OPIS PRZYPADKU CASE REPORT

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Renal artery stenosis of the transplanted kidney as a cause of posttransplant arterial hypertension

Zwężenie tętnicy nerki przeszczepionej jako przyczyna nadciśnienia tętniczego po przeszczepieniu nerki

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Key words

hypertension after kidney transplantation, renal artery stenosis of the transplanted kidney, restenosis after transluminal angioplasty

Słowa kluczowe

nadciśnienie po przeszczepieniu nerki, zwężenie tętnicy nerki przeszczepionej, nawrót zwężenia tętnicy nerki przeszczepionej po angioplastyce

Summary

Hypertension after kidney transplantation is a very common disease and its etiology is usually complex. One of the causes of hypertension after kidney transplantation is transplanted renal artery stenosis (TRAS). The clinical features of TRAS include new-onset and refractory hypertension, allograft dysfunction especially after treatment with ACE inhibitor or AT1blockers, presence of bruit over the graft or arteriosclerosis in other arteries. It should be stressed that TRAS may be also completely asymptomatic. TRAS increases the risk of graft loss, including the patient's death, almost three-fold. Colour Doppler Ultrasonography is the most common, non-invasive, screening method used for the detection of TRAS. Percutaneous transluminal renal angioplasty (PTRA) with stenting is the treatment of choice and restores kidney perfusion in 65-100% of cases. TRAS should be taken into consideration in every case of hypertension in patients after organ transplantation. Early detection and treatment improve function and survival of transplanted kidney and survival of patients.

Streszczenie

Nadciśnienie tętnicze występuje u większości pacjentów po przeszczepieniu nerki. Etiologia nadciśnienia tętniczego w tej grupie pacjentów jest zwykle złożona, a w różnicowaniu jego przyczyn zawsze należy uwzględnić zwężenie tętnicy zaopatrującej graft (ang. *Transplanted Renal Artery Stenosis* – TRAS). Objawy kliniczne nasuwające podejrzenie TRAS to nagłe pogorszenie kontroli ciśnienia tętniczego krwi, nadciśnienie tętnicze oporne na leczenie, zwłaszcza z towarzyszącym upośledzeniem czynności przeszczepionej nerki, szybkie pogorszenie funkcji wydalniczej nerki po rozpoczęciu leczenia inhibitorami konwertazy angiotensyny lub blokerami receptora angiotensyny, szmer w okolicy przeszczepionego narządu oraz współistniejące zmiany miażdżycowe w innych obszarach naczyniowych. TRAS może przebiegać również bez objawów klinicznych. TRAS niemal trzykrotnie zwiększa ryzyko utraty nerki przeszczepionej, włącznie ze śmiercią pacjenta. Ultrasonografia metodą Dopplera jest podstawowym, nieinwazyjnym badaniem przesiewowym w przypadku podejrzenia TRAS. Przezskórna angioplastyka balonowa (ang. *Percutaneous transluminal renal angioplasty* – PTRA) połączona z implantacją stentu w miejscu zwężenia naczynia jest skuteczną w 65-100% metodą leczenia. Uwzględnienie TRAS jako przyczyny nadciśnienia tętniczego u każdego chorego po transplantacji nerki umożliwia wczesne rozpoznanie a następnie skuteczne leczenie, co istotnie wpływa na funkcję i przeżycie graftu oraz przeżycie pacjenta.

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INTRODUCTION

Arterial hypertension (HTN) is common after organ transplantation, affecting from 50 to 85% of kidney transplant recipients (1, 2). As one of the most important non-immunological risk factors of transplant failure, HTN contributes significantly to the development of graft loss in these patients. Moreover, HTN significantly increases the risk of serious cardiovascular events, which are the most common cause of death in kidney transplant recipients (3). A retrospective study conducted in over 1600 patients demonstrated that the risk of graft loss or death increases by 5% for every 10 mmHg increment in blood pressure (4). Generally, HTN etiology in kidney recipients

is complex and includes graft-dependent factors, recipient-dependent factors and the hypertensive effect of some immunosuppressant drugs. The key factors associated with HTN pathogenesis in kidney transplant recipients are shown in table 1.

Table 1. Causes of hypertension in kidney transplant recipients.

