). GCA lesions can progress into thoracic aneurysms, dissection and ischaemia [18]. Non-invasive imaging modalities, such as DUS of the temporal artery may reveal the characteristic "halo sign" which has variable sensitivity and specificity and the "compression sign" [19]. CTA findings in GCA often reveal long tapered stenoses in large vessels, however these abnormalities are not pathognomonic [20]. There is limited utility of MRA in biopsy-proven GCA [21].

PAN is an alternative diagnosis and is a medium-vessel vasculitis typically affecting males at an average age of 50 years. PAN is seen in the branching points of medium-sized vessels and is initially characterised by segmental inflammatory lesions which can progress into diffuse vessel fibrosis, microaneurysm formation and vascular occlusions [22]. PAN can affect any vascular bed, but for reasons unknown involvement in all organs except the lungs have been described [22]. PAN can present with a wide range of features including mononeuritis multiplex, purpuric lesions, subcutaneous nodules and an acute abdomen in 30% cases [22]. PAN can have renal manifestations through infarction or haematoma formation, however it does not cause glomerulonephritis unlike in ANCA-related small-vessel vasculitis. There is limited evidence as to which imaging modality can best detect PAN.

There are no guidelines into the long-term management and surveillance of FMD patients. The specific management of FMD is based on its arterial manifestation. Dissections are medically managed with either antiplatelets or anticoagulation, unless there are significant threats of end-organ complications. Given the possibility of multi-vessel involvement, many authors advocate for a once-off CTA from head to pelvis [5]. In contrast to vasculitic diseases, the management of FMD does not require corticosteroids or other immunosuppression. Thus, making an accurate diagnosis is crucial to avoiding a lifetime of immunosuppression-related complications. It is therefore imperative for clinicians to be aware of FMD given the potential considerable delay in diagnosing this condition and the significant differences in management in comparison with that of its differential diagnoses.

FMD is a systemic vascular disorder with a broad range of vascular phenotypes and territory involvement. It can have a wide variety of clinical presentations including cardiac symptoms. It is largely diagnosed by imaging, for which catheter-based imaging is the gold standard but alternative non-invasive modalities are useful. FMD is a common cause of dissections and aneurysms and has potential for extensive multi-vessel involvement. This should trigger consideration of FMD particularly in the setting of bilateral arterial dissections. Whilst FMD can radiologically appear similar to large and medium-vessel vasculitis and other differential diagnoses, it is important to be aware of the sometimes-subtle differences in presentation and nature/distribution of the affected vessels amongst the disease processes. In contrast to vasculitis, the management of FMD does not require immunosuppression. Thus, an accurate diagnosis is crucial to avoiding a lifetime of immunosuppression-related complications. It is therefore imperative for clinicians to be aware of FMD given the potential considerable delay in diagnosing this condition and the significant differences in management in comparison with that of its differential diagnoses.

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