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Transplant renal artery stenosis: clinical manifestations, diagnosis and therapy

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Abstract

Transplant renal artery stenosis (TRAS) is a well-recognized vascular complication after kidney transplant. It occurs most frequently in the first 6 months after kidney transplant, and is one of the major causes of graft loss and premature death in transplant recipients. Renal hypoperfusion occurring in TRAS results in activation of the renin–angiotensin–aldosterone system; patients usually present with worsening or refractory hypertension, fluid retention and often allograft dysfunction. Flash pulmonary edema can develop in patients with critical bilateral renal artery stenosis or renal artery stenosis in a solitary kidney, and this unique clinical entity has been named Pickering Syndrome. Prompt diagnosis and treatment of TRAS can prevent allograft damage and systemic sequelae. Duplex sonography is the most commonly used screening tool, whereas angiography provides the definitive diagnosis. Percutaneous transluminal angioplasty with stent placement can be performed during angiography if a lesion is identified, and it is generally the first-line therapy for TRAS. However, there is no randomized controlled trial examining the efficacy and safety of percutaneous transluminal angioplasty compared with medical therapy alone or surgical intervention.

Keywords: flash pulmonary edema; hypertensive crisis; Pickering syndrome; renal artery pseudoaneurysm; transplant renal artery stenosis

Introduction

Poorly controlled hypertension is common among renal transplant recipients and associated with graft failure and high mortality [1]. Transplant renal artery stenosis (TRAS) is the narrowing of the transplant renal artery, impeding blood flow to the allograft. It accounts for 1–5% cases of post-transplant hypertension [2–4]. Especially, since the introduction of calcineurin inhibitors and other immunosuppressive agents, the incidence of allograft rejection has substantially decreased [5], making TRAS one of the important causes of graft loss and premature death in transplant recipients. In this study, we describe a case of transplant renal artery narrowing caused by compression of a pseudoaneurysm with clinical features of TRAS, followed by a thorough review on TRAS. The key teaching points are listed in Table 1.

Case presentation

A 42-year-old African-American man, who underwent kidney transplantation for end-stage renal disease due to hypertension, presented to the emergency department with lightheadedness, palpitations and a reported home blood pressure of >220/110 mmHg. Six weeks prior, he had received a kidney from a 30-year-old deceased donor who died from a gunshot wound. The donor renal anatomy was notable for three renal arteries: two main renal arteries on a common aortic patch and a third superior pole renal artery on a separate aortic patch. The superior pole artery supplied ∼20% of the graft. It had been transected during procurement, but was repaired in an end-to-end fashion with running continuous sutures. During transplantation, two separate aortic cuff anastomoses were made to the external iliac artery. Reperfusion of the kidney was normal and the kidney functioned immediately. The immunosuppression regimen included basiliximab induction and

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Table 1. Key teaching points

- TRAS occurs most frequently in the first 6 months, but it can present at any time.
- Patients with TRAS have activated RAAS and usually present with worsening or refractory hypertension, fluid retention and/or allograft dysfunction without evidence of rejection.
- TRAS should be a differential diagnosis of a kidney transplant recipient with hypertensive crisis and flash pulmonary edema. This unique clinical entity has been named Pickering Syndrome.
- Doppler sonography is commonly used as a screening tool for TRAS, whereas angiography provides a definitive diagnosis.
- Percutaneous transluminal angioplasty with stent placement is generally the first-line therapy to correct hemodynamically significant stenosis in TRAS, especially for lesions that are short, linear and distal to the anastomosis.

maintenance tacrolimus, mycophenolate mofetil and corticosteroids. The postoperative course was uncomplicated except for new onset of atrial fibrillation, which was resolved with cardioversion. The blood pressure after kidney transplantation ranged between 125/70 and 175/105 mmHg on metoprolol tartrate 100 mg and nifedipine 90 mg twice daily. After addressing medication compliance, antihypertensive medications were adjusted. On the day of the presentation to the emergency department, the patient's antihypertensive medications included clonidine 0.2 mg three times a day, labetalol 200 mg and nifedipine 90 mg twice daily. He appeared diaphoretic, with a blood pressure of 235/122 mmHg and a heart rate of 87 bpm. Physical examination revealed bilateral lung rales without peripheral edema or abdominal pain.

