Post-transplantation Presentation of ANCA-associated Vasculitis: Granulomatosis with Polyangitis

M. A. Shafiee[1],
G. Parastandechehr[1],
S. Taba Taba Vakili[1],
M. Shahroukh[2],
A. Haghighi[3],
B. Broumand[2]*

[1]*Department of Medicine, Toronto General Hospital, University of Toronto, 200 Elizabeth St, 14 EN-208 Toronto, ON, M5G 2C4, Canada*
[2]*Pars Advanced and Minimally Invasive Manners Center, Pars Hospital, and Department of Nephrology, Iran University of Medical Sciences, Tehran 1415944911, Iran*
[3]*Department of Rheumatology, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran 1445613131, Iran*

ABSTRACT

Granulomatosis with polyangitis (GPA) is characterized by necrotizing granulomatosis of the upper and lower respiratory tract and glomerulonephritis. If GPA does not respond to appropriate management, it might result in end-stage renal disease, which may remit the disease severity. The overall impression is that immunosuppression following renal transplantation would further subside the vasculitis. However, several studies have shown that systemic vasculitis recur in 25% of patients following renal transplantation. This may indicate the perplexing nature of the immune system. One of the key factors in prevention of relapse of GPA is following up of patients by careful immunosuppressive dose adjustment and regular measurement of biomarkers for vasculitis. Herein, we describe an interesting case of biopsy-proven GPA who had a complex long history of several post-transplantation relapses in different organs with anti-neutrophil cytoplasmic antibodies seroconversion. This case emphasizes that vasculitis in particular GPA can mimic various diseases depending on which vessels and organs are affected by the inflammation and is one of the reversible causes of failure of transplanted kidney. Bearing the diagnosis in mind as one of the potential differential diagnoses of failure of renal transplantation will lead to early diagnosis and treatment of recurrent GPA.

KEYWORDS: Granulomatosis with polyangitis; ANCA; Kidney transplant

INTRODUCTION

Currently, pauci-immune crescentic glomerulonephritis is the most common cause of rapidly progressive renal failure [1]. The majority of cases are associated with the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) with a specificity of 99.3% with a wide range of sensitivity (34%–92%) [2, 3]. One of the major subtypes of ANCA-associated vasculitis (AAV) is granulomatosis with polyangitis (GPA). Kidney transplantation has been shown to improve survival and quality of life in GPA patients with end-stage renal disease (ESRD). Several studies have demonstrated that kidney transplantation offers a survival benefit compared with maintenance dialysis in these patients [4, 5]. Transplanted AAV patients also have lower vasculitis relapse rates compared with those who remain on dialysis [6]. Having said that, we describe an interesting case of a 23-year-old white woman with biopsy-proven GPA, who had a complex long history of several post-transplantation relapses in different

*Correspondence: Behrooz Broumand MD, Assistant Professor, Department of Medicine, Toronto General Hospital, University of Toronto, 200 Elizabeth St, 14 EN-208 Toronto, ON, M5G 2C4, Canada
Tel: +1-416-340-4800 ext. 6244
Fax: +1-416-595-5826
E-mail: mohammad.shafiee@uhn.ca

organs such as sinuses, joints, the central nervous system, renal artery of transplanted kidney, and ureteropelvic junction of the transplanted kidney with ANCA seroconversion.

CASE PRESENTATION

A 23-year-old woman presented on March,1998 to the out-patient clinic with morning stiffness, oral temperature of 38 °C, cough, hemoptysis, polyarthritis (including sacroiliac and hip joints), abdominal cramps, hematuria, vaginal bleeding, hematochezia, perianal tender swelling, and paroxysmal nocturnal dyspnea. In physical examination, she was found to have bilateral coarse crackles at the bases of lungs and some maculopapular rashes with palpable purpuras in the perianal area. The patient also had some blisters on the extensor surface of the left knee, along with subcutaneous nodules along left side of her neck, as well as some red maculopapular rashes and palpable purpura on both forearms. There were some infarcted areas in her nail beds in addition to oral aphthous ulcers and petechial lesions on her soft palate.

