De Novo IgA Nephropathy in a Renal Allograft

Amir Shabaka,1 Isabel Pérez-Flores,1 José Antonio Cortés,2 Ana Isabel Sánchez-Fructuoso1

Abstract

Posttransplant glomerulonephritis is a complication of kidney transplant that can impair graft function and long-term graft survival. De novo immunoglobulin A disease in kidney allografts appears to be much less common than the recurrent disease, and in most cases it is diagnosed in protocol biopsies with no clinical evidence of disease or in association with other renal transplant pathologies such as chronic rejection. We present a case of de novo immunoglobulin A nephropathy presenting with overt proteinuria, microscopic hematuria, and progressive deterioration of renal function 30 months after renal transplant.

Key words: Kidney transplant, Long-term survival, mTOR inhibitor, Posttransplant glomerulonephritis

Introduction

Posttransplant glomerulonephritis is a frequent complication of kidney transplant that can impair graft function and long-term graft survival and is considered the third most common cause for graft loss at 10 years after transplant. The prevalence of recurrent or de novo glomerulonephritis is variable along the different series reports and probably underdiagnosed due to the lack of consensus regarding the evaluation of kidney transplant recipients who show slow and gradual worsening of graft function.1

Recurrence of immunoglobulin A (IgA) nephropathy after transplant is common, exceeding 50% in patients who undergo protocol biopsy.2 It leads to considerable graft dysfunction in 36% of patients or graft loss in up to 16% of patients.1,3 Nevertheless, in most patients, the presence of IgA deposits in the biopsy does not translate to clinically evident disease and sometimes is associated to other renal transplant pathologies such as chronic rejection.

There are only sporadic cases of de novo IgA nephropathy reported in the English language literature, which include asymptomatic cases that were incidentally diagnosed and other cases associated with recurrence of another glomerular disease.4 Here, we present a case of de novo IgA nephropathy after renal transplant presenting with overt proteinuria, microscopic hematuria, and progressive deterioration of renal function.

Case Report

A 64-year-old male patient was diagnosed with chronic kidney disease after he developed an episode of cutaneous leukocytoclastic vasculitis with worsening kidney function, nephrotic-range proteinuria, microscopic hematuria, and hypertension. During the study of renal insufficiency, a decrease in C3 levels was observed together with positive cryoglobulins with tests for antinuclear antibody, anti-double-stranded DNA, anti-Sm antibodies, and other immunologic tests being negative. The serologic tests for hepatotropic viruses were negative, and serum protein electrophoresis was normal. A renal biopsy was done that revealed sclerosis in 53% of the glomeruli. The remaining glomeruli showed a diffuse but segmentary pattern of discrete cellular and mesangial proliferation and patches of endocapillary deposits. Neither fibrinoid necrosis nor crescents were found.

Silver staining demonstrated that most of the capillary membranes showed duplication (Figure 1), with presence of moderate acute and chronic inflammatory infiltrate, tubular atrophy, and tubulitis and without apparent signs of vasculitis. Some medium-sized arteries showed parietal
thickening with lumen reduction. With direct immunofluorescence, endocapillary deposits of C3 and C1q were seen in a segmental pattern, along with endocapillary immunoglobulin M (IgM) deposits of less intensity and weak deposits of IgM and IgA on some vascular walls.

Figure 1. Silver Staining of Native Kidney Specimen, Showing Duplication of Glomerular Membranes

After the patient received a diagnosis of membranoproliferative glomerulonephritis, the patient was initiated on treatment with prednisone and cyclophosphamide. However, the patient showed no response to treatment and displayed progression to end-stage kidney disease, resulting in the necessity of initiating renal replacement therapy with peritoneal dialysis.

After 5 months of renal replacement therapy, the patient received a renal transplant from a donor after cardiac death. Immunosuppression was induced with thymoglobulin, mycophenolate, and prednisone, and tacrolimus was started on day 5. Protocol renal biopsy was done on day 17 due to delayed graft function, which only showed acute tubular necrosis. The patient later showed a descent in nitrogenous products, maintaining a stable renal function for 1 year. Serum cryoglobulins were negative at both 1 month and 6 months after transplant.

