Presence of a Failed Kidney Transplant in Patients Who Are on Hemodialysis Is Associated with Chronic Inflammatory State and Erythropoietin Resistance

JUAN M. LÓPEZ-GÓMEZ,* ISABEL PÉREZ-FLORES,* ROSA JOFRÉ,* DIANA CARRETERO,* PATROCINIO RODRÍGUEZ-BENITEZ,* MAITE VILLAVERDE,* RAFAEL PÉREZ-GARCÍA,* GEORGE M. NASSAR,† ENRIQUE NIEMBRO,‡ and JUAN CARLOS AYUS§

*Departments of *Nephrology and ‡Pathology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; †Department of Nephrology, Baylor College of Medicine, and Renal Research Inc., The Kidney Institute, Houston, Texas; and §Department of Nephrology, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas*

Abstract. Patients returning to hemodialysis (HD) after failure of their kidney transplant suffer from high morbidity and mortality rates. It is common practice to keep failed kidney transplants in place. It is not known if these failed kidney transplants induce an inflammatory state that contributes to morbidity and mortality. In a single facility, patients starting on HD with failed kidney transplant were identified (Group A) and screened for the presence of chronic inflammatory state. Those with clinical symptoms attributed to the failed allograft (Group A1) were not offered transplant nephrectomy unless deemed necessary during follow-up. Their clinical and laboratory data were followed up for 6 months. Similar data were obtained from a group of incident HD patients (Group B). Forty-three patients had a failed Kidney transplant (Group A). Of these, 29 comprised Group A1 and 14 Group A2. Group B comprised 121 patients. In comparison with Group B, Group A exhibited worse anemia and erythropoietin resistance index (ERI), had lower serum albumin and prealbumin, and higher CRP. Group A1 had lower Hb and higher ferritin, CRP, and ESR in comparison with Group A2. Following transplant nephrectomy, Group A1 had improvement in ERI, serum albumin, prealbumin, ferritin, fibrnogen, CRP, and ESR. At 6 months, Group A1 had higher Hb and serum albumin levels, and lower CRP and ERI in comparison with Group A2. Group B parameters showed no change during follow-up. Patients returning to HD following failure of their kidney transplant suffer from a chronic inflammatory state. Resection of failed transplants in symptomatic patients is associated with amelioration of markers of chronic inflammation. Transplant nephrectomy should be considered a treatment option for patients with failed kidney transplants, especially if they exhibit signs and symptoms of chronic inflammatory state.

Patients who return to hemodialysis (HD) with a failed kidney transplant are being increasingly recognized as a group of patients with high rates of morbidity and mortality (1–3). Recent data show that the annual adjusted death rates for patients after kidney transplant failure is threefold higher than that of patients with a functioning kidney transplant (1). Cardiovascular and infectious events are most common causes of death, but the exact reasons for such high mortality and morbidity rates are just beginning to receive attention (1–3).

Failed kidney transplants may undergo resection in patients who develop intense pain at the transplant site as a result of uncontrolled immune-mediated rejection. Otherwise, it is common practice to keep failed kidney transplants in place despite loss of kidney function. Consequences of leaving such failed kidney transplants in place have not been well studied. We have recently demonstrated that HD patients, with occult infection of their failed arteriovenous grafts (AVG), experience a chronic inflammatory state (4–9). This characterized by a constellation of signs and symptoms that include failure to thrive, hypoalbuminemia, erythropoietin-resistant anemia, high plasma C-reactive protein (CRP) levels, and increased morbidity and mortality (4–20). Resection of these AVG with occult infection led to resolution of the chronic inflammatory state and general improvement of health (4–9). Influenced by these observations, we hypothesized that failed kidney transplants, by virtue of being a site of persistent immune-mediated reactivity, may similarly be inducing a chronic inflammatory state. We also hypothesized that resection of the failed kidney transplants is associated with amelioration of the chronic inflammatory state.

In this study, we examined the hypothesis that failed kidney transplants are associated with a chronic inflammatory state. We selected a large HD facility and identified all patients who

Received January 31, 2004. Accepted June 15, 2004.
Correspondence to Dr. Juan Carlos Ayus, University of Texas Health Sciences Center at San Antonio, 7703 Floyd Curl Drive, MC #7882, San Antonio, TX 78229-3900. Phone: 713-942-8434; Fax: 713-942-9342; E-mail: ayus@uthscsa.edu
1046-6673/1509-2494
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000137879.97445.6E

started HD after failure of their kidney transplant (group A). Baseline clinical and laboratory data were obtained from these patients and were compared with data obtained from a contemporary group of incident HD patients who never had a kidney transplant (group B). Among group A patients, those with clinical symptoms attributed to the failed kidney transplant were subjected to transplant nephrectomy (group A1). Patients without clinical symptoms attributed to the failed kidney transplant were not subjected to transplant nephrectomy (group A2). Clinical and laboratory data of group A1, group A2, and group B were followed prospectively for 6 mo.