Laboratory tests were significant for a serum creatinine, which had increased from a post-transplant baseline of 1.4 to 2.2 mg/dL over 4 days. The tacrolimus trough level was slightly elevated at 18.3 ng/mL (target 8–15 ng/mL), which suggested against allograft rejection. Urine and blood cultures were negative. Chest X-ray showed evidence of pulmonary edema. Electrocardiogram revealed no evidence of cardiac ischemia or arrhythmia. The patient was admitted to the intensive care unit and administered a nicardipine drip, but his blood pressure remained elevated. Given the presence of refractory hypertension and flash pulmonary edema, TRAS was suspected. Duplex sonography was performed and revealed a hilar pseudoaneurysm adjacent to one of the main donor renal arteries measuring 3.1 × 3.2 × 3.1 cm, with a peak systolic velocity of 457 cm/s in the transplant renal artery. Angiography demonstrated a bi-lobed pseudoaneurysm arising from the distal anastomosis and extrinsically compressing the main transplant artery and limiting flow (Figure 1).

The following day, the patient was taken to the operating room for pseudoaneurysm repair. Due to extensive abdominal adhesions from prior surgeries, repair of the pseudoaneurysm was aborted, and the pseudoaneurysm was controlled by placement of a covered endoluminal stent to the external iliac artery. This led to surgical embolization of the allograft. The blood pressure improved significantly postoperatively. Finally, the allograft was removed. On the pathologic examination of the explanted kidney, there was extensive coagulative necrosis, reactive acute inflammation and vascular thrombi, which was compatible with infarction. In the residual viable kidney parenchyma, there were vascular changes suggestive of malignant hypertension. There was no evidence of rejection. In summary, this is a case of hypertensive crisis and flash pulmonary edema in a kidney transplant recipient, as a result of transplant renal artery narrowing due to compression of a pseudoaneurysm.

Epidemiology

Owing to the difference in diagnostic modalities, the reported incidence of TRAS varies widely, ranging from 1 to 23% [6, 7]. Most of these studies were performed retrospectively in a single center. For example, Rengel *et al.* [8] estimated the incidence of TRAS to be 4.5% among 286 kidney transplant recipients from 1990 to 1997 in their institution. The study published by Hurst *et al.* [9] in 2009 was the only study performed using a national sample of renal transplant recipients. Using the United States Renal Data System (USRDS) registry, they identified 42 403 Medicare primary renal transplant recipients from 2000 to 2005, and found a cumulative incidence of TRAS to be 2% at 3 years and an overall incidence rate to be 8.3 cases per 1000 patient-years [95% confidence interval (CI) 7.8–8.9]. In children, the prevalence of TRAS seems to be lower compared with adults. In a single center, a retrospective study with 216 pediatric patients, the prevalence of TRAS was 4.6% among patients transplanted between 2001 and 2011 [10]. The lower prevalence of TRAS in the pediatric population is likely due to a minor extent of vascular changes in younger donors. TRAS accounts for 1–5% cases of post-transplant hypertension and ∼75% of post-transplant vascular complications [2–4]. It is a major cause of graft loss and premature death in transplant recipients. According to the USRDS registry, the adjusted hazard ratio for death and graft loss was 2.84 (95% CI 1.70–4.72) in transplant recipients with TRAS compared with those without TRAS [9].

