



# Embolización del injerto renal no funcionante: eficacia y control del estado inflamatorio crónico

J. Pérez Martínez\*, E. Gallego\*, E. Juliá\*\*, F. Llamas\*, A. López\*, F. Palao\*\*, I. Lorenzo\*, E. López\*, M. L. Illescas\* and C. Gómez Roldán

\*Nephrology. \*\*Radiology Departments. University Hospital Complex of Albacete.

## SUMMARY

**Background:** The graft intolerance syndrome (fever, pain, haematuria) may lead to a chronic inflammatory disease, with cardiovascular repercussion. Nephrectomy is considered the classical treatment of these cases but nowadays renal vascular embolization has been suggested as a possible alternative treatment. The present study summarizes seven cases treated with renal vascular embolization in our hospital summarizing data of graft intolerance syndrome and the chronic inflammatory disease.

**Material and methods:** Between January 2000 and December 2003 seven renal vascular embolizations were performed in nonfunctioning renal allograft. The procedure was made with calibrated particles of 300-500 $\mu$ . Data about complications related to the technique the same as analytic inflammatory parameters before and after treatment (CRP, ferritin, serum albumin, hemoglobin, erythropoietin) were registered.

**Results:** The patients were two men and five women, with median age of 39,7  $\pm$  8,8 years. The period between the dialysis and the embolization was of 10,0  $\pm$  8,2 months. Comparing the period of admission in the hospital due to nephrectomy which was of 17,86  $\pm$  4,41 days, the period because of embolization was shorter, being 8,14  $\pm$  4,53 days. All analytic parameters studied, clearly improved after embolization with decrease of ferritin and CRP, increase of albumin and better hemoglobin level with lower erythropoietin dose. In five of the seven patients there was no renal captation with CT or gammagraphy. Four patients presented a postembolization syndrome, but no other important complication was registered. Neither reembolization nor renal nephrectomy was necessary in any of the seven cases.

**Conclusion:** Percutaneous renal embolization is a simple, easy, safety and effective technique that must be considered as an alternative treatment to nephrectomy, resolving the chronic inflammatory disease secondary to the graft intolerance syndrome.

Key words: **Renal allograft. Embolization. Nephrectomy. Graft intolerance syndrome. Inflammation. Chronic allograft nephropathy.**

## EMBOUZACION DEL INJERTO RENAL NO FUNCIONANTE: EFICACIA Y CONTROL DEL ESTADO INFLAMATORIO CRÓNICO

### RESUMEN

**Introducción:** El síndrome de intolerancia al injerto (fiebre, dolor, hematuria), conlleva el desarrollo de un estado inflamatorio crónico, con consecuencias a nivel cardiovascular. La embolización percutánea del injerto renal no funcionante ha sido descrita como alternativa a la nefrectomía. Presentamos los resultados de la embolización de injertos renales no funcionantes en nuestro centro, respecto al síndrome de intolerancia al injerto y al estado inflamatorio.

**Material y métodos:** Desde el 1-1-2000 hasta el 31-12-2003 hemos realizado siete embolizaciones de injertos renales no funcionantes. El procedimiento se realizó con partículas calibradas (embosferas) de 300-500  $\mu$ . Se analizaron datos referentes a las complicaciones de la técnica y los parámetros analíticos relacionados con el estado inflamatorio: PCR, ferritina, albúmina, hemoglobina, y dosis de eritropoyetina, antes y después de la embolización.

**Resultados:** Los pacientes, dos varones y cinco mujeres, tenían una edad media de  $39,7 \pm 8,8$  años. Desde el reinicio de la diálisis hasta la embolización transcurrieron  $10,0 \pm 8,2$  meses. La duración del ingreso por embolización fue de  $8,14 \pm 4,53$  días y por nefrectomía de  $17,86 \pm 4,41$  días. No hubo complicaciones importantes, pero cuatro pacientes presentaron un síndrome postembolización. En cinco pacientes se confirmó la ausencia de captación renal por TC o gammagrafía. No ha sido necesaria la reembolización ni la trasplantectomía hasta el momento. Hemos observado una mejoría en todos los parámetros analíticos después de la embolización, con disminución de la PCR y de la ferritina, aumento de la albúmina, y clara mejoría de las cifras de hemoglobina para dosis de eritropoyetina inferiores.

