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CASE REPORT

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Late renal allograft rupture in a patient with small vessel vasculitis following discontinuation of immunosuppression

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Abstract We report the case of a 21-year-old man with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis who experienced spontaneous renal allograft rupture 21 months after engraftment. Because of chronic allograft nephropathy, the patient's immunosuppressive regimen had been discontinued approximately 3 weeks prior to his presentation with abdominal pain and evidence of internal hemorrhage. He was emergently taken to the operating room, where a ruptured allograft was found and transplant nephrectomy was performed. Postoperatively, the cause of rupture was determined to have been acute cellular rejection. This case may be the longest interval reported between renal transplant and spontaneous allograft rupture.

Keywords Renal transplant · Complications · Delayed renal allograft rupture · Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis · Small vessel vasculitis · Kidney rupture

Introduction

Renal rupture presents dramatically with acute onset of abdominal or back pain, hematuria, hypotension, and tachycardia. Major etiologies of spontaneous renal hemorrhage in native kidneys include tumors, vascular disease (most commonly polyarteritis nodosa), and infection [1]. While the most common cause of renal allograft hemorrhage and rupture is acute cellular rejection, usually occurring within 2–3 weeks of engraftment, other etiologies such as acute tubular necrosis may have a considerable role [2, 3]. Renal allograft rupture has become relatively rare in the modern immunosuppression era, but is still a recognized complication of kidney transplantation. We report a case demonstrating that late rupture may occur and must not be overlooked in the differential diagnosis of acute abdominal pain in kidney transplant patients, especially in patients whose immunosuppression has been withdrawn due to allograft nephropathy.

Case report

A 21-year-old man received a living-related kidney transplant from his mother at another institution for antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. Postoperatively,

the patient was initiated on maintenance immunosuppression, including 30 mg qd prednisone, 350 mg b.i.d. cyclosporine, and 2 mg qd sirolimus. His postoperative course was complicated only by hypertension. He was discharged on postoperative day 5, with a serum creatinine of 1.5 mg/dl. Eighteen months after transplantation, his baseline serum creatinine was 2.4 mg/dl.

Approximately 19 months after engraftment, the patient was admitted to an outside hospital with acute renal failure, with a BUN of 107 mg/dl and serum creatinine of 11.2 mg/dl. At this time, the patient was only receiving 6 mg qd tacrolimus for immunosuppression. Laboratory examination revealed a WBC of $19.5\times10^3/\mu l$, hemoglobin of 7.8 g/dl, hematocrit of 22%, and platelets of $149\times10^3/\mu l$. An abdominal ultrasound demonstrated patency of the renal artery and vein, with no evidence of hydronephrosis or calculi. Kidney biopsy revealed 39 glomeruli, of which 17 were completely obsolescent and hyalinized. Marked interstitial lymphocytic infiltration was present in the cortex in a periglomerular distribution, but absent in the medulla. Neither tubulitis nor intimal arteritis was identified. Arterial immunofluorescence staining for C_3 and C_{1q} was present. Staining for C_{4d} was weakly present in the arterioles, but not in the capillaries. Antinuclear antibody titers were negative. The only suggestion of recurrent vasculitis included one episode of hemoptysis and a chest x-ray showing increased opacification of the right upper lung consistent with a consolidative process. A prednisone taper was instituted for possible recurrence of his vasculitis. The patient was initiated on hemodialysis and discharged on 5 mg qd prednisone.

Two months later, the patient was admitted to another hospital with fever, chills, and generalized weakness. Laboratory examination revealed a WBC of $15.5\times10^3/\mu l$, hemoglobin of 7.82 g/dl, hematocrit of 23.9%, platelets of $238\times10^3/\mu l$, BUN of 32 mg/dl, and serum creatinine of 7.5 mg/dl. A right subclavian dialysis catheter was removed for presumptive line sepsis. Immunosuppression was discontinued, and the patient was empirically treated with intravenous vancomycin and gentamicin. Blood and urine cultures obtained during this time were sterile.

