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CASE REPORT

MIXED PULMONARY INFECTION IN A PATIENT WITH SUCCESSFULLY TREATED RECURRENCE OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS ON KIDNEY ALLOGRAFT

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Abstract

Introduction. Recurrence of focal segmental glomerulosclerosis (FSGS) in patients with a kidney transplant (KTx) is a challenging issue. Pulmonary infections can further complicate the clinical course of these patients.
Case presentation. A 36-years-old female with kidney failure due to FSGS had KTx from a living-related donor in 2017, with stable graft function during the follow-up. In 2021, the patient presented with proteinuria and increased serum creatinine. Renal biopsy demonstrated recurrence of FSGS in kidney allograft. She was treated with Rituximab combined with plasma exchanges and achieved complete remission. In 2023, the patient was admitted due to 10-days history of weakness, fever and productive cough with hemoptysis. The computed tomography scan of the lungs revealed bilateral ground-glass opacities with

Résumé

Infection pulmonaire mixte chez une malade greffée ayant récidive de glomerulosclerose segmentaire focale traitée

Introduction. La récurrence de la glomérulosclérose segmentaire focale (GSFS) chez les patients ayant une greffe rénale est une problématique difficile. Les infections pulmonaires peuvent compliquer davantage l'évolution clinique de ces patientes.
Présentation de cas. Une femme de 36 ans atteinte d'insuffisance rénale chronique due à la GSFS a été transplantée d'un donneur vivant en 2017, ayant une fonction de greffe stable. La patiente a présenté une protéinurie et une augmentation de la créatinine sérique, 5 ans après la transplantation. La biopsie rénale a montré une récidive de la GSFS dans l'allogreffe

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cavitary lesion. The bronchoalveolar lavage and immunofluorescence test for detection of atypical pulmonary pathogens were positive for *Acinetobacter* and human *Rhinovirus/Enterovirus*. High β-d-glucan fungal antigen suggested a severe fungal infection. To alleviate "cytokine storm" the patient was treated with hemoadsorption (CytoSorb) with transitory hemodynamic stabilization and improved graft function. Despite the therapy with wide-spectrum antibiotics, antiviral and antifungal drugs, the patient developed respiratory failure and need of mechanical ventilation and died on the 15th day of hospitalization.

Conclusions. Rituximab and therapeutic plasma exchange are effective for FSGS recurrence following KTx. In these patients, the infections are usually caused by multiple microorganisms, and the diagnosis is challenging, because the clinical presentation is non-specific and the diagnostic tools have limited sensitivity and specificity. The mortality is very high despite the treatment.

Keywords: focal segmental glomerulosclerosis, kidney transplant, plasma exchange, fungal infection.

List of abbreviations:
FSGS – focal segmental glomerulosclerosis
ESKD – end-stage kidney disease
KTx – kidney transplant
LRTI – lower respiratory tract infections
PCR – polymerase chain reaction
CT – computed tomography
BAL – bronchoalveolar lavage
LDH – lactate dehydrogenase
LED-FM – light-emitting diode fluorescence microscopy
CMV – cytomegalovirus
BMI – body mass index
MMF – mycophenolate mofetil
CAN – chronic allograft nephropathy

rénale. Elle a été traitée par Rituximab associé à des échanges plasmatiques et a obtenu une rémission complète. En 2023, le patient a été admis en raison d'antécédents de faiblesse, de fièvre et de toux productive et une hémoptysie depuis 10 jours. La tomodensitométrie des poumons a révélé des opacités bilatérales en verre dépoli avec une lésion cavitaire. La lavage broncho-alvéolaire et le test d'immunofluorescence pour la détection des agents pathogènes pulmonaires atypiques ont été positifs pour *Acinetobacter* et *Rhinovirus/entérovirus* humain. Un taux élevé d'antigène fongique β-d-glucane suggérait une infection fongique grave. Pour atténuer la "tempête de cytokines", la patiente a été traitée par une hémoadsorption (CytoSorb) suivi par une stabilisation hémodynamique transitoire et amélioration de la fonction du greffon. Malgré le traitement par des antibiotiques à large spectre, des antiviraux et des antifongiques, le patient a développé une insuffisance respiratoire et avait besoin une ventilation mécanique et est décédée au 15eme jour de son hospitalisation.

