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Bilateral spontaneous renal artery dissection and antiphospholipid antibodies

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Short title: Bilateral spontaneous renal artery dissection

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Key words: spontaneous renal artery dissection; arterial hypertension; anti-phospholipid antibodies; lymphocyte subpopulations;
Abstract

Spontaneous renal artery dissection (SRAD) is a rare disorder with a prevalence of 0.005%, whilst bilateral SRAD is even less frequent. It occurs in about 12-18% of all cases of renal artery dissection and represents a variant entity, whose causes often remain unknown. To our knowledge, only 29 cases of bilateral SRAD have been previously described. Here we report the 30th case of a 46-years-old man with bilateral SRAD dissection and repeatedly positive IgM anticardiolipin antibodies at medium titres that may be pathogenic.

Introduction
Renal arteries are the most common site of dissection involving visceral vessels [1]. Generally, rupture occurs as an extension of aortic dissection or secondary to trauma [2], more rarely arises spontaneously. Spontaneous renal artery dissection (SRAD) is a rare disorder with a prevalence of 0.005% and a predilection for males (M:F ranging from 4:1 to 10:1), smokers, and in the fourth to sixth decades of life. Bilateral SRAD is seen in about 12-18% of all cases [2]. SRAD was first reported by Bumpus [3] and 29 cases of bilateral SRAD have been previously described. Here we report a review of the literature and the 30th case of a 46-years-old man with bilateral spontaneous renal artery dissection and repeatedly positive IgM anti-cardiolipin antibodies (aCL).

Case report

A 46 years old man was admitted to our Emergency Department due to a sudden abdominal pain prevalently localized to right ipocondrium. Pain started in the morning and was followed by diarrhoea. Physical examination of abdomen showed diffuse tenderness at palpation. Bowel sounds were present. Vital parameters were within normal limits. Pain was of intensity 7.5 on a scale ranging from 0 to 10. His past medical history was unremarkable, with the exception of smoking and he was not taking any medication.

Blood analysis showed a neutrophil leucocytosis, whereas anti-thrombin, homocysteine, lactate hydrogenase (LDH), creatinine, urea and 24 hour proteinuria were within normal limits. Fibrinogen, IgM anti-cardiolipin antibodies, C reactive protein and D-dimer levels were also increased (table 1). Fluorescence flow cytometry showed low CD3+ve cells at 0.37x10⁶/ml (reference range 0.96-2.5), normal CD3/CD8+ve cells 0.17x10⁶/ml (0.27-0.93), low CD3/CD4+ cells 0.2x10⁶/ml (0.5-1.7), low CD4/CD8 ratio 1.14 (1.5-3.0), CD19+ve/CD45+ve 0.029x10⁶/ml (0.12-0.63), borderline low CD3-ve/CD16+ve/CD56+ve/CD45+ve cells 0.02x10⁶/ml (0.02-0.74).

Total body CT scan revealed a large infarct involving superior and medial poles of the right kidney. Echocolourdoppler ultrasound of renal artery did not show significant stenosis. Selective arteriography of the right renal artery demonstrated a dissection of the anterior branch of the right renal artery leading to a lack of vascularization at superior and medial kidney portions.
Anticoagulation with subcutaneous low weight heparin was started.

In the week that followed, a complete metabolic profile, coagulation tests and laboratory markers of systemic autoimmunity were performed. Protein C (94%, reference range 70-130%), protein S (70%, reference range 64%-129%), anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-smooth muscle cell antibodies, rheumatoid factors, antibodies to extractable nuclear antigens, anti-β2glycoprotein1 antibodies, and lupus anti-coagulant were all negative. Genetic screening for inherited connective tissue disease, Factor V Lieden was absent, prothrombin G2021A was normal, and methylentetrahydrofolase reductase C677T and A1298T variants were both negative. HIV test was negative. To complete the diagnostic work-up, a trans-thoracic echocardiography was carried out showing a slight increase of aortic root. Cerebral angio-MRI showed no abnormalities, whereas 24 hours monitoring of arterial blood pressure demonstrated a grade 1 hypertension [4], so that a treatment with beta blockers and calcium antagonists was started.

During hospitalization, certain blood tests and a total body computed tomography (CT) scan was repeated, the latter revealing a bilateral dissection of renal artery with consensual areas of renal infarction in both the kidneys (figure 1). Blood analyses normalised, although IgM aCL was still high. The vascular surgeon was in agreement with the interventional radiologist, considering well controlled values of blood pressure, normal creatinine and urea levels and risk of extending dissection by percutaneous intervention on renal artery, suggested an instrumental follow-up and conservative management. Patient was discharged with oral anticoagulation, beta blockers and calcium antagonists and he was advised to monitor his blood pressure and renal function.

