CASE REPORT

An unusual cause of severe persistent neutropenia in a child with nephrotic syndrome

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SUMMARY

A 5-year-old boy presented with neutropenia 9 weeks following the administration of rituximab for management of his steroid-dependent nephrotic syndrome. Extensive investigations failed to identify any underlying cause. In keeping with adult reports, rituximab was thought to be the likely cause for this 'late-onset' neutropenia (LOP). He was treated successfully with granulocyte-colony-stimulating factor. Patients treated with rituximab need to be carefully monitored for LOP.

BACKGROUND

Nephrotic syndrome (NS) is one of the commonest paediatric renal conditions managed by general paediatricians and paediatric nephrologists. Although most cases respond to standard steroid treatment, some cases can prove challenging due to steroid resistance, steroid dependence and the side effects of medications used. Rituximab has recently gained popularity for the treatment of difficult cases of NS, especially steroid dependent NS. Our patient developed late-onset neutropenia (LON) following rituximab infusion. He developed neutropenic sepsis and required hospital admission, intravenous antibiotics and granulocyte-colony-stimulating factor (G-CSF). We report the first case of LON following the use of rituximab in the paediatric age group. Also, in contrast to previous reports in adult literature that suggest that LON associated with rituximab is clinically benign, our patient had clinically significant consequences of LON. With the increasing use of rituximab for various indications within the paediatric population, clinicians using this relatively new drug need to monitor blood counts to detect this complication which can be clinically significant and can occur weeks after rituximab is administered.

CASE PRESENTATION

A 5-year-old Asian boy presented with typical features of NS with generalised oedema, heavy proteinuria, hypoalbuminaemia and hypercholesterolaemia. He had normal serum complement levels and negative antinuclear antibodies. A clinical diagnosis of NS was made. Following the commencement of oral prednisolone at 60 mg/m² daily, he achieved remission after 10 days. He developed a clinical relapse of NS following the reduction of prednisolone to 40 mg/m² on alternate days and failed to achieve remission following 4 weeks of high-dose daily oral prednisolone at 60 mg/m² daily. A percutaneous ultrasound-guided renal biopsy was performed which showed minimal change disease. He achieved

remission soon after receiving 3 days of intravenous methyl prednisolone at 600 mg/m² daily.

Unfortunately, this period of remission was not sustained and he was treated sequentially with steroid sparing agents including oral cyclophosphamide at 3 mg/kg/day for 8 weeks and then mycophenolate mofetil at 600 mg/m² twice a day for 5 weeks, but failed to maintain a sustained period of remission. He was therefore commenced on oral cyclosporine A but developed marked increase in body hair, gum hypertrophy and systemic arterial hypertension as side effects of cyclosporine therapy. Elevated blood pressure was controlled with a single antihypertensive agent, and cyclosporine was substituted with tacrolimus to alleviate these 'cosmetic' side effects of cyclosporine therapy. Tacrolimus and alternate day prednisolone therapy failed to maintain him in sustained remission and he was therefore given two doses of rituximab at 750 mg/m² per dose, administered at fortnightly intervals as part of our unit protocol. He was in relapse at the time of administration of the first dose but achieved remission 4 days prior to the second dose of rituximab. He continued on tacrolimus and alternate day steroid therapy following this and was able to reduce the dose of his steroids by a third from 30 mg on alternate days to 10 mg on alternate days over the following 4 weeks.

At the time of a routine clinic review, while in remission, 63 days following the second dose of rituximab, he was found to have a neutrophil count of $0.8 \times 10^9/l$. His haemoglobin was 10.3 g/dl, total white cell count was $3.6 \times 10^9/l$ and platelet count was $457 \times 10^9/l$. The peripheral film confirmed neutropenia but with no other abnormal findings. The CD19 count was 18 cells/ μl . Neutrophil count prior to rituximab therapy was in the range of $2.6\text{--}8.8 \times 10^9/l$. Tacrolimus was stopped 9 days following the diagnosis of neutropenia. He was managed as an outpatient and given general advice relevant for patients with asymptomatic mild neutropenia. The family was advised to contact the hospital promptly if he became unwell or developed fever.