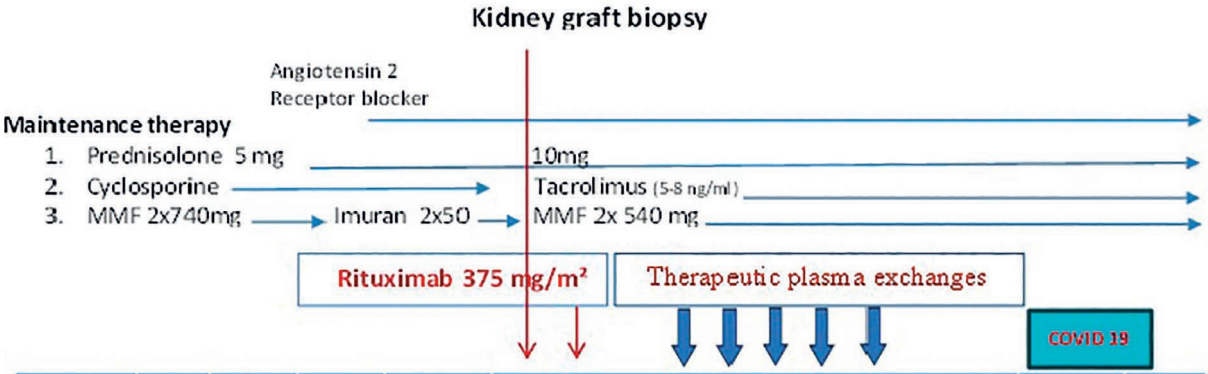
Conclusion. Le rituximab et l'échange plasmatique thérapeutique peuvent être efficaces dans le traitement de la récidive de la GSFS après la transplantation rénale. Chez ces patients, les infections sont généralement causées par plusieurs micro-organismes, le diagnostic est difficile car le tableau clinique n'est pas spécifique et les outils de diagnostic ont une sensibilité et une spécificité limités. La mortalité est très élevée malgré le traitement.

Mots-clés: glomérulosclérose segmentaire focale, transplantation rénale, échange plasmatique, infection fongique

Introduction

Idiopathic focal segmental glomerulosclerosis (FSGS) is one of the leading causes of end-stage kidney disease (ESKD) in adults and a common indication for kidney transplant (KTx) with a high-risk of posttransplant recurrence[1]. The reported rate of recurrence ranged from 17% to 55%, and was higher in younger patients, native kidneys nephrectomies, white race, aggressive primary FSGS with heavy proteinuria prior to transplant, mesangial hypercellularity with fewer sclerotic glomeruli on native kidney biopsy and lower body-mass index (BMI) at transplant[2]. Proteinuria is usually the first sign of FSGS recurrence and could occur within 48-72 hours after KTx as a primary nonfunctional graft or as chronic proteinuria with gradually deterioration of graft function[1,2]. In any case, recurrence of FSGS is associated with lower rate of graft survival and prompt diagnosis and timely treatment are crucial for preservation of kidney function.

Lower respiratory tract infections (LRTI) affect 40-80% of kidney transplant patients at various times after transplantation[3,4]. Usually, these infections are caused by multiple multidrug-resistant microorganisms (bacteria, viruses, and fungi) and often have a rapid and fulminant course with high morbidity and mortality[3,4].



Year after KTx	1	2	3	4	5	6	7
Creatinine µmoll/L	71	94	78	117	104...117.....130.....108.....161.....97	116	107
Proteinuria g/L	< 0.07	< 0.07	0.09	0.3...0.7	0.3.....0.97.....0.5.....0.1	0.2	0.17
Anti HLA ab		neg	neg	neg	DSA (DR52, 1108 MFI)		

Figure 1. Schematic presentation of laboratory data, clinical course and therapeutic interventions in the patient.
MMF – mycophenolate mofetil; CAN – chronic allograft nephropathy; FSGS – focal segmental glomerulosclerosis

