Focal Segmental Glomerulosclerosis and Kidney Transplantation

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The recurrence rate of focal segmental glomerulosclerosis after kidney transplantation is ranging between 20% and 40%. Focal segmental glomerulosclerosis is associated with poor graft survival. In this review, the etiology, pathogenesis, clinicopathological features, risk factors of recurrence, and updated lines of management are discussed.

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Review

INTRODUCTION

Primary focal segmental glomerulosclerosis (FSGS) is the most frequently acquired disease leading to end-stage renal disease (ESRD) in children according to the 2004 annual report of the North American Pediatric Renal Trials and Collaborative Studies.[1-6] Its recurrence rate after kidney transplantation is ranging between 20% and 40%, and it is associated with poor graft survival.[7-13] It portends a rate of graft loss of 20% to 50% of cases.[14,15]

In France, the majority (91%) of pediatric patients exhibited a classical steroid-responsive relapsing disease, without progressive renal insufficiency. Estimates of steroid-responsiveness are somewhat lower (80%) in referral populations or cohorts that include adults.[16,17] On the other hand, in New York City, about two-thirds of steroid-resistant nephrotic syndrome (SRNS) patients were biopsy-proven FSGS.[18] These lesions are associated with a high risk of progressive kidney failure.[19]

The lesion refers to a set of particular histopathological features in which steroid-resistant podocyte injury leads to focal adhesions between the glomerular tuft and the visceral layer of Bowman capsule, followed by progressive glomerulosclerosis and proteinuric kidney failure.[16] Moreover, when profuse proteinuria occurs shortly after transplantation, an early kidney biopsy usually shows minimal or no changes. The podocytopathy that characterizes FSGS can only be detected several days or even weeks later by electron microscopy—which is not always performed—and typical changes of FSGS will only be detected by light microscopy several weeks or months later.[20] On serial biopsies, the incidence of minimal change disease decreased over time, while the incidence of FSGS variants increased. The variant type observed in the native kidneys was not predictive of either recurrence or type of FSGS seen on the allograft. Moreover, patients with complete and sustained remission did not develop FSGS.[15] Therefore, posttransplant FSGS recurrence implies these conditions: pretransplant histopathological diagnosis and profuse proteinuria that appears within weeks or days, if not hours, following the release of vascular clamps. Moreover, kidney biopsy discloses the reappearance of FSGS weeks later following a first stage of minimal glomerular changes.[20]

RISK FACTORS OF RECURRENCE

Some studies have identified some risk factors for recurrent FSGS, which include rapid progression to ESRD, young age of the onset of FSGS, and loss of a previous graft from recurrent disease, but none of these studies can clearly separate the patients who will or will not be affected by recurrence.[21] Age significantly influences the rate of recurrence. It is not clear why teenagers have a poorer graft survival than younger children. However, they have long-term survival rates similar to recipients

older than 65 years.[22]

Despite that the risk of recurrence in Hispanic patients is similar to that of other white patients, patients of African descent, especially in the United States have a genetic inclination to suffer from FSGS.[23,24] Conversely, due to unknown reasons, black patients transplanted for primary FSGS run a less than 50% lower risk of recurrence than their white fellow victims. Golgert and colleagues[25] concluded that if the first graft had failed following recurrence of FSGS, the risk of recurrence in subsequent transplantations would be 100 %. However, Gohh and coworkers[26] found in a limited experience that 3 of 6 cases of preemptive plasmapheresis were credited with the avoidance of relapse following a first failure. However, this is not sufficient to recommend living donor transplantation without concern.

Several mutations of the slit diaphragm complex proteins lead to neonatal (*NPHS1*, nephrin), childhood (*NPHS2*, podocin), or delayed (*ACTN4*, *CD2AP*, and *TRPC6*) forms of steroid-resistant FSGS.[27] It could logically be assumed that sporadic FSGS may recur on a transplant, whereas a genetic form should not, except if antibodies against the donor missing protein develop in the recipient. Most studies on this matter have been carried out in children with podocin mutations. Therefore, fine genetic screening should be carried out in children with SRNS form of FSGS and that podocin mutations do not necessarily preclude the risk of recurrence following kidney transplantation. However, recurrence in genetic forms of FSGS, due to unknown reasons, is rare,[28] and this raises again the issue of the glomerular permeability factor. However, this situation might find an explanation stemming from the concept that inhibitors of glomerular permeability are lost in the urine along with other proteins.[29]