Laboratory results showed a white blood cell (WBC) count of $20\times10^3/mm^3$ with shift to the left, hemoglobin of 5.5–10.3 g/dL, erythrocyte sedimentation rate (ESR) of 85 mm in the 1st hr, 3^+ CRP, and elevated serum IgA levels. C-ANCA was negative in two occasions. Urine analysis disclosed 4^+ proteinuria, hematuria (25–30 RBC/HPF with 45% dysmorphic RBC), and leukocyturia (25–30/HPF). Twenty-four-hour urine contained 7926 mg protein and 1200 mg creatinine. Paranasal, frontal and maxillary sinuses were reported normal in x-ray. Chest x-ray was suggestive of alveolar hemorrhage with no cavity. Pelvic x-ray revealed right sacroiliitis. Electromyography (EMG) and nerve conduction velocity (NCV) studies revealed mixed pattern of myopathy and neuropathy. Echocardiography was normal. Colonoscopy was positive for multiple small ulcers in the rectum. The patient was treated with drainage and antibiotics for her perianal abscesses. She became afebrile upon receiving antibiotic treatment. Prednisolone 40 mg/day and hydroxychloroquine 200 mg/day were started for skin manifestations with the possible diagnosis of GPA or Henoch-Schonlein purpura.

There was a great improvement in general condition over two months. In five-month follow-up increasing proteinuria and rise in her serum creatinine from the baseline value of 1.3 to 4 mg/dL and BUN of 105 mg/dL occurred.

Renal biopsy performed, was interpreted as necrotizing crescentic glomerulonephritis and acute interstitial nephritis. Skin biopsy was also done showing leukocytoclastic vasculitis. Accordingly, the possible diagnosis of vasculitis (likely GPA) was made. Immunosuppressive therapy was started including intravenous (iv) methylprednisolone, 1000 mg/day for three consecutive days, cyclophosphamide, 1000 mg/day for three consecutive days, and five courses of plasmapheresis, once weekly. Oral co-trimoxazole (trimethoprim/sulfamethoxazole) was added for possible AAV.

On follow-up, the patient was referred to our clinic on September 29, 1999 with a serum creatinine of 4 mg/dL and a BUN of 105 mg/dL, while she had already received 1 g iv cyclophosphamide monthly for three consecutive months. After a few months, the patient developed nausea and vomiting.

Then an A-V fistula was created, and immunosuppressive therapy was stopped except for prednisolone therapy of 7.5 mg/day. Five months after hemodialysis, on August 12, 2000, the patient had an uneventful pregnancy and delivered a healthy baby girl. During her pregnancy hemodialysis sessions were increased to five times/wk.

In June 22, 2002, the patient received a renal transplant from a 29-year-old woman unrelated live donor. Her initial immunosuppressive regimens were prednisolone, 7.5 mg, po, qd; cyclosporine 100 mg, po, bid; and Cellcept, 1 g, po, bid. She was also treated with co-trimoxazole 40/400 mg po, bid and nifedipine, 30 mg, po, qd, to treat post-transplantation hypertension. Her serum creatinine was always less than 1.3 mg/dL; the serum cyclosporine A

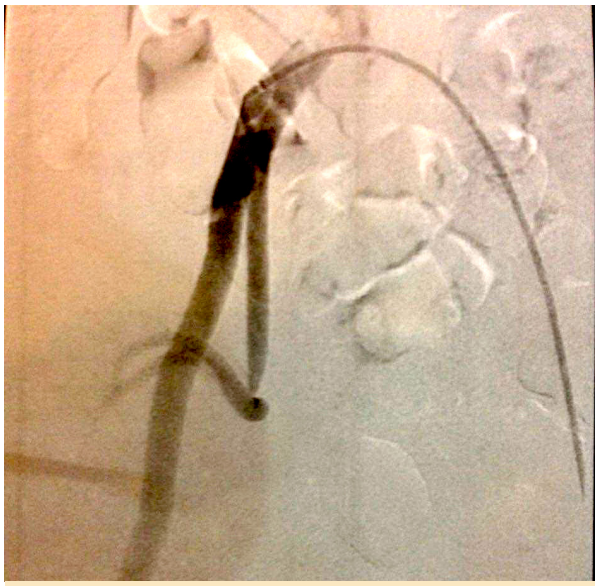

Figure 1: Angiogram of the renal transplant

level was in acceptable range for 12 years post-transplantation.