Materials and Methods

Patient Selection

The first step was to identify incident patients who started HD after failure of their kidney transplant. At the same time, incident HD patients with no history of previous kidney transplant were identified. This was carried out prospectively in a large HD unit in Madrid, Spain, between 1997 and 2000. A total of 43 incident HD patients were identified as returning to HD after failure of their kidney transplant. These patients composed group A. A total of 121 incident HD patients were identified as starting HD but with no history of kidney transplantation. These patients composed group B. In group A, patients were divided into group A1 and group A2 on the basis of the presence or absence of constitutional symptoms, respectively. Thus, group A1 comprised 29 patients in whom fever was present in 25, decrease in appetite in 22, weight loss (>1 kg/mo) in 20, and malaise in all. The remaining 14 patients composed group A2, who had no constitutional symptoms at initial evaluation. In group A1, the patients were advised resection of the failed kidney transplant justified primarily on clinical symptoms attributed to rejection of the failed kidney transplant. All 29 patients complied and underwent transplant nephrectomy. In group A2, patients did not have clinical symptoms at initial evaluation and thus were not offered transplant nephrectomy unless they developed symptoms attributed to the failed kidney transplant during subsequent follow-up. All patients underwent baseline demographic, clinical, and laboratory evaluation. Their laboratory parameters were followed prospectively for 6 mo afterward.

Data Collection and Follow-up

Demographic data were collected on all patients at baseline. Laboratory data obtained at baseline included the following: hemoglobin (Hb) levels, erythropoietin dose, erythropoietin resistance index (ERI), serum CRP, erythrocyte sedimentation rate (ESR), ferritin, transferrin saturation index (TSI), intact parathyroid hormone levels (iPTH), fibrinogen, prealbumin, albumin, and cholesterol levels. CRP was determined using a highly sensitive immunoassay. Serum albumin was measured using green bromocresol method. The rest of the parameters were determined using established routine methods. The ERI was obtained simply by dividing the total weekly erythropoietin dose first by the patient's weight (in kilograms) and then by the patient's Hb level (in g/dl) and was expressed as units/wk per kg per g/dl.

Laboratory data were collected on all patients at 6 mo of follow-up. In group A1, baseline data were obtained within 1 wk before surgery and at 3 and 6 mo after transplant nephrectomy. In addition, data were collected on comorbidities associated with transplant nephrectomy. Specifically, these included data on infectious complications, transfusion requirements, and length of stay in the hospital. Data on intake of prednisone were obtained in group A. Data on intake of antihypertensive medications as well as on type of dialysis vascular access were obtained in groups A and B.

Histopathology of Resected Kidney Transplants

Resected kidney transplant specimens were routinely sent to the pathology department for microscopic examination. Specimens were subjected to standard histologic review by a staff pathologist using routine techniques. Limited microbiologic studies were performed to exclude the presence of infections.

Statistical Analyses

The Kolmogorov-Smirnov test was applied to all of the variables evaluated in this article. This test was NS in any instance. Thus, all of the variables have a normal distribution, and that allowed us to use parametrics *t* test for comparison between groups. The ANOVA test was used for the comparison of parameters at different points of the study when baseline data within a group were compared with subsequent follow-up. The differences found were considered statistically significant at $P < 0.05$.

Results

Between 1997 and 2000, 43 patients (group A) started HD in our unit after failure of their kidney transplant. The mean age in group A was 48.6 ± 14.6 yr; 55.8% were men. The original causes of their end-stage kidney failure were as follows: chronic glomerulonephritis (32.5%), diabetic nephropathy (14%), chronic tubulointerstitial nephropathy (11.6%), adult polycystic kidney disease (20.9%), and unknown in the rest (Table 1). The dialysis vascular access was arteriovenous fistula in 30 (69.7%) and polytetrafluoroethylene arteriovenous graft (PTFE-AVG) in 13 (30.3%), and none had indwelling dialysis catheters. Old clotted PTFE-AVG was present in 4 (9.3%) in whom Indium scan showed no uptake suggestive of inflammation.

Group B comprised 121 contemporary incident HD patients from the same HD unit. The mean age in group B was 62.9 ± 13.8 yr; 63.8% were women. The leading causes of their end-stage kidney failure were similar to group A and were as follows: chronic glomerulonephritis (22.6%), diabetic nephropathy (19.5%), chronic tubulointerstitial nephropathy (20.3%), and adult polycystic kidney disease (16.5%; Table 1). The dialysis vascular access was arteriovenous fistula in 67 (55.4%), PTFE-AVG in 45 (37.2%), and indwelling dialysis catheter in 9 (7.4%). Old clotted PTFE-AVG was present in 25 (20.6%).

