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Short Communication

Possible consequences of non-adherence to immunosuppression: a case of acute T-Cell mediated kidney rejection and IgA nephropathy

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Abstract

Patients with primary immunoglobulin A nephropathy (IgAN) usually represent ideal candidates for a renal transplantation. IgA nephropathy represents the most frequent form of recurrent glomerulonephritis post kidney transplant. The therapeutic effects of post transplant immunosuppressive therapy seem to be related to the ability to regulate T-cell immunity and the Th1/Th2 balance. T-cell dysregulation plays an important role in IgAN pathogenesis and recurrence post kidney transplantation. We describe the case of a 52 years old Asian woman with IgAN who received an unrelated living donor kidney transplant. She had independently withdrawn all immunosuppressive maintenance therapy seven years after transplantation followed by acute kidney dysfunction. Acute T-cell mediated rejection was demonstrated in the first kidney biopsy. High steroid pulses were administered with partial response. Recurrence of native IgAN associated with partial resolution of T-cell mediated rejection was observed, as showed in the second kidney biopsy. We hypothesize that recurrence of primary nephropathy could be a manifestation of T-cells activation in non-adherent patients partially responsive to T-cell anti-rejection therapy.

INTRODUCTION:

RImmunoglobulin A nephropathy (IgAN) is a frequent cause of glomerulonephritis more common in Asia than the rest of the world1,2. IgAN is characterized by polymeric IgA deposition and accumulation in the glomerular mesangium3 . Although IgAN is considered a benign disease, it causes chronic renal failure in 20-40% of patients4,5. Patients with primary IgAN usually represent ideal candidates for renal transplantation because they are often relatively young with little comorbidity6,7. Recurrence of primary glomerular nephropathy after renal transplant occurs in 10-20% of kidney grafts and accounts for graft failure in up to 50% of cases. IgA nephropathy represents the most frequent form of recurrent glomerulonephritis with histological evidence of IgAN recurrence in up to 60% of chronic kidney dysfunction, occurring usually within the first 3-4 years after transplantation6,8. However, factors predicting the recurrence of IgAN remain controversial. Several studies have reported a higher risk of disease recurrence among organs from living-related donors8,9. Therefore, in native IgAN, improvement in increasing of steroid treatment is required after kidney transplantation. T-cell dysregulation plays an important role in IgAN pathogenesis and recurrence. T-cells are involved in IgA production, which accumulate in glomerular mesangium3 . In patients with severe manifestation, immunosuppressive therapy with cyclophosphamide, azathioprine or mycophenolatemofetil (MMF) is usually recommended10-12. Their therapeutic effects seem to be related to the ability to regulate T-cell immunity and the Th1/Th2 balance13. Compliance to immunosuppressive treatment is necessary to prevent rejection and graft loss in solid organ transplantation. Non-adherence to immunosuppressive regimen has been shown in 20 to 37% of kidney transplant recipients14-17. Systematic reviews have shown that an estimated 50% (range 20-73%) of late acute rejections and 15% (range 3-35%) of graft losses are associated with non-adherence to the therapeutic regimen14,15,18. Non-adherence to immunosuppressant therapy is one of the major causes of early and late renal acute rejection and allograft failure. Even if association between recurrent IgAN and acute rejection has not been found8 , we hypothesize that recurrence of primary nephropathy could be a manifestation of T-cells activation in non-adherent patients or in partial responsive T-cell rejection patients. Case report Here we describe a case of a 52 years old Asian woman with an history of end stage renal disease on haemodialysis secondary to IgAN since 2004 who received an unrelated living donor kidney transplant (LDKT) in the Philippines on October 2006 (negative T-cell cross match), as evidenced by patient's medical record from Hospital of Philippine (OrtigasCenter, Pasig City). Her immunosuppressive therapy was based on MMF, steroids and calcineurin inhibitors (cyclosporine then replaced with tacrolimus in December 2006). The patient came to our outpatient nephrology clinic in January 2007. Follow-up visit were scheduled weekly over the first month and every 4-6 weeks thereafter, until 12 months after transplant. Thereafter, follow-up visits were scheduled every 3-4 months. Immunosuppressive drug trough levels, routine bloods and urinalysis were monitored each time. Blood tests and imaging showed satisfactory function of the transplanted kidney with serum creatinine (sCre) levels ranging from 0.5 to 0.7 mg/dL till October 2011. Since then, the patient failed to attend the scheduled appointments and omitted to check immunosuppression level. She returned to our attention on March 3, 2013 when she was admitted to the Emergency Department at the Policlinico Umberto I in Rome for anuria and general maculopapular rash. Laboratory investigation at admission in Nephrology Department and Transplant Unit (March 5, 2013), revealed worsening of renal function, with extremely high sCre levels (20 mg/dL), blood urea nitrogen (BUN) of 148 mg/dL, severe metabolic acidosis, hyponatremia and hyperphosphoremia (Table 1). The chest x-ray showed multiple nodular thickening partially confluent in the right lung and

