Allotransplantation using a diseased kidney: when a swallow makes a summer

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In this issue of Nephrology, Dialysis, Transplantation, Mirza et al. [1] present a very interesting but also puzzling case of membranous nephropathy (MN) transplanted in a patient with a history of long-term diabetes mellitus and severe atherosclerosis. Simultaneous heart and kidney transplantation were carried out at a time when the recipient’s estimated glomerular filtration rate was 28 mL/min and proteinuria 1+. His native kidney histology was unknown and although the aetiology of his nephropathy was multifactorial, it can be safely ascertained that the grafted kidney benefitted, in a broad sense, from a ‘non-immunologic’ environment. This case thus provides a unique opportunity to observe the outcome of immune deposits after cessation of the immunological aggression.

The donor was a young woman who died from a hypertensive subarachnoid haemorrhage. Prior to her death, she was not proteinuric. A pre-transplant biopsy of the donor’s kidney led to the discovery of lesions of Stages II, III and IV MN, a puzzling finding in the absence of proteinuria. The authors hypothesize that the preservation of the glomerular filtration barrier to proteins might be explained by the mild podocyte injury that was observed on the four serial biopsies that were performed up to Day 812. Each yielded a substantial number of glomeruli and showed by light microscopy, electron microscopy and immunofluorescence, a striking improvement of the initially severe membranous lesions. As in the donor, and despite persistence of Stages II and III glomerular basement membrane (GBM) lesions and immunoglobulin and complement staining, proteinuria was never significant and the kidney recipient maintained good function.

This case is exceptional, although not the first one describing progressive wash-out of membranous immune deposits in kidneys transplanted into a non-immunologic environment. Parker et al. [2] reported the case of a patient with end-stage renal disease (ESRD) secondary to Type II diabetes mellitus who received a cadaveric renal transplant from a 37-year-old woman who died of cerebral infarction. A biopsy of the donor’s kidney performed at the time of transplantation showed MN by electron microscopy. There was immediate graft function and the recipient continued to have good kidney function 3 years post-transplantation. Nakazawa et al. [3] presented the case of a 41-year-old man grafted with a cadaver kidney. An allograft biopsy obtained during the operation showed spike formation on periodic acid-silver methenamine staining and deposition of IgG along the glomerular capillary loop on immunoperoxidase staining. Immunofluorescence staining for IgG persisted in the specimens obtained on Day 11 and after 4 weeks, but markedly decreased in the specimen obtained 7 weeks after transplantation. Electron-dense deposits also decreased in amount, but irregular thickening of the glomerular basement membrane with spikes, electron-lucent lesions and small amounts of electron-dense deposits remained 20 months after the transplantation. Akioka et al. [4] transplanted a kidney from a father, diagnosed with MN and mild proteinuria, to his son. At 39 months after transplantation, allograft biopsy showed a wash-out of electron-dense deposits and electron-lucent lesions.

These reports are interesting but were not analyzed as meticulously as Mirza et al. did in their case. Their recipient’s kidney was studied by a pre-transplant histology followed by four biopsies up to 27 months post-transplantation. Along with light and electron microscopy, they used a wide panel of antibodies for immunofluorescence including staining for type-M phospholipase A2 receptor (PLA2R) that was negative. This is suggestive of a secondary aetiology of membranous glomerulonephritis (GN) but does not exclude a PLA2R-unrelated primary form [5]. PLA2R is a major target antigen in autoimmune idiopathic membranous GN. PLA2R is revealed in normal human glomeruli, and in idiopathic MN, PLA2R and IgG4 are shown to co-localize within subepithelial deposits. Early recurrence of MN in kidneys transplanted to recipients with circulating anti-PLA2R antibodies lends credit to a pathogenic role of these antibodies [6-8]. Their decrease
following immunosuppressive therapy portends a good prognosis [9, 10]. In the present case, PL2AR was not identified in capillary wall immune deposits and did not seem to be a significant antigen. The donor was (HLA)-DQA1 negative, a pattern associated with idiopathic MN in patients of white European ancestry [5]. These findings might suggest that the donor’s kidney suffered from another immunologic conflict. The authors did not seek all possible causes of secondary membranous GN [11] but excluded drug-induced MN, hepatitis B virus carriage and more importantly Stage V lupus. An autopsy was not performed on the donor and one cannot exclude the existence of a clinically occult malignancy.