I. Transplant-related hypertension
– hypertension transferred with the transplanted organ from a hypertensive donor
– too small size of the transplanted kidney
– chronic kidney disease of the transplanted organ
– impaired function of the transplant kidney
– transplant renal artery stenosis (TRAS)
– hydronephrosis due to urethral obstruction in the transplanted kidney
– arteriovenous fistula following a graft biopsy
II. Recipient-related hypertension
– hypertension induced by the recipient's own kidneys – elevated renin secretion, sympathetic nervous system hyperactivation
– polycythemia – uncontrolled erythropoietin production
– obesity, metabolic syndrome
– obstructive sleep apnea syndrome
– concomitant endocrine hypertension-inducing disorders (Conn's syndrome, pheochromocytoma)
– presence of angiotensin II type 1 (AT1) receptor-activating antibodies
III. Immunosuppression-related hypertension
– glucocorticosteroids
– cyclosporine A
– tacrolimus

CASE REPORT

A 23-year-old male after kidney transplantation (4 years previously) demonstrated impaired kidney graft excretory function during a routine follow-up visit at the Transplantation Outpatient Clinic (increased serum creatinine levels from 280 to 445 μmol/L; $eGFR_{MDRD}$ = 13 ml/min/1.73 m^2) and high blood pressure values (240/120 mmHg). The patient was urgently admitted to the Department of Nephrology, Endocrinology and Metabolic Diseases, Silesian Medical University in Katowice. On admission, he denied dysuria and fever and reported no decrease in urine volume, no peripheral edema, or pain. Past medical history showed earlier incident of impaired renal excretory function and elevated hypertension after 14 months of kidney transplantation. Doppler ultrasonography and computed tomography angiography (CTA) of the kidney graft allow to make a final diagnosis of transplanted of transplant renal artery stenosis (TRAS) (by approximately 50%) in the vicinity of the anastomosis. Following percutaneous transluminal renal angioplasty (PTRA) of the transplanted kidney with metal stent placement, both the blood pressure and serum creatinine levels returned to the levels observed prior to the described TRAS. During the patient's present stay on the ward (July 2012), due to ineffective control of hypertension with oral antihypertensive drugs (captopril, nitrendipine, doxazosin, metoprolol, furosemide), parenteral urapidil followed by a continuous nitroglycerine were administered; however, complete blood pressure control was not achieved. The Doppler ultrasound examination showed reduced vascularization of the segmental arteries of the kidney graft; the renal artery anastomosis or the segment distal to the anastomosis were not visualized. Due to a suspected restenosis of the stent placed in the graft artery in 2009, the patient was qualified for a double procedure of angiography and angioplasty. Angiography revealed a critical intrastent stenosis of the graft renal artery at the site of its anastomosis with the left external iliac artery, while the distal segment of the graft renal artery was normal (fig. 1). At the same time, a successful 5 x 20 mm balloon angioplasty of the stenosed segment was performed. No complications were observed following the procedure, and the blood pressure did not exceed 150/95 mmHg. After the procedure, dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) and the antihypertensive treatments with metoprolol (at a dose 2 x 50 mg p.o.) and furosemide (at a dose 2 x 40 mg p.o.) were administered to achieve effective blood pressure control. Seven days after the balloon angioplasty, serum creatinine levels decreased from 445 μmol/L measured on admission to the Nephrology ward, to 329 μmol/L. During follow-up visits at the Transplantation Outpatient clinic 1 and 5 months after the procedure, blood pressure did not exceed 140/90 mmHg and the kidney graft excretory function returned to the level observed during the 12 months preceding the described TRAS episode (maximum creatinine level 287 μmol/L).

EPIDEMIOLOGY, PATHOPHYSIOLOGY, CLINICAL PRESENTATION

Depending on the diagnostic methods and criteria, transplant renal artery stenosis (TRAS) is found in 1 to 23% of all kidney transplant recipients (5). A recent study in 41 000 kidney transplant recipients showed the incidence of TRAS to be 8.3 new cases per 1000 patients per year (6). TRAS typically develops 3 months to 2 years after kidney transplantation, most commonly 6 months post transplantation, but it may also occurs long after the procedure (7-9). Clinical manifestations suggestive of TRAS are a sudden blood pressure increase and graft excretory dysfunction, not associated with acute rejection, infection, or obstructive nephropathy. Transplant renal artery stenosis may be suspected when a rapid deterioration in renal excretory function following initiation of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) treatment is observed or there is a presence of vascular bruit over transplanted kidney or concomitant atherosclerosis lesions in other arteries (10). Moreover, due to activation of the renin-angiotensin-aldosterone (RAA) system in the