For seven years, she continued to suffer from recurrent sinusitis and frequent episodes of left knee swelling, otolaryngology consultation was done three times. Sinus computed tomography was ordered and blood work and urine culture for infection were done. Also cerebrospinal fluid (CSF) and synovial fluid analysis, VDRL, and PPD were done, all being negative. There was an excellent improvement with steroid therapy. However, her ANCA remained negative.

On February 10, 2009, with no changes in immunosuppressive regimen, she presented with a high grade fever, cloudy nasal discharge, neck rigidity, severe headache, diplopia, and bilateral papillary edema. Lumbar puncture was performed revealing high CSF pressure (>40 cm H_2O). CSF analysis revealed high protein, 400 RBC, 50 WBC with 20% PMN and 80% lymphocytic predominance. Brain MRI showed a lesion suggestive of lymphocytic hypophysitis (LYH). Accordingly, she was treated successfully with high dose steroids.

In March 2009, the patient was admitted with severe headache. While taking her immunosuppressive, as usual and regularly, her C-ANCA became positive for the first time accompanied by proteinuria of <900 mg/24 hrs. Neurology consultation reported "bilateral papillary edema and high CSF pressure (>40 cm H_2O)," Cerebral pseudo-tumor was therefore suggested and frequent lumbar puncture was recommended. Laboratory data including HBS Ag, HBC Ab, HIV Ab, CMV Ab (IgG and IgM), VDRL, and AFB for Mycobactrium tuberculosis, C_3, C_4, CH50, Wright and Coombs Wright reported within normal limits. In all CSF analyses, WBC was high with lymphocyte predominance, high protein and normal to low glucose. The patient developed cavernous sinus thrombosis, which was treated successfully using heparin followed by warfarin. Headache was subsided with increasing the dose of corticosteroid. In follow up, the patient was doing well and stable until September 2014 when her serum creatinine was 1.3 mg/dL and urinalysis was normal.

In November 2014, while on cyclosporine A, according to blood level and Cellcept 2 g/day plus 7.5 mg prednisolone, the patient developed acute renal failure—an increase in serum creatinine from 1.3 to 2.01 mg/dL—with the therapeutic range of cyclosporine A trough level. In work up for the cause of acute kidney injury in transplanted kidney, color Doppler ultrasonography reported positive for a significant renal artery stenosis of the transplanted kidney at the anastomosis site of the donated renal transplant artery to the right internal iliac artery of the recipient (Fig 1). At this time, there was no evidence of hydronephrosis of the transplanted kidney in ultrasonography.

A stent was inserted via angioplasty procedure, to bypass significant proximal renal artery stenosis in the transplanted kidney on February 18, 2015. Following insertion of the stent in the stenotic site, renal function improved. In June 2015, serum creatinine increased again. Renal ultrasonography revealed a moderate to severe hydronephrosis due to uretero-pelvic junction obstruction (UPJO) in the transplanted kidney. Considering positive C-ANCA with simultaneous inflammation of the right knee and ankle joint, diagnosis of recurrent vasculitis in ureteo-pelvic junction of the transplanted kidney was established. Following percutane-

