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*Vascular and Interventional Radiology* *Case Series*

# Role of failed renal allograft embolization in the treatment of graft intolerance syndrome

Hussam Hindi[1], Ali Harb[1]

[1]Department of Radiology, Wayne State University/DMC, Detroit, Michigan, United States.

***Corresponding author:**
Hussam Hindi,
Department of Radiology,
Wayne State University/DMC,
Detroit, Michigan, United States.

hhindi@dmc.org

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## ABSTRACT

Nearly, 20% of renal allografts fail after 5 years resulting in a return to hemodialysis. These patients subsequently undergo withdrawal of immunosuppressant therapy, and the failed allograft is left *in situ*. However, many patients (40%) develop graft intolerance syndrome, characterized by fever, pain, and hematuria. Conventionally, this is managed with low-dose maintenance immunosuppressant therapy, however, that is not without notable adverse risk. In refractory patients, transplant nephrectomy is the treatment of choice; however, this caries significant morbidity and mortality. Interventional radiology plays a substantial role of treating graft intolerance syndrome while delivering improved patient outcomes.

**Keywords:** Renal, Transplant, Embolization, Graft, Intolerance

## INTRODUCTION

There are approximately 20,000 renal transplants yearly in the US alone.[1] Given that renal allograft failure increases year over year and roughly 40% will go on to develop graft intolerance syndrome, alternative methods of treatments to improve outcomes should be more closely evaluated.[2] Conventional methods of treatment, including low-dose immunosuppression therapy and transplant nephrectomy, have an increased incidence of complications. Minimally invasive transarterial embolization, although described sparingly in the literature for graft intolerance syndrome, should be more heavily considered as a first-line treatment.

## CASE SERIES

### Case 1

A 73-year-old male with medical history of end stage renal disease (ESRD) caused by focal segmental glomerulosclerosis, received a deceased donor kidney transplant (DDKT) in 2013. In 2020, the patient suffered from cardiopulmonary arrest and was intubated secondary to COVID-19 pneumonia and was placed on dialysis due to renal transplant failure. On admission, he presented with fever and painless bright red hematuria for several weeks. The patient's vital signs and hemoglobin were stable. Tacrolimus was discontinued in 2020; however, he continued to take 5 mg prednisone daily. During admission, a cystoscopy showed bloody efflux arising from the renal allograft. The patient's prednisone was increased to 60 mg daily. He was deemed a poor

surgical candidate for renal transplant nephrectomy and interventional radiology was consulted for renal transplant embolization.

During the procedure, an arteriogram depicted a patent renal artery anastomosis arising from the external iliac artery. The transplanted renal artery was selected, and an arteriogram demonstrated poor parenchymal enhancement of the renal transplant [Figure 1]. A 2.8 French microcatheter was advanced coaxially through the base catheter. The renal transplant was embolized utilizing 100–300 μm and 300–500 μm Embospheres (Merit Medical Systems, South Jordan, UT, USA) with no further parenchymal enhancement [Figure 1]. The main renal artery was, then, embolized using two 6 × 2 mm and two 7 × 3mm tornado coils (COOK MEDICAL, Bloomington, IN) [Figure 1]. Post-embolization arteriogram demonstrated complete embolization of the renal artery with no further opacification [Figure 1]. The wires and catheters were removed, and hemostasis was achieved with manual compression. A small access site hematoma was noted. Total fluoroscopy time was 17.5 min and total radiation dose was 1077 mGy.

Postoperatively, the patient had increased hematuria for a few days and was subsequently discharged after 9 days. During short-term clinic follow-up, the patient denied any hematuria and began weaning from prednisone. Unfortunately, the patient passed away 1 month after the procedure due to unrelated comorbidities.

