

Case study

Effective treatment of a post-renal transplantation patient with early recurrent focal segmental glomerulosclerosis and concomitant hemolytic uremic syndrome, a case report

ABSTRACT

While recurrence of primary Focal Segmental Glomerular Sclerosis (FSGS) is common (30%-80%), a concomitant presentation of hemolytic uremic syndrome (HUS) and recurrence FSGS has never been reported. In addition, treatment of recurrent FSGS and HUS post-renal transplantation is challenging; and usually individualized based on center's experience.

Here, we reported a case of a pediatric patient with early recurrence of FSGS and concomitant HUS post-renal transplantation. This patient had a complete hematological and renal response following the administration of Eculizumab and Rituximab, respectively. Both **withdrawal of offending** agent as well as plasmapheresis did not improve kidney function.

Withdrawal of offending agent as well as plasmapheresis did not improve kidney function. Therefore, we concluded that both Eculizumab and Rituximab could achieve remission in comparable cases when administered at fixed intervals.

Keywords: Recurrent Focal Segmental Glomerular Sclerosis; hemolytic uremic syndrome; renal transplantation.

(Note: 1. Case Reports should follow the structure of Abstract, Introduction, Presentation of Case, Discussion, Conclusion, Acknowledgements, Competing Interests, Authors' Contributions, Consent (where applicable), Ethical approval (where applicable), and References plus figures and/or tables. Abstract (not more than 250 words) of the Case reports should have the following sections: Aims, Presentation of Case, Discussion and Conclusion. Only Case Reports have word limits: Papers should not exceed 2000 words, 20 references or 5 figures. Other Type of papers have no word limits.

2. Review papers may have different headings of the sections and are exempted from following these suggestions.

3. Research Papers and Short Notes should follow the structure of Abstract, Introduction, Methodology, Results and Discussion, Conclusion, Acknowledgements, Competing Interests, Authors' Contributions, Consent (where applicable), Ethical approval (where applicable), and References plus figures and/or tables.)



1. INTRODUCTION

Kidney transplantation is the most effective treatment option for End-Stage Renal Disease (ESRD). It provides the best possible outcome with regards to life expectancy and quality of life for ESRD patients (1). However, recurrence of the primary disease following kidney transplantation, such as Focal Segmental Glomerular Sclerosis (FSGS) and Thrombotic Micro Angiopathy (TMA), remains a concern in both pediatric and adult patients (2,3).

Post-transplant nephrotic syndrome after renal transplant is mainly seen in children with FSGS (3). It recurs in 30-80% of all cases, while graft loss is seen in about half of patients with recurrent disease. Most cases of post-transplant nephrotic syndrome occur within the first year of kidney transplant, but they can also occur in the early post-transplant period (4).

Thrombotic Micro Angiopathy (TMA) is an additional complication of kidney transplantation that may occur de novo (PT-TMA) or recur in patients with a previous history of Hemolytic Uremic Syndrome (HUS) (5). The reported incidence of de novo HUS varies (0.8%-14%), as it greatly depends on the definition used (6). HUS is defined in terms of specific clinical features, while TMA is a diagnosis that can only be established on histological examination. The incidence of post-transplant recurrence among HUS ranges from 4-60% (2,5). Recurrent HUS is more common in patients with atypical HUS (aHUS) (>08%) and rarely seen in patients who had developed ESRD caused by Shiga-toxins producing *E. coli* (<1%). The latter has generally favorable renal prognosis, whereas aHUS leads to graft loss in 90% of affected patients, if left untreated (2,5-7).

A concomitant presentation of early FSGS and HUS post-renal transplantation is uncommon and has not been reported in previous literature. Moreover, Treatment of FSGS and HUS post-renal transplantation is challenging and is usually based on single-center experience.

2. CASE HISTORY

A 7-year-old girl with ESRD secondary to steroid-resistant FSGS was admitted to our hospital to undergo a Living Related Renal Transplantation (LRRT). Two years prior to this admission, the patient presented initially with generalized edema. She was received a high dose of Prednisolone (2mg/K) and was in remission after two weeks. After being discharged, she received a daily Prednisolone of 30 mg maintenance dose. Patient was readmitted a few days later due to proteinuria and *E. coli* urinary tract infection. Remission was induced again after three weeks. Despite the high dose of Prednisolone treatment, proteinuria reoccurred, and her response to steroid was poor.

Thereafter, an elective admission was done, and a renal biopsy was taken. It showed FSGS in 12 glomeruli, none of which are globally sclerosed, with mild tubular atrophy and interstitial fibrosis. After that, kidney function started deteriorating and she gradually became anuric. Due to her critical condition, she was eventually admitted to the pediatric ICU where she received continuous renal replacement therapy (CRRT).