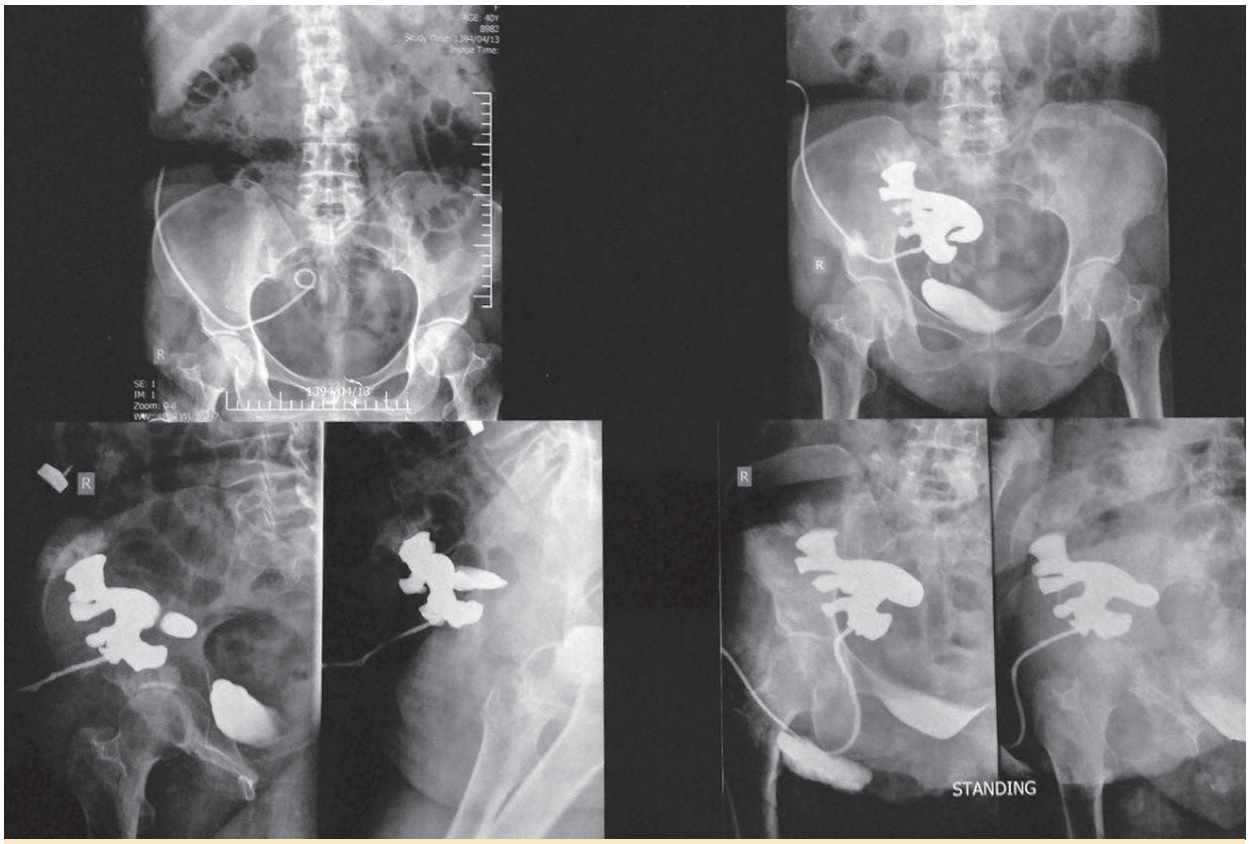

Figure 2: Antegrade pyelography

ous nephrostomy and antegrade pyelography (Fig 2), initiation of corticosteroid therapy as well as 500 mg prednisolone daily, and rituximab every week for four consecutive weeks, complete resolution was achieved. On July 4, 2015, nephrostomography of the transplanted kidney revealed resolution of the uretero-pelvic stenosis in the transplanted kidney (Fig 3) and no more hydronephrosis, thus, nephrostomy catheter was removed. In March, renal ultrasound revealed grade 1–2 hydronephrosis in pyelocaliceal system and hydroureter. Simultaneous laboratory work showed a WBC count of 1500, hemoglobin of 11.9 g/dL, BUN of 25 mg/dL, creatinine of 1.6 mg/dL, and serum potassium of 4.7 mEq/L.

DISCUSSION

To the best of our knowledge, this is the first report of GPA after renal transplantation in a female patient who had a complex long history with several relapses in different organs such as sinuses, joints, the central nervous system, and renal artery and uretero-pelvic junction of the transplanted kidney with ANCA seroconversion post-transplantation. The patient experienced vascular involvement of many organs probably due to a bacterial infection superimposed on her vasculitis.