All patients were on chronic HD three times per week, averaging between 3.5 and 4.0 h per session. Mean KT/V in the HD unit was 1.32 ± 0.19. There were no differences in achieved Kt/V between group A and group B. Their residual renal function was not measured, but all patients were making <400 ml of urine per day, indicating marked impairment of renal function. All patients were undergoing treatment with subcutaneous recombinant human erythropoietin and were being administered intravenous iron, based on protocols established in the HD unit. The target Hb range in the HD unit was between 11 and12 g/dl. The serum vitamin B_{12} and folate levels were normal in group A (serum vitamin B_{12} = 646 ± 313 pg/ml, serum folate = 6.9 ± 4 ng/dl). In group A, 62%

Table 1. Baseline demographic, clinical, and laboratory data of group A and group B[a]

	Group A	Group B
N	43	121
Age (yr)	48.6 ± 14.6[b]	62.9 ± 13.8
Gender (% male)	55.8	63.2
Cause of chronic renal failure	GN (32.5%), DN (14%), CIN (11.6%), APCD (20.9%)	GN (22.6%), DN (19.5%), CIN (20.3%), APCD (16.5%)
Hb (g/dl)	10.4 ± 1.9[b]	12.7 ± 1.4
rHu-EPO dose (U/wk)	8862 ± 3924[b]	6380 ± 3706
ERI (U/kg per wk per g/dl)	16.1 ± 9.0[b]	8.3 ± 5.5
Ferritin (μg/L)	469 ± 382[NS]	412 ± 320
TSI (%)	26.7 ± 10.7[NS]	34.5 ± 15
Albumin (g/dl)	3.2 ± 0.6[b]	3.8 ± 0.4
Prealbumin (mg/dl)	25.3 ± 12.1[b]	32.3 ± 7.8
Cholesterol (mg/dl)	181.3 ± 42.7[NS]	191.4 ± 39.5
CRP (mg/dl)	4.1 ± 4.7[b]	1.3 ± 1.9
iPTH (pg/ml)	258.3 ± 271.3[c]	386 ± 400

[a] Data from group A were obtained within 1 wk before transplant nephrectomy. Data are mean ± SD. GN, glomerulonephritis; DN, diabetic nephropathy; CIN, chronic interstitial nephropathy; APCD, adult polycystic disease; Hb, hemoglobin; ERI, erythropoietin resistance index; TSI, transferring saturation index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; iPTH, intact parathyroid hormone; NS, no significance.

Significance between groups A and B at baseline: [b] $P < 0.001$; [c] $P < 0.05$.

were on antihypertensive medications that included angiotensin-converting enzyme inhibitor in 27.7%, angiotensin receptor blocker in 11.1%, and calcium channel blockers in 59.5%. The use of antihypertensive medications was similar in group B, 56.2% of whom were on antihypertensive medications that included angiotensin-converting enzyme inhibitor in 30.9%, angiotensin receptor blocker in 19.1%, and calcium channel blockers in 55.9%.

Comparison of group A and group B patients revealed several differences. Group A patients at baseline had ERI of 16.1 ± 9.0 U/kg per wk per g/dl, which was significantly higher than group B patients, whose ERI was 8.3 ± 5.5 U/kg per wk per g/dl ($P < 0.001$). In addition to erythropoietin resistance, group A patients had other biochemical abnormalities suggestive of chronic inflammatory state; group A patients had lower levels of serum albumin ($P < 0.001$) and serum prealbumin ($P < 0.001$) and a higher CRP ($P < 0.001$) in comparison with group B. No differences, however, were found in serum ferritin, TSI, cholesterol, and iPTH levels between group A and group B patients (Table 1).

Among group A patients, 29 had clinical symptoms attributed to kidney transplant failure and were subjected to transplant nephrectomy on the basis of clinical judgment. This subgroup of patients is labeled group A1. Among these, 22 (75.8%) patients were on low dosages of prednisone (6.4 ± 3.8 mg/d) but on no other immunosuppressants. The other 14 patients in group A had no clinical symptoms at initial evaluation. They were not offered transplant nephrectomy initially and were labeled group A2. Of these, 8 (57.1%) were on low doses of prednisone (5 ± 2.3 mg/d) and on no other immunosuppressants.

Group A1 patients were more symptomatic than group A2 patients. In parallel with differences in clinical symptoms, group A1 patients had worse biochemical and hematologic profiles than group A2 (Table 2). At baseline, group A1 patients had significantly higher ferritin, CRP levels, and ESR in comparison with group A2 patients. The mean Hb was 9.8 ± 1.8 g/dl in group A1 *versus* 11.6 ± 1.5 g/dl in group A2 ($P < 0.01$), but the ERI was not statistically different between the two groups. There were no statistical differences in albumin, prealbumin, fibrinogen, and iPTH between group A1 and group A2 (Table 2).