ETIOLOGY

Focal segmental glomerulosclerosis is now viewed as a group of clinicopathological syndromes sharing a common glomerular lesion, which is mediated by diverse insults directed to or inherent within the podocyte. It could be a primary (idiopathic) form (80%), which is due to unknown cause, possibly mediated by circulating permeability factors, or it could be secondary to familial or genetic mutations in specific podocyte genes, virus-associated (human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus, and Epstein-Barr virus), drug-induced (heroin, interferons, lithium, pamidronate, sirolimus, calcineurin-inhibitors, and anabolic steroids), adaptive conditions with reduced renal mass (oligomeganephronia, very low birth weight, unilateral renal agenesis, renal dysplasia, reflux nephropathy, sequelae to cortical necrosis, surgical renal ablation, kidney allograft, aging kidney, and any advanced renal disease with reduced functioning nephrons), or conditions with initially normal renal mass (Table 1). The later includes systemic hypertension, acute or chronic vaso-occlusive processes (atheroembolization, thrombotic microangiopathy, and renal artery stenosis), elevated body mass index (obesity, increased lean body mass [eg, body building]), cyanotic congenital heart disease, and sickle cell anemia.

PATHOGENESIS

Primary FSGS is the result of a complex interaction between T and B cells leading to the secretion of a circulating factor targeting podocytes. The presence of a circulating vascular permeability factor implicated in the physiopathology of this disease is extrapolated by (1) early posttransplant recurrence of nephrosis[30]; (2) proteinuria induced in rats by infusing serum from patients with recurrent FSGS[31]; (3) newborn infants belonging to women with FSGS that may show the occurrence of a transient nephrotic syndrome[32]; and (4) the efficiency of plasma exchange or immune-adsorption at inducing remission.[33] Biochemically, this circulating factor is still not clear. Its molecular weight is suspected to be between 30 kDa and 100 kDa; Dantal and colleagues[34] suggested that it could be a part of a complex with immunoglobulins. Recently, Savin and colleagues[35] found that it had a high affinity for galactose and that all its activity was

Table 1. Differences Between Primary and Secondary Causes of Focal Segmental Glomerulosclerosis

Feature	Focal Segmental Glomerulosclerosis	
	Primary	Secondary
Albuminuria	Low (heavy proteinuria)	Normal
Glomeruli	Not enlarged	Enlarged
Sclerosis	Other sites	Perihilar
Effacement of foot processes	More	Milder

eliminated by galactose affinity columns. Several candidate plasma factors have been proposed. Cardiotrophin-like cytokine 1, a member of the interleukin-6 family, has been proposed initially. It has permeability activity in a plasma fraction with a molecular weight of less than 30 kDa and can be enriched by means of galactose affinity chromatography.[36]

Elevated serum levels of soluble urokinase plasminogen activator receptor (> 3000 pg/mL) have been identified in nearly two-thirds of patients with primary FSGS but not in those with minimal change disease. Increased serum levels of soluble urokinase plasminogen activator receptor before renal transplantation were associated with an increased risk of recurrent disease in the allograft. It can induce foot process effacement through the activation of podocyte β3 integrin, and its effect can be blocked in animal models by neutralizing antibodies targeting soluble urokinase receptor.[37,38] It is closely correlated to inflammation, and renal and hepatic dysfunction, which are central pathophysiological and therapeutic targets in critical disease.[30] It is expressed by various immune cells such as monocytes, macrophages, neutrophils, eosinophils,[40] activated T cells and natural killer cells.[41,42] It is also expressed by vascular endothelial cells,[43] megakaryocytes,[44] and certain tumour cells.[5] It is absent on erythrocytes, platelets, B cells and resting T cells.[45]

It is well known that podocytes are postmitotic cells, arrested in G2/M phase of the cell cycle, and do not proliferate. It has been postulated that this circulating factor and/or immune cells directly interact with podocytes causing injury. This included the redistribution of the protein of the slit diaphragm, the loss of nephrin or podocin and the effacement of the foot processes.[46] It has been suggested that foot processes effacement, if reversed, can lead to the restoration of glomerular architecture, which is typically observed in steroid-sensitive minimal change disease. The failure of repair mechanisms promotes podocyte detachment, apoptosis, podocyte depletion, and FSGS.