It is known that GPA is a fatal disease that affects small to medium sized vessels in multiple organs. Infections with micro-organisms, such as bacteria and viruses, as well as genetic background have been implicated in its pathogenesis. There is a general agreement that ANCAs are responsible for the inflammation in GPA. ANCAs can activate neutrophils, increase their adherence to endothelium, and induce their granulation that can damage endothelial cells and induce vascular inflammation.

Bacterial infection such as Staphylococcus aureus infection (SA) may be essentially implicated as a significant risk factor for GPA exacerbation [7]. Chronic nasal carriage of SA has been reported to be three times more frequent

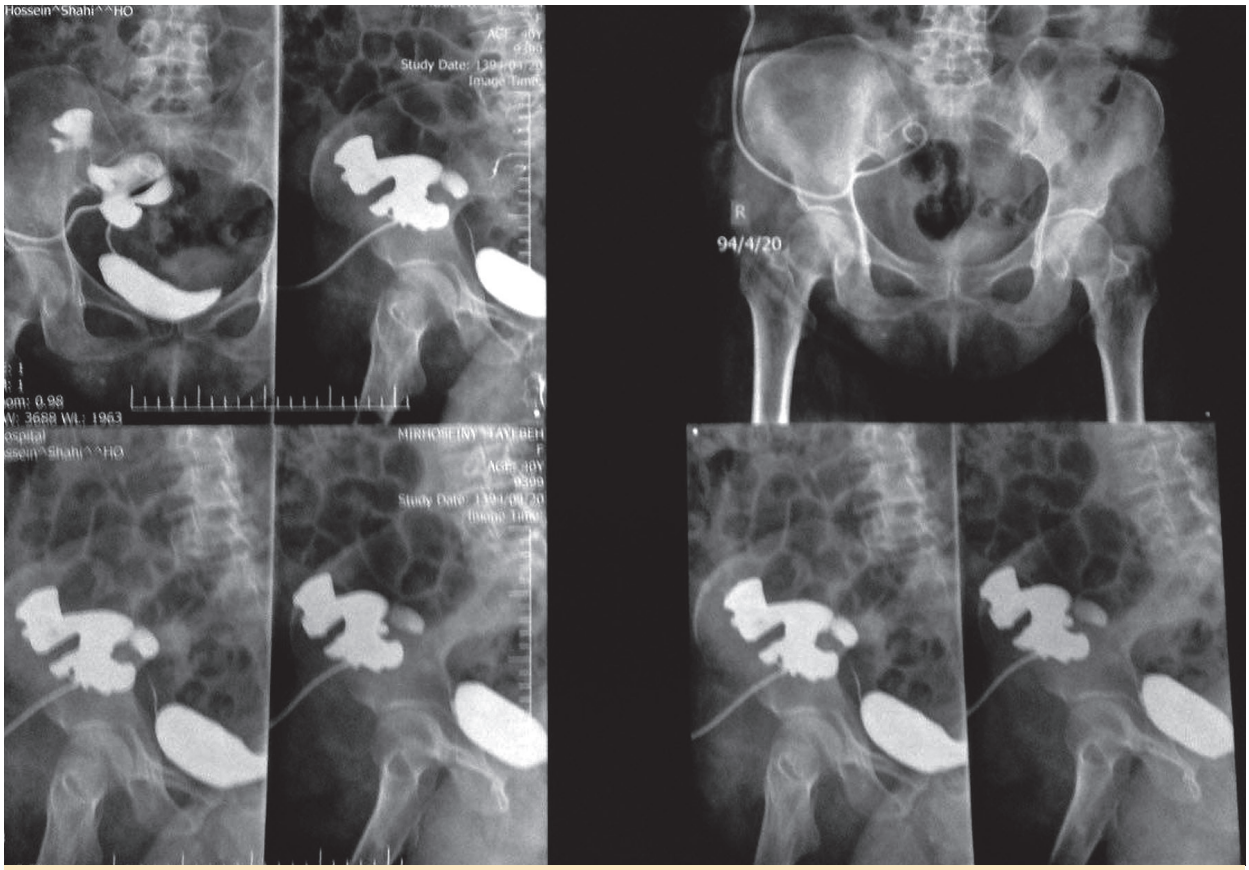

Figure 3: Resolution of the uretero-pelvic stenosis in the transplanted kidney

in GPA patients than healthy individuals [7]. The prevalence of SA carrier has also been shown to be 40%–50% among hemodialysis patients [8], explaining higher contamination rate of SA in transplant recipients, similar to our patient who was a SA-carrier because she had a positive nasal swab for SA and it was also positive again after three months. The mechanism of action of SA infection attributes to its contribution to the pathogenesis of AAV by triggering a break in immune tolerance and the development of sustained or recurrent autoimmunity. SA can potentially act as an immune stimulator, and by proliferation of T cells and B cells to induce autoimmunity [9, 10].

Generally, one would expect that in uremia, ESRD, and post-transplantation, autoimmune diseases including vasculitis would subside, as they are all considered immunosuppressive states. However, relapses occur. This can be due to inadequate immune suppression as a consequence of dose adjustment based on patients' tolerability to medications. Moreover, some of the medications can have an immunomodulatory effect, which may result in ANCA seroconversion. Recurrent SA infection, which could be prevalent in this population as discussed above, could contribute to this pathology. Presence of new systemic vasculitis or rising ANCA titer level during relapse attacks might be useful in detecting the relapse. In addition biopsy of the affected organ can reveal a new vasculitis, and at last, reasonable response to immunosuppressive therapy could be a proof which suggest relapse retrospectively.

Several studies have shown that systemic vasculitis recur in 25% of patients following renal transplantation, which corresponds to 0.04/patient/yr depending on the maintenance of treatment, follow-up and some donor organ-related factors [11]. There is no clear consensus regarding the risk of post-transplantation recurrence of vasculitis (renal or non-renal). However, non-renal post-transplant relapse is more prevalent specifically in skin, upper re-