**Conclusión:** La embolización renal percutánea constituye una técnica sencilla, segura y efectiva, que puede indicarse como alternativa a la nefrectomía quirúrgica, y que resuelve el estado inflamatorio crónico secundario a intolerancia al injerto renal no funcionante.

Palabras clave: **Trasplante renal. Embolización. Nefrectomía. Síndrome de intolerancia al injerto. Inflamación. Nefropatía crónica del injerto.**

### INTRODUCTION

Functional loss of a renal graft forces the patient inclusion in a dialysis program. In this setting, immunosuppression is usually slowly reduced in order to keep the graft in situ. This position may pose two inconveniences: the development of a chronic inflammatory state and, in a variable percentage of cases, the development of a graft intolerance syndrome that obliges to increase and maintain immunosuppression<sup>1</sup>.

The graft intolerance syndrome is involved in the development of an inflammatory state that may become chronic if renal graft activity is not suppressed.

This may lead to the hyponutrition, inflammation and atherosclerosis (HAI) syndrome with systemic cardiovascular involvement in patients with other risk factors already present<sup>2</sup>.

Classically, the treatment for the renal graft intolerance syndrome has been surgical nephrectomy.<sup>3</sup> Complications of transplantectomy are frequent, and may involve up to 20% of patients<sup>4,5</sup>. As an alternative to this high morbidity, some groups have used graft embolization with good results.

We present our experience with embolization of non-functioning renal grafts, with especial attention to the low morbidity of the technique and in analytical improvement of chronic inflammation parameters.

## MATERIAL AND METHODS

### Population

From 01-01-2000 to 12-31-2003 we have performed in our Center seven embolizations of non-functioning grafts. Patients are five women and two men, with a mean age at the time of embolization of  $39.7 \pm 8.8$  years. They had been transplanted for  $92.8 \pm 82.9$  months. Five patients were on hemodialysis program and two on peritoneal dialysis. Time elapsed from dialysis onset until the procedure was  $10.0 \pm 8.2$  months.

Indication for embolization was the development of graft intolerance syndrome when reducing immunosuppression. We define this syndrome as protracted fever, persistent hematuria and/or graft pain, and it may associated with difficult-to-manage hypertension and thrombocytopenia; these clinical manifestations were controlled with reestablishment or increase of corticoids dose.

### Embolization technique

All patients received antibiotic prophylaxis previously. Besides, 3 of them received antihistamines and systemic corticosteroides ( $0.5 \text{ mg/kg}$  as a single dose). The Vascular Radiology Department performed the procedure with following technique: prior local anesthesia, through puncture of the ipsilateral femoral artery by Seldinger's technique, a 5-french short introducer is inserted through which a diagnostic multipurpose catheter is introduced, generally with a 2 cobra curvature or sim 1, depending on the curvature of the renal artery. The renal artery is catheterized and a morphologic study is performed with 8 mL of radio contrast media. The catheter tip is placed in the main artery, just before its division. From that point, embolization starts with 300-500  $\mu\text{m}$  calibrated particles (embospheres) until flow is virtually stopped, when there is the risk for particles reflux, the moment at which the main artery embolization is performed with a metallic coil to accelerate the complete occlusion. A final check is done to verify the procedure effectiveness.

### Parameters assessed

Vital statistics of each patient were gathered: age, gender, time with transplantation, date of dialysis onset, and date of embolization. Parameters related

with the inflammatory state were also recorded at the time of dialysis onset, embolization and 6 months after: CRP, ferritin, albumin, hemoglobin, and weekly erythropoietin dose per kilogram of body weight.

After embolization, the presence of complications was checked, both of the procedure itself and the ones resulting from graft necrosis, which constitute the so-called post-embolization syndrome that includes fever and graft pain 24-48 after embolization, excluding an infectious cause (blood cultures, hemogram and radiologic studies were performed in patients presenting this syndrome).