Collapsing glomerulopathy is a specific variant of FSGS in which podocytes may undergo a proliferative state and phenotypic changes.[47,48] In addition to podocytes, parietal epithelial cells also participate in the collapsing glomerulopathy phenotype.[49] Recently, Reiser and associates[50] described the expression of the costimulatory molecule B7.1 on podocytes. However, its significance is not clearly understood and remains speculative.

Dysfunction of Glomerular Filtration Barrier

Nephrotic proteinuria results from loss of integrity of the glomerular filtration barrier, which regulates selectivity through the intimate association of 3 layers: fenestrated glomerular endothelial cells at the inner blood interface, the glomerular basement membrane in the center, and podocytes at the outer urinary interface. Podocytes look like neurons in their large cell body and elongated cellular extensions, stabilized by a central actin cytoskeleton core. The foot processes interdigitate along the outer aspect of the glomerular capillary wall, linked to their neighbors by slit diaphragms, which are modified adherence junctions aligned in a zipper like array. They provide structural support to the glomerular capillaries and synthesize the proteins of the slit diaphragm and many extracellular components of the glomerular basement membrane. They cannot repair by cell division, therefore its depletion through detachment, apoptosis, or necrosis is a critical mediator of glomerulosclerosis.[51]

The loss of a critical number of nephrons—as in cases with late secondary forms of FSGS—promotes the activation of the rennin-angiotensin system, exacerbating proteinuria and setting the stage for progressive glomerulosclerosis regardless of the initial cause. Angiotensin II has direct proapoptotic effects on podocytes. Excessive protein uptake by podocytes induces podocyte TGF-β,[52] which promotes apoptosis and leads to endoplasmic reticulum stress, cytoskeletal reorganization, and dedifferentiation.[53] Drugs that are aimed at the inhibition of RAS (such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) lower intraglomerular filtration pressures through the inhibition of angiotensin II–mediated vasoconstriction of the efferent arteriole. Angiotensin-converting enzyme inhibition also augments bradykinin, which contributes to efferent arteriolar dilatation. The resulting reduction in proteinuria exerts a protective effect on podocytes and tubular cells.

CLINICAL PRESENTATION

It is found that the time to onset of nephrotic

FSGS and the malignant forms are predictive of an early relapse on the graft,[14,15,54,55] with a histopathological pattern similar to that of the native kidney. However, the first recurring lesions were observed at the beginning of the proximal tubule. This malignant variant often demonstrates high serum creatinine levels and severe glomerular and tubulointerstitial lesions, although the time elapsed between the subclinical onset of FSGS and its discovery when oedema appears and leads to histopathological diagnosis by kidney biopsy is unknown.[56]

The 1999 European Dialysis and Transplant Association Registry Report[57] retrieved 723 cases of transplantation for FSGS with 152 graft failures (24%) at less than 15 years. However, this report is somewhat confusing as there was no clear distinction made between failure due to recurrence and failure due to rejection. Floege,[14] in his review, found an estimate of 20% to 40% clinical recurrence rate in FSGS resulting in a 10% to 20% rate of graft loss after 5 to 10 years. Another review made by Fine,[9] came up with a consensus that 30% of grafts with the recurrence of nephrotic syndrome or FSGS are lost, presumably as a result of the recurrent pathological process.

The most severe form of FSGS identified is the so-called collapsing glomerulopathy. Swaminathan and coworkers[58] found that proteinuria and serum creatinine were significantly higher in this subgroup. The glomerular tip lesions of FSGS appears to be generally benign, following a course similar to that of minimal change disease.[59]

PATHOLOGIC EXAMINATION

More than 80% of FSGS cases recurred in the same pattern as the original disease.[60] However, these findings are not matched with Canaud and colleagues[28] who did not find that the initial histopathological pattern was predictive of that found on the grafted kidney.