Transplant nephrectomy was performed in group A1 at 5.0 ± 5.0 mo (1 to 24 mo) after starting HD. In 14, it was within 3 mo after starting HD. There were no perioperative deaths, and none of the group A1 patients died during the 6 mo of postoperative follow-up. Prospective follow-up of group A1 patients after transplant resection showed significant improvement in anemia (Table 3). Thus, Hb levels improved from 9.8 ± 1.8 at baseline to 12.7 ± 1.1 g/dl at 6 mo after surgery ($P < 0.001$). There was a corresponding improvement in ERI from 16.5 ± 7.9 to 9.9 ± 5.5 U/kg per wk per g/dl ($P < 0.001$), and it became similar to that of group B (Figure 1A). Significant improvement in serum albumin, prealbumin, ferritin, plasma fibrinogen, ESR, and CRP levels were seen after transplant nephrectomy in group A1 (Table 3). Serum albumin improved from 3.1 ± 0.7 to 3.9 ± 0.6 g/dl at 6 mo after surgery ($P < 0.001$) and became similar to group B (Figure 1B). Prealbumin levels improved from 26.0 ± 13.5 to 30.8 ± 8.6 mg/dl ($P < 0.01$). Ferritin levels decreased from 594.3 ± 400.7 to 356.7 ± 268.6 μg/L ($P < 0.05$). Plasma fibrinogen improved from 535.3 ± 218.6 to 400.2 ± 107.9 mg/dl ($P < 0.001$). ESR fell from 88.4 ± 40.4 to 29.2 ± 14.4 ($P < 0.01$). CRP levels decreased from 6.6 ± 5.2 to 0.9 ± 0.5 mg/dl ($P < 0.01$) and

Table 2. Baseline demographic, clinical, and laboratory data of group A1 and group A2[a]

	Group A1 Transplant Nephrectomy Done	Group A2 Transplant Nephrectomy not Done
N	29	14
Age (yr)	43.8 ± 13.0[b]	59.6 ± 12.3
Gender (% male)	58.7	50
Hb (g/dl)	9.8 ± 1.8[b]	11.6 ± 1.5
rHu-EPO dose (U/wk)	8448 ± 2599[NS]	9954 ± 6270
ERI (U/kg per wk per g/dl)	16.5 ± 7.9[NS]	15.1 ± 11.8
Ferritin (μg/L)	594 ± 400[c]	272 ± 259
TSI (%)	23.5 ± 8.0[NS]	30.5 ± 12.4
Albumin (g/dl)	3.1 ± 0.7[NS]	3.4 ± 0.4
Prealbumin (mg/dl)	26.0 ± 13.5[NS]	24.3 ± 10.6
CRP (mg/dl)	6.6 ± 5.2[c]	3.1 ± 4.2
Fibrinogen (mg/dl)	535.3 ± 218.6[NS]	502.3 ± 196.6
ESR (mm/h)	88.4 ± 40.4[c]	48.1 ± 28.7
iPTH (pg/ml)	234.9 ± 250.2[NS]	285 ± 302.9

[a] Data are mean ± SD. ESR, erythrocyte sedimentation rate.
Significance between group A1 and group A2 patients at baseline: [b] $P < 0.01$; [c] $P < 0.05$.

Table 3. Baseline and follow-up laboratory data of group A1[a]

	Baseline	+3 Months	+6 Months
Hb (g/dl)	9.8 ± 1.8	12.2 ± 2.0[b]	12.7 ± 1.1[b]
rHu-EPO dose (U/wk)	8448 ± 2599	7655 ± 2525[NS]	6925 ± 3173[NS]
ERI (U/kg per wk per g/dl)	16.5 ± 7.9	12.4 ± 5.9[b]	9.9 ± 5.5[b]
Ferritin (μg/L)	594.3 ± 400.7	365.2 ± 343.1[NS]	356.7 ± 268.6[e]
TSI (%)	23.5 ± 8.0	39.5 ± 19.8[c]	37.9 ± 14.3[b]
Albumin (g/dl)	3.1 ± 0.7	3.8 ± 0.6[b]	3.9 ± 0.6[b]
Prealbumin (mg/dl)	26.0 ± 13.5	29.6 ± 8.2[NS]	30.8 ± 8.6[d]
CRP (mg/dl)	6.6 ± 5.2	1.3 ± 1.0[d]	0.9 ± 0.5[d]
Fibrinogen (mg/dl)	535.3 ± 218.6	354.8 ± 65.5[NS]	400.2 ± 107.9[b]
ESR (mm first h)	88.4 ± 40.4	35.9 ± 22.8[d]	29.2 ± 14.4[d]
iPTH (pg/ml)	234.9 ± 250.2	379.4 ± 504.0[NS]	526.4 ± 630.3[NS]

[a] Follow-up data were obtained at 3 and 6 mo after transplant nephrectomy. Data are mean ± SD.
Significance with respect to baseline: [b] $P < 0.001$; [c] $P < 0.005$; [d] $P < 0.01$; [e] $P < 0.05$.

became similar to CRP levels in group B (Figure 1C). In contradistinction, group B patients exhibited no improvements in hematologic or biochemical profiles with prospective follow-up (Table 4).

