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CASE REPORT

Organ transplants do not escape paradoxical embolisms

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Summary

Acute renal allograft dysfunction in the first weeks after transplantation primarily requires examination for acute rejection, drug-associated injury, pre-renal failure due to exsiccosis/dehydration, and post-renal problems such as urinary tract obstruction. In rare instances, main renal artery or vein thrombosis may be found, e.g. due to acute rejection of the vessels. Herein, we describe the clinical course of a patient with a recent renal transplantation who presented with an acute enigmatic renal allograft failure which, after intensive diagnostic efforts, emerged as paradoxical embolism with extensive allograft ischemia in consequence of a venous thrombosis and a patent foramen ovale – a so far unreported case.

Introduction

Early acute allograft dysfunction is typically caused by acute rejection, drug-associated injury, exsiccosis/dehydration, urinary tract infections or obstruction. Ischemic injury due to an occlusion of renal vessels is comparably rare. Most of these cases may be related to surgical complications or acute rejection of the main renal artery and vein with subsequent thrombosis [1]. In this report, we describe an unusual case of arterial occlusion leading to acute renal allograft dysfunction.

Case report

A 56-year old Caucasian male who had received a living non-related renal transplantation into the right iliac fossa 4 weeks prior to presentation was referred for evaluation of an increase in serum creatinine levels (baseline value: 115 μmol/l; at referral: 320 μmol/l). His medical history was significant for end-stage kidney disease due to IgA-nephropathy, three-vessel coronary artery disease with coronary artery bypass grafting in 2007, and a long-standing history of arterial hypertension. The patient had no history of atrial fibrillation or any other cardiac arrhythmia. All documented ECGs showed normofrequent sinus rhythm. His medication consisted of tacrolimus, mycophenolate mofetil, prednisolone, cotrimoxazole, metoprolol, amlodipine, pantoprazole, torasemide, low-dose aspirin, doxazosine and oral amphotericin B suspension.

On admission, the patient was without complaints and denied any urinary symptoms. The blood pressure was 166/84 mmHg. The remaining physical examination of this obese patient (BMI 35.1) was unremarkable. Urinary tract infection and inadequate high tacrolimus through levels were excluded. Lactate dehydrogenase was elevated at 791 U/l. Urine analysis showed microscopic hematuria and a protein excretion of 2.0 g/day. Blood hemoglobin was 10.8 g/dl. Ultrasound evaluation showed inhomogeneous and blurry hyperechoic renal parenchyma and no urinary tract obstruction. Notably, the resistance index

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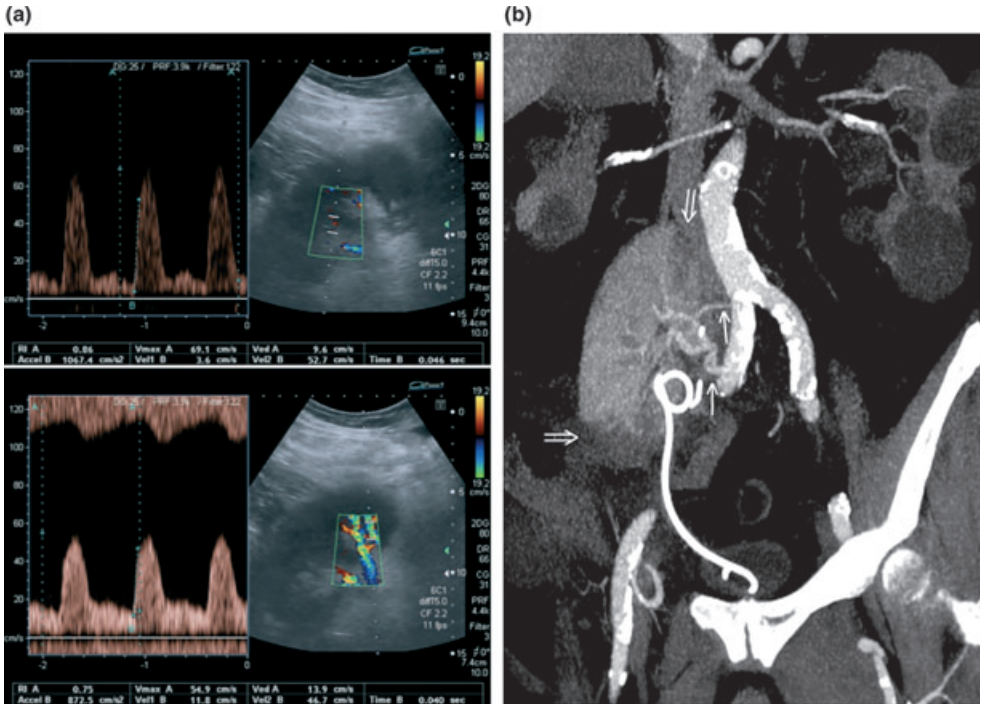