Hospital stay for embolization has been compared to hospital stay for surgical transplantectomies that account for 13 surgical interventions performed at our Center for graft intolerance until 12-31-1999.

### Statistical analysis

Data are expressed as mean  $\pm$  standard deviation. Quantitative variables have been compared by non-parametric Wilcoxon's test for paired data, considering a significance level of  $p < 0.05$ . The statistical software package used has been SPSS 11.0 for Windows.

## RESULTS

Table I shows the patients' data relating to age, duration of renal transplantation, and time elapsed from dialysis onset to embolization. Besides, hospital stay is shown both for embolizations and for nephrectomies in our Center.

This a group of patients in their mid-life, with a female preponderance, preserving graft function for more than 7 years on average. The mean time elapsed from dialysis onset to embolization was 10 months, which is time enough to reverse uremic syndrome and to achieve adequate dialysis parameters (Kt/V, nutrition, anemia, etc.).

**Table I.** Epidemiological data of patients submitted to graft embolization (mean  $\pm$  standard deviation)

Mean age (years)	$39.7 \pm 8.8$
Gender (male/female)	2/5
Renal transplantation duration (months)	$92.8 \pm 82.9$
Time to embolization (months)	$10.0 \pm 8.2$
Hospital stay for embolization (days)	$8.14 \pm 4.53$
Hospital stay for nephrectomy (days)	$17.86 \pm 4.41$

Hospital stay for embolization is shorter than the one needed for nephrectomy.

The procedure was uneventful in all patients. The graft intolerance clinical condition vanished in all patients. In five out of seven patients renal flow absence after the procedure was confirmed by means of CT or scintigraphy. At the time of study conclusion, all patients remain asymptomatic and re-embolization or surgical nephrectomy of no graft has been necessary.

In none of the two patients on peritoneal dialysis program therapy withdrawal was necessary at no time. Both have been transplanted again, with no complications of rejection episodes at the time of study conclusion.

The post-embolization syndrome developed in 4 patients, with well tolerated and self-remitting fever within 48 hours. The studies performed ruled out the infectious origin in all cases.

Data pertaining to the inflammatory state at three different times (at dialysis onset, at embolization, and 6 months after) are shown in table II.

The inflammatory state at the time of restoration of dialysis constitutes a reference for clinical course comparison until embolization. Contrary to what is thought, inflammatory parameters do not improve by adapting dialysis but even worsen as a result of graft intolerance. After embolization, a remarkable improvement in the assessed parameters is observed. At six months, the inflammatory state is even better than at dialysis onset, with normalization of nutritional parameters and anemia optimization.

**DISCUSSION**

Patients with non-functioning renal graft may present two problems derived from the presence of the transplant: the graft intolerance syndrome and a chronic inflammatory state. In the first case, im-

munosuppressive treatment (corticosteroids) must be restored to control it, and in the second case, the development of a hyponutrition, atherosclerosis and inflammation (HAI) syndrome is favored. Both cases oblige to eliminate the non-functioning graft.

The incidence of graft intolerance syndrome varies depending on the series.<sup>6</sup> Classically, the preferred technique for graft elimination has been nephrectomy. The indication is established in hyperacute rejection, irreversible vascular thrombosis, graft rupture, neoplasms, or urological complications<sup>7,8</sup>. However, surgery-associated complications are many, from mild such as wound infection, haematoma or peritoneal manipulation, to severe such as sepsis, shock and death. Although their frequency has been reduced, it still is significant<sup>9,10</sup>.

