INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a glomerulopathy primarily caused by podocyte injury that leads to focal adhesions formation between the glomerular tuft and the visceral layer of Bowman capsule (1,2). The global incidence of FSGS has been estimated at 8 cases/million/year, with 40-60% of patients developing end-stage renal disease (ESRD) within 10 to 20 years after diagnosis (3,4). Nowadays, five forms of FSGS have been recognized – genetic, arising from multiple nuclear or mitochondrial gene mutations; adaptive, associated with disequilibrium in physiological load and glomerular filtration surface; virus-associated; drug-induced; and primary (idiopathic)(5).

Although kidney transplantation (KTx) is the treatment of choice in this specific group of patients, post-transplant recurrence of FSGS remains an obstacle towards satisfactory long-term allograft survival (1). FSGS recurs in 20-50% of kidney allografts, with either early or late occurrence (1,6). Most importantly, only primary FSGS recurs following KTx, supporting the hypothesis of preexisting immune abnormalities which trigger podocyte injury. There are numerous factors associated with an increased risk of recurrence, most of all young age at onset (children < 6 years), severe proteinuria and rapid progression towards ESRD in native kidneys, and prior history of allograft loss due to recurrence (7). It is also worth mentioning that compared to recurrence of other glomerulopathies, patients with FSGS recurrence demonstrate two-fold higher risk of losing the allograft in a 10-year period (8).
The management of FSGS recurrence is challenging and unclear, as there are still no well-established treatment protocols. Thus, the treatment is mostly "empirical," with therapeutic plasma exchange (TPE) and high-dose cyclosporine (CSA) being the cornerstones of therapy (9). Recent studies have reported anti-CD20 chimeric monoclonal antibody (Rituximab, RTX) to be highly effective in treating and preventing the FSGS recurrence, but further efforts are needed to precisely establish its safety/efficacy profile (9-11).

The main aim of this study was to evaluate the outcomes of kidney transplantation in patients with FSGS treated at our Center and discuss available management options for improved outcomes in this group of patients.

PATIENTS AND METHODS

The study was carried out at the Department of nephrology, arterial hypertension, dialysis and transplantation, University Hospital Center (UHC) Zagreb. All patients with histological evidence of FSGS on a native kidney biopsy transplanted during the period between October 2007 and October 2013 were analyzed in this retrospective observational study.

Clinical and laboratory data were obtained from the medical records and charts. Data included dialysis modality and vintage, comorbidities, type of immunosuppressive regimen, complications after KTx, immunological compatibility and laboratory values indicating kidney allograft function and possible FSGS recurrence. Therapeutic plasma exchange was performed on Diapact, B.Braun, with exchange of one plasma volume, and 5% human albumins as replacement fluid.

Statistical evaluation of the data was carried out using SPSS statistical package, version 17.0 for Windows. Baseline data were reported using descriptive statistics. To compare characteristics of two groups Χ² test and t-test were performed, with statistical significance defined as $P < 0.05$.

RESULTS

Patients' characteristics

From October 2007 to October 2013, 786 renal transplantsations were performed at our institution. A total of 30 cases of biopsy-proven FSGS were indentified during the observed period. Among them, 29 had a non-collapsing form of FSGS (ncFSGS), while one had collapsing FSGS (cFSGS). There were 20 female (66.7%) and 10 male (33.3%) patients of mean age 44.74 ± 4.24 years. The mean time spent on dialysis prior to kidney transplantation was 4.03 ± 0.7 years. Comorbidities included predominantly cardiovascular (n=8) and rheumatoid diseases (n=4). Two patients had concomitant hepatitis infection (HBV n=1; HCV n=1), and 8 patients showed no signs of comorbidities.