Histological classification recognizes: not-otherwise-specified,[45] perihilar,[45,48-52] cellular,[52,53] tip,[14,45,54] and collapsing disease[14,15,56,57] variants, and these are applicable to both primary and secondary FSGS (Table 2 and Figure).[54]

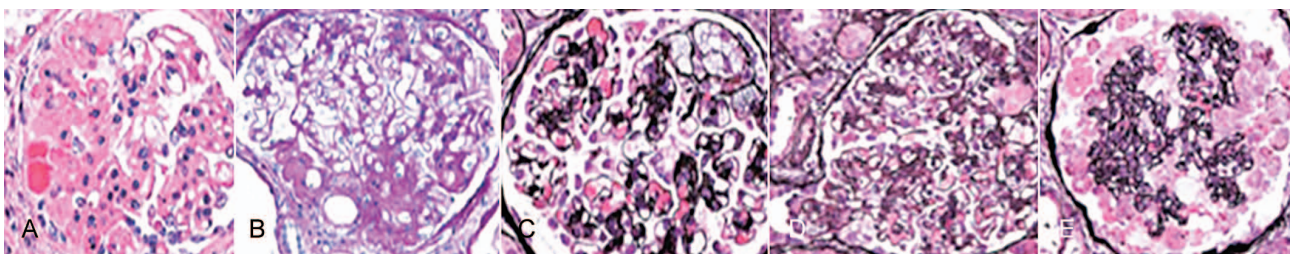
MANAGEMENT OF RECURRENCE

Preemptive Plasmapheresis

A few studies using preemptive plasmapheresis have been reported that it showed inconstant efficacy and lack a control group. In 2005, Gohh and colleagues[28] conducted a prospective study to test whether pretransplant plasmapheresis could

Table 2. Different Types of Focal Segmental Glomerulosclerosis

Feature	Focal Segmental Glomerulosclerosis				
	Not otherwise specified	Perihilar	Cellular	Glomerular tip	Collapsing
Etiology	Primary or secondary	More in adaptive	Usually primary	Primary	Primary or secondary
Features	Usually of genetic origin; the most common	Glomerulomegaly; lesions at vascular pole	Least frequent; endocapillary; hypercellularity	Lesions at tubular pole; less tubular atrophy and interstitial fibrosis	Collapsed tufts; hyperplasia of overlying cells filling U space
Proteinuria	Nephrotic or subnephrotic	Subnephrotic	Nephrotic	Nephrotic; abrupt	Nephrotic
Foot process effacement	Variable	Mild and focal	Severe	Severe	Severe
Prognosis	Fair	Fair	Fair	Best	Worst



Pathologic Features of Focal Segmental Glomerulosclerosis: **A**, not otherwise specified; **B**, perihilar type; **C**, cellular type; **D**, glomerular tip; and **E**, collapsing.

prevent recurrence of primary FSGS in high-risk patients who were defined by a rapid progression toward ESRD (n = 4) or prior allograft loss because of recurrence (n = 6). Patients were subjected to a course of 8 plasmapheresis sessions for 2 weeks in the immediate perioperative period. Recipients of live donor kidneys initiated plasmapheresis treatments 1 week before transplantation and completed their course at the end of the first postoperative week. On the other hand, recipients of cadaver kidneys underwent an initial plasmapheresis within 24 hours of transplantation. They found that FSGS recurred in 3 of 10 patients, each of whom had lost prior kidney graft due to recurrent FSGS. Two of these progressed to ESRD, and the third had significant renal dysfunction. The authors concluded that plasmapheresis may decrease incidence of FSGS recurrence in this particular patients. This therapeutic approach is difficult to organize in case of deceased donors. However, plasmapheresis session before or shortly after transplantation may increase the risk of major bleeding, despite that no adverse events were reported in that study. This approach would also lead to excessive treatment in 50% of patients.

Rituximab

Rituximab is a monoclonal antibody against CD20, a protein located on the surface of B cells. It is used for treatment of certain cancers and autoimmune disorders, but has also treated kidney conditions including FSGS. CD20 was absent in biopsies of patients with recurrent FSGS, suggesting that podocytes do not express CD20 in either healthy or diseased conditions. Rituximab not only recognizes CD20 on B lymphocytes, but might also bind sphingomyelin phosphodiesterase acid-like 3b protein and regulate acid sphingomyelinase activity in podocytes. Therefore, its mechanism of action is not antibody-mediated, but through B lymphocyte-independent mechanism. It regulates the activity of acid sphingomyelinase, which is essential for the organization of receptors and signaling molecules in the podocytes. It acts as a direct modulator of podocyte function, similar to what has been reported for cyclosporin. The number of sphingomyelin phosphodiesterase acid-like 3b-positive synaptopodin-positive cells per glomerulus was lower in biopsies from patients with recurrent disease when compared with non-recurrent biopsies.[61]

