Transplant glomerulopathy. Clinical outcome and follow-up of cases

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Abstract

Objective: We describe the evolution of graft function in patients with transplant glomerulopathy measure by levels of serum creatinine, proteinuria and estimated glomerular filtration rate. Method: Cross-sectional study conducted in the Regional General Hospital No. 46 IMSS. Included patients with kidney allograft and diagnosis of renal biopsy of transplant glomerulopathy grafting between January 1, 2006 to April 31, 2013 serum creatinine, proteinuria and estimated glomerular filtration rate at diagnosis, 6, 12 and 24 was recorded months. The results are shown with numbers, percentages and standard deviations. Results: 42 patients were included. At 6 months of diagnosis, 14% decline in graft function and 7.1% graft loss. At 12 months, 17.9% graft loss, and at 24 months 36.3% had chronic graft dysfunction and graft loss as return to dialysis. Conclusions: Evolution in our patients seems to be better to other series of cases reported in the literature.


Introduction

Chronic kidney disease is the result of different chronic-degenerative conditions and is considered to be a catastrophic disease owing to the growing number of cases, high investment costs, limited infrastructural and human resources, late detection and high morbidity and mortality rates in replacement programs, with kidney transplant being the treatment of choice.

However, the main causes of renal graft loss include graft chronic dysfunction and death of patients with functioning graft for cardiovascular causes. When a clinically-indicated biopsy is performed, the main cause for graft failure is secondary to antibody-mediated (humoral) rejection in patients with poor adherence to immunosuppressant treatment.

Transplant glomerulopathy (TG) has received much attention in the past few years as a manifestation of chronic humoral rejection, described by Porter et al. in 1967 and characterized by thickening or duplication of the glomerular basement membrane (in the absence of other conditions that may cause this histological pattern). It is often diagnosed at late post-transplantation stages and it is associated with poor graft survival.

Several studies have investigated the clinical meaning of different parameters (both clinical and histologic) in relation to TG, in an attempt to identify a subgroup of patients with slower disease progression and to determine the group of patients in need for immunomodulatory therapy. Average 5-year post-biopsy with TG diagnosis estimated survival is only 16.7%.

It is important pointing out that the glomerular filtration rate (GFR) reduction, once the biopsy is performed, tends to decrease. Cosio et al. found that, after one year of follow-up, 27% of TG-diagnosed patients had already a GFR decrease of 50%.

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To date, there isn’t an effective therapy available for TG. There is strong evidence that blood pressure control and angiotensin II inhibition are effective measures and decrease disease progression. Furthermore, additional immunosuppression has been suggested to likely be useful, with this being based on pathogenesis and in isolated cases of management, which is why this is still considered preliminary evidence. Change in the immunosuppressant scheme (association of tacrolimus and mycophenolate mofetil) has been used, with a sustained decrease in antibody titers.

Recent strategies with the same purpose are based on the use of plasma exchange, intravenous immunoglobulin and T and B-cell depleting agents, including anti-lymphocyte globulin or rituximab, but the results have not been as good as expected, with optimal treatment protocol still pending to be defined. Among rituximab-treated patients, 50% experience graft loss in a 26-month period, with serum creatinine (SCr) values stabilization and important proteinuria decrease in the remaining 50% at 3 years of follow-up.

The purpose of the study was to know graft function evolution at 6, 12 and 24 months in TG-diagnosed patients by means of the SCr, proteinuria and estimated GFR (eGFR) values.

**Method**

Cross-sectional descriptive study carried out at the Hospital General Regional No. 46 of the Mexican Institute of Social Security in Guadalajara, Jalisco. Among patients with kidney transplant on follow-up as outpatients, those with TG whose diagnosis was established between January 2006 and April 2013, who met the inclusion criteria (age between 16 and 60 years of age, either gender), who had a renal graft biopsy report with optical microscopy description, immunofluorescence and C4d by immunohistochemical staining establishing the TG diagnosis, as well as proteinuria and SCr determination at baseline and at 6, 12 and 24 months, according to the follow-up time, were included.

Patients with incomplete renal graft biopsy report, with the received treatment not specified in the medical note, who were lost to follow-up as nephrology-department outpatients or who had SCr and proteinuria not reported in the medical notes were eliminated.

To determine the evolution, creatinine and proteinuria were recorded at baseline and at 6, 12 and 24 months after the TG diagnosis, with the same tests being systematically performed in kidney transplant patients’ follow-up. In addition, GFR was estimated at baseline and at 6, 12 and 24 months with the Modification of Diet in Renal Disease 4 (MDRD-4) formula.

Evolution was concluded as: a) no deterioration in graft function: SCr increase lower than 50% from baseline value or eGFR decrease < 10 mL/min; b) with graft function deterioration: SCr increase higher than 50% or eGFR decrease > 10 mL/min; or c) graft loss of function, return to to dialysis or kidney retransplantation.

**Statistical analysis**

Numerical variables are shown as averages with standard deviations; nominal variables are shown as numbers and percentages. Descriptive statistics was carried out with absolute frequencies. The SPSS program, version 15 in Spanish, was used.