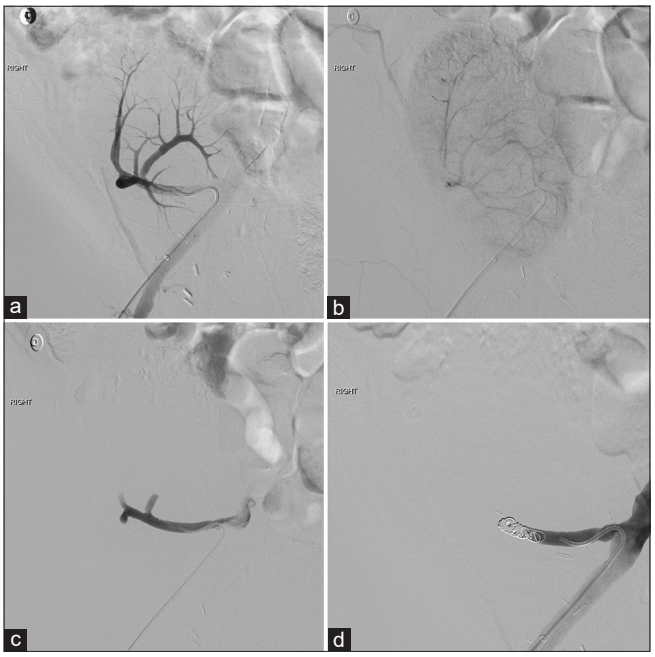


**Figure 1:** A 73-year-old male with failed deceased donor kidney transplant after cardiopulmonary arrest secondary to COVID-19 pneumonia. (a) Digital subtraction angiography demonstrates a patent renal artery anastomosis in the early arterial phase. (b) There is poor parenchymal enhancement secondary to renal allograft rejection. (c) Arteriogram shows almost complete renal transplant embolization after administering 100–300 um and 300–500 um particles. (d) Distal coil embolization was also performed.

**Case 2**

A 70-year-old male with medical history of ESRD caused by membranous nephropathy, received a DDKT in 2014. He returned to dialysis in 2015 due to recurrent membranous nephropathy and renal allograft failure. The patient presented with several weeks of hematuria and pain around the transplanted kidney site approximately 1 year after transplant failure. The patient was taking prednisone 10 mg daily, mycophenolate mofetil 1000 mg twice daily, and cyclosporine 50 mg twice daily for immunosuppression. His hemoglobin was decreased from 9 to 7.5 on admission. During cystoscopy, he was noted to have bloody efflux from the transplant kidney. Prednisone was increased to 50 mg daily and interventional radiology was subsequently consulted for renal transplant embolization.

During the intervention, an arteriogram depicted a patent renal anastomosis arising from the external iliac artery [Figure 2]. The catheter was exchanged for an occlusion balloon to prevent non-target embolization. 10 mL of dehydrated ethanol was injected. Arteriogram showed mild stasis of flow and repeat embolization with 10 mL of dehydrated ethanol demonstrated satisfactory embolization [Figure 2]. The balloon catheter was removed, and the access site was closed using the MYNX device (Cordis, Miami Lakes, FL, USA). Total fluoroscopy time was 15.2 min.

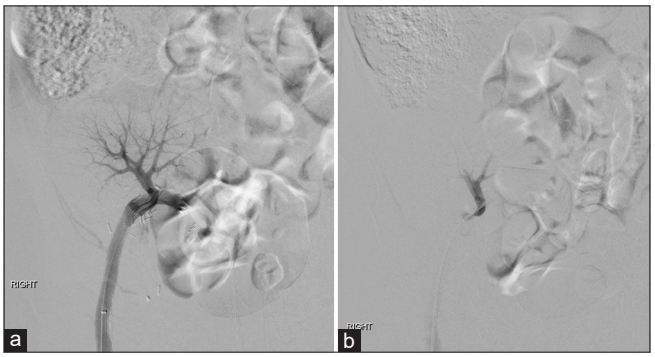


**Figure 2:** (a) A 70-year-old male with failed deceased donor kidney transplant secondary to recurrent membranous nephropathy. (a) Digital subtraction angiography demonstrates a patent renal artery anastomosis in the early arterial phase. (b) There is complete renal transplant embolization after administering 20 mL of dehydrated ethanol with supporting balloon occlusion catheter.

Postoperatively, the patient complained of abdominal pain and continued hematuria for several days. However, the pain subsided, and the hematuria resolved before discharge after 4 days. The patient was weaned from prednisone and

at 2 months had continued cessation of hematuria and pain.