In 2006, Pescovitz and associates[62] reported complete remission after infusion of rituximab in a young transplant recipient. After kidney transplantation, this child rapidly developed FSGS recurrence resistant to plasmapheresis and cyclosporine and at the 5th month he developed a posttransplantation lymphoproliferative disease. After 6 infusions of rituximab to treat posttransplantation lymphoproliferative disease, proteinuria disappeared, suggesting a possible interaction between Band T cells that leads to the secretion of permeability factor.

Since that report, many transplant teams have tested the ability of rituximab to treat FSGS recurrence.[63-66] In fact, rituximab seems to induce remission in about 50% of cases, but some questions remain unsolved. When should the infusion begin: as an induction therapy or at time of recurrence? How many infusions should be administered, given that depletion of circulating B cells does not always correlate with lymphoid organ depletion[67]? What are the long-term side effects of this treatment? To date, no consensus has emerged, and double-blind studies are needed to determine the therapeutic potential of rituximab.

Fornoni and colleagues[61] have demonstrated that rituximab treatment of high-risk FSGS patients is associated with lower incidence of posttransplant proteinuria and could directly protect podocytes in a SMPDL-3b–dependent manner.

Anti-Cytotoxic T-Lymphocyte Antigen 4

The costimulation molecule B7.1 is normally expressed on antigen-presenting cells and B cells. Recently, Reiser and colleagues[52] found that B7.1 is also expressed on podocyte and could be upregulated in many proteinuric states. Again, the significance of the presence of this molecule is not clearly understood and remains speculative. To date, no published studies have evaluated blockade of this costimulation pathway for the treatment of FSGS recurrence.

Anti-Tumor Necrosis Factor-α

Tumor necrosis factor-α (TNF-α) mRNA was found to be upregulated in macrophages preceding the development of nephrotic syndrome in Buffalo/Mna rats.[68] Furthermore, a high level of TNF-α mRNA was detected in mononuclear cells from patients

with FSGS.[69] Anti-TNF-α therapy was recently tested in a child with resistant FSGS recurrence[70] and induced transient complete remission; however, every relapse was anti-TNF-α infusion dependent.

Retinoic acid, Roscovitine, and Cyclin-dependent Kinase Inhibitor

Collapsing glomerulopathy recurrence is a situation, in which podocytes can proliferate. Using in vitro and in vivo mouse models, retinoic acids were found to be efficient at reducing podocyte proliferation and proteinuria.[71] An ongoing study is evaluating treatment of collapsing glomerulopathyin native kidneys using retinoic acid (NCT00098020).

Galactose

Recently, Savin and coworkers[37] found that the circulating factor has a high affinity for galactose and that its activity can be nullified using galactose affinity columns. This group and one another reported a significant reduction inproteinuria after administration of galactose along withother therapeutics.[14,37] A clinical trial (NCT00098020) is recruiting patients to treat primary FSGS in native kidney with galactose. Galactose has an excellent safety profile and could be an interesting therapeutic candidate.

PROGNOSIS

It was perceived that posttransplantation lymphoproliferative disease does not necessarily mean loss of the graft. The 1999 European Dialysis and Transplant Association Registry Report 31 retrieved 723 cases of transplantation for FSGS with 152 graft failures (24%) at less than 15 years. Floege,[60] reviewing the literature, found a similar estimate of 20% to 40% clinical recurrence rate of FSGS with 10% to 20% graft loss rate within 5 to 10 years. Moreover, Fine[23] gave a consensus that 30% of patients with recurrent FSGS will lose their grafts as a result of the pathological process. Recent reviews are equally or more distrustful. Higher incidence of recurrence (up to 50%) was reported by Golgert and colleagues[60] among paediatric and young adults' patients with primary FSGS. Similarly, Raafat and colleagues[72] found a recurrence incidence in children of 67% (16 of 24) between 1991 and 2003. They added that the risk of recurrence was more or less similar in collapsing glomerulopathy compared to other histological subsets. The recurrence rate after failure of a first graft may reach 80%.