**Results**

Out of 906 on kidney transplant follow-up, 42 were diagnosed with TG and met the inclusion criteria, and a TG frequency of 4.6% was therefore calculated in this population. Average time from kidney transplant to diagnosis was 90.8 ± 41.7 months (Table 1). All 42 patients completed a minimal period of 6 months after TG diagnosis, 39 patients 12 months and only 33 patients 24 months.

The TG evolution outcomes are shown (Table 2), as well as the creatinine, proteinuria and MDRD-4-measured values throughout the follow-up period (Table 3).

Average time to graft loss after diagnosis was 16.35 months (range: 6-44 months). Graft survival was 92.8%, 82.05% and 63.6% at 6, 12 and 24 months, respectively.

Of total patients, 18 received treatment; in 66.6%, shift was made to tacrolimus, and in the rest, therapy based on biologicals. Importantly, 72.2% of patients who received any type of treatment remained with a functioning graft for the entire 24-month follow-up.

The main indication for performing a biopsy was creatinine elevation in 28 patients (66.7%); however, 57.14% also showed proteinuria at diagnosis.

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The first study carried out at the Hospital General Regional No. 46, which has 906 patients on kidney transplant follow-up, with the purpose to determine the prevalence and evolution of patients with TG, is presented.

The international literature reports a TG prevalence ranging from 1.6 to 20%\(^6,10\); this broad variation is related to the type of patients in whom the diagnosis is established. In our study, the prevalence of TG was 4.6%, which in spite of falling within the reported range, tends to be low, but we cannot rule out underdiagnosing of this pathology, given that we included only patients with indicated rather than per protocol biopsies.

TG has been described with presentations as early as only 2 months from kidney transplant, although it is more common at later stages. In this group of patients, the earliest diagnosis was made at 21 months from the kidney transplant, with a mean of 7.5 years; the latter is within that which is expected since, although it is higher than the value reported by authors such as Shimizu et al.\(^{14}\), whose diagnosis is earlier (4.4 years) they included patients who underwent biopsy both owing to graft function deterioration and owing to proteinuria and per protocol in their study, in contrast with ours, where only patients with indicated biopsies were included, which influences on the time elapsed until the diagnosis is established, since up to 5% of kidney transplant-recipient patients have been observed to develop this lesion within the first post-transplant year with no renal graft function manifestations that impact on the graft survival range at diagnosis\(^6,10,13-15\).

The most common presentation form in our patients was graft function deterioration, with an increase in usual creatinine of 40%, with creatinine usual values being 1.5 ± 0.54 mg/dL and 2.1 ± 0.94 mg/dL at TG diagnosis, which is consistent with values reported in other series\(^15,16\).

The presence of proteinuria in 57.14% of cases is also similar to that described in the world literature, where it ranges from 36 to 93%\(^{14-16}\); however, proteinuria occurred at nephrotic ranges in 45.8% of patients, which more than doubles the value reported by Sun et al.\(^{17}\) (18.6%), probably influenced by the type of immunosuppression used in our patients, since 69% of them use sirolimus, as well as anti-proteinuria measures that might have not been used by the patients.

In our series, the most common histopathologic finding is IF/TA, although its frequency is below to that reported, which ranges from 81 to 90% of cases. Capillaritis and glomerulitis, which have been described by Shimizu et al. among the most common TG-associated findings (84 and 81%, respectively), do not agree with that what was found in the present or other studies, where the frequency of both is lower, probably as a result of the known interrater variability there is in biopsy interpretation\(^14,17\). We consider a similar

### Table 1. Demographic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
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</thead>
<tbody>
<tr>
<td>Age (years) (\bar{x} \pm s)</td>
<td>26.2 ± 8.7</td>
<td></td>
<td></td>
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<tr>
<td>Male/female gender, n/n (%)</td>
<td>29/13 (31/69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg) (\bar{x} \pm s)</td>
<td>61.9 ± 14.50</td>
<td></td>
<td></td>
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<tr>
<td>LRD LT, n (%)</td>
<td>34 (81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDD LT, n (%)</td>
<td>5 (11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD LT, n (%)</td>
<td>3 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of rejection, n (%)</td>
<td>19 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBP, n (%)</td>
<td>3 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>2 (4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual Cr (mg/dL) (\bar{x} \pm s)</td>
<td>1.54 ± 0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr at diagnosis (mg/dL) (\bar{x} \pm s)</td>
<td>2.19 ± 0.95</td>
<td></td>
<td></td>
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<tr>
<td>Proteinuria at diagnosis (g/24 h) (\bar{x} \pm s)</td>
<td>3.35 ± 2.6</td>
<td></td>
<td></td>
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<tr>
<td>eGFR at diagnosis (mL/min) (\bar{x} \pm s)</td>
<td>42.2 ± 20.9</td>
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</tbody>
</table>

**BD DL T**: brain dead donor liver transplantation; **Cr**: creatinine; **DM**: diabetes mellitus; **eGFR**: estimated glomerular filtration rate; **HBP**: high blood pressure; **LAD LT**: living related donor liver transplantation; **LR DL T**: living related donor liver transplantation.

