

Spontaneous Renal Artery Dissection in Ehler–Danlos Syndrome



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Received 13 July 2019; revised 4 August 2019; accepted 6 August 2019; published online 14 August 2019

Kidney Int Rep (2019) 4, 1649–1652; <https://doi.org/10.1016/j.ekir.2019.08.003>

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INTRODUCTION

Renal infarction is a relatively infrequent condition, most commonly occurring in the presence of predisposing factors, including atherosclerosis, valvular or ischemic heart disease, atrial fibrillation, endocarditis, hypercoagulability, malignancy, vasculitis, and kidney trauma.^{1,2} About 30% of renal infarctions, however, occur in the absence of these classic risk factors and are usually called “idiopathic.”¹ In this noncategorized group, an emerging diagnosis is spontaneous renal artery dissection (SRAD), which may account for several, if not the majority of cases. The largest series so far published reports on 17 cases, mostly in males in their fourth or fifth decade of life, usually without any underlying disease.^{3,4}

Strenuous exercise may be a facilitating factor, and SRAD is associated with diseases and conditions affecting the vascular tunica media, including fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome, polyarteritis nodosa, and cystic medial necrosis.⁵

The clinical and laboratory presentation is shared with all other types of kidney infarction, with sudden-onset flank pain, which radiates to the epigastrium or groin, and high lactate dehydrogenase. Retroperitoneal hemorrhage may be a rare presentation of SRAD, whereas new onset, occasionally severe hypertension may suggest SRAD in the context of kidney infarction.^{3,5}

The case reported here highlights this emerging diagnosis as a cause of kidney infarction and suggests that it should be considered in the case of symptoms that appear suddenly after physically strenuous activities or sexual intercourse.^{6,7}

CASE PRESENTATION

A 48-year-old Caucasian male, in apparent good health, with normal body mass index, normotensive, and no recent history of disease, sought medical attention for sudden excruciating back pain after sexual intercourse. His clinical history showed surgery for clubfoot in childhood, and for trigger finger at the age of 33, allergic asthma, mild hypercholesterolemia, and psoriasis.

In the emergency room, the patient was found to be afebrile (37 °C), with blood pressure of 140/100 mm Hg, and left costovertebral tenderness was noted. Renal ultrasounds ruled out kidney stones and hydronephrosis. Laboratory data showed neutrophilic leukocytosis, and a mild reduction in kidney renal function (Table 1). A computed tomography scan with contrast media, performed because of the persistence of severe pain, demonstrated a large kidney infarction in the left kidney, further characterized by nuclear magnetic resonance (Figure 1). Cardiac evaluation and echocardiography were normal (no hypertrophy; ejection fraction 67%; no valvular abnormalities). Immunologic tests (antinuclear antibody, antineutrophil cytoplasmic antibody, anti-dsDNA, extractable nuclear antigen) were negative, with the exception of borderline positive (1:80) antinuclear antibodies and lupus-like anticoagulant (antiphospholipid antibodies were negative). Screening for thrombophilia was also negative, and positron emission tomography showed no evidence of occult neoplasia or large vessel vasculitis (Table 1).

Computed tomography angiography, performed 2 months after the acute episode, showed an eccentric

Table 1. Main biochemical data at referral or first assessment

Test	Result	Reference range
Creatinine (mg/dl)	1.26	0.6–1.2
Estimated GFR (ml/min per 1.73 m ²)	64.51	>90
White blood cells (mm ³)	15,480	4000–10,000
Neutrophils (%)	93.6	50–75
Hemoglobin (g/dl)	16.4	13–17
Platelets (n/mm ³)	200,000	150,000–400,000
Na (mEq/l)	137	135–145
K (mEq/l)	4.2	3.5–5
Bicarbonate (mEq/l)	23	20–30
LDH (U/l)	650	140–250
HbA1C (%)	6.10	4–6
Cholesterol (mg/dl)	248	<200
Triglycerides	140	<150
Protein C (%)	118	80–130
Protein S anticoagulant (%)	89	70–140
Antithrombin III activity (%)	108	80–130
Activated protein C resistance (ratio)	3.1	>2.2
PT (%)	100	80–100
INR	1	
Factor V Leiden mutation	Absent	Absent
Prothrombin gene mutation (g.20210G>A)	Absent	Absent

GFR, glomerular filtration rate; INR, international normalized ratio; LDH, lactic dehydrogenase; PT, prothrombin time.

endoluminal defect, associated with harmonic dilatation downstream. In the absence of signs of atherosclerosis, such a lateral perfusion deficit, with downstream dilatation, was suggestive of SRAD (Figure 2).