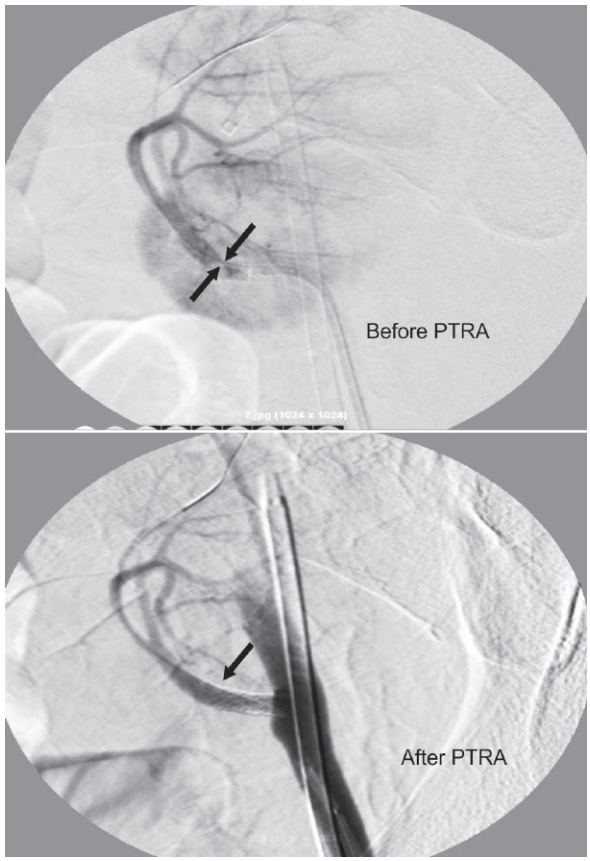

Fig. 1. Arteriography of the transplant renal artery (the arrow marks the site of stenosis).

course of renal artery stenosis, there may be signs of fluid retention for instance peripheral edema or congestive heart failure. It is important to remember that critical TRAS may occurs despite a lack of the clinical manifestations mentioned above. Introduction of routine Doppler ultrasound examinations in kidney transplant recipients helped increase the rate of TRAS diagnosis by 10% in the total population of kidney transplant recipients, the majority of whom were asymptomatic (11). In a study conducted in 823 patients with TRAS, Hurst et al. demonstrated that TRAS increased the risk of graft loss, including the patient's death, almost three-fold compared to the rate in patients without TRAS (6). Risk factors for TRAS include: advanced age of the donor and/or recipient, kidney from an expanded criteria donor (donor > 60 y.o. or donor > 50 y.o. with 2 out of 3 associated factors: history of hypertension, creatinine levels ≥ 1.5 mg/dL, stroke-related death), delayed graft function, ischemic heart disease, induction immunosuppressive therapy, cytomegalovirus infection (6, 12, 13). The method of kidney harvesting, degree of vessel damage, vessel length (e.g. long artery and short vein of the transplant kidney), atherosclerosis in donor vessels, and probably the method of anastomosis between the recipient's own vessels and the vessels of the graft (the use of clamps, type of anastomosis) (6). TRAS generally develops in the area of surgical anastomosis of the graft artery with the recipient's artery, but it may also develop proximally or distally to the anastomosis. TRAS occurring at the site of anastomosis is typically directly associated with the transplantation surgery and may be a result of donor or recipient vessel damage (e.g. during kidney harvesting or during vessel preparation for anastomosis), due to subsequent fibrosis and scarring at the site of anastomosis or due to an inappropriately conducted anastomosis procedure. The latter reason for TRAS occurs typically soon after transplantation. Non-anastomotic TRAS is mostly associated with atherosclerotic lesions in the donor or recipient arteries and typically develops later after kidney transplantation. The so-called pseudo-TRAS, which is associated with atherosclerotis narrowing of iliac arteries impairing transplant artery perfusion, should also be considered in differential diagnosis.