Fourteen days following the initial finding of neutropenia, he developed fever and vomiting.

INVESTIGATIONS

Blood and urine cultures were sterile, but he remained febrile over the following 10 days. His total white cell count ranged from 2.9 to $4.9 \times 10^9/l$, and his neutrophil count ranged from 0.1 to $0.9 \times 10^9/l$. There were no abnormalities of white cell morphology on peripheral blood film.

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Haemoglobin and platelet counts remained normal. The CD19 count was 8 cells/ μ l (representing B-cells), CD3 count was 1578 cells/ μ l (representing T-cells), direct antiglobulin test was negative and there were no detectable serum granulocyte-specific and antilymphocyte antibodies to suggest auto-immune neutropenia.

TREATMENT

He was admitted to hospital, underwent a septic screen and was treated with intravenous antibiotics co-amoxiclav and gentamicin. He was given a single dose of G-CSF 83 days following the second dose of rituximab.

OUTCOME AND FOLLOW-UP

Twenty-four hours following G-CSF, his neutrophil count improved and has remained at normal levels since. He was discharged home while in remission on low-dose prednisolone.

At the time of a clinical relapse 53 days following recovery of his neutrophil count, his CD19 count was 29 cells/ μ l at the time, suggesting that the effect of rituximab had diminished. He achieved remission following the commencement of oral prednisolone at 60 mg/m² daily, in 7 days. He currently remains steroid sensitive and is currently in remission on tacrolimus and low-dose prednisolone.

DISCUSSION

NS has traditionally been considered a T-cell-mediated disease, although its pathogenesis is now thought to involve both T and B lymphocytes.¹ Rituximab, a chimaeric monoclonal antibody against CD20 lymphocytes, has gained increasing popularity for the management of severe steroid-dependent NS in children.²⁻⁵ The results are less encouraging in cases of steroid-resistant NS.^{2,4}

The adverse effects of rituximab are usually mild and transient. One multicentre trial reported adverse reactions in 10 out of 22 cases,² given rituximab as a treatment for a steroid-dependent or steroid-resistant but cyclosporine-sensitive NS. Five patients had mild effects including cutaneous eruptions, abdominal pain, headache and mild hypotension that did not necessitate the cessation of drug infusion. One patient had transient atrial arrhythmia during the first infusion, not requiring treatment, and that did not reappear with subsequent infusions. Two other patients had malaise and bronchospasm.² Transient neutropenia was reported in one patient, although the interval following rituximab infusion is not described.² This was not associated with bacterial infection, and the same patient went on to develop *Pneumocystis carinii* pneumonia later on, while on steroids and tacrolimus. Eight other patients had hypogammaglobulinaemia attributed to rituximab in four patients.²

Another study of 22 cases with NS⁶ reported dizziness, tachypnoea and tachycardia, necessitating cessation of the infusion and restarting at a lower dose in two patients. They also reported unusual side effects like hepatic cytolysis, gastroenteritis, peripheral venous thrombosis, transient thrombocytopenia and fever without an identifiable source in one patient each. One patient developed neutropenia 2 weeks following the second infusion requiring 3 days of granulocyte macrophage-colony-stimulating factor for neutrophil recovery.

Rarely, more serious and sometimes fatal adverse effects can occur following rituximab. Severe pulmonary complications have been reported in 62 cases in the literature.⁴ Almost all subjects (60/62) had pre-existing respiratory problems. Interestingly, of the two children with pulmonary complications, both had NS, which raises the possibility that this group of patients may be more susceptible to this particular adverse effect. One

14-year-old boy had interstitial pneumonitis, which was successfully treated with prednisolone and antibiotics,⁷ and the other developed pulmonary fibrosis 3 days following rituximab infusion and died later despite extracorporeal membrane oxygenation.⁸ Some authors therefore suggest that a pre-treatment chest x-ray screen be used and to avoid rituximab in patients with pre-existing respiratory problems.⁴