Figure 1 Renal findings. (a) Varying resistance indices (RI) of renal segmental interlobular arteries at different locations of the allograft using colour-coded duplex examination. (b) Contrast enhanced CT in the late arterial phase in coronal oblique maximum intensity projection. Wedge-shaped areas of absent contrast enhancement (⇒) can be appreciated especially at the lower pole, representing areas of renal infarction. Both renal arteries are patent (→).

was quite variable in different segmental interlobular arteries, ranging from 0.75 to 0.86 (Fig. 1a). An allograft biopsy showed only minor, focal acute tubular epithelial injury, but no signs of acute rejection. On the following day, shortly after micturition the patient complained of heavy claudication and numbness of the left lower leg, which appeared cool and pale with absent popliteal pulses. Duplex ultrasonography detected bilateral deep venous thromboses of posterior tibial veins. CT angiography revealed an embolic occlusion of the left common femoral artery and a thrombus in the right popliteal artery (Fig. 2a). The CT also demonstrated a wedge-shaped hypoperfused region of the lower pole of the allograft and several patchy areas in the remaining organ (Fig. 1b). An immediate embolectomy revealed a fresh mixed thrombus of 8 cm length. Oral anticoagulation therapy with phenprocoumon was initiated. The finding of multiple arterial emboli prompted us to perform an

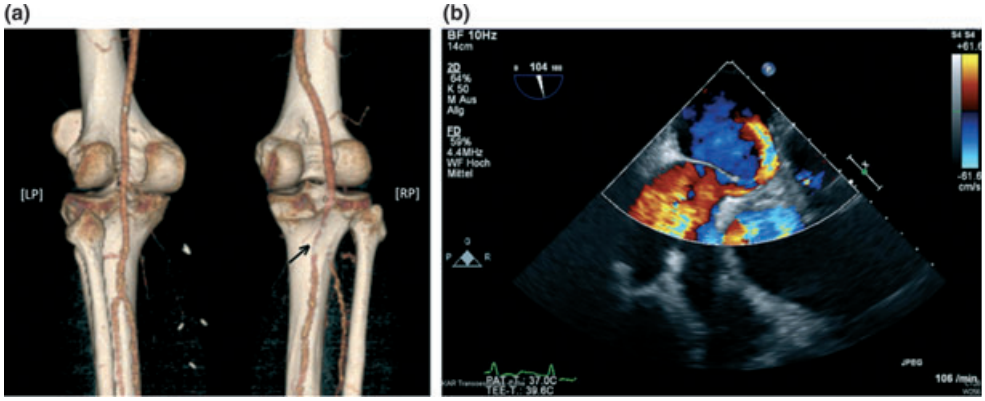

Figure 2 Findings supporting the putative paradox embolic disease in the patient. (a) CT-Angio depicting a thrombus in the right popliteal artery (→). (b) Transesophageal echocardiogram with colour-coded duplex demonstrating a patent foramen ovale with a spontaneous right-to-left atrial shunt.