One year after transplant, the patient showed evidence of active replication with BK polyomavirus in blood and urine, leading to discontinuation of tacrolimus and conversion to a mammalian target of rapamycin inhibitor (everolimus). The patient was maintained on this agent for the next 15 months and showed a stable renal function with no evidence of proteinuria or microscopic hematuria. Everolimus was then suspended temporarily for tacrolimus for 1 month due to a planned surgical procedure. After returning to treatment with everolimus, the patient presented with gradual progressive worsening of renal function, appearance of significant subnephrotic-range proteinuria, and microscopic hematuria. Immunosuppressor blood levels were always within therapeutic range, complement levels were normal, no circulating donor-specific antibodies were detected, serum cryoglobulins were negative, serologic tests for hepatotropic viruses and human immunodeficiency virus persisted negative, and both serum and urinary viral loads of BK polyomavirus measured by polymerase chain reaction were negative. Renal graft biopsy was done, which revealed an increase in mesangial matrix with mesangial hypercellularity, presence of mononuclear cells in some capillary loops, and fibrous thickening of Bowman’s capsule (Figure 2). There were areas of interstitial fibrosis and tubular atrophy (around 10%) with no evidence of tubulitis, and intraluminal red blood cell casts were present in some of the tubules. There were no arteriolar changes. On direct immunofluorescence, granular mesangial deposits of IgA and C3 were seen (Figure 3), with less intense levels of IgM deposits. No deposits of IgG were observed. These histopathologic changes were diagnostic of mesangial IgA nephropathy (Oxford MEST classification M1E1S0T0).

Figure 2. Masson Trichome Stain of Renal Graft Showing Increase in Mesangial Matrix and Mesangial Hypercellularity With Presence of Mononuclear Cells in Some Capillary Loops

Once this diagnosis was made, everolimus was discontinued and tacrolimus was reinitiated, with treatment with renin-angiotensin system blockade intensified. The patient then showed a gradual
improvement in renal function and complete remission of proteinuria, with persistent microscopic hematuria to this date.

Discussion

There have been reports of gradual loss of renal function due to recurrent IgA nephropathy with progressive course and crescentic pattern, but there have been no reports of de novo IgA nephropathy presenting in this fashion.

De novo IgA disease in kidney allografts appears to be much less common than the recurrent disease but should not be unexpected, since IgA nephropathy is one of the most common glomerular diseases worldwide. In view of the high frequency of asymptomatic IgA nephropathy, it is speculated that some patients with de novo posttransplant IgA nephropathy have received a kidney that already had latent IgA nephropathy.

Both de novo and recurrent IgA deposition have been associated with reduced allograft function. The course of de novo IgA nephropathy may be favorable in cases of mild mesangial cell proliferation but may be rather poor in the presence of crescents, which can lead to allograft loss within a short time. Carneiro-Roza and associates suggested that, in de novo IgA nephropathy, specific immunosuppression (cyclosporine in their study) showed a better initial response than renoprotection in lowering proteinuria, but without improvement of renal function.

There have been retrospective studies that have shown an association between sirolimus-based immunosuppression regimens and the recurrence of IgA nephropathy, and there are reports of development of de novo focal and segmental glomerulosclerosis lesions in patients who were on a sirolimus-based regimen or after conversion from a calcineurin inhibitor to sirolimus. In some cases of rapamycin-associated posttransplant glomerulonephritis, reintroduction of calcineurin-inhibitor therapy showed remission of proteinuria and stabilization of renal function.

In our patient, stable renal function together with the absence of proteinuria or microscopic hematuria within the first 2 years after transplant argues against donor-derived IgA nephropathy and suggests a de novo origin of the disease. Also, the recipient of the mate kidney, although never biopsied, has had stable kidney function with neither proteinuria nor microscopic hematuria after 3 years of transplant. Together with the lack of known past medical history of the donor, the uneventful clinical signs in our patient in the first 2 years after transplantation and the lack of evidence of IgA nephropathy in the native kidney biopsy would favor our diagnosis of de novo rather than transmitted or recurrence of IgA nephropathy.

Robles and associates described a case of IgA nephropathy with rapidly progressive deterioration of kidney function, proteinuria, and microscopic hematuria after renal transplant of a patient with chronic kidney disease secondary to membranoproliferative glomerulonephritis. However, in that case, immunofluorescence was not done in the native kidney biopsy. There have been sporadic cases describing de novo Henoch-Schönlein purpura after renal transplant that led to rapid allograft loss. This is, to the best of our knowledge, the first case describing de novo IgA mesangial proliferative glomerulonephritis after renal transplant with no other associated glomerulopathy and presenting with gradual progressive renal dysfunction, overt proteinuria, and severe hematuria. In our case, potentiating immunosuppressive therapy with a calcineurin inhibitor and intensifying renin-angiotensin system blockade led to a complete remission of proteinuria and improvement of renal function.

References


