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REVIEW

De novo membranous nephropathy (MN) in kidney allografts. A peculiar form of alloimmune disease?

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Conflicts of Interest
CP has been consultant for Novartis Italy until December 31st, 2011 (Inactive) and received honoraria from QuesCor (Inactive). RJG is active consultant for Genentech, Genzyme, Bristol-Myers Squibb, QuestCor, Bio-Marin- Eli Lilly, ChemoCentrix- Vifor, LightHouse Learning, UpToDate and Novartis.

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Summary

De novo membranous nephropathy (MN) is an uncommon complication of kidney transplantation, which shows histological findings similar to those seen in recurrent MN, but with some distinct differences. The clinical presentation may be variable, from asymptomatic to nephrotic proteinuria. The disease may run an indolent course or may have an accelerated course leading to allograft loss. *De novo* membranous nephropathy (MN) can develop in transplant recipients with viral hepatitis, Alport syndrome, ureteral obstruction, renal infarction, or in conjunction with recurrent IgA nephritis. Histologic signs of allograft rejection are often associated with or can antedate *de novo* MN. These findings suggest that donor-specific antibodies and antibody-mediated rejection might play a pathogenetic role in some patients with *de novo* MN. However, signs of rejection were absent in a number of cases, and in some instances the disease developed in recipients of ''full house'' HLA- matched kidneys. Thus, it seems possible that *de novo* MN is not because of allograft rejection *per se*, but is triggered by different injuries that can create an inflammatory environment, activate innate immunity, and expose hidden (cryptic) antigens, probably different from those observed to be involved in idiopathic MN. These events can lead to the production of circulating antibodies and *in situ* formation of immune complexes (IC) and the morphological lesion of MN.

Patients whose original disease leading to end-stage renal failure (ESRF) was idiopathic membranous glomerulonephritis (iMN) may develop a recurrence of the disease in renal allografts. Recurrent iMN has been observed in 25–40% of such patients after kidney transplantation [1–4]. However, a lesion of MN may also develop in the renal allograft of patients originally affected by other renal diseases, often referred to as *de novo* MN. Such *de novo* MN is rare, but not exceptional. In a collaborative French study, 19 cases of *de novo* MN were detected in a series of 1000 kidney graft biopsies [5]. A similar percentage (1.8%) was also reported in another French study [6]. In a German series, *de novo* MN was diagnosed in 14 of 611 (2.3%) transplant recipients [7] and in the United Kingdom, *de novo* MN represented the second most frequent cause of nephrotic syndrome observed after kidney transplantation [8]. In a pediatric series, in which control allograft biopsy was performed even in the absence of signs of nephropathy, a *de novo* MN was found in 9% of cases [9]. Overall, recurrent and de *novo* MN are about equally common post-transplant, but a patient with iMN as the original disease and post-transplant MN is overwhelmingly likely to be have recurrent rather than *de novo* disease.

Pathology

Although the optical microscopical findings of recurrent MN and *de novo* MN can often be very similar [10,11], however, *de novo* MN can also show distinct differences from recurrent MN. For example, *de novo* MN often reveals mild-to-moderate mesangial cell proliferation, focal segmental distribution of subepithelial deposits, and the contemporaneous presence of different stages of the disease [9,12,13], often in conjunction with the features of chronic allograft nephropathy [14,15]. It has also been reported that the histological findings of *de novo* MN were frequently associated with signs of antibody-mediated rejection, such as peritubular capillaritis and C4d deposition in peritubular capillary [16,17] or transplant glomerulopathy [12].

The diagnosis of recurrent or *de novo* MN by optical microscopy should always be confirmed by the presence of subepithelial immune deposits using immunofluorescence and/or electron microscopy. The distribution of granular immunoglobulin (IgG) deposits along the capillary walls is usually diffuse, but can also be segmental [9,12]. The IgG subclass distributions are very different in recurrent and *de novo* MN in allograft kidneys. In a recent study, IgG4 was the dominant or co-dominant IgG subclass in capillary loop deposits in all the seven cases of recurrent MN, whereas IgG1 staining was dominant in three of the four cases of *de novo* MN and were codominant with IgG4 in the fourth [18]. Thus, *de novo* MN can often be efficiently separated from recurrent MN by careful immunopathological examination of transplant renal biopsy specimens. However, in some cases, a *de novo* MN may be secondary to malignancy or exposure to drugs post-transplant, and these uncommon cases need to be identified and separated from the more common forms of *de novo* MN.

