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Case Report

A case report on usage of rituximab on complicated steroid-dependent nephrotic syndrome

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ABSTRACT

Nephrotic syndrome (NS) is one of the common yet challenging childhood disease. Treating NS with immunosuppressants like corticosteroids is typically effective. However, there are significant evidences which displayed resistance patterns to the former drugs. Here in this case, a male patient came to the nephrology department with the history of steroid dependant nephrotic syndrome with complaint of its infrequent relapse. The condition was complicated since, the patient was on multiple steroids even after which there were recurrent episodes of syndrome. Considering the status, Mycophenolate mofetil was added as a supportive treatment for the management of the disease along with steroids, still the outcome was unremarkable. Hence, rituximab was ordered (four cycles). The outcome this time was appreciable, rituximab administration produced a positive result. No events were recorded during the treatment duration.

Keywords: Nephrotic syndrome, Immunosuppressants, Relapse, Resistant patterns

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is considered to be one of the most common chronic glomerular diseases in children. A total of 80-90% of patients with childhood idiopathic nephrotic syndrome achieves remission with steroid therapy (steroid-sensitive nephritic syndrome (SSNS)). However, approximately 50% of children with SSNS develop frequently relapsing nephritic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS). About 20% of children who are receiving immunosuppressive agents still show frequent relapses or steroid dependence during or after treatment, which can be defined as complicated FRNS or SDNS.¹

Treatment of steroid-dependent nephrotic syndrome, particularly in patients who have failed to respond to multiple immunosuppressive drugs, remains challenging.²

Corticosteroids have been the main treatment for decades and are effective in most children with INS but, about 15% of these children become resistant to steroid. There might have an increased risk of developing steroid toxicity in sensitive children who are receiving steroids yet frequently relapse occurs where alternative immunosuppressive medicines such as cyclophosphamide, mycophenolate mofetil (MMF) and calcineurin inhibitors (CNIs) can be used to induce and/or maintain remission of INS and hence helps in improving their clinical course.

Among the immunosuppressive agents Rituximab, a chimeric anti-CD20 monoclonal antibody that was originally developed to treat patients with B-cell non-Hodgkin's lymphoma, but it also showed significant benefits in children and adults with a variety of renal disorders, including vasculitis, lupus nephritis, and NS is currently used for treating SSNS.³ Although the exact

mechanism(s) underlying primary NS is not yet well-established, however earlier studies suggested that podocyte foot process effacement and heavy proteinuria occurs when T cells becomes the main effector cells. However, more recent evidence suggests that B cells may play a previously unrecognized yet significant role in the development of INS.⁴

CASE REPORT

A 5 years old male child came to department of nephrology with a known case of SDNS frequent relapse and last relapse was on November 2019. On the day of admission patient's vitals were recorded as- blood pressure (BP) 100/70 mmHg and pulse 116 bpm. Upon laboratory investigation it was found that patient's hemoglobin, packed cell volume, platelet count and erythrocyte sedimentation rate (ESR) were abnormal. Urine analysis showed abnormal counts in serum creatinine (0.2 mg/dL), serum albumin (2.7 g/dL), total serum protein (5.6 g/dL) and also protein and creatinine ratio spot urine (9.07) which signifies proteinuria. The child was currently on steroid regimen (tablet prednisolone) with calcium and vitamin D3 supplements.

The past history shows that the child was diagnosed on December 2018 as SDNS at the age of 2 (protein ~4 g/dL) and was on steroid regimen which is tablet prednisolone 15 mg once daily (in morning) till the urine albumin is negative and then the dose was reduced to 10 mg OD for 2 weeks and then further reduced to 7.5 mg OD for another 2 weeks followed by 5 mg OD daily till the next review. But when the dose of steroid was tapered, patient's condition relapsed (protein ~4 g/dL and lower limb edema) and therefore it was necessary to start the use of tablet levamisole 50 mg once daily every alternative days on April 2019 with the steroid regimen (Prednisolone 10 mg OD for 2 weeks then 7.5 mg OD till next review) with routine spot urine analysis.

As previously mentioned, as the dose was tapered, patient was seen with oedematous condition in face and lower limb (protein >4 g/dL and edematous face). Thus, the patient was advised on July 2019 to start with Mycophenolate mofetil (MMF) therapy, where patient received MMF at a dose of 250 mg twice daily orally with steroid regimen. Tablet prednisolone was initially given at a dose of 25 mg OD in first week, 20 mg OD dose at second week and 15 mg OD dose till next review was planned along with the routine spot urine tests. During the next visit the nephrologist reduced the dose of Prednisolone to 12.5 mg OD for 2 weeks followed by 10 mg OD till next review along with Pantoprazole and calcium supplement. On October 2019, as urine protein was <3.5 g/dL, Prednisolone dose was further reduced to 7.5 mg OD for 2 weeks followed by 7.5 mg OD for 2 weeks and 5 mg OD till next visit along with tablet MMF 250 mg BD, pantoprazole and calcium supplement.