DIAGNOSTICS

Doppler ulrasonography is the main screening diagnostic procedure in TRAS, evaluating hemodynamic parameters in the organ. Doppler parameters characteristic for TRAS are shown in table 2. Renal Doppler ultrasound is a noninvasive, easily accessible and repeatable examination with 87-94% sensitivity and 86-100% specificity (11). However, Doppler ultrasonography is a time-consuming examination that should be conducted only by a very experienced specialist. Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) are also used in diagnosis of TRAS. These imaging methods allow to find the precise location and to conduct an accurate assessment of the degree of vascular stenosis, and are characterized by a 98 and 83% sensitivity and 94 and 97% specificity, respectively (9). Despite continuous advances in the imaging techniques mentioned above, intra-arterial arteriography still remains the 'gold standard' of TRAS diagnosis. However, this is an invasive procedure, requiring puncturing a major arterial vessel and associated with increased risk of complications, including contrast-induced nephropathy. The alternative to conventional arteriography with iodine-based contrast media may be carbon dioxide arteriography (carbon dioxide has no nephrotoxic effects); this imaging method should be considered especially in patients with highly impaired graft excretory function (14).

Table 2. Doppler-ultrasound-based diagnostic criteria of TRAS (18).

– increased maximum blood flow velocity at the site of stenosis – Vmax > 2 m/s.
– lowered pulsatility index (PI) and resistive index (RI)
– longer acceleration time (AT) in intrarenal arteries (> 100 ms)
– the ratio of Vmax in the graft artery to Vmax in the iliac artery proximal to the anastomosis > 1.8

TREATMENT

There are 3 methods used in TRAS treatment: pharmacological antihypertensive therapy, percutaneous transluminal renal angioplasty (PTRA) with or

without stent implantation and surgical treatment. The first therapeutic option involving only pharmacological antihypertensive therapy is recommended for patients with TRAS with stable graft excretory function and no evidence of hemodynamically significant TRAS in Doppler ultrasound (Vmax < 1.8 m/s, resistive index 0.5). In these patients, small doses of short-acting ACE-inhibitors may be used (11), with serum creatinine and potassium level monitored during treatment. Additionally, supportive treatment may include statins and acetylsalicylic acid (10). The remaining two therapeutic options of percutaneous revascularization and surgery typically require complementary pharmacological antihypertensive treatment. Percutaneous transluminal renal angioplasty (PTRA) is recommended in the case of TRAS with refractory hypertension and/or deteriorating graft excretory function. In the majority of cases, percutaneous balloon angioplasty is performed together with stent placement, as this method is associated with a lower risk of restenosis. Restenosis occurs in less than 10% of patients who underwent PTRA with stent placement, whereas the rate of restenosis with PTRA alone ranges from 16 to 62%. The effectiveness of percutaneous balloon angioplasty with stent placement ranges from 65 to 100% (15). However, it is important to remember that these procedures are associated with a risk of complications, such as: arterial dissection, embolism, hematoma, pseudoaneurysm, as well as the already mentioned restenosis. PTRA complications may occur in up to 10% of patients treated with this method. Surgical treatment of TRAS is conducted in patients after unsuccessful PTRA and in those with a very significant stenosis or other technical problems inaccessible to PTRA. Surgical treatment effectiveness and the rate of restenosis are comparable to those of PTRA with stent placement, although the rate of complications is higher with surgery. These complications include graft loss (15-20%), ureteral damage (14%), reoperation (13%) and death (5%) (11). Like in the case of recipient's own renal artery stenosis, TRAS has no specific indications to qualify a patient for revascularization and there are no large prospective studies comparing the efficacy and long-term benefits of the individual treatment options, and the results of earlier studies are inconsistent. A recent retrospective study in 67 patients with TRAS compared long-term results of three therapeutic options of TRAS: conservative treatment (pharmacological therapy), percutaneous balloon angioplasty with stent placement and surgical treatment (16). Assessed at 1 and 5 years of follow-up, graft survival after balloon angioplasty with stent placement was 93 and 81%, respectively, which was significantly higher in comparison to that in patients undergoing conservative (75 and 65%, respectively) or surgical treatment (85 and 63%, respectively). All three study groups achieved a reduction in hypertension, however, only the percutaneous angioplasty group demonstrated this effect to be maintained long-term. A study by Geddes et al., who evaluated the treatment efficacy in 27 patients undergoing PTRA and 16 patients receiving conservative treatment, demonstrated different results. The study revealed no differences in terms of hypertension values, the number of antihypertensive drugs used, or renal graft function at 5 years of follow-up (17). Similarly, in a retrospective study in 823 patients with TRAS, Hurst et al. showed no significant differences in graft survival between the conservative treatment group and the percutaneous balloon angioplasty group (6). Long-term prospective studies are needed in order to answer the questions of when and how to treat patients with TRAS.