Clinical presentation and prognosis

De novo MN usually occurs months or years after transplantation [12,15,16,19]. However, rare cases have been described to occur early after transplantation [20–22]. The clinical presentation may be variable from asymptomatic to severe nephrotic proteinuria. In the report of a pediatric series of protocol transplant renal biopsies by Antignac *et al.* [9] (predominantly a study of *de novo* MN), a quarter of children showed no clinical signs of renal disease and another quarter had only a mild proteinuria. A number of patients already show renal allograft dysfunction at presentation.

The prognosis as well as the risk factors that may predict a poor outcome in *de novo* MN are not well established. In the series of Antignac *et al.* [9], most pediatric patients developed a nephrotic syndrome, but about 20% of them did not develop any proteinuria. However, in the long-term, about 60% of children lost their graft on average 6 years after the diagnosis. Of note, four of seven patients who received a second graft redeveloped *de novo* MN [18]. In adults, the prognosis of *de novo* MN has been more varied. A large French series reported that the development of *de novo* MN had no deleterious effect on graft function [5] and Schwarz *et al.* [7] reported that the 5-year graft survival rate was similar in 21 patients with *de novo* MN and in 851 other renal transplant recipients. However, in the series of Monga *et al.* [12], repeated biopsies showed progression of the stage and extension of deposits to a larger number of glomerular capillaries. Truong *et al.* [15] found that 42% of patients with *de novo* MN lost their allograft (from rejection or *de novo* MN) on average 3 years after the diagnosis. Dische *et al.* reported an accelerated loss of graft function in three patients [14]. In most cases, with an unfavorable outcome, signs of chronic rejection were reported in kidney graft biopsy.

The treatment of *de novo* MN remains elusive. There is no evidence that intensification of immunosuppressive treatment or introduction of cytotoxic agents is of any benefit [7,23]. Experience with Rituximab therapy is too limited to draw any conclusion.

Etio-pathogenesis

In a number of cases, *de novo* MN is associated with hepatitis B (HBV) or hepatitis C (HCV) infection [6,10,24–27], but in most cases ,the cause(s) of the lesion in the transplanted kidney remain(s) unknown. Sporadic cases of *de novo* MN occurred in renal transplant recipients with renal infarction [10], Alport's syndrome [28], ureteral obstruction [29,30], or recurrent IgA nephritis [31], and even the post-transplant emergence of cancer. A possible role for immunosuppressive drugs has also been hypothesized. *De novo* MN developed in a patient after conversion from cyclosporine to sirolimus; the glomerular lesion reversed after the patient stopped sirolimus and was reconverted to cyclosporine [32].

The pathogenesis of *de novo* MN is far from being established. Early investigations suggested that the disease was an autoimmune disorder. Ward and Kovie [33] studied seven sera from patients with *de novo* MN. They were able to detect small preformed (circulating) IC use of monoclonal rheumatoid factor reagents. These IC had cationic IgG spectrotypes by isoelectric point determination using chromatofocusing, and they found antibodies reactive with brush border or tubular epithelial/interstitial antigens using indirect immunofluorescence. Five of the seven sera demonstrated the presence of each of these immunopathologic features, whereas sera from normal transplant patients, and

those with chronic rejection did not display such features. However, further studies confirming these data have not yet been reported. Moreover, the current view is that both idiopathic and secondary MN are caused by circulating antibodies directed against endogenous or exogenous antigens planted in the podocytes not by circulating IC trapped into the glomerular barrier [34]. Bansal *et al.* reported a case of *de novo* MN in patient who received the kidney from her craniopagus conjoint Siamese twin. According to the authors, the original cause of renal failure requiring transplantation was probably a postinfectious glomerulonephritis, hence, excluding that MN could be caused by rejection or recurrence. However, in the biopsy of the native kidney immunofluorescence staining was not performed and an electron microscopy showed subepithelial deposits, so that it is not possible to rule out that the original disease, in this peculiar case, was actually a MN that recurred after transplantation [35].

