Case Report

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Local release of renin unveils intrarenal arterial fibromuscular dysplasia

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A previously healthy young man developed severe hypertension requiring triple antihypertensive therapy. Initial evaluation identified hyperreninemic hyperaldosteronism, mild hypokalaemia, hypodensity within the right kidney at computed tomography (CT), normal renal arteries at echography. He was referred to Verona ESH Centre were angio-CT revealed significant stenosis of an aberrant branch artery of the right kidney with hypo-perfused area colocalizing with a hypo-oxygenated area, as assessed by BOLD-MR imaging. Super-selective sampling found high plasma renin concentrations only in the vein draining the lower pole of the right kidney. Renal angiography confirmed tightened stenosis of an aberrant branch artery supplying the lower arterial segments, consistent with unifocal medial fibromuscular dysplasia, successfully treated with angioplasty. Investigating extra-renal sites, angio-MR found an S-shaped loop of extracranial left internal carotid artery, consistent with multisite fibromuscular dysplasia. This clinical case underscores the importance of comprehensive functional and imaging tests to identify elusive causes of secondary hypertension.

Keywords: arterial fibromuscular dysplasia, arterial hypertension, branch renal artery stenosis, cervical arteries, multisite, renal artery angioplasty, renovascular disease, unifocal

Abbreviations: BOLD, Blood oxygenation level dependent; CT, Computerised Tomography; DSA, Digital Subtraction Angiography; ESH, European Society of Hypertension; FMD, fibromuscular dysplasia; MR, Magnetic Resonance; MRA, Magnetic Resonance Angiography

CLINICAL CASE

An otherwise healthy 33-year-old male was referred urgently to the local hospital for sudden-onset headache and blurred vision. Blood pressure was 180/145 mmHg. Previously, his blood pressure did not to exceed 130/80 mmHg, with no diagnosis of arterial hypertension or any relevant clinical conditions. He was a non-smoker and alcohol intake lower than 10 g daily. Any pharmacological treatment or exposure to illicit drugs were denied. He referred a family history type-2 diabetes mellitus, ischemic cardiopathy and arterial hypertension associated with unilateral kidney agenesis.

At admission to the emergency room, physical examination did not reveal any pathological signs. Mild hypokalaemia (3.3 mmol/l) with normal plasma creatinine (0.89 mg/dl; eGFR >90 ml/min/1.73 m^2) was found (Table 1). A preliminary screening for secondary hypertension performed in the local hospital revealed hyperreninemic hyperaldosteronism (peripheral plasma renin: 184 μU/ml, plasma aldosterone: 1380 pmol/l, Table 1). Normal were the abdominal aorta and the renal arteries at colour Doppler ultrasound. An abdominal computer tomography (CT) scan showed regular morphology and dimensions of adrenal glands and kidneys, with slightly reduced volume in the inferior-middle third of the right kidney, interpreted as previous pyelonephritis. Three antihypertensive agents (ACE inhibitor, calcium channel blocker and reduced-dose beta-blocker) were required to maintain his blood pressure below 140/90 mmHg.

He was referred to our European Society of Hypertension (ESH) Centre. The revision of the abdomen CT doubted the diagnosis of pyelonephritic outcomes. During hospitalization, the patient underwent a thorough investigation for secondary forms of hypertension, including endocrine and inflammatory vascular diseases that were excluded (Table 1). Super-selective sampling from the three right intrarenal veins revealed a renal venin renin ratio >7 between blood collected from the right inferior renal vein and the other right and left renal veins (Table 1, Figure 1, Supplemental Digital Content, http://links.lww.com/HJH/C661). A new Abdominal angio-CT scan confirmed slowed perfusion of the apical and lower segments of the kidney (Fig. 1, panel a and Figure 2, Supplemental Digital Content, http://links.lww.com/HJH/C661), especially revealing anterior aberrant branch for these segments with tightened

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TABLE 1. Laboratory tests performed before and at the admission to the ESH excellence centre