Two weeks later, the patient returned to the same hospital complaining of severe acute abdominal pain in the right lower quadrant, hematuria, fevers, and chills and was transferred to our institution. Upon arrival, the patient was hypotensive and tachycardic, with a blood pressure of 93/56 mmHg and a heart rate of 127 bpm. His hemoglobin was 4.3 g/dl, decreased from 7.69 g/dl at the transferring institution. Further laboratory examination revealed a WBC of $27.1\times10^3/\mu l$, PT of 17.9 s, PTT of 36 s, fibrinogen of 411 mg/dl, BUN of 32 mg/dl, serum creatinine of 8.0 mg/dl, and ANCA titers of less than 1:16. The patient was resuscitated with crystalloid fluids and packed red blood cells. A chest x-ray demonstrated infiltrative changes in the left base posteriorly. A retroperitoneal computed tomography (CT) scan with oral and intravenous contrast revealed massive retroperitoneal and intra-abdominal hemorrhage originating from an enlarged and hemorrhagic transplanted kidney (Fig. 1). An exploratory laparotomy was performed. A ruptured renal allograft with a subcapsular hematoma and massive retroperitoneal hemorrhage was found, necessitating a transplant nephrectomy. On gross inspection, the kidney weighed 245 g (normal 125–170 g). There were two 4-cm tears, one close to the hilum and one in the lower pole. There also was a 9-cm Z-shaped defect in the hilar area. Histologic examination of the allograft revealed extensive interstitial hemorrhage and severe acute cellular rejection superimposed on chronic rejection. The patient's postoperative course was uneventful and he was discharged 7 days later.

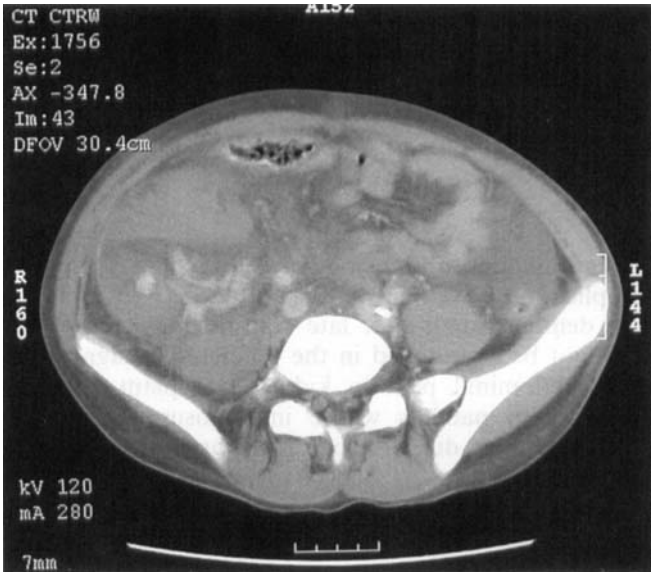

Fig. 1 CT scan showing active extravasation of contrast material and massive retroperitoneal and intra-abdominal hemorrhage originating from an enlarged renal allograft in the right iliac fossa

Discussion

The reported incidence of renal allograft rupture ranges from 0.3 to 9.6% [3]. In 1968, Murray et al. [4] reported four cases of allograft rupture among a series of 110 renal transplant patients, all occurring within days of transplantation. More recently, Ramos et al. [5] reported an allograft rupture incidence of 1.2% in a retrospective study of 934 renal transplants performed between 1983 and 1999. Szenohradszky et al. [6] reported an 8.4% renal allograft rupture incidence among 628 consecutive renal transplants. In these studies, more than 90% of the cases occurred within 3 weeks of engraftment. Longer intervals between renal transplant and rupture are uncommon, but have been reported.

Ajao et al. [7] reported renal allograft rupture in a 51-year-old African-American male with end-stage renal disease from malignant hypertension that became manifest 4 years after his second kidney transplant. As he presented with 4 days of graft pain after falling down a few days earlier, trauma probably initiated the rupture. Lord et al. [8] reported a late spontaneous rupture of a renal allograft in a 19-year-old male 170 days after transplantation that was attributed to acute cellular rejection. The allograft ruptured across its convex border along the avascular plane, but did not involve a previous biopsy site. In addition to prednisone, this patient also received radiation therapy (450 rads) for a previous episode of acute cellular rejection. Another patient with frequent urinary tract infections had spontaneous calyceal rupture associated with abscess formation in a localized area of the lower pole of a renal allograft 133 days after transplantation, probably resulting from an episode of acute cellular rejection 14 weeks earlier that had resulted in polar ischemia [9]. This patient was successfully treated with a

nephrostomy, wound drainage, and antibiotics. Dux et al. [10] reported an allograft rupture 8 days after a kidney biopsy in a 50–year-old woman with immune complex disease suggestive of systemic lupus erythematosus. As there were no signs of intrarenal hematoma, infarction, or communication between the biopsy and rupture site, the rupture was thought to be independent of the biopsy.