CONCLUSIONS

Most kidney transplant recipients develop hypertension, and its etiology is typically complex. Transplant renal artery stenosis (TRAS) should always be considered when differentiating causes of hypertension in this group of patients. TRAS may manifest as refractory hypertension with or without impaired graft excretory function, but it may also be completely asymptomatic. TRAS increases the risk of graft loss, including the patient's death, almost three-fold. Therefore, routine Doppler ultrasound examinations of the graft, which are easily accessible and non-invasive screening assessments, seem to be warranted in each kidney transplant recipient.

BIBLIOGRAPHY

1. Zhang R, Leslie B, Boudreaux JP et al.: Hypertension after kidney transplantation, impact, pathogenesis and therapy. Am J Med Sci 2003; 325: 202-208.
2. Campistol JM, Romero R, Paul J, Gutiorrez-Dalmau A: Epidemiology of arterial hypertension in renal transplant patients: changes over the last decade. Nephrol Dial Transplant 2004 Jun; 19 (suppl. 3): ii62-66.
3. Ojo AO: Cardiovascular complications after renal transplantation and their prevention. Transplantation 2006; 82: 603-609.
4. Kasiske BL, Anjum S, Shah R et al.: Hypertension after Sidney transplantation. Am J Kidney Dis 2004; 43: 1071-1081.
5. Fervenza FC, Lafayette RA, Alfrey EJ, Petersen J: Renal artery stenosis in kidney transplants. Am J Kidney Dis 1998; 31: 142-148.
6. Hurst FP, Abbott KC, Neff RT et al.: Incidence, predictors and outcomes of transplant renal artery stenosis after kidney transplantation: analysis of USRDS. Am J Nephrol 2009; 30: 459-467.
7. Seratnahaei A, Shah A, Bodiwala K, Mukherjee D: Management of transplant renal artery stenosis. Angiology 2011; 62: 219-224.
8. Voiculescu A, Schmitz M, Hollenbeck M et al.: Management of arterial stenosis affecting kidney graft perfusion: a single-centre study in 53 patients. Am J Transplant 2005; 5: 1731-1738.
9. Munoz Mendoza J, Melcher ML, Daniel B, Tan JC: Multiple renal arteries and non-contrast magnetic resonance angiography in transplant renal artery stenosis. Clin Kidney J 2012; 5: 272-275.
10. Piecha G, Wiecek A, Januszewicz A: Epidemiology and optimal man-

agement in patients with renal artery stenosis. J Nephrol 2012; 25: 872-878.
11. Bruno S, Remuzzi G, Ruggenenti P: Transplant Renal Artery Stenosis. J Am Soc Nephrol 2004; 15: 134-141.
12. Audard V, Matignon M, Hemery F et al.: Risk factors and long-term outcome of transplant renal artery stenosis in adult recipients after treatment by percutaneous transluminal angioplasty. Am J Transplant 2006; 6: 95-99.
13. Humar A, Uknis M, Papalois V et al.: Is there an association between cytomegalovirus and renal artery stenosis in kidney transplant recipients? Transplantation 2000; 69: S386.
14. Spinosa DJ, Matsumoto AH, Angle JF et al.: Gadolinium-based contrast and carbon dioxide angiography to evaluate renal transplants for vascular causes of renal insufficiency and accelerated hypertension. J Vasc Interv Radiol 1998; 9: 909-916.
15. Leonardou P, Gioldasi S, Pappas P: Transluminal angioplasty of transplanted renal artery stenosis: a review of the literature for its safety and efficacy. J Transplant 2011; 2011: 693820; doi: 10.1155/2011/693820.
16. Ghazanfar A, Tavakoli A, Augustine T et al.: Management of transplant renal artery stenosis and its impact on long-term allograft survival: a single-centre experience. Nephrol Dial Transplant 2011; 26: 336-343.
17. Geddes CC, McManus SK, Koteeswaran S, Baxter GM: Long-term outcome of transplant renal artery stenosis managed conservatively or by radiological intervention. Clin Transplant 2008; 22: 572-578.
18. De Morias RH, Muglia VF, Mamere AE: Duplex Doppler sonography of transplant renal artery stenosis. J Clin Ultrasound 2003; 31: 135-141.

received/otrzymano: 20.11.2013
accepted/zaakceptowano: 08.01.2014