After a six months follow-up, the patient was in good general conditions, renal function remained within the normal limits and arterial blood values were well controlled by treatment. aCL IgM persisted at medium titres (table 1). Total body CT scan demonstrated the persistence of a focal dissection of the anterior branch of the right renal artery with regular flow after the dissected tract and a reduction of the extension of the ischaemic area in the superior pole of the kidney. Moreover, a slight reduction of calibre of left renal artery with sign of partial revascularization in the medial
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pole of left kidney was found (figure 2). In view of stable clinical, laboratory and instrumental tests, further invasive interventions were excluded and medical treatment was continued.

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Patient gave his written informed consent to publish his case

Discussion

A PubMed search using as key words “spontaneous bilateral renal artery dissection” and “spontaneous renal artery dissection” was performed. We found 29 cases of bilateral SRAD.

Bilateral SRAD is a rare disease, of still unknown aetiology [5]. SRAD can occur chronically, and since its symptoms are non-specific, more than half of patients with SRAD will already have had renal infarction at diagnosis. Lumbar or abdominal pain represents the onset clinical presentation in 77% of the cases. Moreover, severe arterial blood hypertension, poorly responsive to anti-hypertensive treatments, can develop because of renal ischaemia. Nausea, vomiting, dysuria, renal failure, haematuria and testicular and/or groin pain can also occur [5,6]. Clinical features of SRAD not distinguishable from those occurring in the most common diseases involving abdomen and urogenital tract such as infections, trauma and nephrolithiasis. A new onset arterial hypertension can represent a signal of an underlying SRAD, mainly when associated with abdominal pain.

SRAD, has been mostly associated with atherosclerosis and fibromuscular dysplasia. However, no inflammatory, no atherosclerotic segmental arterial mediolysis (SAM), trauma and inherited tissue connective diseases such as Marfan and Ehlers-Danlos syndromes, are pathological conditions predisposing renal artery to dissection [5,6]. Moreover, in one patient with SRAD positive antiphospholipid antibodies (aPLs) have been found [7]. In this case, renal artery dissection was related to aPLs both throughout a direct effect on endothelium and by their pro-thrombotic actions [7]. Also in our patient repeatedly positive aCL IgM antibodies at medium titres were found, suggesting a possible relationship between aPLs and SRAD. It is well known that thrombotic complications of antiphospholipid antibodies syndrome (APS) can affect renal arteries and veins,
intrarenal arteries and arterioles, and glomerular capillaries [8]. Accordingly, renal vasculopathy is included among APS classification criteria [9] and comprise a wide spectrum of vascular diseases ranging from large renal vessels occlusion to thrombotic microangiopathy [8,9]. Renal infarction represents a possible complication of APS related to ischemic kidney damage. Patients typically present with sudden-onset or uncontrolled systemic hypertension, or the diffuse abdominal or flank pain in the cases of renal infarct. Recently, also renal artery stenosis without evidence of thrombosis has been described in the context of APS [10], suggesting that vascular features of renal APS can be wider than expected. Interestingly, in our patent left renal artery dissection evolved towards a vascular stenosis as demonstrated by abdomen CT scan. The hypothesis of a relationship between aPLs and bilateral SRAD is attractive, mainly considering that in our patient, other causes potentially related to renal artery dissection and renal ischemia such as vasculitis, cardiogenic embolism, atrial fibrillation, cardiomyopathy, valvular heart disease, endocarditis, thromboembolism, haematologic disorders, renal artery injury by trauma or angiographic procedures, were excluded. Atherosclerosis, fibromuscular dysplasia, and SAM were also excluded because of epidemiological feature and no evidence of atherosclerotic lesions at any arterial site. Moreover, arteriography was not consistent with radiological features of fibromuscular dysplasia SMA [1]. However, considering that positive aPLs have been evaluated only in two patients affected by SRAD, including our case, we can only suggest a possible relationship between positive aPLs and SRAD.