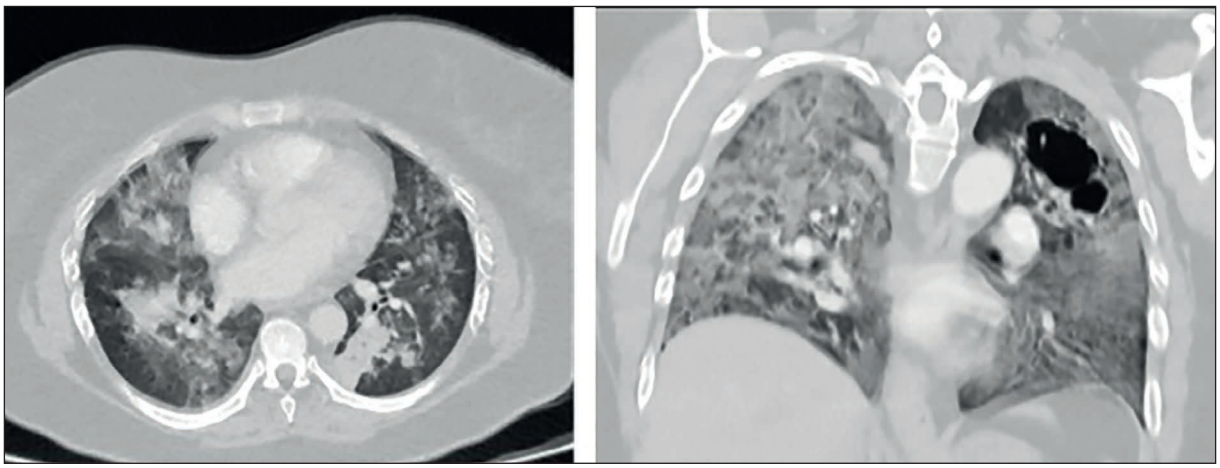
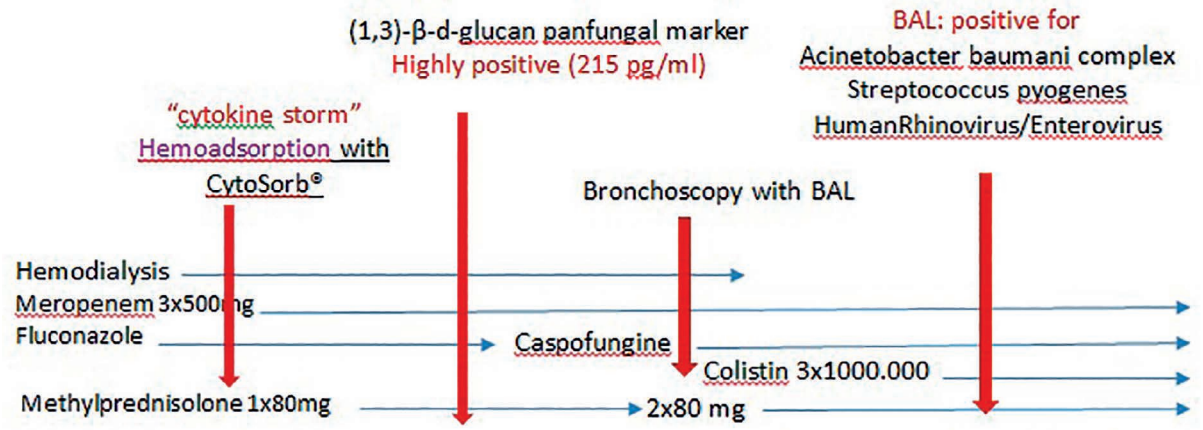


Figure 2. The computed tomography (CT) scan of the lungs with bilateral ground-glass opacities with massive infiltration and cavitary lesion.

We present an aggressive mixed pulmonary infection in a kidney transplant patient who developed severe systemic inflammatory response and respiratory failure despite the treatment.

Case presentation

A 36-years-old female with kidney failure due to FSGS had kidney transplant from a living-related donor in 2017. She received standard induction therapy and standard triple maintenance immunosuppressive therapy. In the follow-up period, the patient had stabile graft function without proteinuria (Figure 1). Four years after transplantation, the patient developed proteinuria (0.97 g/diuresis, ref. range < 0.2g /diuresis) and increased serum creatinine (130 µmol/L, ref. range 45-109 µmol/L). The standard microbiological work-up for infectious causes including urine culture and polymerase chain reaction (PCR) assay for detection of cytomegalovirus, Mycobacterium tuberculosis and Epstein-Barr virus were negative. The color Doppler test showed allograft in right iliac fossa with dimension of 119x59 mm, parenchymal thickness of 21 mm, renal artery flow of 113 cm/s (resistive index 0.59), renal parenchymal artery flow of 63 cm/s (resistive index 0.40). Renal allograft biopsy was obtained, which demonstrated chronic allograft nephropathy, no evidence for rejection, and typical foot process effacement changes consistent with recurrent FSGS in the kidney allograft. The patient was treated with