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echocardiogram which showed a patent foramen ovale (PFO) with a spontaneous right-to-left atrial shunt (Fig. 2 b). Left atrial or ventricular thrombi were not detected. Considering the triad of (i) systemic arterial embolus in the absence of left-sided cardiac sources, (ii) the evidence of a right-to-left shunt and (iii) venous thrombosis, a paradoxical embolism most likely accounted for the ischemic damage of the renal graft and the arterial occlusion of the lower extremity in our patient. Therefore, the patient received an interventional closure of the PFO by implantation of a 30 mm Amplatzer®-occluder (Plymouth, MN, USA). Follow-up evaluations in the following months showed serum creatinine values between 149 and 165 mmol/l. Ultrasound of the graft showed scarring alteration of the caudal parenchyma, consistent with the previous renal infarction but otherwise normal perfusion of the kidney.

Discussion

In the presented case, common complications like acute rejection, drug-associated injury, exsiccosis/dehydration (prerenal failure), transplant pyelonephritis and urinary tract obstruction were excluded during the regular work-up for acute allograft impairment. The biopsy findings with mild acute tubular injury were not sufficient to explain the decline in renal function. The biopsy size was representative according to the requirements of the BANFF classification [2], however, in view of the CT diagnosis with multiple but focal infarctions the biopsy must have been originated from a non-affected area. To this end, the Doppler findings with variable resistance indices could have been a clue to the focal nature of the allograft injury.

Paradoxical arterial embolism causing acute renal allograft dysfunction has not been reported to our knowledge. Nevertheless, lack of other plausible explanations and the combination of deep vein thrombosis, PFO and the extent of infarcted areas in the allograft leaves paradoxical embolism as the most likely cause of acute allograft failure in our case. Although uncommon, such complication may be not unlikely: According to an autopsy study (of 965 hearts), the prevalence of PFO may be as high as 27% in the general population [3]. In younger patients (<55 years) with stroke of unidentified causes ('cryptogenic stroke'), embolism via a PFO accounts for 46% of the cases [4]. On the other hand, deep venous thrombosis (DVT) is quite frequent after renal transplantation affecting 6.2–9.1% of the patients [5–7] and embolic disease may occur in about a quarter of these cases [5]. Most often, the deep vein thrombosis develops on the side to the allograft implantation [6].

We do not have a clear explanation why the PFO of such size and with spontaneous right-to left shunt was not detected in the regular pretransplant work-up while being on the transplant waiting list. Unfavorable sonographic conditions (obesity) or lacking examiner's experience are potential explanations. Nevertheless, despite the fact that the PFO must have been present at that time, prophylactic occlusion would have been – most likely not performed. According to the guidelines of the European Society of Cardiology '…patients with significant shunt (signs of right ventricle volume overload) and pulmonary vascular resistance <5 WU should undergo ASD closure regardless of symptoms' [8]. In the present case, we do not know whether or not these criteria were present pre-transplant but the echocardiogram which was performed after the incident did not show RV volume overload. After occurrence of the embolic disease, we decided to perform the occlusion of the PFO. Alternatively, oral anticoagulation would have been an option which is probably not inferior according to uncontrolled studies [9], however, ongoing prospective, randomized and controlled trials are still awaiting final results to clarify this point [10].

Considering the enhanced risk of thrombotic events after kidney transplantation, anticoagulation prophylaxis with heparin for at least 2–3 weeks to prevent late-onset thrombosis has been suggested. In this regard, Ubhi *et al.* demonstrated that treatment with 5000 U b.i.d of standard heparin significantly reduced the incidence of DVT following transplantation [11]. In view of these findings, kidney transplant patients, in particular with reduced mobility, should be advised of anti-thrombosis prophylaxis for at least 2–3 weeks in addition to wearing compression stockings [11]. In our case, standard low-dose prophylactic heparin therapy was stopped 10 days after surgery at the end of the hospital stay. In the presence of this additional risk factor, obesity it would have been reasonable to prolong this prophylaxis to at least 3 weeks.

Our case and the reviewed studies underscore the importance of an individually based evaluation of potential risk factors for thrombosis and an appropriate prophylaxis. Moreover, presence of DVT and or patent foramen ovale in a patient with acute allograft impairment should prompt one to consider paradoxical embolism as a possible underlying cause.

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