More recent study has suggested that *de novo* MN is not an autoimmune disease, but can be an expression of chronic allograft rejection. As mentioned above, the histological lesions of rejection may be associated with or may even antedate *de novo* MN [12,15]. Moreover, histological findings of antibody-mediated rejection (AMR) and circulating donor-specific antibodies (DSA) were detected in five patients with *de novo* MN at the time of biopsy. In one of these cases, a donor-derived human leukocyte antigen (HLA) was identified in the subepithelial IgG deposits on the glomerular capillary walls [16]. Another kidney transplant recipient developed *de novo* MN with heavy proteinuria in the context of a DAS directed against HLA DQ7. Proteinuria resolved and the titer of the DSA fell in parallel with resolution of the proteinuria following treatment with mycophenolate mofetil and an angiotensin receptor blocker [36]. These reports suggest that DSA and AMR might play a pathogenetic role in some patients with *de novo* MN after kidney transplantation. However, this hypothesis may be challenged by the observation that signs of chronic allograft rejection were absent in a substantial number of cases of *de novo* MN reported in the literature. Moreover, in a study reporting nine cases of *de novo* MN after kidney transplantation, the disease developed in four patients with ''full house'' HLA-A,B matches, two with none, and two with only one HLA-A,B mismatch [19].

Considering the fact that the disease may develop in a variety of circumstances, such as chronic allograft rejection, viral infection, renal infarction, drug-reactions, and cancer, it seems possible that *de novo* MN is not because of allograft rejection *per se*, but to a peculiar form of immune response triggered by exposure of hidden (cryptic) antigens. However, the antigens and the corresponding antibodies operative in *de novo* MN are probably different from those observed in idiopathic MN (iMN). About 60–80% of patients with i MN have circulating antibodies directed against a conformation-dependent epitope in muscle-type phospholipase A2 receptor 1, which is present in the cell membrane of normal podocytes and in immune deposits in patients with MN [37]. Debiec *et al.* [38] detected anti- membrane-type phospholipase A2 receptor 1 antibodies in five of 10 patients with recurrent MN, but in none of the nine patients with *de novo* MN. This may depend on the fact that most cases of iMN are caused by autoantibodies that react with a genetically determined conformational antigen [39], which is not the case for patients with *de novo* MN. Thus, other cytoplasmic or membrane-associated podocyte proteins involved in the function of the glomerular barrier may be involved. In this setting, it is interesting to point out that in iMN not only antibodies directed against membrane-type phospholipase A2 receptor 1, but also antibodies against other podocyte enzymes, such as super-oxide dismutase, aldose reductase [40], and alpha-enolase [41] have been detected. Recently, cases of MN have been reported in patients with IgG4-related disease, a new autoimmune disease that may affect the kidney in various patterns [42].A number of other antigens may trigger the production of antibodies in secondary forms of MN [43]. Moreover, in a mouse model polyclonal sheep anti-mouse podocyte antibodies caused a severe nephrotic syndrome associated with subepithelial immune complex formation. Electron microscopy revealed 60–80% podocyte foot process effacement, enlarged podocytes, and subepithelial deposits. Nephrin and synaptopodin staining was severely disrupted, and podocyte number was reduced, indicating severe podocyte damage. Immunohistochemistry detected the injected anti-podocyte antibody exclusively along the glomerular filtration barrier [44]. Ubiquitin C-terminal hydrolase-L1 activity might also be involved. Expression of ubiquitin C-terminal hydrolase-L1, a member of ubiquitin-proteasome pathway, has been discovered in parietal epithelial cells of Bowman's capsules, in tubular epithelial cells, and in podocytes of kidneys affected by immune complex-mediated nephritis, suggesting that immune injury may stimulate podocytes to express ubiquitin C-terminal hydrolase-L1 [45]. Finally, a novel regulatory protein of the podocyte foot process, called p dlim2, has been identified. The expression of this protein is reduced in the podocytes of patients with MN suggesting a possible role of p dlim2 in the pathogenesis of glomerular diseases [46].

