
*Viewpoint***Recurrence of Glomerulonephritis after Kidney Transplantation**

Dimitrios S. Goumenos

Department of Nephrology and Renal Transplantation, University Hospital of Patras, Patras, Greece

The recurrence of glomerulonephritis after kidney transplantation is a cause of graft loss. The true incidence of recurrent disease is difficult to be estimated because not all patients have undergone native kidney biopsy [1]. The risk of graft loss from recurrence is estimated from 0.6% at first post-operative year to 8.4% at the 10th post-operative year. Other potential problems in the diagnosis of recurrence are the difficulty to differentiate between de novo and recurrent disease and the coexistence of histological features of chronic allograft nephropathy or nephrotoxicity due to calcineurin inhibitors [2]. The recurrence rate, clinical course and impact on graft survival vary between different types of glomerulonephritis [1,3].

Recurrence of IgA nephropathy is observed after transplantation in about 30% of patients. However, the recurrence rate fluctuates between 10% and 60% in various studies because of the differences in the follow-up of patients and biopsy policy of different transplant centers. Most centers perform biopsies only in patients with proteinuria, hematuria or decline in renal function. Clinical manifestations are similar to primary IgA nephropathy and typically occur 5-10 years after transplantation. The estimated 10-year incidence of graft loss due to recurrence is about 10% and there is no significant difference in the survival of grafts from living or deceased donors [2,4]. However, potential donors should be carefully evaluated to exclude familial IgA nephropathy, which has a higher risk for progression to end-stage renal failure. In patients with loss of first graft due to recurrent disease the risk of recurrence is significantly higher in the second graft and potential living donors should be discouraged in such cases. No effective therapy exists for prevention or treatment of recurrent IgA nephropathy. New immunosuppressive drugs, steroid free regimen or rapid steroid withdrawal show no influence on the risk of recurrence. Converting enzyme inhibitors and angiotensin receptor blockers are commonly used for reduction of proteinuria and preservation of renal function [2].

Primary focal and segmental glomerulosclerosis (FSGS) has a recurrence rate of 20-50% leading to graft failure in 13-20% of patients, 10 years after transplantation. In

patients with graft loss due to recurrent disease the recurrence rate reaches 80%-100% in a subsequent transplant. Secondary FSGS due to an underlying condition causing progressive nephron loss and hereditary FSGS due to mutations of podocyte and slit diaphragm protein genes do not recur after transplantation [2]. Clinical presentation of recurrent FSGS includes early onset of massive proteinuria, usually sometimes hours to days post-transplantation, hypertension and graft dysfunction. A circulating permeability factor is considered responsible for proteinuria. Serum soluble urokinase receptor (suPAR), which activates podocyte $\beta 3$ integrin, represents a possible permeability factor. Risk factors for recurrence include younger age, rapid progression of the original disease with development of end-stage renal failure within 3 years, mesangial hypercellularity of native kidney and a history of previous graft failure due to recurrence. Living donation for patients with idiopathic FSGS is better to be restricted to patients who are not at high risk for progression [5]. Institution of a short course of plasma exchange pre-emptively should also be considered in this setting. The management of recurrent FSGS is difficult and controversial [5,6]. High doses of either intravenous or oral cyclosporine have achieved satisfactory results. High doses of steroids and cyclophosphamide have not been proved to be beneficial in recurrent FSGS. Plasma exchange or immunoabsorption using protein A columns applied early showed promising results. Rituximab might be a rescue therapy for patients resistant or unable to be treated with cyclosporine and/or plasma exchange but it needs further investigation. Membranoproliferative glomerulonephritis (MPGN) type I and II have high rates of recurrence after transplantation. Recurrent MPGN should be differentiated from de novo MPGN, which occurs as part of the histological changes in patients with chronic transplant nephropathy. MPGN type I due to viral hepatitis C and systemic diseases has reduced risk of recurrence after treatment of the original disease. MPGN type I recurs in 20-50% of patients whereas MPGN type II in 80-100% of patients. No effective treatment is available for prevention or treatment of recurrent MPGN.

Idiopathic membranous nephropathy recurs in 10-30% of patients after kidney transplantation [1]. The clinical presentation of recurrent disease is characterized by nephrotic range proteinuria. M-type phospholipase A2 receptor (PLA2R) has been identified as a target antigen for idiopathic membranous nephropathy. Recurrence usually occurs 2-3 years after transplantation [2-7]. No risk factor for recurrence has been identified. Graft failure from recurrence occurs in 10-15% of patients after 10 years. In contrast to idiopathic membranous nephropathy in native kidneys spontaneous remission is rare among post-transplantation cases. Cyclosporine and mycophenolate mofetil, which are used in the management of the primary disease, do not prevent or change the course of recurrent disease. Tacrolimus and cyclophosphamide are not superior to cyclosporine. Rituximab seems promising as in small number of patients with recurrent disease it was followed by partial or complete remission [2].

