



# Renal Graft Embolization as a Treatment for Graft Intolerance Syndrome

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## ABSTRACT

**Background.** Renal graft intolerance syndrome is an inflammatory process that occurs in up to 40% of patients with graft loss. It is characterized by fever, graft pain, hematuria, and anemia. Traditionally, the treatment has been nephrectomy; however, this procedure is associated with high morbidity and mortality rates. As an alternative, graft embolization is associated with success rates of up to 92%. In this study, we describe the graft embolization experience of 1 center, its clinical outcomes and complications.

**Methods.** An observational, retrospective study was conducted. It included all patients with graft intolerance syndrome undergoing graft embolization between 2012 and 2018. The success of the procedure was defined by the resolution of the symptoms that motivated the embolization.

**Results.** We found 12 cases of patients undergoing embolization. The time of presentation of the graft intolerance syndrome after admission to dialysis was 6 months (range, 0.6-13). The main clinical manifestation was pain in the area of the graft and macroscopic hematuria. Except for 1 patient, all continued with the immunosuppressive treatment regimen after graft loss for 4 months (range, 0.6-9), received antibiotics for 5.5 days (range, 2-14), and 10 patients received steroid treatment for 6.5 days (range, 5-10). The main complication, secondary to the procedure, was hematoma at the puncture site in 3 patients. Only 1 patient had postembolization syndrome, which resolved with steroid administration. Two patients required postembolization nephrectomy due to persistent renal blood flow and symptoms such as pain and hematuria. The average hospital stay was 5.5 days (range, 1-24).

**Conclusions.** Renal graft embolization is an effective technique as a treatment strategy in patients with clinical signs of intolerance syndrome, with a success rate  $\geq 83.3\%$ , low morbidity, and short hospital stay; furthermore, it avoids the potential complications of a surgical nephrectomy. Graft infection should be ruled out before embolization, and the use of prophylactic antibiotics and steroid therapy is recommended to reduce the risk of postembolization syndrome and infectious complications.

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**R**ENAL graft intolerance is an inflammatory process that occurs in some failed grafts that are left in situ [1]. About 10% of patients who start dialysis each year have a dysfunctional renal graft and at least one-third of them develop graft intolerance syndrome [2,3].

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Table 1. Characteristics of Patients Taken to Graft Embolization

Patient No.	Age at Transplant, y	Time from Dialysis to Intolerance Syndrome, mo	Graft Survival, mo	Time With Immunosuppression After Admission to Dialysis, mo	Fever	Pain in Graft Area	Hematuria	Type of Sclerosing Agent	Postembolization Nephrectomy	Complication Associated to Puncture	
										Yes	No
1	56	8	10	1.5	No	Yes	Yes	Polyvinyl alcohol	No	Yes	Hematoma
2	34	4	2	3	Yes	Yes	Yes	Microspheres	No	No	No
3	49	4	15	3	Yes	Yes	Yes	Microspheres	No	Yes	Bleeding and hematoma
4	51	9	41	8	No	Yes	Yes	Microspheres	No	No	No
5	28	4	41	4	Yes	Yes	No	Metallic coils	No	No	No
6	47	0.6	98	0.6	Yes	Yes	No	Microspheres	No	No	No
7	12	8	57		No	No	Yes	Polyvinyl alcohol	No	No	No
8	49	9	10	4	No	Yes	Yes	Polyvinyl alcohol	No	No	No
9	19	6	90	6	Yes	Yes	Yes	Metallic coils	Yes	No	No
10	30	2	81	2	Yes	No	Yes	Microspheres, polyvinyl alcohol and metallic coils	Yes	No	No
11	53	1	123	6	No	Yes	Yes	Metallic coils	No	No	No
12	39	13	82	9	No	Yes	No	Polyvinyl alcohol	No	Yes	Hematoma

There are different options, with varying degrees of complexity, that have been developed to address the needs of patients with renal graft intolerance syndrome, from surgical nephrectomy to new techniques of embolization of the nonfunctioning graft's renal artery [4-6].

Traditionally, the treatment of renal graft intolerance syndrome has been surgical nephrectomy. However, it is associated with high morbidity and mortality rates [1,7,8]. Up to 20% of patients undergoing this procedure may have some complications related to the procedure [6].

As a therapeutic alternative to this high morbidity, embolization using ethanol or polyvinyl alcohol microspheres followed by the insertion of metallic coils has been used [9]. Various case series report success rates between 65% and 92% with lower hospital stay and lower complication rates compared to nephrectomy [10,11]. The most frequent complication is postembolization syndrome, characterized by pain in the graft area, fever, and leukocytosis 24 to 48 hours after the procedure [7,9,12]. Another complication is graft infection, which can be prevented by prophylactic antibiotic administration [13,14].