CONCLUSIONS

Recurrent FSGS remains a major unsolved problem for nephrologists. Plasmapheresis, in order to remove a circulating factor possibly responsible for the primary disorder, in addition to increased maintenance immunosuppression provides some success for preserving the survival of the grafted kidney. However, such therapies do not explain the mechanism of disease but make it more complicated.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Habib R, Levy M, Gubler MC. Clinicopathologic correlations in the nephrotic syndrome. Paediatrician. 1979;8:325-48.
2. Cameron JS. The enigma of focal segmental glomerulosclerosis. Kidney Int Suppl. 1996;57:S119-S131.
3. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. Am J Kidney Dis. 1997;30:621-31.
4. Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA, Jr., Germain MJ. Changing incidence of glomerular diseases in adults. Am J Kidney Dis. 2000;35:878-83.
5. Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis. 2004;44:815-25.
6. Filler G, Young E, Geier P, Carpenter B, Drukker A, Feber J. Is there really an increase in non-minimal change nephrotic syndrome in children? Am J Kidney Dis. 2003;42:1107-13.
7. Cameron JS, Senguttuvan P, Hartley B, et al. Focal segmental glomerulosclerosis in fifty-nine renal allografts from a single centre; analysis of risk factors for recurrence. Transplant Proc. 1989;21:2117-8.
8. Dantal J, Baatard R, Hourmant M, Cantarovich D, Buzelin F, Soulillou JP. Recurrent nephrotic syndrome following renal transplantation in patients with focal glomerulosclerosis. A one-center study of plasma exchange effects. Transplantation. 1991;52:827-31.
9. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis posttransplantation in 42 allografts in children--a single-center experience. Transplantation. 1991;51:401-5.
10. Dantal J, Soulillou JP. Relapse of focal segmental glomerulosclerosis after kidney transplantation. Adv Nephrol Necker Hosp. 1996;25:91-106.
11. Tejani A, Stablein DH. Recurrence of focal segmental glomerulosclerosis posttransplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. J Am Soc Nephrol. 1992;2:S258-S263.