After two years of peritoneal dialysis, she received a living donor kidney transplant from her uncle. As per standard of care, an induction with immunosuppressive medications was given which consisted of Methylprednisolone and anti-thymocyte, next to IVIG pre-operation. Immunosuppressive therapy was based on findings of non-direct class II donor specific antibodies (DSA) at 2300 mfi with associated HLA of donor but not direct and known to be less immunogenic as per tissue typing, as well as being complement dependent cytotoxicity assay (CDC) crossmatch negative.

The immediate post-operation graft function was excellent in the first 24 hours with urine output (>20ml/kg/hr) and serum creatinine (45 micromoles/L from > 600 micromoles/L).

However, on the morning of day one, urine dipstick showed 3+ protein as well as blood test showed significant decrease in serum-albumin (16 g/L). During day one urine output decreased sharply to < 2.6ml/kg/hr and she ultimately became anuric. Serial abdominal ultrasound was done to ensure patent graft vascularity and to evaluate free fluid collections which was unremarkable. Laboratory findings indicated severe hemolysis: hemoglobin dropped sharply by >20 gram, decreased platelet count (<50 103/microliter), elevated lactate dehydrogenase (LDH)(400 U/L), very low haptoglobin level (<40 mg/dL) and doubled serum creatinine level (80 micromoles/L). In addition, a repeated flow cross-matching was done to exclude other potential diagnosis such as acute rejection and lymphocyte rejection which produced negative results, with donor specific antibodies being less than 1000 mfi. Also, a lab work-up for TMA was sent to identify the underlying cause of bicytopenia. Laboratory tests for ANCA, Anti-GBM, ANA, Ds-DNA CH50 showed later to be normal; yet C4 and C3 were found to be low.

On the night of day two, Tacrolimus was stopped, and plasmapheresis was initiated to treat for both possible hemolytic uremic syndrome (HUS) and recurrent FSGS. After plasmapheresis, an induction dose of Eculizumab was administered. In addition, pulse therapy of Methylprednisolone was administered for three days. Due to persistent oliguria and alarming laboratory results on day six, she was put on CRRT, and three sessions of plasmapheresis were planned every other day. The second session was aborted because of hemodynamic instability and blood products were transfused. Hereafter, a second induction dose of Eculizumab was given; followed by Rituximab after two days. A total of six Rituximab doses were given, starting with weekly doses due to heavy proteinuria. Spacing the doses of Rituximab and Eculizumab was applied to avoid interactions. Also, routine laboratory tests were done to monitor the effect of Rituximab by evaluating CD19 activity.

A Renogram test was done during the first week post-transplantation; it revealed good perfusion, parenchymal retention, and no signs of urine leakage. Due to the patient's hemodynamic status, biopsy was later taken which was inconclusive.

On day fourteen, the patient started improving and urine production returned gradually back to normal levels. Creatinine levels decreased gradually, and she was discharged with a serum creatinine level of 43 micromoles/L.

3. DISCUSSION

In this case report, the patient showed signs of recurrent FSGS as well as HUS, yet Kidney biopsy was delayed due to hemodynamic instability and severe thrombocytopenia. Based on the clinical picture and laboratory findings, multiple therapeutic plasmapheresis sessions were planned, and the patient underwent the first session without any complications. The second session was, however, brought to a halt due to subcutaneous bleeding from intravenous lines and surgical site. Also, Eculizumab and Rituximab were administered at fixed moments to avoid interactions, which attained a complete response, and no adverse events were reported.

Plasmapheresis and rituximab are the mainstays of treatment for recurrent FSGS. they are commonly applied based on center experience (8-11). Although plasmapheresis is shown to induce remission in many cases with recurrent FSGS post-renal transplantation, controlled trials evaluating the efficacy of plasmapheresis are still missing (12-14). Moreover, early intensive, and prolonged plasmapheresis was found to be effective in treating recurrent FSGS and preventing graft loss without using immunosuppressants as demonstrated in a retrospective study of 29 pediatric kidney transplant patients with recurrent FSGS (15). Pre-emptive plasmapheresis has been also utilized in many centers as a prophylactic strategy in patients with high risk of recurrence with variable rates of success, but large multicenter studies are needed to evaluate the efficacy of pre-emptive plasmapheresis (16-18). In a

retrospective study of 66 patients (19), a preventative therapy with plasmapheresis and/or Rituximab did not decrease the recurrence rate, but prompt treatment of recurrence post transplantation with these therapies resulted in improved outcomes.