This study aims to describe our experience in transcatheter embolization therapy of nonfunctioning renal grafts in patients with intolerance syndrome, including clinical outcomes, complications, and procedure success rate.

## METHODS

An observational, retrospective study was conducted at the San Ignacio University Hospital between January 2012 and December 2018. The study included patients with a history of renal transplantation who experienced graft loss and intolerance syndrome managed with embolization. The diagnosis of intolerance syndrome was based on the presence of clinical criteria such as fever, hematuria, pain, and graft size increase in the absence of underlying infectious disease. In all cases, a Doppler ultrasound of the graft was performed to verify the presence of arterial flow. The success of the procedure was defined by an improvement in the symptoms that initially led to the embolization. Renal embolization was performed under local anesthesia, with an ipsilateral or contralateral approach to the femoral artery. After arteriography and analysis of the graft anatomy, 5 F angiographic catheters were advanced within the artery. Polyvinyl alcohol or a mixture of microspheres and contrast medium was then injected to embolize the distal circulation until flow reduction was achieved. In some cases, metallic coils were inserted at the end of the procedure.

Among the topics analyzed were the cause of graft loss, the length of time of immunosuppressive treatment from admission to dialysis, the time elapsed between graft loss (admission to dialysis), and embolization and symptoms of graft intolerance syndrome. Complications of the procedure were described, such as hemorrhage, hematoma, infection, pain, and postembolization syndrome.

This study was approved by the ethics committee of the institution. The results are presented in Table 1 with the individual data. Quantitative variables are presented within the text using median values and ranges.

## RESULTS

Within the study population, there were 12 cases of graft intolerance syndrome that led to embolization. Eight patients were men, with a median age at transplant of 43 years (range, 12-56), and all were deceased-donor transplantations except for 1 patient. The duration of the graft function was 49 months (range, 2-123). The most commonly used immunosuppressive scheme was tacrolimus, mycophenolate, and prednisone at the time of graft loss.

The time from admission to dialysis and intolerance syndrome was 6 months (range, 0.6-13). Except for 1 patient, all continued with the immunosuppressive treatment regimen after graft loss, with a median time of 4 months (range, 0.6-9).

The main clinical manifestation was pain in the area of the graft and macroscopic hematuria. Fever occurred in half of the patients, and leukocytosis and neutrophilia were not common manifestations. However, 7 patients had a high C-reactive protein (9.4 mg/dL; range, 1.6-22) and elevated erythrocyte sedimentation rate (58 mm/h; range, 23-116).

Before the embolization, an acute infectious process of the urinary tract was ruled out. Ten patients received antibiotics for 2 days prior to the procedure, with a total duration of 5.5 days (range, 2-14). No patient presented with postembolization bacteremia or pyelonephritis. Ten patients received a steroid prior to embolization, for 1.5 days (range, 1-6) with a dose of 30 mg per day (range, 6-30). Of those who received steroids, 9 continued after embolization along with 1 additional patient who had not received it, with a total treatment time of 6.5 days (range, 5-10). Only 1 patient experienced postembolization syndrome despite receiving steroids. The main complication derived from the procedure was hematoma at the puncture site in 3 patients. Two patients required postembolization nephrectomy due to persistent renal blood flow and symptoms such as pain and hematuria. The median hospital stay was 5.5 days (range, 1-24). None of the patients died.

## DISCUSSION

Renal graft intolerance syndrome is an inflammatory process that occurs in up to 40% of patients experiencing graft loss. It is characterized by fever, graft pain, hematuria, and refractory anemia. Renal graft intolerance is a common event, especially within the first year of returning to dialysis therapy, and it has been associated with an accumulated risk of 28%, 38%, and 40% at 6, 12, and 24 months, respectively [1]. Graft nephrectomy has been the accepted method of treatment; however, studies report significant morbidity, increased hospital stay, infectious complications, and the need for transfusion [10,15]. Chowanec et al [16] report that 37.9% of patients who presented with graft failure were managed with nephrectomy, mainly due to graft intolerance syndrome, and 38% had some complication as a result.

Our study shows that graft embolization, as a way of managing intolerance syndrome, is a therapeutic alternative to nephrectomy. It achieves the complete remission of

symptoms in more than 80% of cases, with a low failure rate (only 2 patients required transplantectomy because of the persistence of symptoms) and a low number of complications (mainly due to puncture) and without any infectious process. These results indicate that graft embolization is a procedure associated with low morbidity and short hospital stay.