## DISCUSSION

Graft intolerance syndrome is an immune-mediated condition characterized by the presence of symptoms after a failed renal graft is left *in situ*. This is the main indication for transplant nephrectomy in late kidney graft failure. Symptoms on average begin within 6 months after graft failure and include fever, hematuria, anemia, and localized pain at the graft site.[2]

Gradual immunosuppression weaning or continued low dose immunosuppressive therapy may suppress graft intolerance syndrome; however, in one single-center study, immunosuppression weaning led to a seven-fold risk ($P$ = 0.017) for admission within 6 months of graft failure with symptomatic rejection.[3] Many patients on continued low-dose immunosuppression are also at increased risk for metabolic disorders (diabetes, hypertension, and dyslipidemia), infection, cardiovascular complications, and malignancies including skin cancer and non-Hodgkin's lymphoma.[3-5]

Transplant nephrectomy has high morbidity (17–60%) and mortality (1.5–14%) rates.[6]

Hemorrhage and hematoma were the most common complications, and the procedure subsequently leads to prolonged hospital stays.

There are several studies that support embolization as first-line treatment due to the poor outcomes of transplant nephrectomy. A study of 2421 patients demonstrated a 4% versus 0.1% mortality rate and 18% versus 1.2% morbidity rate in transplant nephrectomy and embolization cases, respectively. However, post-embolization syndrome characterized by fever, nausea, vomiting, and pain was present in 68% of patients in the embolization group, although symptoms typically resolved at 1 week. Furthermore, 20% of patients post-embolization underwent nephrectomy for residual graft intolerance symptoms.[7] Embolization was successful in 28 of 33 patients in another study with a mean hospital stay of 5 days and no significant complications.[8] Delgado *et al*. described embolization in 48 patients, 31 of which were successful (65%). A second embolization was necessary in eight patients; however, no deaths or severe complications were observed. Of 48 patients, eleven (22%) underwent transplant nephrectomy due to persistent graft intolerance syndrome or graft infection.[9] Complications specific to renal allograft embolization includes post-embolization syndrome, hematoma, infection, pseudoaneurysm, and non-target embolization. Transient increased post-operative hematuria secondary to vascular occlusion and sloughing typically resolves within a few weeks.

Embolization is likely served best for patients who are poor surgical candidates who will not undergo repeat renal transplant. A study from Spain described 62 kidney transplant patients; 31 patients underwent selective embolization for failed renal allograft and were compared to 31 patients with preserved failed renal allograft. Renal allograft embolization patients showed an increased percentage of panel reactive antibodies levels than before (19.2–46.2%, $P$ = 0.09).[10] Necrosis secondary to embolization may also exacerbate underlying infectious processes including pyelonephritis. Embolization should be reconsidered in this patient population as well.

Transarterial embolization of the renal transplant begins with access of the ipsilateral common femoral artery and the renal artery anastomosis is typically selected from the external or internal iliac artery. Embolization has been described by multiple methods including coil embolization, absolute ethanol injected at 0.1 mL/kg of body weight, N-butyl cyanoacrylate (N-BCA) glue, and particle embolization. Coils are packed tightly and covered with thrombogenic material to promote thrombosis. Coils are typically placed distally to allow a surgical margin for resection in the setting of treatment failure. Absolute ethanol is a liquid embolic agent that penetrates the distal capillary bed levels, infarcting tissue, and disrupting collateral flow formation. This is routinely combined with contrast to create a radiopaque solution that can be monitored during embolization. N-BCA glue is a monomer that polymerizes and creates a strong adhesive bond on contact with ionic mediums such as blood. The monomer is mixed with ethiodized oil to allow fluoroscopic opacification in ratios ranging from 1:1 to 1:9 depending on the rate of polymerization needed. To prevent early polymerization within the catheter, 5% non-ionic dextrose is flushed to remove the ionic contents in the catheter. Simultaneous administration of N-BCA and 5% dextrose also decreases polymerization rate and allows for a more distal embolization. Due to the increased risk of non-target embolization with absolute ethanol and N-BCA, a supporting balloon catheter may be used to prevent the reflux of these embolic agents. Tris-acryl gelatin microspheres cause permanent vascular occlusion by lodging into vessels and come in a variety of different size ranges.

## CONCLUSION

This case series describes two patients who demonstrated complete resolution of graft intolerance syndrome with minimal reported complications. Although the follow-up time is within a few months, it supports the current limited literature of the efficacy of failed renal allograft embolization with improved outcomes from conventional management. Patient selection is a key determining factor; however, embolization is a viable treatment option that should be more heavily considered.

### Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

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