Deceased donor kidney allograft received 96.7% of patients, while one patient was transplanted preemptively from a living-related donor. Two patients received second KTx, their first allografts lost due to FSGS recurrence. Immunological compatibility was favorable. All patients received basiliximab induction, followed by the standard immunosuppressive regimen composed of calcineurine inhibitor, mycophenolic acid and corticosteroids. Demographic data are summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± std), years</td>
<td>44.74 ± 4.24</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>33.3</td>
</tr>
<tr>
<td>Dialysis modality (n)</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>19</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>11</td>
</tr>
<tr>
<td>Dialysis vintage (mean ± std), years</td>
<td>4.03 ± 0.7</td>
</tr>
<tr>
<td>Number of HLA mismatches</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
<td>7</td>
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<tr>
<td>3</td>
<td>18</td>
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<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Immunosuppression protocol (n)</td>
<td></td>
</tr>
<tr>
<td>CSA + MPA + steroid</td>
<td>20</td>
</tr>
<tr>
<td>TAC + MPA + steroid</td>
<td>10</td>
</tr>
</tbody>
</table>

CSA – cyclosporine A; TAC – tacrolimus; MPA – mycophenolic acid

Patient and graft survival

Overall patient survival was 90% during the follow-up period. Two patients died from infectious complications and one after the acute myocardial infarction.

Eighty percent of patients have satisfactory allograft function, with median allograft survival of 49.15 months (range 0.5-84 months). Delayed allograft function (DGF) occurred in 4 cases, but without negative impact on the long-term allograft survival.

Posttransplant complications and FSGS recurrence

One allograft was lost in the early posttransplant period due to severe surgical complication (rupture of external iliac artery) demanding prompt artery ligation and graphtectomy. Acute rejection episode was record-
ed in 8 patients – acute cellular rejection (ACR; n=7) was successfully treated with high-dose corticosteroid therapy. One patient presented with combined acute cellular and humoral rejection diagnosed after a kidney biopsy performed due to development of nephrotic range proteinuria. Combined therapy with corticosteroid boluses and TPE was applied, with proteinuria reduction and significant improvement in graft function. However, three months later proteinuria reappeared and the second biopsy, showing no signs of rejection, pointed towards something else – cFSGS. TPE was commenced once more, followed by RTX therapy, but the graft function rapidly declined and finally failed.

The incidence of recurrence was 20% (6/30), with 3 allografts lost rapidly due to cFSGS. The most sudden onset of heavy proteinuria was recorded on day 5 posttransplant, in a young patient with previously diagnosed cFSGS on the native kidney biopsy (Fig. 1). TPE was initiated but without improvement. 3 patients with ncFSGS recurrence have stable allograft function, two of them are treated regularly with TPE. There was no significant difference in age, gender distribution, number or severity of comorbidities, dialysis modality, DGF and immunological matching between the groups with the recurrence of either ncFSGS or cFSGS. All patients with FSGS recurrence received deceased donor allograft. In comparison to cFSGS group, patients with ncFSGS had longer dialysis duration prior to KTx (46±12.28 months vs. 5±1.73 months), cFSGS group had higher urine protein excretion (16.37±20.46 g/dU vs. 4.06±3.84 g/dU; P < 0.001) earlier in the post-transplant period (1.71 months vs. 10.38 months; P < 0.05), which resulted with more severe clinical presentation and early allograft loss (3-6 months posttransplant). As previously mentioned, TPE was successfully employed in 2 patients with ncFSGS, while 2 patients in the cFSGS group did not respond to intensified treatment (response rate 50%).

The main intention of our study was to comprehensively evaluate pretransplant characteristics and outcomes of patients with FSGS treated at our Center. The results are encouraging with 80% of allografts showing satisfactory function and the overall patient survival of 90% during the observed period. The incidence of recurrence was similar (20%) when compared to previous studies (6,15-17). Moreover, Francis et al. showed even better results when studying the largest FSGS cohort by date – only 7.5% of adult population had biopsy-proven recurrent FSGS (18). Unfortunately, in our cohort 3 allografts were lost rapidly due to cFSGS with no response to therapy.

cFSGS is a distinct histological variant of FSGS characterized by the occurrence of heavy nephrotic range proteinuria, progressive deterioration of kidney function and quick evolvement towards ESRD (14). It has been described in native as well as transplanted kidneys, as a recurrent or de novo process, previously linked to possible viral (HIV, parvovirus B19, polyomavirus species) infection (19,23). Swaminathan and colleagues demonstrated that cFSGS represented a more severe

**DISCUSSION**

FSGS is one of the most common causes of primary glomerular disease in adults, its clinical course usually unpredictable and characterized by the sudden onset of nephrotic syndrome followed by the progression towards ESRD (1-4). The pathogenesis of FSGS is not known, and experimental studies so far support the concept of a circulating factor causing podocyte foot-process effacement (12,13). It seems only primary FSGS recurs following KTx, additionally supporting the hypothesis of preexisting immune abnormalities which trigger podocyte injury (8). Because of its high occurrence rate after KTx FSGS remains a challenge and a major frustration among nephrologists worldwide (1,9).