Renal graft embolization has been described as an effective, less invasive method with a lower complication rate. The first description for the management of intolerance syndrome was made by Lorenzo et al [17] in which the authors reported having injected absolute ethanol in 14 patients and inserted a steel coil in 7 patients, achieving the remission of symptoms. This was done without major complications; however, 11 patients developed postembolization syndrome. Subsequently, Gonzalez-Saute et al [18], in a cohort of 33 patients, showed that intolerance syndrome resolved in 28 (85%) patients, but 5 patients required nephrectomy due to persistent symptoms after the embolization. A similar situation occurred in the study by Cofan et al [7], where investigators performed embolization in 30 patients using a polyvinyl alcohol microspheres injection, followed by the insertion of a steel coil in the renal artery, achieving an 80% success rate, with symptoms of remission. However, due to the recurrence of symptoms after  $40 \pm 18$  days (13-66), 6 (20%) patients needed a nephrectomy. Atar et al [13] performed embolization in 25 patients using absolute alcohol or polyvinyl alcohol and inserted metallic coils in all cases; they reported a 92% remission of symptoms, with 1 patient requiring nephrectomy and another needing a re-embolization, and 2 infectious complications. Al Badaai et al [10], in a retrospective cohort, compared the safety and efficacy of embolization as a first-line treatment over surgical removal with an embolization success rate of 84.4%; their study was associated with a lower complication rate and shorter hospital stay. A meta-analysis reviewed the cases of 2421 patients; of these, 2232 underwent transplantectomy and 189 underwent percutaneous embolization. Findings showed that the mortality rate in the nephrectomy group was 4% (95% confidence interval [CI], 2-7;  $I^2 = 87\%$ ), which is higher than the 0.1% (95% CI, 0.1-0.5;  $I^2 = 0\%$ ) of the embolization group. Likewise, the morbidity rate was higher in the transplantectomy group: 18% (95% CI, 13-26;  $I^2 = 79.7\%$ ) vs 1.2% (95% CI, 0.7-2.1;  $I^2 = 26.4\%$ ) in the embolization group [8]. All that information shows that the use of substances such as ethanol, microparticles, or coils for embolization results in success rates between 65% and 92%, with a low complication rate. Nevertheless, in some cases, the lack of symptom remission along with the subsequent requirement of re-embolization or nephrectomy can be explained by distal revascularization, which could occur through collateral supply between the host and the graft; therefore, a careful distal embolization seems to be mandatory [5,7].

In our series, only 1 case of postembolization syndrome was presented, probably because most patients received steroids before and after the procedure, a smaller number than reported in the literature. In the period prior to the use

of steroids, Lorenzo et al [17] documented a 78% (11 of 14 patients) incidence. However, after including the use of steroids, the incidence has decreased to 47% to 68% [7,8]. The pathogenesis is probably related to tissue necrosis with the release of cytokines and other inflammatory molecules [7]. This syndrome is self-limited and is controlled with the use of anti-inflammatory and analgesic medications [6].

In the study, most cases of graft intolerance syndrome occurred in the first 6 months after the graft loss. It should be noted that all patients continued taking immunosuppressive medications on admission to dialysis, with an average of 4.5 months of treatment. Currently, there is no consensus about the weaning of immunosuppressive treatments for patients with a nonfunctioning graft [12]. The risk of maintaining the immunosuppression therapy, which involves more infections, cardiovascular complications, and metabolic disturbances compared to suspending it, should be balanced. Also, the higher risk of graft intolerance syndrome and allosensitization related to a subsequent transplantation should be considered [19,20]. If there is no apparent risk, it is recommended to continue immunosuppressive treatment at low doses. Patients with early graft failure (<1 year) are usually given a nephrectomy and immunosuppression treatment is immediately discontinued. In those with late graft failure, the decrease in treatment is done in weeks or months [21]. The guidelines of the British Transplant Society recommend suspending immunosuppression after nephrectomy and progressive weaning of the steroid. However, if the patient has the possibility of transplantation with a living donor or if the transplantation can be performed in <1 year, they suggest continuing the immunosuppression to avoid sensitization. Additionally, they only recommend performing graft embolization in cases of high surgical risk for nephrectomy [19]. Kassakian et al evaluated immunosuppression weaning schemes, such as abrupt suspension or elimination of the antimetabolite vs the anticalcineurinic drug first, and continuing the steroid medication for 6 to 12 months [19,22]. Currently, the most commonly used scheme is the suspension of the antimetabolite and a decrease in the calcineurin inhibitor over 8 to 12 weeks, after steroid weaning for 12 to 24 weeks [21,23,24]. The absence of infectious complications in our study may be the result of the careful exclusion of an infectious process from the urinary tract prior to the embolization, along with the administration of antibiotic prophylaxis during an average of 72 hours before the procedure.

## CONCLUSIONS

In summary, our series documents that embolization of a nonfunctioning renal graft is an effective technique in the treatment of patients with clinical signs of intolerance syndrome, with a success rate greater than 80%, a low morbidity, and a short hospital stay. Additionally, embolization avoids the potential complications related to a surgical nephrectomy. Infectious complications of the graft

before embolization should be excluded, and the use of a prophylactic antibiotic and steroid antibiotic therapy is recommended to reduce the risk of postembolization syndrome and infectious complications.

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