Clinical manifestation

TRAS usually occurs between 3 months and 2 years after renal transplantation, with the highest frequency in the first 6-month post-transplant but it may present at any time [9, 11, 12]. Patients with TRAS usually present with worsening or refractory hypertension, fluid retention and/or graft dysfunction without evidence of rejection [7]. Similar to bilateral renal artery stenosis or unilateral stenosis in a solitary kidney, the renin–angiotensin–aldosterone system (RAAS) is activated in TRAS. This leads to sodium and fluid retention, and patients may develop edema, congestive heart failure or recurrent bouts of pulmonary edema. In the present case, the patient presented with hypertensive crisis and flash pulmonary edema. Patients with flash pulmonary edema classically present with sudden onset of severe, unprovoked dyspnea with normal left ventricular systolic function [13]. Renal artery stenosis and flash pulmonary edema is a unique entity with distinct pathophysiological, clinical and therapeutic features. It has been named Pickering Syndrome to honor Thomas G. Pickering, who first described it [13]. In 1988, Pickering *et al.* [14] reported a series of 11 patients with atheromatous renovascular hypertension and history of multiple episodes of pulmonary edema. Since then, there have been a number of case reports confirming this entity. In the present case, the presence of flash pulmonary edema in the setting of hypertension crisis led to prompt

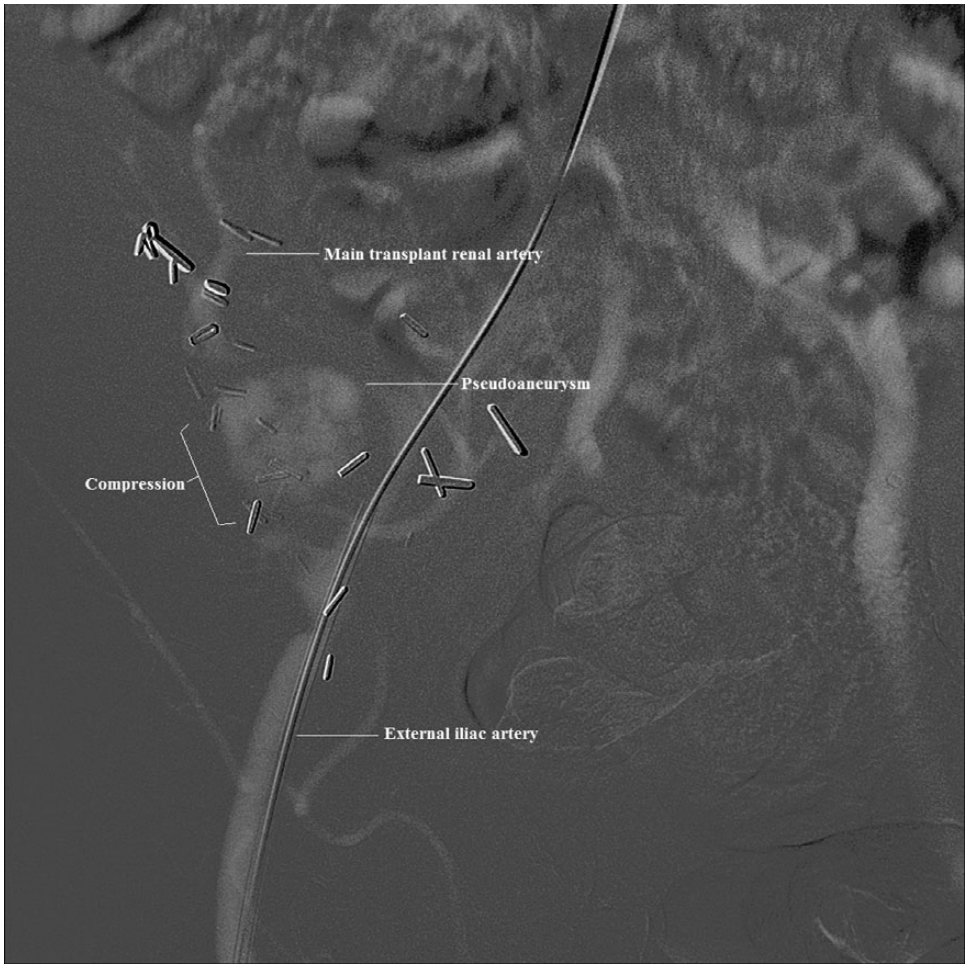

Fig. 1. Angiography of the transplant renal artery with digital subtraction angiography. A large pseudoaneurysm measuring 3.1 × 3.2 × 3.1 cm causing extrinsic compression on the main transplant renal artery limiting flow.

diagnosis of TRAS followed by therapeutic interventions, specifically surgical embolization of the allograft and then transplant nephrectomy, thus preventing potential complications from the hypertensive crisis.