Prospective follow-up data between groups A1 and A2 revealed important findings. At 6 mo of follow-up, group A1 exhibited superior hematologic and biochemical profiles in comparison with group A2 (Table 5). The Hb levels were 12.7 ± 1.1 g/dl in group A1 *versus* 10.9 ± 1.4 g/dl in group A2 ($P < 0.05$). The ERI was 9.9 ± 5.5 U/kg per wk per g/dl in group A1 *versus* 20.2 ± 12.3 U/kg per wk per g/dl in group A2 ($P < 0.05$). Group A1 had lower CRP ($P < 0.01$) and higher albumin ($P < 0.05$) and prealbumin ($P < 0.05$) in comparison with group A2.

Group A1 patients exhibited a general improvement in overall health. This is reflected by a significant weight gain among group A1 patients after transplant nephrectomy. Thus, at 6 mo after surgery, there was a significant increase in the dry weight of group A1 patients from 57.0 ± 10.5 to 58.2 ± 11.3 kg ($P = 0.01$). This was not associated with changes in BP. There were no deaths in group A1 during 6 mo of follow-up. In group A2, there were no deaths during the initial 6 mo of follow-up. However, by the end of 1 yr of follow-up, three patients developed rejection of the renal allograft, characterized by the clinical symptoms of malaise, fever, weight loss, and pain at the site of the kidney transplant. Two of these patients required urgent resection of the kidney transplant, and one died because of progressive malnutrition before having a chance at resection of the kidney transplant.

Patients who underwent transplant nephrectomy (group A1) required an average of 19 ± 11 d of hospitalization. Blood transfusions were needed in 58.6% of the patients. Transfusion

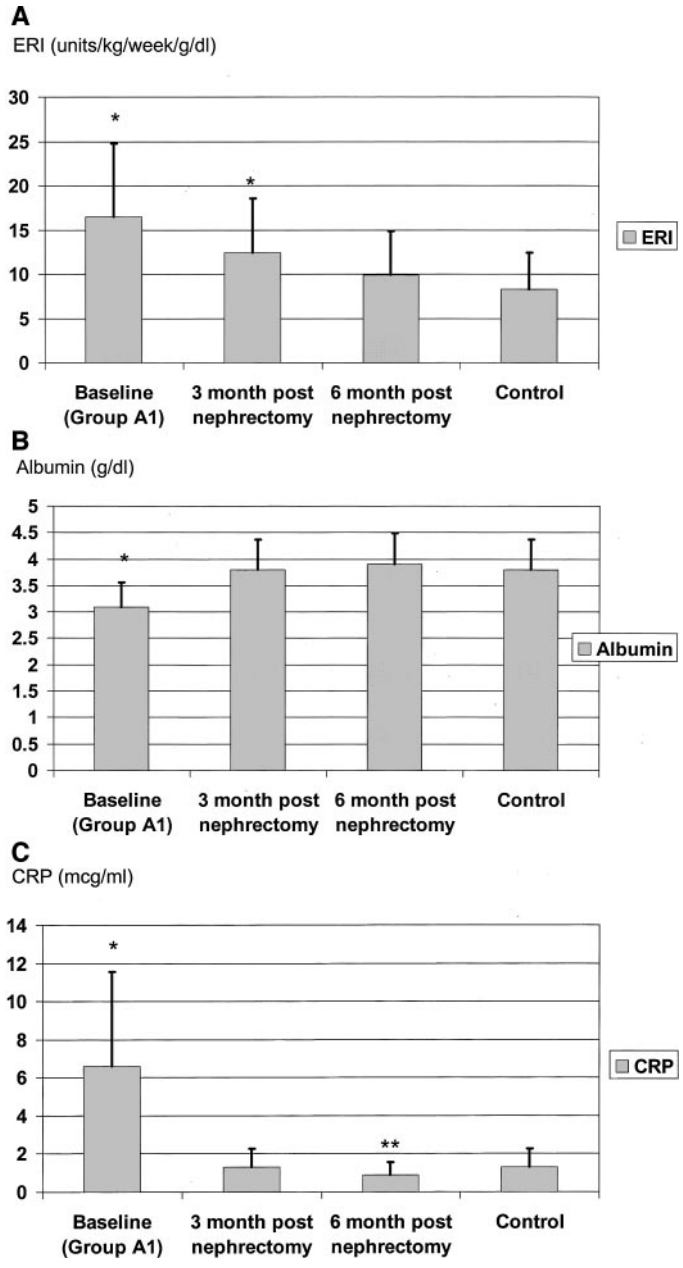

Figure 1. Prospective follow-up of erythropoietin resistance index (ERI; A), serum albumin levels (B), and C-reactive protein (CRP) in group A1 (C). Comparison with group B is provided. *Significantly worse than group B ($P < 0.01$); **significantly better than group B.