Standard biochemical profile	Local hospital	At ESH centre	Normal range
s-Sodium (mmol/l)	138	137	135–145
s-Potassium (mmol/l)	3.3*	3.97	3.40–4.80
s-Creatinine (mg/dl)	0.91	0.94	0.59–1.29
p-Renin (μU/ml) upright position	184		4.4–46.1
p-Aldosterone (pmol/l) upright position	1380		194–554
Second level diagnostic tests		At ESH Centre	Normal Range
p-Renin (μU/ml) right kidney upper vein		186	Not available
p-Renin (μU/ml) right kidney middle vein		157	Not available
p-Renin (μU/ml) right kidney lower vein		>1000	Not available
p-Renin (μU/ml) left kidney		134	Not available
p-Renin (μU/ml) distal inferior vena cava		156	Not available
p-Renin (μU/ml) proximal inferior vena cava		159	Not available
Renal vein renin ratio (right LV/left kidney)		>7	<1.5

stenosis at 3-dimentional reconstruction (Fig. 1, panel b and Figure 3, Supplemental Digital Content, http://links.lww.com/HJH/C661).

To confirm the diagnosis of stenosis of a branch artery causing renovascular hypertension, further tests were performed, while low-dose acetylsalicylic acid was added to therapy. Blood oxygenation level dependent (BOLD) MR imaging and dynamic renal scintigraphy with Tc-99m DTPA confirmed hypo-oxygenation and hypo-perfusion of the same vascular segment located in lower area of the right kidney.

Selective Digital Subtraction Angiography (DSA) of the right renal artery confirmed the aberrant anterior branch with stenosis located in the distal third (Fig. 1, panel c and Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/C661). This aberrant artery (anatomical variant) vascularizes the entire inferior pole (which corresponds to the vascular segment), part of the anterior vascular segments and part of the superior pole. Downstream of the origin of the aberrant branch, the renal artery divides into anterior posterior segmental branches and for the superior pole. Thus, the vascularization of the inferior pole derives from the aberrant artery alone (Fig. 1, panel d and Figures 3 and 4, Supplemental Digital Content, http://links.lww.com/HJH/C661).

The angiographic characteristics of the lesion were those of focal medial fibromuscular dysplasia (FMD) with severe stenosis (Fig. 1, panels c and d and Figure 3 and 4, Supplemental Digital Content, http://links.lww.com/HJH/C661). Percutaneous artery angioplasty was then performed without complications (Figure 4, Supplemental Digital Content, http://links.lww.com/HJH/C661). Antihypertensive therapy was reduced to two drugs (angiotensin receptor blocker and calcium channel blocker), while clopidogrel was added to acetylsalicylic acid for 6 months. At the 6-month follow-up visit, blood pressure was 115/75 mmHg and treatment with only an angiotensin receptor blocker was prescribed. MR performed 6 months after angioplasty showed reperfusion of the whole vascular segments.

A thorough imaging of systemic arteries was performed to investigate potential extrarenal sites of FMD. Magnetic resonance angiography (MRA) of the cervical vessels revealed an S-shaped loop of the extracranial left internal carotid artery (Figure 5, Supplemental Digital Content, http://links.lww.com/HJH/C661).

DISCUSSION

In the present case, the diagnostic process revealing focal, aberrant renal branch artery FMD, causing renovascular hypertension prompted from the clinical evidence of severe hypertension associated with hyperreninemic hyperaldosteronism and hypokalaemia. In the absence of treatment with loop diuretics or renal tumour-secreting renin, the reninoma, this finding could be compatible with renovascular disease causing arterial hypertension. The clinical presentation of FMD interesting the renal arterial circulation is typically grade 3 hypertension, or hypertension resistant to treatment, arising before the age of 30 years, especially in women, although data from international registries also describe different patterns of presentation [1]. The present case could be classified as multisite, since including a S-shaped curve of the internal carotid arteries, a typical finding in cervical FMD [1].