Pathophysiology

TRAS has multiple causes, and usually occurs close to the sites of surgical anastomoses. In a case series of 38 patients, stenosis at different sites was recognized: stenosis of the recipient artery (pre-anastomotic, in the iliac artery), stenosis of the suture line and stenosis of the donor renal artery [12]. The causes that have been identified include atheroma in the donor artery, suture techniques, trauma to the donor or recipient artery during procurement or transplantation as well as immune-mediated vascular damage [7, 12]. Suture errors were thought more likely to occur in end-to-end anastomoses because of the difference in texture and caliber between the donor and recipient vessels [12]. In addition, end-to-end anastomoses may cause turbulent flow or disturbed hemodynamics, which could be responsible for the development of stenosis. However, the evidence is contradictory [15, 16]. Stenosis that occurs years after transplantation usually reflects atherosclerotic disease either of the transplant renal artery or of the adjacent proximal iliac artery [17]. Diffuse stenosis may reflect immune-mediated endothelial damage. This was evidenced by the similar histologic changes seen between the stenosed arteries and the vessels of renal allograft rejection [12, 18]. Furthermore, post-anastomotic TRAS has been shown to be associated with *de novo* Class II donor-specific antibodies [19]. In rare cases, TRAS or narrowing can occur due to extrinsic mechanical compression. For example, there has been a case report of transplant renal artery compression by enlarged native polycystic kidneys causing clinical features [20]. Similarly, in the present case, mechanical compression of a pseudoaneurysm caused transplant renal artery narrowing and the clinical features of TRAS.

Renovascular hypertension that occurs in the setting of TRAS is similar to Goldblatt's 'one-kidney, one-clip' experimental model on hypertension [21]. Pathologist Harry Goldblatt established the first animal model of hypertension in 1934, by testing the effect of experimentally induced renal ischemia on blood pressure in dogs [22]. In his 'two-kidney, one-clip' model, a clip is applied to the renal artery of one kidney to induce ipsilateral renal hypoperfusion. This activates the RAAS, causing hypertension with sodium and fluid retention. The elevated blood pressure leads to pressure natriuresis in the contralateral

normal kidney. Therefore, the overall volume status is normal or decreased, and the renin level is high in the 'two-kidney, one-clip' model. In the 'one-kidney, one-clip' model, a clip is applied to one kidney's artery while the contralateral kidney is removed. Renal hypoperfusion again results in activation of the RAAS leading to sodium retention and volume expansion, but there is no compensatory mechanism. Thus, in a steady state, there is sustained hypertension and volume expansion, and plasma renin activity is normal or low. One difference between TRAS and the 'one-kidney, one-clip' model is that the transplant kidney is denervated, thus kidney hypoperfusion does not directly elicit the sympathetic response that is normally triggered by renal ischemia [23]. In dogs, the critical degree of renal artery stenosis to cause a decrease in renal perfusion pressure was determined to be >50% of the diameter, and the minimum degree of stenosis needed to cause hypertension was 70% of the diameters, with the kidney being either innervated or denervated [24].

In Pickering Syndrome, flash pulmonary edema develops in patients with critical bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. It occurs when there is an abrupt imbalance of pulmonary fluid homeostasis and damage to the pulmonary capillary endothelium, leading to accumulation of fluid within the pulmonary interstitium and alveoli [25]. It is a dramatic form of acute decompensated heart failure. Flooding of the alveolar space can occur within minutes resulting in a life-threatening condition. Messerli *et al.* [13] proposed three pathophysiological mechanisms that may predispose patients with bilateral renal artery stenosis to develop flash pulmonary edema. The three mechanisms were defective natriuresis leading to sodium and fluid retention, exacerbation of diastolic dysfunction from increased blood pressure and damage of pulmonary capillary blood-gas barrier from increased intracapillary pressure and release of neurohumoral mediators, such as angiotensin II, catecholamines and endothelin-1. In other words, RAAS activation and sympathetic nervous system overactivity in TRAS could lead to damage to pulmonary capillary and fluid accumulation in pulmonary interstitium and alveoli, thus the development of flash pulmonary edema.