spiratory tract and joints. One study reported an AAV recurrence rate of 17% on an average of 31-month follow-up [12, 13]. Accordingly, in order to prevent the relapse in vasculitis, it is crucial to following up of patients by careful immunosuppressive dose adjustment and regular biomarkers measurement. It is important to have high index of suspicion for recurrence of vasculitis in the transplanted kidney when present with renal failure and not just focus on rejection or drug toxicity in such cases.

Some other important factors in relapse are genetic factors, such as PR3, MPO, α$_1$-antitrypsin, CD8 T cells, and CTLA4, which can play important role in AAV [14]. In autoimmune lymphocytic hypophysitis, a known (but rare) consequence of GPA, specific human monoclonal antibodies, which antagonize CTLA4, could result in autoimmune and auto-inflammatory system disorders by induction of unrestrained T-cell activation [7, 11]. Lymphocytic hypophysitis is an autoimmune disorder of the pituitary gland. Symptoms include headache, visual disturbance, pituitary dysfunction, and neurological deficits [15]. In this case, the first manifestation of headache in addition to evidence of increased intracranial pressure requiring frequent lumbar puncture and suspicious of pituitary tumor was compatible with lymphocytic hypophysitis, managed by frequent lumbar puncture after pituitary tumor was ruled out by MRI.

The pathogenesis includes multi-vasculitis episodes in the brain, like other organs, of which more than 90% abnormalities happen in hypothalamic region (anterior, posterior, and stalk) [16]. Pituitary gland is also vulnerable to arterial injury, edema and swelling, leading to vasculitis. Pituitary is a highly vascular organ with extensive small size capillary sinuses and portal vessels [17]. Therefore, inflammation can result in serious conditions. Ischemia results in a cascade of activation of leukocytes/platelets, inflammatory mediators, calcium influx, disruption of cell membrane and fluid transudation that cause a rise in pressure resulting in more edema and consequently lower perfusion as a vicious cycle. Moreover, inflammatory mediators increase capillary permeability and activate coagulation cascade [18] to culminate in excess fluid formation and edema in the closed space (the gland is located in the middle of the sella turcica and covered by meningeal layer on top, which make it like a box) that can imitate as a compartment to produce further tissue damage and ischemia. Furthermore, as all of the pituitary circulation goes through the stalk, passing through a narrow orifice, inflammatory phase in vasculitis could cause an increase in the thickness of the stalk and result in strangulation of the vessels, further ischemia, vascular wall damage and inflammation [14]. Steroids (glucocorticoid) could be considered an efficient therapy (with a 75% reduction in size of hypophysis) in lymphocytic hypophysitis by decreasing the inflammation, edema and improving the perfusion [19].