Percutaneous embolization of the non-functioning renal graft represents a therapeutic alternative to graft nephrectomy, with few complications and low morbidity<sup>11</sup>. Renal embolization has been done on native kidneys in dialysis patients, in cases of treatment-refractory hypertension, nephrotic syndrome, and even non-resectable neoplasms<sup>6</sup>. However, there are circumstances that contraindicate the performance of this procedure such as the existence of urinary tract infection, graft intolerance not responding to corticosteroids and irreversible acute rejection, where surgical nephrectomy would be the treatment of choice. In our experience, the complication rate is low, only highlighting the occurrence of the post-embolization syndrome in 4 patients. This syndrome is self-limited and adequately controlled with anti-inflammatory and fever lowering drugs. In the two patients that were on peritoneal dialysis, therapy withdrawal was not necessary, although during the first days the peritoneal effluent was mildly hematic. The possible complications of surgical nephrectomy were thus avoided that many forces the interruption of peritoneal dialysis and switch the patient to a hemodialysis program.

Hospital stay ( $8.14 \pm 4.53$  days) was shorter than that for surgical nephrectomy in our Department ( $17.86 \pm 4.41$  days), with the subsequent lower morbidity. This data compare favorably with those obtained by others<sup>12,13</sup>.

The technique was safe and effective, the graft intolerance syndrome disappeared in all cases, being possible to withdraw corticosteroids therapy. In five cases we later verified by CT or scintigraphy the absence of graft vascular flow. In no case re-emboli-

**Table II.** Results at dialysis re-start, before and after embolization

	<i>Dialysis</i>	<i>Embolization</i>	<i>6 months</i>
CRP (mg/L)	4.51 ± 3.85	20.03 ± 16.29	9.83 ± 15.03*
Ferritin (ng/mL)	376.57 ± 419.26	426.14 ± 355.32	164.00 ± 52.45*
Albumin (g/dL)	3.39 ± 0.19	3.27 ± 0.45	3.64 ± 0.21*
EPO U/kg/week	132.73 ± 64.79	121.18 ± 36.56	116.60 ± 46.06
Hemoglobin (g/dL)	9.63 ± 0.95	9.31 ± 1.18	11.90 ± 1.26*

\*p < 0.05.

zation or nephrectomy for recurrence of graft intolerance were necessary.

The renal graft that does not induce rejection may remain safely in these patients. In the case of irreversible acute rejection, renal extraction has been demonstrated to significantly reduce morbimortality. Some authors describe a decrease in survival with the second renal transplantation after nephrectomy of the previous graft due to a greater patient sensitization and greater antibodies rate, which negatively affect the course of the following transplant<sup>14</sup>. In our series, the second transplantation was normally performed in two cases, in the contralateral iliac cavity, and currently with no evidence of nephropathy or graft rejection after more than two years since transplantation.

Different materials such as pure alcohol, polyvinyl, or metallic coils have been described in the literature as useful for percutaneous embolization, with similar results and success, in some series greater than 90%.<sup>15</sup> The embolization technique with embospheres used in our Center allows safely occluding the collateral branches, being a simple technique with a low rate of complications and recurrences.

The graft intolerance syndrome produces its defining symptoms and a chronic inflammatory state that may condition the onset of the HAI syndrome, affecting the patient's survival in case of perpetuating<sup>16</sup>. Besides, it is accompanied by erythropoietin resistance<sup>17</sup>.

Grafts embolization produced an improvement in analytical parameters indicative of an inflammatory state. This improvement cannot be attributed to dialysis onset since by the time the procedure was performed average elapsed time from dialysis onset was 10 months. So, at 6 months post-embolization, there has been a clear increase in hemoglobin levels using the same erythropoietin doses, albumin has normalize and CRP has also improved, normalizing in all patients but one. The statistical analysis shows that both CRP and ferritin decrease and albumin and hemoglobin increase are significant ( $p < 0.05$ ). For that reason, we believe that another indication for embolization of a non-functioning renal graft, besides the graft intolerance syndrome, may be the existence of a chronic inflammatory state since, if the latter were due to graft presence, one would resolve and prevent the development of an HAI syndrome by means of a procedure with low co-morbidity and high efficacy.

In conclusion, percutaneous renal embolization, in the case of graft intolerance in non-functioning transplants, represents a simple, safe and effective tech-

nique that may indicated as an alternative to surgical nephrectomy, does not interfere with peritoneal dialysis and may resolve that chronic inflammatory state.