Differential diagnosis

There are several causes of hypertension after kidney transplantation. The risk factors for post-transplant hypertension include native kidney disease in the recipients, donor age, cold ischemia time, delayed graft function, allograft rejection and use of immunotherapy such as corticosteroid and calcineurin inhibitors [26]. Calcineurin inhibitors, cyclosporine more than tacrolimus, play a dominant role in raising blood pressure after kidney transplantation [27, 28]. This is also true in other solid organ transplantation. Among heart transplant recipients, Shiba *et al.* [29] found a 10-year incidence of 83.8% in developing hypertension in the cyclosporine era. One of the mechanisms that calcineurin inhibitors raise blood pressure by is increasing the release of vasoconstrictors, such as endothelin [30, 31]. In this patient, worsening hypertension was initially attributed to the use of immunotherapy, specifically tacrolimus and corticosteroids. However, despite escalating the dosage of antihypertensive medications, he still developed hypertensive crisis.

In the present case, Page kidney was also a differential diagnosis after renal ultrasound revealed a large mass located adjacent to the allograft. Page kidney occurs when a large subcapsular hematoma causes pressure-induced ischemia, leading to RAAS activation and systemic hypertension [32, 33]. Page kidney was first described by Irvine H. Page in 1939 when he wrapped kidneys in cellophane to cause renal parenchymal compression and noted the induction of hypertension [34]. Page kidney is often associated with blunt trauma [35] and iatrogenic intervention, such as allograft or native kidney biopsy [36, 37]. Although spontaneous Page kidney has been described in the kidney transplant literature [38], it usually occurs as a complication of allograft biopsy [39, 40]. Page kidney in an allograft is generally associated with acute hypertension and renal insufficiency [35, 37]. Surgical evacuation of the subcapsular hematoma is sometimes warranted to preserve renal function and normalize renin-mediated hypertension. In this patient, Page kidney became a differential diagnosis for hypertensive crisis and acute kidney injury after a large mass was discovered adjacent to the allograft on ultrasound. However, subsequent computed tomographic (CT) scan revealed that hematoma was not subcapsular and therefore did not cause renal parenchymal compression or Page kidney.

Diagnosis

The definitive diagnosis of TRAS requires the use of invasive angiography: conventional or digital subtraction angiography [3, 41]. Conventional angiography utilizes a relatively large amount of iodinated contrast, and thus poses a risk of developing contrast-induced acute kidney injury [42, 43]. Digital subtraction angiography has been shown to correlate highly with conventional angiography and uses a smaller amount of contrast material. This makes digital subtraction angiography a more suitable choice in the evaluation of TRAS [44, 45]. Although angiography procedures are diagnostic, they are invasive and may cause various complications, such as thromboembolism, pseudoaneurysms, traumatic arteriovenous fistulas and hematomas [3]. Therefore, angiographic techniques are not used as a screening tool, but are reserved for either patients with inconclusive results on the non-invasive screening tests or patients with TRAS requiring treatment [3].

The following non-invasive tests are reasonable alternatives for initial testing of TRAS: duplex sonography, isotope renography, CT angiography and contrast-enhanced magnetic resonance angiography (MRA). Duplex sonography is commonly utilized as an initial tool to investigate allograft dysfunction since it can be performed safely regardless of renal function [46]. Acceleration time in the transplant renal and intrarenal arteries $\geq$0.1 s, peak systolic velocity in the transplant renal artery >200 cm/s and a ratio of peak systolic velocity in the transplant renal-to-external iliac arteries >1.8 are used to diagnose TRAS [47]. Elevated peak systolic velocity in the transplant renal artery is the most sensitive Doppler criterion for the detection of high-grade TRAS [48]. In the present case, peak systolic velocity in the transplant renal artery was 457 cm/s. This led to the diagnosis of TRAS and the subsequent digital subtraction angiography. However, Duplex sonography is highly operator-dependent, and there may be technical difficulties in assessing transplant vessels [3, 46]. Contrast-enhanced ultrasound can complement standard