Rituximab, a chimeric monoclonal antibody that targets the CD20 receptor on the surface of B-lymphocytes, has been used in the treatment of post-renal transplant recurrent FSGS, with conflicting results (19-25). Several authors reported favorable outcomes when used in combination with plasmapheresis (20,26-28). In other reports, Rituximab therapy was recommended for cases with recurrent FSGS post-kidney transplantation that were not responsive to either the initial treatment, or following plasmapheresis (22,25,29). Other case reports and case series of adult and pediatric patients, with recurrent FSGS post renal transplantation, showed that Rituximab was ineffective and could not induce remission (21,30). Although good response to Rituximab therapy is more common in the pediatric population (>75%) as observed in current reports (22-24,28), most of the reported early recurrences post-renal transplantation were in pediatric patients and fewer adult cases were described. Considering the extreme heterogeneity of the mechanisms leading to PT-TMA and its variable pathologies, a specified course of treatment should be individualized for each patient (31). A stepwise approach was suggested by several authors which depends on diagnosis, as well as patient's response (31-33). This approach starts with reduction or elimination of the offending agent such as Calcineurin Inhibitors (CNI) and Mammalian target of Rapamycin inhibitors (mTORi), by switching from a CNI to a different CNI or to a mTORi. Although many authors have documented full remission of TMA after implementing this strategy (34-37), Satoskar et al found no difference in outcomes (38).

Plasmapheresis with or without intravenous immunoglobulin is the next step in treating patients with PT-TMA. In a case series of 29 patients with biopsy-proven PT-TMA, a graft salvage rate of 80% was achieved by eliminating CNI and applying plasmapheresis (39). In a second case series of 5 patients, a 100% response with no relapse was reported. 4 patients underwent plasmapheresis, 2 were administered Eculizumab and 1 patient Rituximab. All patients experienced CNI withdrawal (34). It has been postulated that plasmapheresis yields favourable outcomes for the following reasons: removal of vasoconstrictors such as thromboxane A2, elimination of mutant complement proteins, and providing deficient factors such as PGI2-stimulating factor and normally functioning complement components (39). However, other authors claimed that the use of plasmapheresis in a large proportion of patients does not improve kidney function and is associated with 20-40% graft loss (40,41).

In a retrospective study of 21 patients with biopsy-proven PT-TMA, the majority (62%) had systemic TMA, whereas a subset had only a TMA localized to the graft (38%) (42). Almost 89% of patients with localized TMA responded to decreasing, changing, or temporarily withdrawing CNI without undergoing plasmapheresis. Also, this study showed no difference in incidence of graft loss between both groups, regardless of whether they had received plasmapheresis (42).

Eculizumab, a fully humanized anti-C5 monoclonal antibody that blocks the generation of the lytic membrane complex. This recombinant monoclonal antibody is shown to be successful in the treatment and prevention of recurrent aHUS after transplantation (43). In PT-TMA, Eculizumab plays a role in the inhibition of the complement system (44), which is shown to be excessively active in PT-TMA patients (45-47). The efficacy of Eculizumab in treating PT-TMA has been only demonstrated in case reports and case series (40,41,48). It has been more frequently used in the treatment of cases unresponsive to plasmapheresis, assisting in the recovery of kidney function, and reducing the risk of graft loss with few adverse effects. In a large case series of 29 patients with PT-TMA, Eculizumab treatment was initiated due to deterioration of renal function and persistent TMA despite treatment of underlying cause and plasmapheresis (41). This study showed rapid resolution of kidney function in 20 patients with >49% decrease in serum creatinine at the last follow-up. In

another large series 22 patients with PT-TMA were subdivided into two groups; 16 with early PT-TMA (<1 month post-transplant) and 6 with late PT-TMA (> 1 month post-transplant) (40). All patients presented with systemic as well as renal manifestations. Almost 77% of early and 100% of late patients received plasmapheresis and achieved complete hematological response but incomplete or absent renal improvement. After administering Eculizumab, complete response was seen in 8 patients and 2 partial responses from the early group. In the late group, 1 complete response and 2 partial responses were reported. In this study, a shorter time interval between diagnosis and the beginning of the treatment was associated with better outcomes. Eculizumab was withdrawn in both previously mentioned studies without relapses (40,41).

A relatively newly emerging therapeutic agent called abatacept has been used in the treatment of both recurrent FSGS and PT-TMA, with conflicting results (28,49-52). It has been speculated to be an effective immunosuppressive agent that allows the withdrawal of offending agents, instead of treating the underlying endothelial injury (32,49,50). This agent appears to be a promising alternative, yet large studies are still lacking.

4. CONCLUSION

This case presented with a rare early recurrent FSGS combined with HUS within the first 24 hours post kidney transplantation. The administration of both Eculizumab and Rituximab at regular intervals resulted in the complete resolution of graft function and complete hematologic response. Conversely, plasmapheresis appeared to be ineffective and non-tolerable. However, effectiveness of both agents is yet to be established in large, controlled studies

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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