The diagnosis of FMD is preferentially based on angio-CT scans or contrast-enhanced MRA with a possible contribution from ultrasonographic examination, only in centres with experienced personnel, which likely proves very poor for the diagnosis of branch renal artery FMD. The study of renal perfusion by scintigraphy or MRA with BOLD technique has been advocated as an additional diagnostic tool to recognize hypo-perfused or hypo-oxygenated areas within renal vascular segments [1–3].

Angio-CT in FMD of segmental branches is capable of directly visualizing arterial stenosis in the angiographic phase. In the parenchymal phase, the area vascularized by the stenotic segmental branch shows a delay and a reduction in density compared to the renal parenchyma vascularized by the normal branches. New CT scans can demonstrate the functional effects of morphological lateralization [4].

Once the diagnosis has been obtained with angio-CT, MR imaging can confirm the morphological finding and hypo-perfused segments, but is less manageable than angio-CT. However, after treatment it allows diffusion weighted imaging and apparent diffusion coefficient to better objectify perfusion improvements.

The assay of renin in the plasma from peripheral veins is not recommended as primary diagnostic criterion because plasma renin, although increased, does not exceed the normal range in most cases [1,5]. However, when increased, the selective intrarenal sampling for plasma renin can provide information concerning the site and the biological consequences of branch arterial stenosis [1]. In the present case, consistently with the anatomy of renal vasculature, the aberrant anterior branch supplied blood to the apical and lower segment, while the anterior and posterior branches perfused the superior, medial and posterior segments. The inferior renal vein, where the highest plasma renin concentration was found, drained the lower pole corresponding largely to the lower lobe. The superior vein drained blood