requirements correlated with the degree of anemia and inflammation in these patients at the time of hospitalization. Patients who received transfusions had lower Hb levels (9.0 ± 1.6 *versus* 11.0 ± 1.5; $P = 0.003$) and higher ESR (118.2 ± 31.3 *versus* 58.6 ± 21.9; $P = 0.008$) at the time of transplant nephrectomy compared with patients who did not require transfusions. Infectious complications appeared in 48%. Of these, the most common was surgical wound infection (59%), followed by hospital-acquired upper and lower respiratory infection (26%). Patients who developed postoperative infectious complications maintained considerably lower serum albumin levels before surgery than those who did not have any postoperative infectious episodes (2.9 ± 0.8 g/dl *versus* 3.5 ± 0.4 g/dl; $P = 0.05$).

Histologic examination of resected kidney transplants was available in 25 of 29 cases. In one case, there was a massive hemorrhagic infarction that prevented further histologic examination. In all remaining 24 cases, there was evidence of chronic rejection characterized by the existence of variable degrees of glomerulitis and tubulitis. Characteristic findings included (*1*) the presence of chronic interstitial mononuclear cell infiltrate, (*2*) subendothelial lymphocytic and monocytic cellular infiltrate, (*3*) intimal vascular fibrosis, and (*4*) moderate to severe interstitial fibrosis (Figure 2). None of the specimens had viral inclusions or findings suggestive of infection. A summary of the major histologic findings is provided in Table 6.

Discussion

Until the late 1990s, there were few data on the outcomes of patients after loss of the kidney transplant. Recent epidemiologic studies on large numbers of kidney transplant patients clearly show that patient survival after graft loss is poor. Ojo *et al.* (3) followed a cohort of 19,208 kidney transplant patients for >10 yr and found that loss of kidney transplant is associated with poor 5-yr survival rates. especially in patients with type 1 diabetes (36% *versus* 65% in nondiabetic patients). Repeat transplantation reduced death rates by 45% and 23% in patients with and without type 1 diabetes, respectively. Kaplan and Meier-Kriesche followed 78,564 patients from the U.S. Renal Data System and found overall annual adjusted death rates to be threefold higher after kidney transplant loss as compared with before graft loss (9.42% *versus* 2.81%) (1). Although these important studies highlighted the gravity of the problem, there were no firm conclusions regarding optimizing the care of patients with failed kidney transplants after return to dialysis.

The first important finding that emerges from our study is that our group of HD patients with a failed kidney transplant (group A) experience erythropoietin resistance and malnutrition and have elevated plasma CRP, ferritin, and ESR. In comparison with HD patients with no history of kidney transplantation (group B), HD patients with failed kidney transplant exhibited worse anemia, erythropoietin resistance, and hypoalbuminemia and had more profound disturbances in CRP, ferritin, and ESR (Table 1). Our data are in agreement with Almond *et al.* (21), who reported that failed kidney transplant patients who restart HD have greater erythropoietin requirements in comparison with the rest of the dialysis population. Our data are also in agreement with Gill *et al.* (2), who found profound anemia and significant hypoalbuminemia among failed kidney transplant recipients who returned to dialysis. This was largely attributed to suboptimal care among these patients before resumption of HD. These hematologic and biochemical disturbances are known to be associated with poor clinical outcomes. In this regard, several studies show that low serum albumin and high CRP are markers for increased cardiovascular and global morbidity and mortality in the general

Table 4. Baseline and follow-up laboratory data of group B[a]

	Baseline	+3 Months	+6 Months
Hb (g/dl)	12.7 ± 1.4	12.6 ± 1.2	12.7 ± 1.1
rHu-EPO dose (U/wk)	6380 ± 3706	6120 ± 3457	6243 ± 3652
ERI (U/kg per wk per g/dl)	8.3 ± 5.5	8.1 ± 5.4	8.2 ± 5.5
Ferritin (μg/L)	412 ± 320	344 ± 257	368 ± 287
TSI (%)	34.5 ± 15	33.9 ± 14.4	38.8 ± 15.2
Albumin (g/dl)	3.8 ± 0.4	3.9 ± 0.4	3.7 ± 0.3
Prealbumin (mg/dl)	32.3 ± 7.8	31.4 ± 8.8	34.8 ± 10.1
CRP (mg/dl)	1.3 ± 1.9	1.2 ± 1.6	1.3 ± 1.7
Cholesterol (mg/dl)	191.4 ± 39.5	187.0 ± 38.6	190.0 ± 42.1
iPTH (pg/ml)	386 ± 400	486 ± 396	488 ± 422

[a] There was no statistical significance of any of the parameters in comparison with baseline. Data are mean ± SD.