Recurrence of renal involvement in patients with ANCA-associated vasculitis occurs in about 17% of kidney transplant recipients after 2-3 years post-transplantation [8,9]. Among patients with ANCA-associated vasculitis treated with dialysis, a relapse rate of 0.09 episodes per patient/year has been reported vs. 0.02 episodes per patient/year in transplant recipients. A lower relapse rate of 0.005 per patient per year has been reported with the new drugs tacrolimus and MMF. Pre-transplantation disease course, ANCA titer and donor type do not predict recurrence. However, kidney transplantation is better to be considered in patients with inactive disease. Patients with renal relapses show good response to cyclophosphamide [8,9].

In patients with anti-glomerular basement membrane disease (anti-GBM) recurrence has been reported in up to 50% of patients when kidney transplantation is performed while circulating anti-glomerular basement membrane antibodies are still present. With the current practice of deferring transplantation until the disease become quiescent and circulating anti-GBM antibody levels become undetectable for at least 6-12 months, clinical recurrence is rare and consists of isolated case reports only. Recurrent anti-GBM disease in the renal allograft should be treated with steroids, cyclophosphamide and plasma exchange. A form of anti-GBM glomerulonephritis in the renal allograft is rarely seen in patients with Alport's syndrome, who develop auto-antibodies in response to the new epitope of type IV collagen a-chain displayed on the graft.

Recurrence of lupus nephritis has been reported in up to 30%. Clinically significant recurrent disease occurs in 2-9% [2,10]. However, the frequency and clinical impact of recurrent lupus nephritis after transplantation vary among centers. Mean time to relapse is 3 years. Although lupus nephritis recurrence in kidney recipients is rela-

tively uncommon, it may increase the risk of graft failure in the long run. Transplantation in patients with end-stage renal failure due to lupus nephritis should be postponed until achieving complete and persistent remission for at least 6-9 months. There are anecdotal reports on the efficacy of mycophenolate mofetil in the recurrent lupus nephritis. Long-term patient and graft survival are similar to kidney allograft recipients with other underlying diseases.

In conclusion, with improving long-term renal allograft survival, recurrent glomerular disease shows an increased incidence as a cause of late graft loss. Apart from plasmapheresis for patients with recurrent FSGS, there is no consensus on strategies to prevent or treat recurrent glomerular disease in the kidney allograft. It is important to emphasize that the majority of patients with primary glomerulonephritis as the underlying cause of renal failure show good graft and patient survival. Thus, living related kidney donation can still be encouraged in carefully selected patients. Caution should be exercised in patients with recurrent disease in the first graft in view of the markedly increased risk for recurrence in subsequent transplants.

Conflict of interest statement. None declared.

References

1. Choy BY, Chan TM, Lai KN. Recurrent glomerulonephritis after kidney transplantation. *Am J Transplant* 2006; 6: 2535-2542.
2. Mariknaki S, Lionaki S, Boletis JN. Glomerular disease recurrence in the renal allograft: A hurdle but not a barrier for successful kidney transplantation. *Transplant Proc* 2013; 45: 3-9.
3. Briganti EM, Russ GR, McNeil JJ, et al. Risk of allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002; 347(2): 103-109.
4. Ortiz F, Gelpi R, Koskinen P, et al. IgA nephropathy recurs early in the graft when assessed by protocol biopsy. *Nephrol Dial Transplant* 2012; 27: 2553-2558.
5. Ulinski T. Recurrence of focal segmental glomerulosclerosis after kidney transplantation: strategies and outcome. *Curr Opin Organ Transplant* 2010; 15(5): 628-632.
6. Moroni G, Gallelli B, Quaglini S, et al. Long-term outcome of renal transplantation in adults with focal segmental glomerulosclerosis. *Transpl Int* 2010; 23(2): 208-216.
7. Debiec H, Martin L, Jouanneau C, et al. Autoantibodies specific for phospholipase A2 receptor in recurrent and de novo membranous nephropathy. *Am J Transplant* 2011; 11(10): 2144-2152.
8. Elmedhem A, Adu D, Savage CO. Relapse rate and outcome of ANCA-associated small vessel vasculitis after transplantation. *Nephrol Dial Transplant* 2003; 18(5): 1001-1004.
9. Geetha D, Eirin A, True K, et al. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation* 2011; 91(12): 1370-1375.
10. Contreras G, Mattiazzzi A, Guerra G, et al. Recurrence of lupus nephritis after kidney transplantation. *J Am Soc Nephrol* 2010; 21(7): 1200-1207.