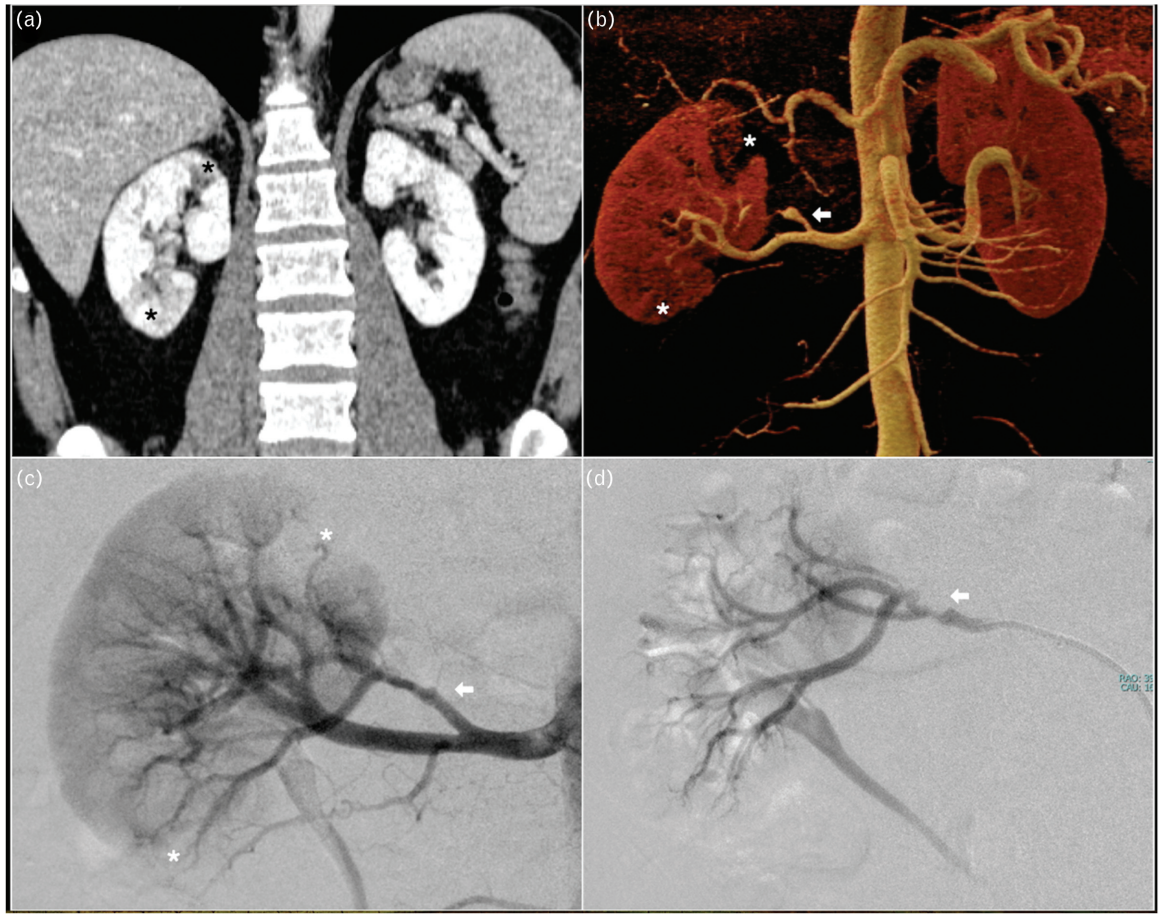

FIGURE 1 (a) Coronal CT scan in the arterial phase shows lower density at the upper and lower poles of the right kidney (asterisks in a). CT 3D VR reconstruction shows an aberrant branch for anterior segments of the kidney with ectasia followed by tight stenosis (arrows in b). The upper and lower poles of the right kidney are hypo-perfused (asterisks in b). Selective DSA of the right renal artery confirms the renal aberrant branch with irregular profiles for the anterior segments of the kidney (arrows in c) and hypo-perfusion at the upper and lower poles (asterisks in c). Super-selective DSA of the aberrant branch highlights fibrodysplastic stenosis (arrow in d). DSA, digital subtraction angiography.

from the upper third of the kidney mixed with that from the apical vascular segment, likely containing more abundant renin. After angioplasty the whole kidney was therefore persistently reperfused, as demonstrated by postprocedural RM and the reduction in blood pressure.

Indeed, a linear relationship exists between renal artery lumen, blood flow and renin secretion [6]. The severity of the stenosis determines the amount of released angiotensin II, responsible for increased oxidative stress and platelet activation that are determinants of renal ischemic damage in the hypo-perfused kidney, thus explaining the therapeutic efficacy of renal revascularization and the protection offered by inhibitors of the renin-angiotensin system towards blood pressure and progression of renal injury [7].

Measurement of the trans-stenotic gradient of blood pressure is recommended to define the actual severity of the stenosis and its pathogenicity as a cause of parenchymal hypoperfusion [1]. The functionality of the stenosis can be defined prior to intervention by evidence of hypoxemia-hypoperfusion in an area downstream of the stenosis by CT or MR. The present case and some previous clinical cases describe the feasibility of identifying significant stenosis due to FMD localized in branches of renal arteries by using super-selective sampling from intrarenal veins, in addition to imaging, for therapeutic decision (Table 2).

FMD lesions located in branches of the renal arteries are found in adults and paediatric cases. Series of clinical cases and FMD registries described the involvement of single or multiple accessory and branch renal arteries associated with arterial hypertension and, in some cases, with renal infarction as clinical presentation [1,8].

Partial nephrectomy, bypass surgery and vascular reconstruction, renal auto-transplantation, or chemical embolization have been used for complex intrarenal FMD. Endovascular treatment is recommended and angioplasty is preferable to stent implantation [1]. Treatment is more effective in reducing blood pressure when performed at a younger age, with a chance of cure or improvement in more than 90% of cases (3). Pharmacological treatment with inhibitors of the renin-angiotensin system is recommended and an option when surgical procedures are not feasible. Given the risk of arterial thromboembolism, lifelong antiplatelet treatment, usually a low dose of aspirin, is recommended to patients with FMD, independently of intervention [1].