The major intention of our study was to comprehensively evaluate pretransplant characteristics and outcomes of patients with FSGS treated at our Center. The results are encouraging with 80% of allografts showing satisfactory function and the overall patient survival of 90% during the observed period. The incidence of recurrence was similar (20%) when compared to previous studies (6,15-17). Moreover, Francis et al. showed even better results when studying the largest FSGS cohort by date – only 7.5% of adult population had biopsy-proven recurrent FSGS (18). Unfortunately, in our cohort 3 allografts were lost rapidly due to cFSGS with no response to therapy.

**B The hyperplastic podocytes contain numerous intracytoplasmic, red protein resorption droplets (SFOG stain, magnification 400x)**

**Fig. 1. Pathohistology changes seen in patient with early cFSGS recurrence (A and B)**

A The glomerulus shows almost global collapse of the tuft, with hyperplastic podocytes (PAS stain, magnification 200x)
form of disease but provided no evidence of viral involvement in its pathogenesis (24). Although our study is limited by the relatively small size of the cohort (30 cases) which disabled more thorough statistical analysis, the sudden and highly aggressive nature of cFSGS could be clearly seen. cFSGS group had significantly higher protein excretion early posttransplant, resulting in rapid deterioration of allograft function despite prompt diagnosis and targeted treatment. Similar observations were made in the study of Laurin et al., although after adjusting for baseline characteristics and immunotherapy they showed similar long-term kidney survival between the two FSGS variants (25). We did not observe significant difference in age, gender distribution, number or severity of comorbidities, dialysis modality, DGF and HLA matching between the groups. In comparison to cFSGS group and patients without recurrence, patients with cFSGS had shorter dialysis duration prior to KTx which is consistent with findings of previous reports (26,27).

The management of FSGS recurrence includes “empirically” used combinations of high-dose CSA, RTX and TPE aiming the still unidentified circulating factor (6). TPE has been used frequently since the late 1980s, after first studies showing benefits of TPE were reported (27,28). Its efficacy varies, with the average response rate of about 50-60% (15). RTX is not only an anti-CD20 monoclonal antibody but also appears to be a regulator of acid sphingomyelinase activity essential for the expression of receptors and signaling molecules in podocytes (30). Its benefits were noted in 2006 after complete remission of early recurrent FSGS was achieved in a young patient suffering posttransplantation lymphoproliferative disease (31). In the systematic review Araya and Dharnidharka showed that remission occurred in 64% treated with RTX (10). Therapeutic response rate in our cohort was 50%, with TPE successfully employed in 2 patients with cFSGS. 2 patients in the cFSGS group did not respond to intensified treatment (one patient treated with TPE, the other treated with the combination on TPE and RTX). In this light, it is interesting to discuss the case of a young 22-year-old patient (not included in this study), with the first allograft lost due to FGSG recurrence. Insufficient vascular access for dialysis brought KTx as a „rescue“ therapy, but with a major risk of FSGS reoccurring once more. We decided to prepare the patient by doing preemptive PP combined with RTX as induction therapy. Regardless of the carefully planned protocol, he developed nephrotic range proteinuria on day 4 posttransplant. PP were started immediately, along with the second application of RTX on day 7. After the discharge PP had continued twice a week for 3 months until proteinuria declined to non-nephrotic range (0.41 g/dU) and remained unchanged since. Carefully planned pretransplant therapy led to preserving satisfactory allograft function despite early FSGS recurrence confirmed by biopsy.