Further confirming the role of immune system in arterial wall weakening, in our case a marked decrease of peripheral blood T and B subpopulations was observed, suggesting that in SRAD immune response undergoes to such peculiar modifications, that have also been described in Stanford-A acute aortic dissection (AAD) [11]. It is well known, indeed, that a depletion of cells related to acquired immunity with a prevalent neutrophil and macrophage natural response, occurs in the peripheral blood and within aortic wall of patients with AAD [11]. Such pattern of immune response favourites pro-inflammatory cytokine and metalloproteinases release, that in turn, leads to
matrix degradation and arterial wall rupture [12,13]. In agreement, in our case the transient increase of neutrophils, platelet, C-RP, erythrocyte sedimentation rate and fibrinogen levels were observed, confirming that a systemic pro-inflammatory environment occurs also in acute phases of SRAD [14] (table 1).

Management options of SRAD include a wide spectrum of alternatives ranging from medical treatment to endovascular intervention or surgical re-vascularization [1,8]. Patients require a close follow-up for monitoring arterial blood pressure, creatinine values, urinalysis and appearance of spontaneous dissection at other vascular sites. Invasive therapeutic approaches are recommended only when arterial hypertension becomes uncontrollable or renal function worsens, since several case report demonstrated successful conservative management [15]. Moreover, angioplasty and stenting can be dangerous in the acute phases of dissection since vessels are extremely friable. In our patient preserved renal function, well controlled arterial hypertension and evidence of revascularization at imaging, discouraged further invasive interventions, whereas standard oral anticoagulation was continued since aCL IgM antibodies were still positive.

In conclusion, we suggest considering bilateral SRAD among differential diagnosis in young/middle aged men with of abdominal pain and new onset arterial hypertension. Prevalence of SRAD, indeed, can be underestimated, whereas a well-timed therapeutic approach is fundamental to prevent the onset of potential life threatening complications such as uncontrolled arterial hypertension and renal insufficiency.

**Disclosure Statement**

The Authors have no conflicts of interest to declare
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References

Figure 1. Angio-CT examination with axial MIP reformat clearly shows to the right the origin of the anterior division affected by a stenotic tract with contextual dissection flaps and post-stenotic dilation. On the left side the extended stenotic tract of the anterior branch with associated downstream dilation

Figure 2. Six weeks follow up MDCT. A stable bilateral arterial pathological condition with more defined ischemic areas.

Table 1. Laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>1 week</th>
<th>1 month</th>
<th>6 months</th>
<th>Reference range</th>
</tr>
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<tbody>
<tr>
<td>White blood cell count (10^6/ml)</td>
<td>18.3</td>
<td>7.65</td>
<td>7.45</td>
<td>7.2</td>
<td>4.3-10.8</td>
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<tr>
<td>Neutrophils (10^6/ml)</td>
<td>14.3</td>
<td>4.4</td>
<td>4.0</td>
<td>4.5</td>
<td>1.8-7.5</td>
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<tr>
<td>Lymphocytes (10^6/ml)</td>
<td>1.6</td>
<td>1.1</td>
<td>2.2</td>
<td>1.9</td>
<td>1.2-4.0</td>
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<td>Fibrinogen (mg/dL)</td>
<td>702</td>
<td>638</td>
<td>304</td>
<td>289</td>
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<tr>
<td>d-dimer (mg/dL)</td>
<td>604</td>
<td>394</td>
<td>92</td>
<td>102</td>
<td>&lt;243</td>
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<tr>
<td>Anti-thrombin (%)</td>
<td>98%</td>
<td>97%</td>
<td>97%</td>
<td>-</td>
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<tr>
<td>Homocysteine (mmol/L)</td>
<td>7.3</td>
<td>-</td>
<td>-</td>
<td>5.3</td>
<td>5-12</td>
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<td>Urea (mmol/l)</td>
<td>1.5</td>
<td>1.8</td>
<td>3.0</td>
<td>2.7</td>
<td>0.8-4.2</td>
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<tr>
<td>Creatinine (µmol/L)</td>
<td>75</td>
<td>77</td>
<td>83</td>
<td>76</td>
<td>62-110</td>
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<tr>
<td>24 h proteinuria (mg/24 h)</td>
<td>108</td>
<td>-</td>
<td>-</td>
<td>103</td>
<td>&lt;150</td>
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<tr>
<td>CRP (mg/dL)</td>
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<td>6.1</td>
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<td>ESR (mm/h)</td>
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<td>49</td>
<td>14</td>
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<td>LDH (U/L)</td>
<td>229</td>
<td>405</td>
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<td>Anti-CL IgM (MPL)</td>
<td>45</td>
<td>-</td>
<td>58</td>
<td>33</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Anti-β2GPI IgM (CU)</td>
<td>-</td>
<td>-</td>
<td>7.5</td>
<td>14</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase, CL = anti-cardiolipin, GPI = β−2−glycoprotein-1
FIG 2