Lesions due to FMD are frequently present in different vascular sites [1,8]. This necessitates extensive screening by

TABLE 2. Summary of clinical cases of branch renal artery fibromuscular dysplasia in which diagnosis was supported by selective blood sampling from intrarenal veins for renin measurement (search keywords renal artery stenosis, branch artery, fibromuscular dysplasia, renin, sampling, different combinations)

Clinical case	Diagnostic procedure	Treatment	Reference
Severe hypertension in a girl with no evidence of parenchymal renal disease. Segmental stenosis and saccular aneurysm affecting a branch of the left renal artery at arteriography.	Segmental renal vein renin sampling demonstrated markedly increased rate of renin secretion from the ischemic portion of the left kidney.	Blood pressure normalized after partial nephrectomy. Striking hyperplasia of the juxtaglomerular apparatus and medial fibromuscular dysplasia at histology.	[9]
A male patient with new-onset, accelerated hypertension secondary to dissection of the anterior division of the right renal artery.	Unstimulated plasma renin activity and serum aldosterone level markedly elevated.	Blood pressure levels normalized without antihypertensive therapy following right nephrectomy. Isolated dissection of the anterior branch of the vessel between the muscularis and adventitia with marked reduction in luminal diameter and renal ischemia at histology.	[10]
Six cases of paediatric hypertension.	Increased renin level at selective segmental renal vein sampling in the area of the renal lesion in 2 cases. Lateralization of renin secretion in 3 cases.	All 6 patients underwent upper, lower or mid segment partial nephrectomy. All patients became immediately normotensive at a mean 10 years of follow-up	[11]
Renovascular hypertension in a 12-year-old girl caused by annular stenosis of the intrarenal arterial branch.	Colour duplex ultrasound, MR and CT angiography and measurement of plasma renin activity in renal veins.	Angioplasty with dilation of stenosis, complete restoration of artery lumen and flow and decrease of blood pressure.	[12]
An 8-month-old boy presenting with shock secondary to renal haemorrhage due to aneurysm of the main renal artery and distal branches FMD.	Elevation of plasma renin activity and aldosterone, pathological findings and the results of renal angiography.	Urgent removal of one kidney. Intimal type FMD with aneurysmal formation.	[13]
A 16-year-old girl referred for hypertension with normal creatinine, mild proteinuria, hypokalaemia and inappropriately high levels of plasma rennin activity and aldosterone.	Segmental ischemia in the right kidney at CT and MRI. Markedly high renin activity in the vein draining the hypo-perfused area.	Endovascular angioplasty attempt failed because of technical difficulties. Antihypertensive treatment controlled the blood pressure, normalized serum potassium and reduced proteinuria.	[3]
Two cases of severe stenosis of the caudal branch from the right renal artery, a tight stenosis on a secondary branch of the left renal artery, caused by FMD.	Increased renin in peripheral veins and lateralization to the right kidney in case 1.	Both successfully treated with angioplasty	[2]
A 16-year-old patient presented with abdominal pain and sustained hypertension. severe branch artery stenosis with poststenotic dilatation consistent with focal FMD.	Thorough evaluation including renography with and without captopril and renal vein renin sampling were normal. Duplex ultrasound raised suspicion of a renal artery stenosis.	Successfully treated with angioplasty. Blood pressure normal without medication and the abdominal pain has only sporadically returned.	[14]
A 20-year-old woman with hypertension and hypokalaemia due to branch artery fibromuscular dysplasia.	Plasma renin activity and plasma aldosterone concentration within normality range. Focal stenosis with adjacent aneurysmal dilation and tortuosity in the proximal branch of the right renal artery at selective reno-angiography.	Successfully treated with percutaneous transluminal angioplasty, free from hypertension and hypokalaemia without any medications.	[4]

imaging, including cervical, intracerebral, splanchnic and iliac circulation, looking for vascular malformations, aneurysms and dissections [1]. In the present case, a typical nonstenotic lesion was found only at the level of the internal carotid artery, but follow-up is recommended.

In conclusion, selective sampling of blood for the determination of plasma renin could help define the functionality of the stenosis of branch arteries as a determinant of the pathophysiology of renovascular disease and hypertension. However, this needs to be integrated by evidence of colocalized parenchymal hypoperfusion and confirmed by measurement of vascular stenosis by direct angiography.

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Conflicts of interest

There are no conflicts of interest.

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