Episodes of severe acute cellular rejection are the cause of 60–80% of renal allograft ruptures [2, 6]. The mechanism of allograft rupture appears to be increased intrarenal pressure caused by impaired lymphatic flow and hypoxia-induced interstitial edema. Impaired intrarenal lymphatic flow results from arteritis involving the interlobular and arcuate arteries [6]. Intrarenal measurements using fine-needle manometry have revealed that acute cellular rejection episodes are usually associated with high levels of intrarenal pressure. This elevated pressure causes longitudinal tearing along the convex renal border, where tension is the greatest [11].

Other reported causes of rupture include arterial or venous occlusion, acute tubular necrosis (ATN), polyarteritis nodosa, defects in the vascular elastic membranes, and trauma [1, 2, 5, 6, 12, 13, 14, 15, 16]. The incidence of venous occlusion increased after the introduction of cyclosporine, perhaps as a result of its thrombogenic effects [14]. ATN was responsible for 36% of ruptures in a case series by Ramos et al. [5]. Six of 12 kidneys that ruptured had severe ATN with edema and minimal acute cellular rejection in the case series by Azar et al. [2]. Szenohradszky et al. [6] retrospectively reported concomitant ATN in 70% of ruptured grafts originally attributed solely to acute rejection. In this study, ATN was the primary cause of rupture in three allografts; furthermore, venous thrombi were present in 57% and urinary tract obstruction in 37% of rejecting kidneys. These data suggest that, although acute cellular rejection is reported to be the most common cause, it may coexist with other lesions that significantly contribute to renal allograft rupture.

Histologic analysis of our patient's ruptured renal allograft demonstrated severe acute cellular rejection superimposed on chronic rejection; however, there were no histologic signs of vasculitis or acute tubular necrosis. Our patient had no predisposing factors for renal allograft rupture, such as advanced age, donor-recipient race mismatch, delayed allograft function requiring dialysis, cadaveric donor, or prolonged cold ischemia time [2]. The only clinical manifestation of recurrent vasculitis was the isolated episode of hemoptysis a few months prior to graft rupture. Pulmonary disease is found in at least half of patients with ANCA-associated vasculitis, commonly presenting as localized pulmonary infiltrates that have not responded to antibiotic therapy [17]. It was thought that the kidney biopsy findings at the previous hospital were suggestive of recurrent Wegener's granulomatosis of the kidney. While there have been reports of allograft failure from recurrence of vasculitis, there have been none of rupture in patients with ANCA-associated small vessel vasculitis [18, 19]. However, polyarteritis nodosa, which only affects medium-sized or small arteries and is not associated with ANCA, is the third most common cause of spontaneous peri-renal hemorrhage, suggesting that a relationship may exist between vasculitis and kidney rupture [1, 17].

The recurrence rate of ANCA-associated vasculitis in immunosuppressed transplant patients is 17%, which is significantly lower than the recurrence rates of 30–45% in the general population [19, 20]. Recurrence of ANCA-associated vasculitis may have resulted in initial allograft failure and facilitated rupture by compromising intrarenal lymph flow, contributing to hypoperfusion and edema formation. Discontinuation of immunosuppression may have not only made the allograft more susceptible to rupture, but also increased the risk of recurrence of vasculitis. However, the patient had no detectable antinuclear cytoplasmic antibodies, and histological evaluation of the excised kidney failed to reveal any evidence of active vasculitis within the allograft itself. Therefore, we believe that the allograft rupture was most likely caused by acute cellular rejection, probably as a result of sudden discontinuation of immunosuppressive medication.

In conclusion, we present a late renal allograft rupture, 21 months following engraftment in a patient with a history of ANCA-associated small vessel vasculitis. Experience with this disease and kidney transplantation is limited; however, to our knowledge, this is the first reported case of renal allograft rupture in a patient with ANCA-associated small vessel vasculitis and may be the longest reported interval between renal transplantation and spontaneous allograft rupture. Since there is a relative lack of published experience in renal transplant patients with a history of ANCA-associated small vessel vasculitis, additional caution must be exercised when minimizing immunosuppression in this patient population.

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