## REFERENCES

1. Critsch HA, Rosenthal IT: La operación del trasplante y sus complicaciones quirúrgicas. En: Danovitch GM, ed. *Trasplante Renal*, 3.ª ed, Marbán, Madrid 146-162, 2002.
2. Pecoits-Filho R, Lindholm B, Stenvinkel P: The malnutrition, inflammation, and atherosclerosis (MIA) syndrome-the heart of the matter. *Nephrol Dial Transplant* 17 (Supl. 11): 28-31, 2002.
3. Keller FS, Coyle M, Rosch J, Dotter CT: Percutaneous renal ablation in patients with end-stage renal disease: alternative to surgical nephrectomy. *Radiology* 159: 447-451, 1986.
4. Ballesteros-Sampol JJ: Systematic extracapsular transplantectomy of nonfunctioning renal graft. *Actas Urol Esp* 18: 532-540, 1994.
5. Chiverton SG, Murie JA, Allen RD, Morris PJ: Renal transplant nephrectomy. *Surg Gynecol Obstet* 164: 324-328, 1987.
6. Cofán F, Real M, Vilardell J, Montanya X, Blasco J, Martín P, Oppenheimer F, Gutiérrez R, Talbot-Wright R, Alcover J: Percutaneous renal artery embolisation of nonfunctioning renal allograft with clinical intolerance. *Transpl Int* 15: 149-155, 2002.
7. Díaz Gallo C, Grino JM, Serón D, Castela AM, Franco E, Alsina J: Routine allograft in late renal failure. *Transplantation* 49: 1204, 1990.
8. Thomas PP, Jacob CK, Kirubakaran MG, Pandey AP, Gopalakrishnan G, Shastry JC: Indication for routine allograft nephrectomy in cases of irreversible rejection. *Transplantation* 48: 155, 1989.
9. Lechevallier E: Kidney transplantectomy: a multicenter study of the Committee of Transplantation of the French Urology Association. *Prog Urol* 5: 204-210, 1955.
10. Voesten HG, Slooll MJ, Hooykaas JA, Tegzess AM, Kootstra G: Safe removal of failed transplanted kidneys. *Br J Surg*. 69: 480-481, 1982.
11. Riera L, Viguds F, Franco E, Montaña J, Blancafort JM, Griño JM, López Costea MA, Serrallach N: Embolization of non-tolerated non-functioning kidney graft: alternative to surgical removal. *Transpl Int* 7 (Supl. 1): 301-302, 1994.
12. Cofán F, Vilardell J, Gutiérrez R, Real M, Montanya X, Oppenheimer F, Talbot-Wright R: Efficacy of renal vascular embolization versus surgical nephrectomy in the treatment of nonfunctioning renal allografts. *Transplant Proc* 31: 2244-2245, 1999.
13. González-Satué C, Riera L, Franco E, Escalente E, Domínguez J, Serrallach N: Percutaneous embolization of the renal allograft in patients with graft intolerance syndrome. *BJU Int* 86: 610-612, 2000.
14. Abouljoud MS, Deierhoi MH, Hudson SL, Diethelm AG: Risk factors affecting second renal transplant outcome, with special reference to primary allograft nephrectomy. *Transplantation* 60: 138-144, 1995.
15. Atar E, Belenky A, Neuman-Levin M, Yussim A, Bar-Nathan N, Bachar GN: Nonfunctioning renal allograft embolization as an alternative to graft nephrectomy: report on seven years' experience. *Cardiovasc Intervent Radiol* 26: 37-39, 2003.

## EMBOLIZATION OF RENAL GRAFT: EFFICACY AND INFLAMMATION

16. Stenvinkel P: Inflammation in end-stage renal failure: could it be treated? *Nephrol Dial Transplant* 17 (Supl. 8): 33-38, 2002.
17. Stenvinkel P: The role of inflammation in the anaemia of end-stage renal disease. *Nephrol Dial Transplant* 16 (Supl. 7): 36-40, 2001.