12. Artero ML, Sharma R, Savin VJ, Vincenti F. Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in patients with recurrent focal glomerulosclerosis. Am J Kidney Dis. 1994;23:574-81.
13. Pardon A, Audard V, Caillard S, et al. Risk factors and outcome of focal and segmental glomerulosclerosis recurrence in adult renal transplant recipients. Nephrol Dial Transplant. 2006;21:1053-9.
14. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. Nephrol Dial Transplant. 2003;18:1260-5.
15. Canaud G, Dion D, Zuber J, et al. Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histological variants of focal and segmental glomerulosclerosis (FSGS). Nephrol Dial Transplant. 2010;25:1321-8.
16. Gbadegesin R, Hinkes B, Vlangos C, et al. Mutational analysis of NPHS2 and WT1 in frequently relapsing and steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2007;22:509-13.
17. Tejani A, Phadke K, Nicastri A, et al. Efficacy of cyclophosphamide in steroid-sensitive childhood nephrotic syndrome with different morphological lesions. Nephron. 1985;41:170-3.
18. Churg J, Duffy JL. Classification of glomerulonephritis based on morphology. Perspect Nephrol Hypertens. 1973;1 Pt 1:43-61.
19. Torban E, Bitzan M, Goodyer P. Recurrent focal segmental glomerulosclerosis: a discrete clinical entity. Int J Nephrol. 2012;2012:246128.
20. Meyrier A. Post-transplant recurrence of nephrotic primary focal segmental glomerulosclerosis. Eur Nephrol. 2011;5:68-71.
21. Canaud G, Martinez F, Noel LH, Mamzer MF, Niaudet P, Legendre C. Therapeutic approach to focal and segmental glomerulosclerosis recurrence in kidney transplant recipients. Transplant Rev (Orlando). 2010;24:121-8.
22. Ulinski T. Recurrence of focal segmental glomerulosclerosis after kidney transplantation: strategies and outcome. Curr Opin Organ Transplant. 2010;15:628-32.
23. Fine RN. Recurrence of nephrotic syndrome/ focal segmental glomerulosclerosis following renal transplantation in children. Pediatr Nephrol. 2007;22:496-502.
24. Kopp JB, Smith MW, Nelson GW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet. 2008;40:1175-84.
25. Golgert WA, Appel GB, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol. 2008;3:800-7.
26. Gohh RY, Yango AF, Morrissey PE, et al. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. Am J Transplant. 2005;5:2907-12.
27. Chiang CK, Inagi R. Glomerular diseases: genetic causes and future therapeutics. Nat Rev Nephrol. 2010;6:539-54.
28. Weber S, Gribouval O, Esquivel EL, et al. NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephrotic syndrome and low post-transplant recurrence. Kidney Int. 2004;66:571-9.
29. Ghiggeri GM, Artero M, Carraro M, Perfumo F. Permeability plasma factors in nephrotic syndrome: more than one factor, more than one inhibitor. Nephrol Dial Transplant. 2001;16:882-5.
30. Hoyer JR, Vernier RL, Najarian JS, Raij L, Simmons RL, Michael AF. Recurrence of idiopathic nephrotic syndrome after renal transplantation. Lancet. 1972;2:343-8.
31. Zimmerman SW. Increased urinary protein excretion in the rat produced by serum from a patient with recurrent focal glomerular sclerosis after renal transplantation. Clin Nephrol. 1984;22:32-8.
32. Lagrue G, Branellec A, Niaudet P, Heslan JM, Guillot F, Lang P. [Transmission of nephrotic syndrome to two neonates. Spontaneous regression]. Presse Med. 1991;20:255-7.
33. Dantal J, Bigot E, Bogers W, et al. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. N Engl J Med. 1994;330:7-14.
34. Dantal J, Godfrin Y, Koll R, et al. Antihuman immunoglobulin affinity immunoadsorption strongly decreases proteinuria in patients with relapsing nephrotic syndrome. J Am Soc Nephrol. 1998;9:1709-15.
35. Savin VJ, McCarthy ET, Sharma R, Charba D, Sharma M. Galactose binds to focal segmental glomerulosclerosis permeability factor and inhibits its activity. Transl Res. 2008;151:288-92.
36. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol. 2010;5:2115-21.
37. Wei C, El HS, Li J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med. 2011;17:952-60.
38. Wei C, Moller CC, Altintas MM, et al. Modification of kidney barrier function by the urokinase receptor. Nat Med. 2008;14:55-63.
39. Koch A, Voigt S, Kruschinski C, et al. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. Crit Care. 2011;15:R63.
40. Nykjaer A, Moller B, Todd RF, III, et al. Urokinase receptor. An activation antigen in human T lymphocytes. J Immunol. 1994;152:505-16.
41. Nykjaer A, Petersen CM, Moller B, Andreasen PA, Gliemann J. Identification and characterization of urokinase receptors in natural killer cells and T-cell-derived lymphokine activated killer cells. FEBS Lett. 1992;300:13-7.
42. Bianchi E, Ferrero E, Fazioli F, et al. Integrin-dependent induction of functional urokinase receptors in primary T lymphocytes. J Clin Invest. 1996;98:1133-41.
43. Haddock RC, Spell ML, Baker CD, III, et al. Urokinase binding and receptor identification in cultured endothelial cells. J Biol Chem. 1991;266:21466-73.
44. Bariety J, Nochy D, Mandet C, Jacquot C, Glotz D, Meyrier A. Podocytes undergo phenotypic changes and express macrophagic-associated markers in idiopathic collapsing glomerulopathy. Kidney Int. 1998;53:918-25.

45. Wohn KD, Kanse SM, Deutsch V, Schmidt T, Eldor A, Preissner KT. The urokinase-receptor (CD87) is expressed in cells of the megakaryoblastic lineage. Thromb Haemost. 1997;77:540-7.

46. Kim BK, Hong HK, Kim JH, Lee HS. Differential expression of nephrin in acquired human proteinuric diseases. Am J Kidney Dis. 2002;40:964-73.

47. Canaud G, Bruneval P, Noel LH, et al. Glomerular collapse associated with subtotal renal infarction in kidney transplant recipients with multiple renal arteries. Am J Kidney Dis. 2010;55:558-65.

48. Barisoni L, Kriz W, Mundel P, D'Agati V. The dysregulated podocyte phenotype: a novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 1999;10:51-61.

49. Dijkman HB, Weening JJ, Smeets B, et al. Proliferating cells in HIV and pamidronate-associated collapsing focal segmental glomerulosclerosis are parietal epithelial cells. Kidney Int. 2006;70:338-44.