sonographic examination in the evaluation of TRAS by providing a quick and non-invasive assessment of graft perfusion [49–51]. Longer time of contrast agent inflow indicates the presence of stenosis, and the rate of contrast agent inflow has been shown to be positively correlated with severity of arterial stenosis on cross-sectional imaging [49]. Isotope renography (basal or after renin-angiotensin system stimulation) can also be used as a non-invasive screening procedure for TRAS, but it is limited by its relatively low specificity of 67% [52]. CT angiography is a widely available and utilized tool for accurate and non-invasive diagnosis of TRAS [53, 54]. This technique provides three-dimensional images of the vascular anatomy and depicts stenotic areas that are highly correlated with the findings on selective angiography [3, 55]. In addition to being non-invasive, CT angiography requires lesser volume of iodinated contrast than angiography [3, 55]. Similar to CT angiography, contrast-enhanced MRA can also accurately depict arterial anatomy, detect and grade transplant artery stenosis with the advantage of avoiding radiation exposure and uses relatively non-nephrotoxic gadolinium-based contrast agents [46, 56–58]. In a small study ($n = 27$), no significant difference was observed in diagnostic accuracy between contrast-enhanced CT angiography and gadolinium-enhanced MRA in the assessment of hemodynamically significant TRAS [59]. However, impaired renal function may prevent administration of gadolinium-based agents due to the risk of nephrogenic systemic sclerosis [58, 60]. Advanced non-contrast MRA techniques also allow imaging of post-transplant vascular anatomy with a high degree of accuracy [61–63]. For instance, an MRA technique using spatial labeling and multiple inversion pulses was reported to have a positive predictive value of 91% for diagnosing high-grade stenosis in the transplant artery, while electrocardiogram-gated non-enhanced three-dimensional steady-state free precession MRA also had 91% in diagnostic accuracy [61, 62]. The pros and cons of the non-invasive tests are listed in Table 2. Duplex sonography is typically the initial test of choice to diagnose TRAS.

Therapy

If a patient presents with Pickering Syndrome, hemodynamic unloading using antihypertensive drugs usually results in the prompt resolution of flash pulmonary edema. A loop diuretic may be used to initiate natriuresis to overcome sodium retention [13]. Although inhibitors of the RAAS could improve flash pulmonary edema empirically, they may further compromise renal perfusion. Therefore, these should not be used unless serum creatinine and potassium levels are in the normal range. In this patient, he developed oliguric acute kidney injury and ended up needing emergent renal replacement therapy to avoid acute respiratory decompensation.

Recognition of TRAS is important because it is potentially treatable. There are three treatment modalities: medical therapy alone, percutaneous transluminal angioplasty and surgical revascularization each with medical therapy. If renal function is stable and there is no hemodynamically significant stenosis on imaging, conservative treatment with antihypertensive medications can be used to control blood pressure [3]. If there is uncontrolled hypertension, worsening renal function or progression of stenosis, revascularization is warranted. In dogs with hypertension induced by constriction of the renal artery to a sole remaining kidney, release of renal artery constriction decreased the mean arterial blood pressure over a 3-day period and resulted in a significant negative sodium and fluid balance [64]. Renal revascularization improves renal perfusion, and decreases circulating angiotensin and aldosterone levels. This results in improvement in kidney function, natriuresis and a decrease in blood pressure.

Percutaneous transluminal angioplasty with stent placement is thought to be the first-line therapy to correct the stenosis. In general, it works well for lesions that are short, linear and distal from the anastomosis [65]. In a retrospective review of 547 renal transplants performed over a 6-year period, Greenstein *et al.* [16] reported that percutaneous transluminal angioplasty resulted in immediate cure or improvement in 76% of patients at a mean follow-up period of 30 months. Similarly, Chew *et al.* [66] reported an overall clinical success rate of 76.9% in a 10-year retrospective study. However, there are also other studies reporting a lower success rate. For example, Merkus *et al.* [67] reported only a third of percutaneous transluminal angioplasty procedures resulted in a definitive correction of the stenosis in their case series. Furthermore, in the USRDS registry, 145 of the 823 patients with TRAS underwent an angioplasty procedure, and no significant improvement in overall allograft survival was observed with angioplasty compared with without angioplasty ($P = 0.4$) [9]. There are also several complications associated with percutaneous intervention. They include renal artery dissection, stent restenosis, thromboembolism, hematoma and pseudoaneurysms at the puncture site [68]. There is currently no randomized controlled trial examining the efficacy of percutaneous transluminal angioplasty over medical therapy alone.