Thus, it is likely that in *de novo* MN different types of injury (viral, immunological, mechanical, ischemic) can cause a podocyte damage and expose cryptic antigens, which can be different from those seen in iMN. Examples of hidden antigens are the cases of MN occurring in the alloimmune setting of newborns from mothers deficient in neutral endopeptidase [47–49], or cases of MN devel-

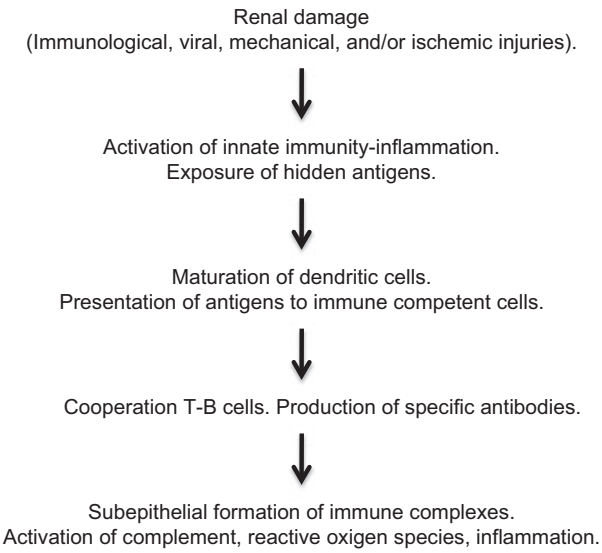

Figure 1 Any type of kidney injury can cause tissue damage. The danger signals released by the damaged tissue alert the recognition receptors, which activate the inflammatory cells and mediators of the innate immunity system. In this inflammatory environment, hidden podocyte antigens may be exposed, whereas dendritic cells become mature, migrate to lymphatic system, and present the antigen to immune competent cells. T cells cooperate with B cells favoring the production of antibodies directed against the exposed antigens planted in the subepithelium, with *in situ* formation of immune complexes, activation of complement, formation of free oxygen radicals, and inflammation.

oping after allogenic hematopoietic stem cell transplantation [50]. The damaged cells would generate danger signals that are intercepted by toll-like receptors and other cellular receptors. These recognition receptors originate a cascade of signals that eventually activate transcription factors that encode inflammatory genes [51]. The inflammatory cells of the innate immunity (polymorphonuclear cells, monocyte-macrophages, natural killer cells) release cytokines, inflammasomes, pentraxins, and other mediators. In this inflammatory environment, dendritic cells become mature and present the antigen to immunocompetent CD4 T cells, which are needed for B cell-driven antibody production. The final result is *in situ* (subepithelial) formation of IC, local complement activation, and injury induced by both circulating and resident glomerular effector cells [52] (Fig. 1).

Summary and conclusions

Taken together, the available data suggest that *de novo* MN is not caused by an immunologic response to a single antigen, but may be triggered by widely different antigens. The frequent association of *de novo* MN with signs of allograft rejection, viral hepatitis, or non immune-mediated kidney diseases strongly suggests that alloimmune responses, viral infections, and possibly mechanical injuries may produce an environment in the kidney allograft that predisposes to the exposure of hidden (cryptic) autologous podocyte-related antigens and thereby stimulate the production of circulating auto- or allo-antibodies (typically of the IgG_1 subclass) eventually leading to *in situ* immune complex formation, subepithelial deposits, and the morphological lesion of MN.

Authorship

CP had the original idea, both the authors contributed to write the paper.

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References

1. Cosyns JP, Couchoud C, Pouteil-Noble C, Squifflet JP, Pirson Y. Recurrence of membranous nephropathy after renal transplantation: probability, outcome and risk factors. *Clin Nephrol* 1998; **50**: 144.
2. Moroni G, Gallelli B, Quaglini S, *et al.* Long-term outcome of renal transplantation in patients with idiopathic membranous glomerulonephritis (MN). *Nephrol Dial Transplant* 2010; **25**: 3408.
3. El-Zoghby ZM, Grande JP, Fraile MG, Norby SM, Fervenza FC, Cosio FG. Recurrent idiopathic membranous nephropathy: early diagnosis by protocol biopsies and treatment with anti-CD20 monoclonal antibodies. *Am J Transplant* 2009; **9**: 2800.
4. Ponticelli C, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. *Clin J Am Soc Nephrol* 2010; **5**: 2363.
5. Charpentier B, Lévy M. Cooperative study of de novo extramembranous glomerulonephritis in renal allografts in humans: report of 19 new cases in 1550 renal transplant patients of the transplantation group of the Ile de France. *Nephrologie* 1982; **3**: 158.
6. Aline-Fardin A, Rifle G, Martin L, *et al.* Recurrent and de novo membranous glomerulopathy after kidney transplantation. *Transplant Proc* 2009; **41**: 669.
7. Schwarz A, Krause PH, Offermann G, Keller F. Recurrent and de novo renal disease after kidney transplantation with or without cyclosporine A. *Am J Kidney Dis* 1991; **17**: 524.
8. Davison AM, Johnston PA. Allograft membranous nephropathy. *Nephrol Dial Transplant* 1992; **7**(Suppl. 1): 114.
9. Antignac C, Hinglais N, Gubler MC, *et al.* De novo membranous glomerulonephritis in renal allografts in children. *Clin Nephrol* 1988; **30**: 1–6.
10. Steinmuller DR, Stilmant MM, Idelson BA, *et al.* De novo development of membranous nephropathy in cadaver renal allografts. *Clin Nephrol* 1978; **9**: 210.