50. Reiser J, von GG, Loos M, et al. Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest. 2004;113:1390-7.

51. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365:2398-411.

52. Abbate M, Zoja C, Morigi M, et al. Transforming growth factor-beta1 is up-regulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. Am J Pathol. 2002;161:2179-93.

53. Inagi R, Nangaku M, Onogi H, et al. Involvement of endoplasmic reticulum (ER) stress in podocyte injury induced by excessive protein accumulation. Kidney Int. 2005;68:2639-50.

54. Chailimpamontree W, Dmitrienko S, Li G, et al. Probability, predictors, and prognosis of posttransplantation glomerulonephritis. J Am Soc Nephrol. 2009;20:843-51.

55. Ponticelli C, Glassock RJ. Posttransplant recurrence of primary glomerulonephritis. Clin J Am Soc Nephrol. 2010;5:2363-72.

56. Golgert WA, Appel GB, Hariharan S. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Clin J Am Soc Nephrol. 2008;3:800-7.

57. Briggs JD, Jones E. Recurrence of glomerulonephritis following renal transplantation. Scientific Advisory Board of the ERA-EDTA Registry. European Renal Association-European Dialysis and Transplant Association. Nephrol Dial Transplant. 1999;14:564-5.

58. Swaminathan S, Lager DJ, Qian X, Stegall MD, Larson TS, Griffin MD. Collapsing and non-collapsing focal segmental glomerulosclerosis in kidney transplants. Nephrol Dial Transplant. 2006;21:2607-14.

59. Stokes MB, Markowitz GS, Lin J, Valeri AM, D'Agati VD. Glomerular tip lesion: a distinct entity within the minimal change disease/focal segmental glomerulosclerosis spectrum. Kidney Int. 2004;65:1690-702.

60. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis. 2004;43:368-82.

61. Fornoni A, Sageshima J, Wei C, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. Sci Transl Med. 2011;3:85ra46.

62. Pescovitz MD, Book BK, Sidner RA. Resolution of recurrent focal segmental glomerulosclerosis proteinuria after rituximab treatment. N Engl J Med. 2006;354:1961-3.

63. Gossmann J, Scheuermann EH, Porubsky S, Kachel HG, Geiger H, Hauser IA. Abrogation of nephrotic proteinuria by rituximab treatment in a renal transplant patient with relapsed focal segmental glomerulosclerosis. Transpl Int. 2007;20:558-62.

64. Hristea D, Hadaya K, Marangon N, et al. Successful treatment of recurrent focal segmental glomerulosclerosis after kidney transplantation by plasmapheresis and rituximab. Transpl Int. 2007;20:102-5.

65. Kamar N, Faguer S, Esposito L, et al. Treatment of focal segmental glomerular sclerosis with rituximab: 2 case reports. Clin Nephrol. 2007;67:250-4.

66. Yabu JM, Ho B, Scandling JD, Vincenti F. Rituximab failed to improve nephrotic syndrome in renal transplant patients with recurrent focal segmental glomerulosclerosis. Am J Transplant. 2008;8:222-7.

67. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford). 2005;44:1542-5.

68. Le BL, Herve C, Buzelin F, Usal C, Soulillou JP, Dantal J. Renal macrophage activation and Th2 polarization precedes the development of nephrotic syndrome in Buffalo/Mna rats. Kidney Int. 2005;68:2079-90.

69. Bakr A, Shokeir M, El-Chenawi F, El-Husseni F, Abdel-Rahman A, El-Ashry R. Tumor necrosis factor-alpha production from mononuclear cells in nephrotic syndrome. Pediatr Nephrol. 2003;18:516-20.

70. Leroy S, Guigonis V, Bruckner D, et al. Successful anti-TNFalpha treatment in a child with posttransplant recurrent focal segmental glomerulosclerosis. Am J Transplant. 2009;9:858-61.

71. He JC, Lu TC, Fleet M, et al. Retinoic acid inhibits HIV-1-induced podocyte proliferation through the cAMP pathway. J Am Soc Nephrol. 2007;18:93-102.

72. Raafat RH, Kalia A, Travis LB, Diven SC. High-dose oral cyclosporin therapy for recurrent focal segmental glomerulosclerosis in children. Am J Kidney Dis. 2004;44:50-6.

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