On careful questioning, he reported that 1 of his 2 daughters had been diagnosed with Ehlers-Danlos syndrome hypermobility type. He had been hyperflexible in his youth but never underwent formal genetic counseling. The genetic assessment (*COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *SMAD3*, *TGFB2*, *TGFB1*, *TGFB2*) found a variant of uncertain significance

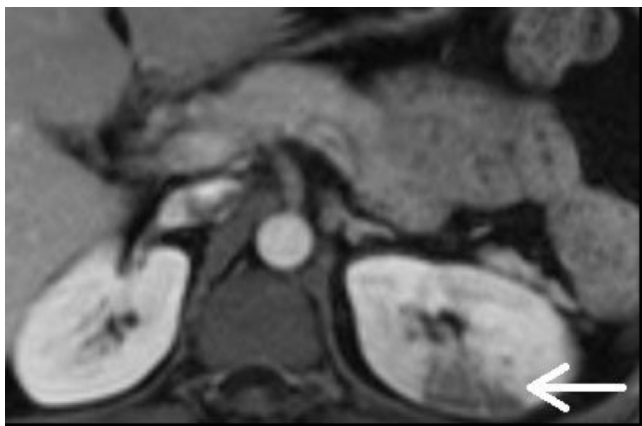


Figure 1. Arterial phase of T1-weighted contrast-enhanced magnetic resonance imaging after endovenous administration of gadolinium showing a large area of hypointensity in the left kidney, with loss of corticomedullary differentiation and absence of contrast enhancement (arrow). The absence of fluid collections in the perinephric space and the sharp demarcation are consistent with acute kidney infarct.

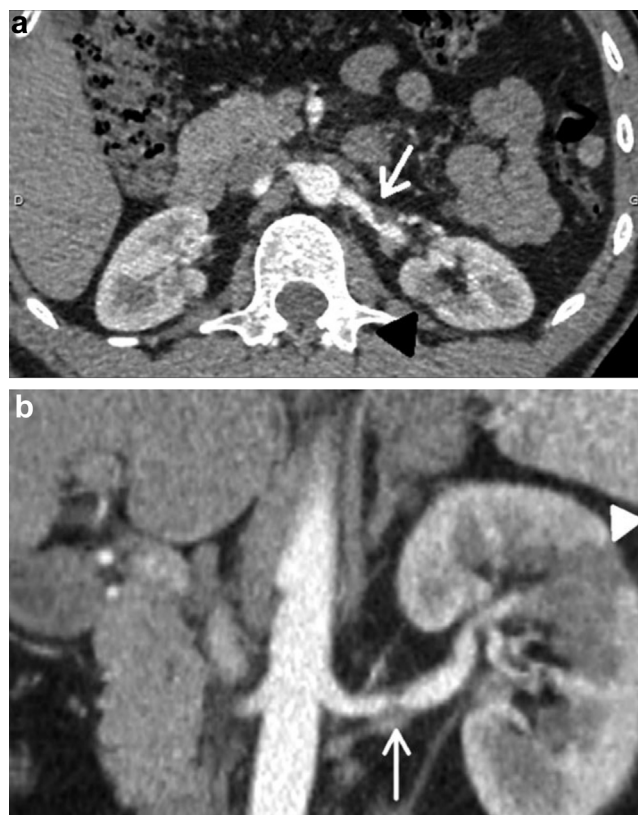


Figure 2. Axial (a) and coronal (b) image from a computed tomography angiography (arterial phase) scan, performed 2 months after the acute episode, show an endoluminal defect of the middle third of the left renal artery (white arrows), associated with harmonic dilatation downstream, in a patient without signs of atherosclerotic involvement. This picture does not suggest an atheromatous plaque, which usually involves the proximal tract of large and medium-size arteries, nor arterial embolism (embolus is usually trapped in small arteries or at vascular bifurcations); a lateral perfusion deficit, in a medium-sized vessel, is suggestive of vascular dissection. The downstream arterial dilatation also evokes dissection, which evolved into focal thrombosis of the false lumen. The vessel is now partially recanalized. Kidney infarction: cuneiform cortical hypodensity, with initial cortical retraction (arrowhead): distal progression of the arterial dissection or blood clots have presumably occluded segmental vessels.

(Class 3 —ACMG) in the *COL5A1* gene, exon 6 (heterozygote substitution: c.791C>T, p [Thr264Met]). Ultrastructural analysis of the skin biopsy, in the patient and in his daughter, showed collagen fibrils with a variable diameter and occasional “flower-like” fibrils, which were considered to be support for the clinical diagnosis (Supplementary Figure S1).

DISCUSSION

In the context of a clinical and imaging picture suggestive of kidney infarction, and in the absence of the classic predisposing cardiovascular or immunologic risk factors, diagnosis of SRAD should be considered. This diagnosis may be particularly frequent in relatively young patients, as in our case.

Clinically, the association with strenuous exercise and sudden onset of hypertension may support the suspicion of SRAD. Diseases affecting the collagen matrix may also be associated and should be searched for in these cases.