11. Briner J, Binswanger U, Largiadèr F. Recurrent and de novo membranous glomerulonephritis in renal cadaver allotransplants. *Clin Nephrol* 1980; **13**: 189.
12. Monga G, Mazzucco G, Basolo B, *et al.* Membranous glomerulonephritis (MGN) in transplanted kidneys: morphologic investigation on 256 renal allografts. *Mod Pathol* 1993; **6**: 249.
13. Sebire NJ, Bockenhauer D. Posttransplant de novo membranous nephropathy in childhood. *Fetal Ped Pathol* 2005; **24**: 95.
14. Dische FE, Herbertson BM, Melcher DH, Morley AR. Membranous glomerulonephritis in transplant kidneys: recurrent or de novo disease in four patients. *Clin Nephrol* 1981; **15**: 154.
15. Truong L, Gelfand J, D'Agati V, *et al.* De novo membranous glomerulonephropathy in renal allografts: a report of ten cases and review of the literature. *Am J Kidney Dis* 1989; **14**: 131.
16. Honda K, Horita S, Toki D, *et al.* De novo membranous nephropathy and antibody-mediated rejection in transplanted kidney. *Clin Transplant* 2011; **25**: 191.
17. Lim BJ, Kim MS, Kim YS, Kim SI, Jeong HJ. C4d deposition and multilayering of peritubular capillary basement membrane in posttransplantation membranous nephropathy indicate its association with antibody-mediated injury. *Transplant Proc* 2012; **44**: 619.
18. Kearney N, Podolak J, Matsumura L, Houghton D, Troxell M. Patterns of IgG subclass deposits in membranous glomerulonephritis in renal allografts. *Transplant Proc* 2011; **43**: 3743.
19. Cosyns JP, Pirson Y, Squifflet JP, *et al.* De novo membranous nephropathy in human renal allografts: report of nine patients. *Kidney Int* 1982; **22**: 177.
20. Heidet L, Gagnadoux MF, Beziau A, *et al.* Recurrence of de novo membranous glomerulonephritis on renal grafts. *Clin Nephrol* 1994; **41**: 314.
21. Teixeira Costa F, Pinto JR, Carvalho F, Galvão MJ. An early case of de novo membranous nephropathy in a renal transplant patient. *Transplant Proc* 2002; **34**: 364.
22. Gough J, Yilmaz A, Yilmaz S, Benediktsson H. Recurrent and de novo glomerular immune-complex deposits in renal transplant biopsies. *Arch Pathol Lab Med* 2005; **129**: 231.
23. Poduval RD, Josephson MA, Javaid B. Treatment of de novo and recurrent membranous nephropathy in renal transplant patients. *Semin Nephrol* 2003; **23**: 392.
24. Lai KN, Li PKT, Lui SF, *et al.* Membranous nephropathy related to hepatitis B virus. *N Engl J Med* 1991; **324**: 1457.
25. Morales JM, Pascual-Capdevila J, Campistol JM, *et al.* Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. *Transplantation* 1997; **63**: 1634.
26. Cruzado JM, Carrera M, Torras J, Grinyò JM. Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant* 2001; **1**: 171–178.
27. Ozdemir BH, Ozdemir FN, Sezer S, Colak T, Haberal M. De novo glomerulonephritis in renal allografts with hepatitis C virus infection. *Transplant Proc* 2006; **38**: 492–5.
28. Prasad GV, Sweet JM, Cole EH, Cardella CJ. Allograft de novo membranous nephropathy complicating Alport's syndrome. *Nephron* 2000; **86**: 227.
29. Hoitsma AJ, Kroon AA, Wetzels JF, Assmann KJ, Berden JH, Koene RA. Association between ureteral obstruction and de novo membranous nephropathy in renal allografts. *Transplant Proc* 1990; **22**: 1388.
30. Robles NR, Gomez-Campdera FJ, Anaya F, Niembro E, Rengel MA, Valderrabano F. Is the development of 'de novo' allograft membranes nephropathy linked to ureteric obstruction? *Nephrol Dial Transplant* 1993; **8**: 883.
31. Koselj-Kajtna M, Rott T, Koselj M, *et al.* Recurrent immunoglobulin A nephropathy complicated with de novo membranous glomerulonephritis in renal allografts. *Transplant Proc* 2002; **34**: 3117.
32. Dittrich F, Schumaldienst S, Soleiman A, Horl W, Pohanha E. Rapamycin-associated posttransplantation glomerulonephritis and its remission after reintroduction of calcineurin inhibitor therapy. *Transplant Int* 2004; **17**: 215.
33. Ward HJ, Kovie MA. Immunopathologic features of de novo membranous nephropathy in renal allografts. *Transplantation* 1988; **45**: 524.
34. Glassock RJ. The pathogenesis of membranous nephropathy: evolution and revolution. *Curr Opin Nephrol Hypertens* 2012; **21**: 235.
35. Bansal VK, Koseny GA, Fresco R, *et al.* De novo membranous nephropathy following transplantation between conjoint twins. *Transplantation* 1986; **41**: 404.
36. El Kossi M, Harmer A, Goodwin J, *et al.* De novo membranous nephropathy associated with donor-specific alloantibody. *Clin Transplant* 2008; **22**: 124.
37. Beck LH, Bonegio R, Lambeau G, *et al.* M-type phospholipase A_2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361**: 11.
38. Debiec H, Martin L, Jouanneau C, *et al.* Autoantibodies specific for the phospholipase A2 receptor in recurrent and De Novo membranous nephropathy. *Am J Transplant* 2011; **11**: 2144.
39. Stanescu HC, Argos-Burgos M, Mediar A, *et al.* Risk HLA-DQA1 and PLRA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; **364**: 616.
40. Prunotto M, Carnevali ML, Candiano G, *et al.* Autoimmunity in membranous nephropathy targets aldose reductase and SOD2. *J Am Soc Nephrol* 2010; **21**: 507.
41. Bruschi M, Carnevali ML, Murtas C, *et al.* Direct characterization of target podocyte antigens and auto-antibodies in human membranous glomerulonephritis: alfa-enolase and borderline antigens. *J Proteomics* 2011; **74**: 2008.
42. Cornell LD. IgG4-related kidney disease. *Curr Opin Nephrol Hypertens* 2012; **21**: 279.