bilaterally emphasizing of bronco-vascular structures.

Discussion

The availability of new immunosuppressive protocols has allowed a significant improvement in the survival of transplanted kidney. Acute rejection by non-adherence to immunosuppressive therapy may occur at any time after transplantation, and can be either cellular-mediated (named T-cell involvement) or humoral (B-cell involvement). Our clinical case suggests that non-adherence to immunosuppressive therapy has not only determined T-mediated rejection, but also the emergence of a primary IgAN, which is recognized to be characterized by a T-cell deregulation20-22 In previous studies, increases in IgA-containing B lymphocytes, IgA-specific T-helper cells, and decreased activity of IgA-specific suppressor T-cells were observed in IgAN patients20-22. These results implicate lymphocyte dysregulation in IgAN suggesting an important role for T lymphocytes in the development of IgAN. In our patients in fact, non clinical or biochemical signs of glomerulonephritis were observed after transplantation, neither IgA mesangial deposits resulted on the first kidney biopsy performed seven years after transplantation. Diffuse IgA deposition appeared only on the second kidney biopsy associated to creatinine elevation, presumably as complication of incomplete response to anti-re jection therapy resulting from T-cells activation. Partial T-cell response associated to the presence of risk factor for IgAN, as suggested by the native IgAN, and non-adherence to immunosuppression, may have facilitated IgAN recurrence after T-cell rejection. The development of complications such as diffuse interstitial fibrosis and Herpetic infection discouraged additional immunosuppressive interventions. Mesenchymal stem cells (MSCs) have been studied in the context of nephrology23. These cells can differentiate into various cell types, migrate to sites of tissue injury, and enhance repair by secreting antifibrotic and proangiogenic factors23-25. Mesenchymal stem cells treatment showed no evidence of adverse events such as procedure-related events, acute toxicity, organ system complications, infection, death, or malignancy. Results of recent clinical trials supported safety and promising effects of autologous and allogeneic MSCs in solid organ transplantation reducing ischemia-reperfusion injury and promoting immune tolerance. In particular, in patients undergoing living-related donor kidney transplants the use of MSCs was compared with anti-IL-2 receptor antibody induction therapy and standard-dose of calcineurin inhibitors showing reduced risk of opportunistic infection, lower incidence of rejection, Bone marrow transplantation has showed evidence to attenuate kidney diseases including lupus nephritis33 and IgAN ((34)) in experimental models. Their therapeutic effect is related to their ability to regulate T-cell immunity and the Th1/Th2 balance. In fact, ASCs therapy significantly decreased Th1 cytokine activity in the kidney and caused a shift to Th2 responses in spleen T-cells as determined by fluorescence-activated cell sorter analysis13. Only recently it has been postulated the application of peripheral blood stem cells. However, this technology could be extended to administer other cell-based therapies.

Conclusions

With our case we want to describe the effects of non-adherence to immunosuppressive therapy after kidney transplantation on T-cells activation causing the onset of cellular rejection and IgAN in a patient with history of IgAN. Non-adherence to immunosuppressive therapy is the major cause of rejection and in this case it could also have led to recurrence of primary nephropathy resulting in a synergic negative impact on the transplant outcome. The poor response to therapy promptly performed did not modify the IgAN recurrence and the related poor graft outcome. In our case, the use of stem cells might have a role both on T-cell mediated rejection and on IgAN recurrence, which is known to be linked to T-cells dysregulation. We suggest the use of stem cells as possible therapeutic choice to improve the renal outcome in T-cells dysfunction in kidney transplant complications.