Table 5. Comparison of hematologic and biochemical data between group A1 and group A2 at 6 mo of follow-up[a]

	Group A1 Transplant Nephrectomy Done	Group A2 Transplant Nephrectomy not Done
N	29	14
Hb (g/dl)	12.7 ± 1.1[c]	10.9 ± 1.4[c]
rHu-EPO dose (U/wk)	6925 ± 3173[c]	12714 ± 8693[c]
ERI (U/kg per wk per g/dl)	9.9 ± 5.5[c]	20.2 ± 12.3[c]
Ferritin (μg/L)	356.7 ± 268.6[NS]	235 ± 119[NS]
TSI (%)	37.9 ± 14.3[NS]	38.7 ± 18.1[NS]
Albumin (g/dl)	3.9 ± 0.6[b]	3.3 ± 0.4[b]
Prealbumin (mg/dl)	30.8 ± 8.6[c]	27.6 ± 7.9[c]
CRP (mg/dl)	0.9 ± 0.5[b]	3.6 ± 6.0[b]

[a] Data are mean ± SD.
Significance between group A1 and group A2: [b] $P < 0.001$; [c] $P < 0.005$.

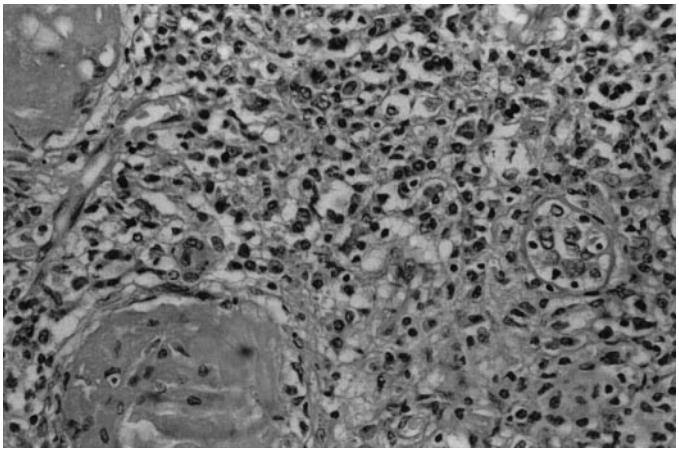

Figure 2. Typical chronic mononuclear cell interstitial infiltrate is present. In addition, there are few scattered polymorphonuclear cells, evidence of tubulitis, and glomerular sclerosis. Magnification, ×250 (hematoxylin and eosin).

Table 6. Summary of histopathologic findings in 24 resected kidney transplant specimens[a]

Findings	Grade 0	Grade 1+	Grade 2+
Chronic inflammation (interstitial MN infiltrate)	0	13	11
Acute inflammation (interstitial PMN infiltrate)	16	3	5

Findings	Absent	Present
Arteriolopathy (intimal hyperplasia, parietal thickening)	15	9
Vascular thrombosis (arterial and venous thrombi)	19	5

[a] Grade 0 is negative; grade 1+ is mild-moderate; grade 2+ is moderate-severe; PMN, polymorphonuclear; MN, mononuclear.

population as well as in patients who undergo chronic dialysis (10–13,17–19,22–26). Many epidemiologic studies have shown an association between CRP and arteriosclerosis, thereby establishing a possible link among inflammation, arteriosclerosis, and malnutrition in patients with kidney disease (13,27,28). Thus, patients who have failed kidney transplants and are on HD exhibit a constellation of hematologic and

biochemical abnormalities characteristic of a chronic inflammatory state, which is associated with increased morbidity and mortality.

The second important finding relates to improvement in the hematologic, biochemical, and clinical parameters of patients with failed kidney transplant after resection of the allograft. Surgical resection of the failed renal allograft was performed in a subgroup (group A1) of patients who exhibited clinical signs and symptoms of allograft rejection. The 6-mo follow-up data after transplant nephrectomy of these patients was very informative. It showed that surgical resection of failed kidney transplants was associated with enhanced erythropoietin responsiveness, resolution of hypoalbuminemia, and marked improvement in biochemical markers of chronic inflammation (Table 3). Thus, by the end of 6 mo after transplant nephrectomy, the biochemical and hematologic profile of study group A1 patients became similar to that of group B (Figure 1). At initial evaluation, group A1 patients exhibited worse hematologic and biochemical profiles in comparison with group A2 (Table 2). The impact of transplant nephrectomy in group A1 was so favorable that by the end of 6 mo of follow-up, there was reversal of the superiority of the hematologic and biochemical profiles in favor of group A1 patients (Table 5). However the hematologic and biochemical profiles of group B patients did not improve despite 6 mo of dialysis (Table 4). Collectively, these data refute the possibility that the improvements seen in group A1 were a result of 6 mo of hemodialytic therapy and support the hypothesis that resection of failed kidney transplants is associated with resolution of parameters of the chronic inflammatory state.