### Table 2. Renal graft function evolution in 42 cases

<table>
<thead>
<tr>
<th>Time of appearance</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No function deterioration, n (%)</td>
<td>33 (78.6)</td>
<td>21 (53.8)</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>Function deterioration, n (%)</td>
<td>6 (14)</td>
<td>11 (28.2)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Loss of function, n (%)</td>
<td>3 (7.1)</td>
<td>7 (17.9)</td>
<td>12 (36.3)</td>
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</tbody>
</table>

Most frequently reported histopathologic finding was interstitial fibrosis and tubular atrophy (IF/TA) in 28 patients, of which in 14 it was mild, in 9 it was moderate and in 5 it was serious; followed by glomerulitis in 54.8%, C4d in 40.5%, tubulitis in 28.6% and capillaritis in 4.8%.

As an additional analysis, the frequency of histopathologic and biochemical findings associated with poor graft survival was determined both in patients with graft function loss and in those who remain with a functioning graft (Table 4).

### Discussion

The prevalence and evolution of patients with TG, is related to the type of patients in whom the diagnosis is established. In our study, the prevalence of TG was 4.6%, which in spite of falling within the reported range, tends to be low, but we cannot rule out underdiagnosing of this pathology, given that we included only patients with indicated rather than per protocol biopsies. TG has been described with presentations as early as only 2 months from kidney transplant, although it is more common at later stages. In this group of patients, the earliest diagnosis was made at 21 months from the kidney transplant, with a mean of 7.5 years; the latter is within that which is expected since, although it is higher than the value reported by authors such as Shimizu et al.\(^{14}\), whose diagnosis is earlier (4.4 years) they included patients who underwent biopsy both owing to graft function deterioration and owing to proteinuria and per protocol in their study, in contrast with ours, where only patients with indicated biopsies were included, which influences on the time elapsed until the diagnosis is established, since up to 5% of kidney transplant-recipient patients have been observed to develop this lesion within the first post-transplant year with no renal graft function manifestations that impact on the graft survival range at diagnosis\(^6,10,13-15\).
situation occurs with C4d staining, where there are wide positivity variations, which range from 34 to 69.7% in peritubular capillaries, depending on the cohort in question; in our cases, peritubular capillary C4d falls within this range14,16-18.

There is strong evidence with regard to TG poor prognosis, but the results in terms of evolution are diverse, with reports of graft loss ranging from 60% 6 months after diagnosis to 69.4% at 26 months, the latter in a 4-year follow-up study conducted by John et al. 10. In the present study, graft loss is much lower than that previously mentioned, but higher than that described by Cosio et al. 8 who, 24 months after TG diagnosis, report graft loss to be lower than 20%, but with an important increase at 36 months, when more than 50% of their patients experienced graft loss. However, we should take into account that in their study they included patients with TG diagnosed with protocol-induced biopsies, so that there was no graft function initial deterioration, as in our patients. In this same study they found that, after one year of follow-up, only 33% maintained a stable GFR, 27% had a 30% decrease, 8% a decrease between 30 and 50%, and 27% had a GFR decrease of 50%8.

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In our case series, at one year of follow-up, 28.2% of patients showed graft function deterioration, 53.8% were considered to have stable renal function and 17.9% had graft loss, which was increased to 36.3% at 24 months of follow-up.

John et al. 10 report a 5-year graft survival of 16.7%; we, at six months, found it to be 92.8%, at 12 months, 82.05% and at 24 months, 63.6%, which is why continuing these patients’ follow-up will be important, since survival mean has been estimated at 43 ± 7 months, and higher graft loss within the following two years might therefore be expected.

Several findings, both histopathologic and biochemical, have been associated with worse graft survival. Kieran et al. 19 conclude in their study that C4d alone does not predict graft loss, but it does it when it is found together with TG, being then a strong predictor of graft loss, with a relative risk of 9.3. The most powerful combination to predict graft loss is TG, positive C4d and SCr > 2.3 mg/mL.

Cosio et al. 5, 8 have associated graft survival and function with proteinuria at diagnosis and basement membrane duplication severity. We found that patients who experienced graft loss during follow up had nephrotic-range proteinuria, IF/TA and peritubular capillary positive C4d more frequently.

An important proteinuria and creatinine increase (and hence it is expressed as lower GFR) is shown at diagnosis, but at one-year and 2-year follow-up, the renal function appears to stabilize and even to improve.

The improvement in the GFR drop can be associated with an intensification of immunosuppressant therapy and patient surveillance, a situation that is similar to that reported by John et al. 10.

It is also important to consider that follow-up in this study, as previously mentioned, is shorter than the mean survival reported after diagnosis. In addition, we are aware of the loss of 21% of the sample at 24 months’ follow-up for not complying with time. However, evolution in our patients appears to be better than that described in the literature, with an important number of functioning grafts at 24 months of TG diagnosis, which is why broadening follow-up time will be important.

**Funding**

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**References**

C. Orizaga-de la Cruz et al.: Transplant glomerulopathy