In our patient, clubfoot and trigger finger were clues, as was the diagnosis of Ehler-Danlos type hypermobility in his daughter. Ehler-Danlos syndrome is an autosomal dominant disease complicated by arterial dissection in multiple sites, including the renal artery.⁸

Indeed, the genes involved in the development of Ehlers-Danlos syndrome are only partially known, and the gene causing hypermobile Ehlers-Danlos syndrome is unknown. Diagnosis is based upon the clinical characteristics, supported by ultra-structural analysis of dermal collagen. In this case (Supplementary Figure S1A), collagen fibrils presented a variable diameter with occasional “flower-like” fibrils. The patient met the Villefranche and Brighton diagnostic criteria as well as the 2017 classification criteria.⁹ Flower-like collagen fibers, variable collagen fiber diameters, and irregular interfiber spacing are 3 primary morphologic abnormalities that can be observed alone in disorders not related to Ehlers-Danlos syndrome. The 3, however, are present in all patients with typical hypermobile Ehlers-Danlos syndrome, as well as in members of their family.⁹

Whether or not in the setting of a genetic disorder, several trigger factors for SRAD have been identified, including hypertensive crises, trauma, and strenuous exercise. For obvious reasons, sexual intercourse may be an underreported trigger, as the case discussed here suggests. Interestingly, it was the second one observed by the corresponding author (Supplementary Case S1, Supplementary Figures S2–S4), and another case was recently published.⁷

As a consequence of its rarity, there is limited experience regarding SRAD management. Symptomatic management includes painkillers and control of the hypertensive crisis; although systemic anticoagulation or anti-aggregation is debated, strict blood pressure control and correction of vascular risk factors are advised in the long-term. Endovascular stenting and surgical intervention have been attempted in some cases, but SRAD may evolve spontaneously with vessel recanalization, as it did in our patient (Figure 2).

CONCLUSION

This case shows the need for attention to SRAD, a rare, possibly underdiagnosed condition, and its association with genetic collagen disorders (Table 2). It is also a reminder of the importance of obtaining a detailed

Table 2. Teaching points

SRAD is an emerging cause of kidney infarction that accounts for a relevant portion, if not the majority, of the cases occurring in the absence of the classic risk factors for kidney infarction.

SRAD may be associated with strenuous exercise, retroperitoneal hemorrhage, and sudden onset of hypertension, in particular in young males without risk factors.

Diseases affecting the collagen matrix, such as Marfan disease and Ehler-Danlos syndrome, are associated with SRAD.

The genetics of Ehler-Danlos syndrome are only partially known, and diagnosis rests upon clinical features, which are supported by the ultrastructural analysis of dermal collagen.

SRAD management is usually conservative, as spontaneous revascularization occurs in many cases. Symptomatic management includes painkillers and control of the hypertensive crisis; systemic anticoagulation or anti-aggregation is debated. Strict blood pressure control and correction of vascular risk factors are advised in the long-term.

SRAD, spontaneous renal artery dissection.

clinical history, so that time-consuming, expensive, and stressful evaluations can be avoided.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Professor Xavier Jeunemaitre, Service de Génétique et Centre Maladies Vasculaires Rares, Hôpital Européen Georges Pompidou, for the genetic analysis of our case. The publication fee was taken in charge by the Centre Hospitalier Le Mans.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. (A) Collagen fibers in our patient. Variability in fiber diameters, irregular interfiber spacing, and occasional flower-like collagen fibers. (B) Normal picture. (C) Classic appearance of Ehler-Danlos syndrome, with irregular fibrils and large flower-like fibrils.

Case S1. A young man with spontaneous renal artery dissection.

Figure S2. Coronal reformatting of the arterial phase of T1-weighted DIXON sense contrast enhanced magnetic resonance image (MRI), obtained after endovenous administration of gadolinium, shows multiple areas of hypointensity in the right kidney, mostly in the upper pole, with loss of corticomedullary differentiation because of the absence of contrast enhancement (arrows). Note the absence of fluid collections in the right perinephric space and the “cortical enhancement” due to the thin rim of capsular enhancement (arrowheads), which is consistent with acute infarct.

Figure S3. Coronal reformatting of the nephrographic phase of computed tomography, obtained after endovenous administration of contrast medium, shows a large hypodense region with loss of corticomedullary differentiation in the right kidney and small areas with no contrast enhancement in the upper pole (arrows). The cortical rim sign is also appreciable in the scan (arrowheads).

Figure S4. Axial scan and coronal reformatting of computed tomography angiogram (maximum intensity projection images; slice thickness: 5 mm) shows double renal arteries of the right kidney arising from the abdominal aorta. Computed tomography angiogram demonstrates a short linear filling defect along the middle tract of the upper renal vessel (black arrow) and intramural hematoma (dotted white arrow), consistent with dissection. Note the increase in vessel size after the intimal flap or renal dissection (white arrowhead).

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