Day of hospitalization	1	2	3	4	5	6	7		9	10
Creatinine µmoll/L	367	268		221		195	190			230
HBG (g/l)	83	95	97	80	89	116	108	109	109	
Le (x10⁹)	5.1	2.9	2.8		2.6	2.5	3	6.9	4.6	
LDH (U/L)	502		889		668		956			965
CRP (mg/l)	107	320		116		36		56		10
IL – 6 (pg/ml)	180			57			65			
Procalcitonin (ng/ml)	45			0.883						

Figure 3. Schematic representation of laboratory data, clinical course and therapeutic interventions in the patient.
HBG – hemoglobin; LDH – lactate dehydrogenase; CRP – C-reactive protein; IL-6 – interleukin –6

single dose of rituximab and five therapeutic plasma exchanges. Few months after treatment, the patient experienced complete remission with normalization of serum creatinine and proteinuria (Figure 1).

In November 2023, the patient was admitted in our Nephrology department, because of 10-days history of weakness, fever and productive cough with hemoptysis. The computed tomography (CT) scan of the lungs revealed bilateral ground-glass opacities with massive infiltration and cavitary lesion (Figure 2).

The laboratory tests showed impaired graft function with serum creatinine level of 367 µmol/L (ref. range 45-109 µmol/L), anemia, high lactate dehydrogenase (LDH), and systemic inflammatory response with high C-reactive protein of 107 mg/L (ref. range < 6 mg/L), high serum interleukin-6 of 180 pg/mL (ref. range < 6 pg/mL) and high serum procalcitonin of 45 ng/mL (normal value < 0.5 ng/mL). Hemodialysis was initiated and treatment with parenteral corticosteroid, a broad-spectrum antibiotic, and an antifungal agent (Figure 3). To alleviate excessive systemic inflammation "cytokine storm" the patient was treated with three sessions of hemoadsorption (CytoSorb) with transitory hemodynamic stabilization and improved graft function. The bronchoalveolar lavage (BAL) and immunofluorescence test for detection of atypical pulmonary pathogens (pneumoslide) were positive for Acinetobacter and human rhinovirus/enterovirus. The β-d-glucan fungal antigen was highly elevated, suggesting severe invasive fungal infection. Light-emitting diode fluorescence microscopy (LED-FM) for tuberculosis resulted negative. Despite therapy with parenteral wide-spectrum antibiotics, antiviral and antifungal drugs (caspofungin) the patient had continuous worsening with development of respiratory failure. She was transferred to Central Intensive Care Unit, put on inotropic support with noradreneline and dopamine and mechanical ventilation. The patient died on the 15th day of hospitalization (Figure 3).

Discussion

The reappearance of glomerular-type proteinuria, with or without nephrotic syndrome, after excluding other potential causes of proteinuria in a patient with FSGS on native kidneys, is indicative for recurrence of FSGS on kidney allograft. The median time of FSGS recurrence was 0.5 months, but it was reported as late as > 5 years posttransplant (varying from 1 to 4745 days after KTx)[5]. The recurrence of

the non-genetic form of FSGS was considered to be due to the so-called circulating "permeability factor" (e.g., cardiotrophin-like cytokine 1, antiCD40 antibody, soluble urokinase-type plasminogen activator receptor) secreted by T lymphocytes. This factor and/or the absence of its inhibitor were associated with disruption in cytoskeletal proteins and impaired function of endogenous nitric oxide synthetase in podocytes, with their injury and detachment from glomerular basement membrane, glomerular hypertrophy, release of cytokines and progressive glomerulosclerosis[2].

Although our patient was a young, Caucasian female, she did not have the other traditional risk factors associated with a higher rate of FSGS recurrence[1,2]. Four years after KTx, the patient developed subnephrotic proteinuria and increased serum creatinine. The kidney allograft biopsy demonstrated changes consistent with recurrence of FSGS. In the early posttransplant period, the differentiation of the etiology of proteinuria is difficult and acute rejection, ischemia-reperfusion injury, drugs effect, and infections should be excluded; in the later period it is necessary to differentiate from proteinuria as a consequence of chronic allograft nephropathy, diabetes and long-standing hypertension. Hence, a renal biopsy is often needed for definitive diagnosis[2].