43. Glassock RJ. Secondary membranous glomerulonephritis. *Nephrol Dial Transplant* 1992; **7**(Suppl. 1): 64.
44. Meyer-Schwesinger C, Dehde S, Klug P, *et al.* Nephrotic syndrome and subepithelial deposits in a mouse model of immune-mediated anti-podocyte glomerulonephritis. *J Immunol* 2011; **187**: 3218.
45. Liu Y, Wu J, Wu H, *et al.* UCH-L1 expression of podocytes in diseased glomeruli and in vitro. *J Pathol* 2009; **217**: 642.
46. Sistani L, Dunér F, Udumala S, *et al.* Pdlim2 is a novel actin-regulating protein of podocyte foot processes. *Kidney Int* 2011; **80**: 1045.
47. Debiec H, Guigonis V, Mougenot B, *et al.* Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med* 2002; **346**: 2053.
48. Debiec H, Nauta J, Coulet F, *et al.* Role of truncating mutations in MME gene in fetomaternal alloimmunisation and antenatal glomerulopathies. *Lancet* 2004; **364**: 1252.
49. Ronco P, Debiec H, Guigonis V. Mechanisms of disease: alloimmunization in renal diseases. *Nat Clin Pract Nephrol* 2006; **2**: 388.
50. Stevenson WS, Nankivell BJ, Hertzberg MS. Nephrotic syndrome after stem cell transplantation. *Clin Transplant* 2005; **19**: 141.
51. Medzhitov R. Toll-like receptors and innate immunity. *Nat Rev Immunol* 2001; **1**: 135.
52. Couser WG. Basic and translational concepts of immune-mediated glomerular diseases. *J Am Soc Nephrol* 2012; **23**: 381.