On January 2019, the patient was seen with relapse of condition like edematous face and lower limbs and thus was admitted in Apollo Children's hospital. Since relapse was seen with MMF therapy, the nephrologist planned to start with injection rituximab at a dose of 350 mg/m² weekly once with a total of 4 cycles. Medicines like injection Avil 1 mL intravenous (IV) STAT, injection hydrocortisone 50 mg IV STAT, tablet paracetamol 350 mg per oral (PO) STAT/SOS, nebulizer budesonide 0.5 mg and nebulizer levofololol 0.63 mg given as STAT 1 hour prior to the rituximab therapy as a prophylaxis therapy. Injection Rituximab 300 mg (Based on patient BSA) has been mixed with 300 mL of normal saline (NS) for dilution. The total of 300 mg in 300 mL NS was administered as 10 mL/hour at 1st hour, 20 mL/hour at 2nd hour, 30mL/hr at 3rd hour, 40 mL/hour at 4th hour, 50 mL/hour for next 4 hours to bring up 300 mL over 8 hours. No events were recorded during the treatment duration.

DISCUSSION

In patients with steroid-dependent nephrotic syndrome, treatment remains quiet challenging especially for those who experience failure responding to multiple immunosuppressive drugs. Also, NS is considered to be more seen in Asian children rather than in American and Caucasian children.³ As per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines states that if a patient is having Urine protein >3.5 g/d and serum albumin ≤2.5 g/dl with edema then the patient can be said to have NS.⁵ For the current case as the steroid dose was tapered, the urine protein was seen to be >3.5 g/dL in multiple occasions and hence concluded as Complicate SDNS and started steroid regimen protocol.

In earlier studies it was clearly mentioned that levamisole is well tolerated with minimal side effects in patients who are having NS.⁶ As the dose of steroids tapered, relapse seen and was forced to initiate tablet levamisole 50 mg given OD.

Rituximab, an anti-CD20 monoclonal antibody, has been successfully used in the last decade to treat patients with refractory NS, including SDNS.⁷⁻⁹ However, the place of RTX in the treatment of SDNS remains to be established because of the low quality of evidence according to the recently issued clinical practice guideline for kidney diseases by KDIGO5 where it suggested that RTX can be considered only in children with SDNS, who have continuing frequent relapses despite optimal combinations of prednisolone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy.¹⁰

Case series report that RTX has considerable efficacy against childhood SDNS, although many patients tend to relapse within 1 year consistently with the re-emergence of B cells if receiving RTX at a dose of 375 mg/m² BSA once weekly for 4 weeks.¹¹

It appears that RTX is a very effective drug for childhood SDNS or FRNS to maintain remission (average duration of remission is 12–20 weeks based on previous studies), which reduces the frequency of relapses and enables the reduction or discontinuation of corticosteroids and other immunosuppressive agents. It may also be more cost effective than taking a daily medication with all of its needed monitoring and may contribute for improving the growth of children.¹²⁻¹⁴ Four weekly doses of RTX may improve the chances of response by compensating for the amount of medication lost in the urine in some children with NS (90). However, several studies have demonstrated no significant difference in the response rate in children between 1 and 2 doses versus three to four doses.¹⁵

CONCLUSION

Idiopathic NS is one of the most frequent glomerular diseases in childhood. Although most cases respond to steroid treatment, approximately 40% of children with NS develop refractory NS. These patients are commonly treated with immunosuppressants, such as cyclosporine-A, cyclophosphamide, mizoribine (MZB) and MMF. However, the immunosuppressants used are having significant adverse effects in children and hence it is difficult to use for a prolonged duration in children. RTX is an effective and increasingly used as a treatment option to induce or prolong clinical remission of NS in children. Although the exact mechanism is unknown, RTX may very well exert its beneficial effects through multiple mechanisms of action. There is now growing evidence for supporting its safety and efficacy in children with SDNS or FRNS in inducing prolonged remission, which enables in reduction of corticosteroid exposure and its side effects. Also, these immunosuppressive agents such as MMF and calcineurin inhibitors has been proven to be effective in children with SDNS, they need to be taken twice daily to maintain remission. Thus, using an IV medication such as RTX may prove additionally valuable in children where adherence to medications is in question.

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