Finally, the importance of early native kidney biopsy in all patients with suspected renal disease should be emphasized. Glomerulonephritis is the primary cause of ESRD in 30-50% of patients receiving kidney allograft. While constant improvement in immunosuppressive therapy led to decreased number of rejection episodes, it did not affect the occurrence of recurrent or de novo glomerulopathies as the third most common cause of allograft loss during the 10-year period (32-34). Two patients from our cohort did not have precise primary disease diagnosis. One patient was characterized as „chronic glomerulonephritis without biopsy“ and the second as „nephroangiosclerosis“. Nevertheless, they were included in the study. First of all, these were young patients who started hemodialysis shortly after presenting abruptly with marked edema and hypertensive crisis. Secondly, they developed nephrotic range proteinuria within the 3 months posttransplant, with allograft biopsy showing clear signs of FSGS. One patient had nc FSGS variant, positively responding to TPE, while the other was mentioned previously as combined ACR/AHR with cFSGS described after the second biopsy. She lost the allograft 6 months posttransplant, although prompt TPE combined with RTX administration was started. As early recurrence is mainly linked to recurrent FSGS, bearing in mind severity of clinical presentation and quick progression towards ESRD before KTx diagnosis of FSGS as primary glomerulopathy is most likely. De novo FSGS appears fairly late, at a mean of 57 months posttransplant and proteinuria 2.4 g/dU, and is hard to differentiate from chronic allograft nephropathy (35). Thus our future efforts should lead towards precise diagnose of underlying kidney disease and careful choice of posttransplant treatment strategy in order to improve and optimize allograft longevity.

CONCLUSION

Although an increased risk of recurrence exists, kidney transplantation remains the treatment of choice for patients with FSGS. Thorough treatment planning should be made before undergoing KTx, with preemptive TPE and RTX induction as possible options. Urinary protein excretion should be closely monitored on a daily basis in the early posttransplant period and then slowly tapered in the first transplant year when the risk of recurrence is the highest. Immediate allograft biopsy should be performed in all patients developing proteinuria and prompt therapy should be started. Despite no clear evidence, intensive TPE regimen should be started in every patient, followed by
RTX administration in patients showing no response to previous treatment attempts. Sometimes prolonged treatment is needed before achieving remission.

Further studies are needed in order to precisely define FSGS pathophysiology and provide stronger evidence of TPE and RTX treatment benefits.

REFERENCES


Uvod i ciljevi: Povratak fokalne segmentalne glomerularne skleroze (FSGS) u presadak i dalje ostaje važna prepreka u postizanju dugoročno zadovoljavajućih rezultata transplantacije bubrega. Glavni cilj istraživanja bio je procijeniti ishode bolesnika praćenih u našem Centru te raspraviti nove mogućnosti u liječenju ove skupine bolesnika. Ispitanici i metode: U istraživanje su uključeni svi bolesnici (n=30; 33,3 % muškaraca) s dijagnozom FSGS vlastitih bubrega, liječeni transplantacijom u razdoblju od listopada 2007. i listopada 2013. Svi istraživani parametri prikupljeni su iz dostupne medicinske dokumentacije. Rezultati: 29 bolesnika imalo je nekolabirajuću FSGS (ncFSGS), dok je u jednog bolesnika ustanovljena kolabirajuća varijanta bolesti (cFSGS). Kadaverični presadak primilo je 96,7 % bolesnika. Ukupno preživljenje bolesnika tijekom praćenja iznosilo je 90 %. Osamdeset posto bolesnika imalo je zadovoljavajuću funkciju presatka uz medijan preživljenja 49,15 (0,5-84) mjeseci. Incidencija povratak bolesti u presadak bila je 20 % (6/30), a 3 presatka su promptno izgubila svoju funkciju zbog cFSGS. Skupina bolesnika sa cFSGS varijantom izražavala je višu proteinuriju značajno ranije u posttransplantacijskom razdoblju (P <0,05), što se u konačnici odradio težom kliničkom slikom i ranim gubitkom presatka (3-6 mjeseci nakon transplantacije). Terapijskim izmjenama plazme uspješno su liječena dva bolesnika s ncFSGS, dok dva bolesnika s cFSGS varijantom nisu odgovorila na terapiju (50 %-ni odgovor na terapiju). Zaključak: Iako je rizik za povratak FSGS u presadak visok, transplantacija bubrega i dalje je zlatni standard u liječenju bolesnika s FSGS. Neophodno je bez odgađanja učiniti biopsiju presatka u svih bolesnika s razvojem proteinurije kako bi se na vrijeme započela specifična terapija i poboljšao ishod.

Ključne riječi: fokalna segmentalna glomerularna skleroza; transplantacija bubrega; ishod