Open revision surgery is considered as a rescue therapy and reserved for cases of unsuccessful angioplasty. Surgical techniques include resection and revision of the

Table 2. Comparison of non-invasive tests for transplant renal artery stenosis

Non-invasive tests	Advantage	Disadvantage
Duplex sonography [3, 46]	No use of contrast agents, no radiation, inexpensive, high sensitivity (87–94%), high specificity (86–100%)	Operator-dependent, time-consuming, can be technically difficult especially in patients with complex anatomy of vessels
Isotope renography [52]	Good sensitivity (75%) may be predictive of physiologically meaningful renal artery stenosis	Low specificity (67%)
Computed tomography angiography [53–55]	Three-dimensional images allow direct visualization of vessels in optimal projection, shorter examination, not operator- dependent	Radiation, use of iodinated contrast
Magnetic resonance angiography [3, 46, 53, 54, 56–58]	Three-dimensional images, high sensitivity (67–100%), high specificity (75–100%), no radiation, no iodinated contrast	Artifacts from adjacent surgical clips, claustrophobia, high cost, patient hardware compatibility, use of gadolinium, limited availability

anastomosis, saphenous vein bypass graft of the stenotic segment, localized endarterectomy and excision/reimplantation of the renal artery [69]. Success rate seems to be comparable with percutaneous transluminal angioplasty [3]. However, there is a high risk of surgical complications that can result in graft loss and high mortality.

In the present case, transplant renal artery narrowing was caused by compression of a pseudoaneurysm. There were three donor renal arteries. Two of them were on a common aortic patch, while the third one was on a separate aortic patch. The third renal artery was transected during procurement and repaired. Two separate aortic cuff anastomoses were made to the external iliac artery. These multiple anastomoses could have contributed to the development of the pseudoaneurysm. Because transplant renal artery narrowing in this case was caused by the extrinsic compression of the pseudoaneurysm, the therapeutic strategy was different from a typical case of TRAS. Therefore, we focused the treatment on the control of the renal artery pseudoaneurysm, which can be repaired through either open or endovascular techniques. Historically, open repair was the standard of the care, but endovascular techniques are becoming more popular nowadays [70]. In this case, renal ultrasound with duplex showed the radiographic features of TRAS and the presence of a pseudoaneurysm. This was confirmed and further characterized by angiography. During the angiogram, endovascular repair such as coil embolization or balloon-assisted coiling [71] was not attempted, because patient continued to have hypertensive crisis and developed respiratory distress. The following day, he went to the operating room after he received renal replacement therapy with ultrafiltration. In the operation room, we attempted endovascular repair of the pseudoaneurysm, but were unsuccessful due to the complexity of the transplant renal vessel anatomy. In addition, due to extensive abdominal adhesion from prior surgeries, open surgical repair such as aneurysmectomy or arteriorrhaphy could not be performed either. Finally, a covered endoluminal stent was placed to the external iliac artery, and this led to surgical embolization of the allograft and subsequent allograft nephrectomy.

Conclusion

It is important to recognize TRAS in patients with post-transplant hypertension because it is associated with allograft loss and high mortality rate, and more importantly because it is potentially treatable. TRAS should be high on the differential diagnosis list especially when a kidney transplant recipient presents with hypertensive crisis and flash pulmonary edema, or Pickering Syndrome. Duplex sonography is commonly used as a screening tool, but a more definitive diagnosis requires invasive angiography. Percutaneous transluminal angioplasty with stent placement is generally thought to be the first-line therapy for TRAS. However, due to the nature of the disease, most of the studies were retrospective and the conclusions were drawn based on single-center experience. There is no randomized controlled trial to examine the efficacy and safety of percutaneous transluminal angioplasty compared with medical therapy alone or surgical intervention.

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