Concerns have also been raised regarding the reactivation of JC virus and progressive multifocal leucoencephalopathy in patients who have received rituximab therapy. As the incidence of this complication is currently unknown, some authors recommend careful clinical monitoring with spinal fluid analysis if indicated.²

Side effects involving the haematopoietic system secondary to rituximab have been reported extensively in adult literature. These reports primarily involve adult patients with haematological malignancies such as B-cell lymphoma and chronic lymphocytic lymphoma who have received rituximab therapy as part of their management.⁹ These reports define LON as a neutrophil count $\leq 1 \times 10^9$ cells/l, at least 4 weeks following the administration of rituximab, without any other identifiable cause. The reported incidence in these studies is between 6% and 27%, and the time to develop LON can vary from 70 to 191 days following rituximab.^{9,10} LON secondary to rituximab has also been reported in rheumatological patients with recovery after a median of 6.5 days and low risk of recurrence of neutropenia on re-challenge.¹¹

Various mechanisms have been proposed. These include anti-neutrophil antibody production and expansion of T-cell large granular lymphocyte population leading to apoptosis of neutrophils.⁹ Some authors⁹ have investigated the role of stromal-derived factor-1 (SDF-1), which is a chemokine having a central role in both early B-cell lymphopoiesis and neutrophil egress from the bone marrow. It has been proposed that during B-cell recovery following rituximab treatment, SDF-1 is consumed, and this delays/prevents its availability for neutrophil egress from the bone marrow causing neutropenia. Another proposed mechanism suggests haematopoietic competition between B-cell lymphopoiesis and granulopoiesis, favouring the former.⁹

Our patient developed neutropenia 63 days following the second dose of rituximab. At the time of the initial finding of neutropenia, he was asymptomatic and in remission from his NS while taking tacrolimus and alternate day prednisolone therapy. Fourteen days later, he was unwell with fever. Importantly, signs of overt sepsis including high-grade fever and vomiting developed several days following neutropenia, suggesting that the cause of neutropenia was not sepsis but that sepsis resulted because of prevalent neutropenia.

He had no evidence of auto-immune neutropenia and he responded to G-CSF and has maintained a normal neutrophil count since. In the absence of any other identifiable process, we believe our patient developed LON secondary to rituximab. Apart from the two cases of early-onset neutropenia (with transient thrombocytopenia) described previously,⁶ only two other cases of haematological side effects in children who received rituximab have been reported. These children received rituximab as part of their management of autoimmune haemolytic anaemia (AIHA).¹² The first patient was diagnosed with AIHA as part of autoimmune lymphoproliferative syndrome type 1 at 3 months of age. He was treated with steroids and cyclosporine for 18 months before he received four doses of rituximab over 4 weeks. One week after the last dose, he developed fever, hepatosplenomegaly and lymphadenopathy and was found to be neutropenic. He responded to antibiotics and 3 doses of G-CSF,

and the neutrophil count returned to normal 9 days after the onset of fever. The second patient was a 3-year-old boy with AIHA who received 15 packed cell transfusions and intensive steroid treatment followed by 3 doses of rituximab over 3 weeks. One week after the last dose, he developed thrombocytopenia and epistaxis. He was given one platelet transfusion, and a week later, his blood counts returned to normal. These patients developed thrombocytopenia and neutropenia 7 days following rituximab infusion¹² and thus not LON by definition.

Learning points

- ▶ Our patient with nephrotic syndrome developed clinically significant late-onset neutropenia (LON) following rituximab infusion. This is in contrast to previous reports and suggests that LON may have serious adverse clinical outcomes. Our patient developed clinical sepsis and required intravenous antibiotics and granulocyte-colony-stimulating factor.
- ▶ With the increasing use of rituximab for various indications within the paediatric population, we recommend monitoring of blood counts several weeks following infusion, particularly if the patient is travelling or has fever of unknown cause.

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Competing interests None.

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