However, these limits do not cast doubt on the interest of the authors’ exceptional case that demonstrates the reversibility of MN when a kidney with severe subepithelial and intramembranous immune deposits is transplanted in a non-immunologic environment. This observation is reminiscent of the reabsorption of immune deposits and restoration of the glomerular capillary wall ultrastructure in rituximab-responsive patients. It is also striking that in rituximab-responsive patients there is a lag-time of several months from the immunologic remission attested by disappearance of anti-PLA2R antibodies to the renal remission defined by decrease or disappearance of proteinuria [12]. Thus, the repair process takes time and requires extinction of the immunologic aggression. Incidentally, we doubt that the immunosuppressive treatment applied to prevent rejection of the graft played more than an ancillary role in the observed regression of the native donor’s kidney [13]. These comments lead to a wider discussion. Other glomerulopathies may undergo a similar wash-out of lesions when a diseased kidney is transplanted in an immunologically different or naïve environment. Among such cases, IgA GN is a good example of kidney transplantation considered as a form of heroic treatment of an immune-complex disease. Few cases have been published that have shown by serial biopsies of the transplanted kidney, rapid —a matter of weeks—disappearance of the IgA deposits [14, 15]. This particular case of Henoch–Schönlein purpura is more difficult to interpret as it seemed that this wash-out accompanied acute rejection [16].

In the same line, it has been shown that once grafted in a euglycemic patient, such as one with polycystic disease [17], severe diabetic nephropathy may show a regression of glomerular lesions and more generally that kidneys with a diabetic glomerulopathy may be used for transplantation [18].

Another example of renal transplantation using a diseased kidney sheds an exciting light on the pathophysiology of primary, nephrotic focal–segmental glomerulosclerosis (FSGS) and on the quest of the ‘Holy Grail’, that is, the elusive FSGS factor that causes first proteinuria and within a short period of time the podocytopathy which characterizes this clinicopathologic entity [19, 20]. The first one is pregnancy, the oldest known model of semi-compatible transplantation. In neonates born to nephrotic mothers proteinuria was present at the time of birth and waned progressively within weeks following delivery, meaning that once removed from the noxious effect of the ‘glomerular permeability factor’ their podocytes recovered a normal permselectivity to serum albumin [21, 22]. In the same line, Rea et al. [23] observed in two cases of FSGS transplanted kidneys that proteinuria decreased from nephrotic amounts to <1 g/24 h within 3 weeks to 1 year post-transplantation.

A fascinating case was published by Gallon et al. [24]. A 27-year-old man with ESRD caused by primary FSGS (Patient 1) received a kidney transplant from his healthy 24-year-old sister. Although the renal allograft functioned immediately, marked proteinuria developed on the second post-transplantation day. A biopsy from the allograft on Day 6 revealed normocellular glomeruli with prominent podocytes, marked podocyte foot-process effacement and loss of the interdigitating arrangement, indicating FSGS recurrence. The allograft was removed on Day 14 because of persistent nephrotic syndrome and rising creatinine. At this time, the kidney with severely relapsing FSGS was removed and grafted to a 66-year-old man with ESRD caused by Type 2 diabetes mellitus (Patient 2). Immediately after the allograft was retransplanted it regained function, with serum creatinine levels decreasing from 466 to 163 μmol/L and proteinuria decreasing from 25 to 1.2 g per 24 h. Allograft biopsies performed on Days 8 and 25 after retransplantation showed a reversal of the histopathologic lesions. Eight months after retransplantation Patient 2 continued to have excellent allograft function and mild proteinuria.

These cases demonstrate that a swallow does make a summer. Once removed from a hostile environment, lesions of FSGS, provided they have not reached the point of no return, that is, irreversible fibrosis [25], may regress, demonstrating the strong capacity of glomeruli to heal their podocyte lesions. Similarly, the case elegantly analysed by Mirza et al. shows that even when the antigen–antibody conflict has not been identified in a patient with MN, removing the kidney from its black box allows resolution of the GBM insult.

This leads to the wider discussion of our current approach to treating glomerulopathies such as FSGS or MN. Their pathophysiology is still poorly understood and their treatment rests on drugs whose mode of action is essentially based on their immunosuppressive properties. They do influence the kidney environment but their effect is often transient or incomplete because they target the bullet, i.e. the antibody or the permeability factor, not the trigger. Moreover, some of these immunosuppressive regimens such as calcineurin inhibitors and corticosteroids have the capacity to reduce proteinuria through a non-immunologic, pharmacologic effect [26]. In any event, observations like the cases described by Mirza et al. and by Gallon et al. are an incentive to pursue actively the quest for identifying and counteracting the acquired factors that induce the glomerulopathy. More importantly, these exceptional cases show that once this goal is achieved the lesions may be reversible, a strong encouragement to pursue ongoing research on their pathophysiology, even if these endeavours do not yet translate into a definite benefit in terms of patient care [27].

**CONFLICT OF INTEREST STATEMENT**

None declared.

(See related article by Maas et al. Permeability factors in idiopathic nephrotic syndrome: historical perspectives and lessons...

REFERENCES


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