Despite the absence of clinical symptoms in group A2 patients at initial evaluation, their subsequent follow-up is concerning for two reasons. First, they demonstrated no improvement in their hematologic and biochemical profiles at 6 mo of follow-up despite receiving adequate dialytic therapy. Second, three (21%) patients developed signs and symptoms of chronic inflammatory state within 1 yr of follow-up, leading to death in one patient and requiring urgent transplant nephrectomy in two patients. These findings are in agreement with data recently reported by Vanderbilt University investigators on a group of 345 patients with failed kidney transplants. In this large, retrospective analysis, Langone *et al.* (29) found that transplant nephrectomy became necessary, mostly as a result of clinical symptoms, in 273 (79%) at some point during follow-up. Histologic examination of resected kidney transplant specimens in their series as well as in our patients shows that the vast majority of patients had evidence of significant inflammation (Table 5).

Many of our patients were undergoing treatment with prednisone at the time of transplant nephrectomy. Corticosteroids play an important anti-inflammatory role, but they are not free of side effects. Of particular interest is that among group A1 patients; those who were receiving prednisone had higher serum albumin levels. Other investigators have similarly reported on treatment of erythropoietin resistance with immunosuppressive therapy (30). It is a widely common practice to keep patients with a failed kidney transplant on a low-dose immunosuppression protocol. However, controversy regarding maintenance immunosuppression continues to be present. For example, in a multicenter cohort study on 197 failed kidney transplants, Smak Gregoor *et al.* (31) found increased incidence of infections and cardiovascular disease in association with low-dose maintenance immunosuppression. Also, such therapy did not lead to fewer rejections; hence, the authors argued in favor of stopping immunosuppression when patients with failed renal allografts return to dialysis. Because transplant nephrectomy is subsequently required in the majority of patients with failed kidney transplants (29) and because chronic low-dose immunosuppression is neither effective nor safe, elective transplant nephrectomy emerges as both a safe and an effective alternative measure to treat or prevent the development of a chronic inflammatory state in these patients.

Shortcomings of our data include that groups A and B were not specifically matched for age. Unfortunately, this was not possible in our single-center study. We enrolled all incident patients who entered the HD unit in either group regardless of age differences. It may not be surprising that group A patients were younger than group B because they were previous kidney transplant recipients. Of interest is that the age of group B patients matched the mean age of patients on HD in Spain (62.9 ± 13.8 *versus* 63.8 ± 14.2 yr), indicating that group B was a true representation of national HD patients (32). A similar argument could be made that groups A1 and A2 were not matched for age, but, again, it was not feasible to do so in our single-center study. Nevertheless, despite the younger age of group A1 patients, they had worse hematologic and biochemical profiles at the beginning of the study. It is difficult to envision that the younger age of group A1 had a significant impact on the data at baseline as well as during 6 mo of follow-up. Another criticism of the study is that one may not be able to generalize the favorable impact of transplant nephrectomy demonstrated in symptomatic patients (group A1) to all HD patients with failed kidney transplant. Although this is true, one cannot totally ignore two facts: The first is that a high percentage of initially asymptomatic patients subsequently developed constitutional symptoms that required transplant nephrectomy. This was shown in our follow-up of group A2 as well as in the literature (29). The second emerges from our 6-mo follow-up data showing hematologic and biochemical superiority of group A1 (initially symptomatic and underwent transplant nephrectomy) in comparison with group A2 (initially asymptomatic and did not undergo transplant nephrectomy). Clearly, this is the first report demonstrating the benefit of transplant nephrectomy in HD patients with failed kidney transplant, and, obviously, additional, larger studies would be necessary to further our understanding on the subject.

In conclusion, our data show that HD patients with a failed kidney transplant commonly experience a profound chronic inflammatory state. Resection of the failed kidney transplant in symptomatic patients is associated with amelioration of clinical and laboratory parameters of the chronic inflammatory state. Resection of failed kidney transplants should be considered in HD patients who exhibit clinical or biochemical signs of chronic inflammatory state. Larger, multicenter, prospective

studies are recommended to examine further the relationship between resection of the failed kidney transplant in both symptomatic and asymptomatic HD patients.

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