Transplant renal artery stenosis (TRAS) is a recognized, potentially curable cause of post-transplant arterial hypertension, allograft dysfunction, and graft loss. It usually occurs between three months and two years after transplantation, but earlier or later presentations are not uncommon. The prevalence ranges widely from 1% to 23% in different series, reflecting the heterogeneous criteria used to establish the diagnosis, the different manner of preservation of the graft, and surgical expertise. Reported cases are progressively increasing in parallel with the use of non-invasive procedures such as Doppler ultrasonography and magnetic resonance (MR) angiography, which arouse the suspicion of the disease even in less symptomatic cases [20]. Vasculitis relapse TRAS are less common, but it could be one of the consequences of trauma and other mechanisms of injury to vessels such as initial intimal damage by vascular clamps, rough handling and stretching of the artery, which might lead to inflammation, ischemia and recurrence of vasculitis (as in our patient). Also, turbulence flow resulting from kinking, which by torsion of the allograft plus cold ischemia in deceased donor transplantation, may cause arterial injury and inflammation and could be the start point of relapse ending in fibrosis and stenosis/stricture [21].

Uretero-vesicular junction obstruction is the most common urinary complication after renal transplantation with incidence of 3%–8%, caused by reduced blood supply, due to renal and pelvic vascular injury during the transplantation [22, 23]. However, cases of ureteral stenosis and obstructive uropathy due to granulomatous vasculitis at the ureterovesical junction resulting from significant relapse after renal transplantation have been reported [24, 25]. This relapse could be secondary to AAV resulting from TRAS vasculitis or ureteral vasculitis which causes ischemia and fibrosis ending in stricture.

In the present case, stenosis has been the cause of hydronephrosis of the transplanted kidney at the level of uretero-pelvic junction. In this case uretero-vesical junction was patent and there was no evidence of uretero-vesicular junction stenosis. So far, we could not find any reported case of uretero-pelvic junction obstruction as cause of obstructive uropathy due to AAV at the junction of ureter of pelvis of the transplanted kidney. Uretero-pelvic junction obstruction in this case completely recovered after treatment with high dose of corticosteroid and rituximab. Due to response to antivasculitis treatment in transplanted patient with several non-renal manifestation of recurrent disease, we propose that uretero-pelvic junction obstruction in this case was most likely due to vasculitis in arteries of ureteropelvic tissue. Indeed, it is the first report of non-renal relapses of AAV in a transplant recipient with diagnosis of crescentic glomerulonephritis as the cause of end-stage renal failure requiring renal replacement therapy in several organs. Published papers of recurrence of vasculitis in transplant recipients usually just reported involvement of one non-renal organ.

Different immunosuppressive regimens have been tried for the treatment of relapse of AAV in transplanted kidney. Among the patients treated with cyclophosphamide, 27% experienced relapse in 10.5 months, while 50% had relapse in 4.5 months by discontinuation of the medication [16]. Tacrolimus (TAC)-based regimen post-renal transplantation is known to decrease the relapse rate by 4%. On the other hand, cyclosporine has failed to decrease relapse rate compared to azathioprine and revealed higher rate of relapse (22%) compared to TAC regimen [11]. The treatment of choice for AAV currently is repeated cycles of prednisolone and cyclophosphamide [25, 26]. Plasmapheresis may also be used in cases with pulmonary involvement [27, 28].

In conclusion, this case indicated that in certain cases, the degree of immunosuppression could be enough for the transplanted organ but might be inadequate for controlling the vascular disease activity.

CONFLICTS OF INTEREST: None declared.

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