The optimal management of recurrent FSGS is still controversial because there are no controlled clinical trials comparing different treatment strategies. Currently, the combination of plasmapheresis and rituximab is the most promising regimen, with highest response rate. If inadequate response is achieved, other apheresis modalities (immunoadsorption, low-density lipoproteins apheresis) and use of high dose cyclosporine should be considered[6]. In a meta-analysis of 413 kidney-transplant recipients who had relapsing primary FSGS, Kashgary et al. found complete or partial remission in 71% (95% CI 66–75%) of patients after treatment with plasma exchange and median follow-up of 19 months. Age and type of kidney transplant (living vs. deceased) did not associate with remission, but males and patients treated within 2 weeks of recurrence had higher likelihood of remission (OR = 2.16; 95% CI: 0.93 to 5.01)[7]. Lanaret et al. showed that although there was no difference in the rates of complete and partial remission between patients who received plasmapheresis (82.6%; 109 patients) and patients who received combined plasmapheresis with rituximab (71.8%; 39 patients), the addition of rituximab in patients after failure of plasma-exchange therapy (n = 31), leaded to complete or partial treatment response in more than 57% of the patients with similar incidence of severe infections[8]. The number of performed plasma-exchange sessions typically varied from 5 to 13 treatments; regimens of one to six doses of rituximab have been reported[7,8]. Rituximab and plasmapheresis prophylaxis prior to transplantation might have positive effects on preventing FSGS recurrence after KTx[9].

The imbalance between pathogens' exposure and the net state of immunosuppression over years makes KTx patients prone to infections of various organs and systems. Urinary tract infections (61%), followed by respiratory tract infections (8%), intra-abdominal infections (6%), and cytomegalovirus (CMV) infection (6%) are the most common infections among kidney transplant patients[3]. Lower respiratory tract infections (LRTI) were associated with the highest risk of hospitalization and highest mortality[3,4]. In the study of Jain et al., 206 out of 1051 kidney transplant patients had an episode of LRTI requiring admission, nearly 20% over 9 years. The symptoms were non-specific and included fever, productive cough, hemoptysis and dyspnea. More than half of the patients had hypoxemia and need for non-invasive ventilation (36.8%) or mechanical ventilation (30.5%) and vasopressors. Graft dysfunction was seen in 86 (41.7%) patients at presentation, and 46 (22.3%) patients underwent hemodialysis. Bacterial infection was the most common etiology (53%), and Staphylococcus was the most common species. Among the fungal causes (14%), 68% had Aspergillus infection which led to dead in 50% of the cases. The presence of sepsis, septic shock, and the need for mechanical ventilation independently predicted higher mortality. The rate was also higher in patients who received some form of heightened immunosuppression due to history of rejection[3].

In a small study performed by Wang et al., mixed pulmonary infection, either as bacterial infection or bacterial, viral and fungal co-infection, were noted in 18 out of 29 kidney transplant patients. In all cases, the CT findings were diverse and complex, lacking characteristic signs which made their timely diagnosis difficult[10]. To alleviate the systemic inflammation "cytokine storm" in our patient, we performed hemoadsorption (CytoSorb) which led to transitory hemodynamic stabilization and improved graft function. Although it is not part of standard treatment, hemoadsorption (CytoSorb) was also used by Maiorano et al. in a kidney transplant patient with gas gangrene of left foot (two consecutive treatments before intervention and one treatment early after) with reduction in inflammation/infection markers and a complete restoring of diuresis and graft function after the third treatment[11]. However, larger meta-analysis failed to demonstrate a significant positive effect of hemoadsorption (CytoSorb) on mortality[12].

Conclusions

Rituximab and therapeutic plasma exchange are effective treatments for FSGS recurring following kidney transplant. Infections remain the most important cause of death among KTx patients. Infections in these patients are usually caused by multiple microorganisms and diagnosis can be challenging because the clinical presentation is non-specific and the diagnostic tools have limited sensitivity and specificity and must be interpreted in the context of clinical settings. The management is difficult, and mortality is very high despite the treatment.

Author Contributions:

G.S., S.S., Z.S.M., I.G.N., L.T., I.R.-B. and G.S. were responsible for the diagnostic procedures, clinical diagnosis, and treatment decisions. V.T. and B.A. were involved in the treatment of the patient at the Unit for Anesthesiology, Resuscitation and Intensive Care. V.K., A.T., A.K., S.F. and N.G. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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