

A case of autoimmune haemolytic anaemia achieving complete response with rituximab

Maha Dev, Naureen Mushtaq, Ali Faisal

Abstract

Autoimmune haemolytic anaemia is characterised by the formation of auto-antibodies that bind to the erythrocyte surface membrane, leading to haemolysis. It is the main cause of acquired extracorporeal haemolysis in children. It can be classified according to the characteristic temperature reactivity of the red blood cell auto-antibody in warm-antibody autoimmune haemolytic anaemia (reacting at 37°C) and cold-antibody autoimmune haemolytic anaemia (reacting optimally at lower temperature). Glucocorticoids and/or intravenous immunoglobulins are the mainstay of treatment in majority of patients with warm autoimmune haemolytic anaemia, but when these treatments fail, patients often require cytotoxic drugs or splenectomy. Rituximab, an anti-CD 20 monoclonal antibody, has gained widespread acceptance in the management of B-Cell malignancies. Additionally, it has been used to treat the disorders associated with auto-antibody production. We describe a 9-year-old boy with warm autoimmune haemolytic anaemia resistant to the standard treatment who was successfully treated with Rituximab.

Keywords: Autoimmune hemolytic anaemia, Rituximab.

Introduction

Autoimmune haemolytic anaemia (AIHA) is an acquired clinical condition characterised by the production of antibodies that bind to the surface of circulating erythrocytes, leading to haemolysis, and shortened red blood cell (RBC) survival with elimination by the reticuloendothelial system. The estimated yearly incidence of AIHA is 1-3 per 100,000 persons in the general population.¹ AIHA occurs slightly less frequently in children than adults, but is not rare in the paediatric population, particularly in the early years of life when it can develop following viral infections and vaccinations.² The hallmark of this group of diseases is the positive result

of the direct antiglobulin test (DAT), which detects a coating of immunoglobulin or components of complement on the RBC surface. Sometimes free antibody can be demonstrated in the serum (indirect Coombs test).³ In suspected cases of AIHA, a positive DAT is predictive in 83% of patients, but not all cases of AIHA are DAT positive. Special tests like surface immunoglobulin-A (IgA) using gel card testing are required to detect the antibody in cases of "Coombs-negative" AIHA.²

Warm auto-antibodies are responsible for up to 70% of AIHA cases.⁴ In warm-antibody AIHA, Immunoglobulin-G (IgG) antibodies opsonise RBCs and are predominantly cleared in the spleen being recognised by mononuclear phagocytic cell Fc receptors (extravascular haemolysis).⁵

For some authors, infectious causes of AIHA predominate in children.^{6,7} For others, most cases of AIHA are primary.^{7,8} The underlying pathogenic mechanisms are poorly individualised.

In acute phases, haemolysis may be life-threatening. In chronic phases, immunosuppressive treatments are not consistently effective and may have major, life-threatening, secondary effects.⁹

Glucocorticoids decrease the rate of haemolysis by blocking macrophage function, decreasing the production of auto-antibodies and perhaps enhancing the elution of antibody from the RBCs.³ When haemolytic anaemia remains severe despite glucocorticoid therapy, or if very large doses are necessary to maintain a reasonable haemoglobin (HB) level, intravenous immunoglobulin (IVIg) may be tried.

Rituximab, a monoclonal antibody that targets B lymphocytes, the source of antibody production, has been useful in chronic cases refractory to conventional therapy.³ Experience on the use of Rituximab in AIHA has been mostly limited to smaller series.

We are reporting the case of a 9-year-old boy with AIHA who responded successfully to Rituximab. The patient is still in remission at 10 months following treatment.

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Division of Pediatric Hematology and Oncology, Department of Pediatric and Child Health, Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Naureen Mushtaq. Email: naureen.mushtaq@aku.edu

Case Report

A previously healthy 9-year-old boy presented to the emergency department (ED) in March 2012 with history of fever, pallor and lethargy for the preceding two weeks. His medical history was non-contributory. There was no family history of haematological problems or autoimmune disorders.

The physical examination revealed severely pale, icteric and febrile (38.5°C) young boy with height and weight at 50th centile. He was having no rashes but hepatosplenomegaly. His laboratory reports revealed a profound anaemia with haemoglobin (Hb) 3.9g/dl, RBC $1.21 \times 10^{12}/L$, MCV 103 fL, Reticulocyte count 24.4%, white blood cells (WBC) $7.3 \times 10^9/L$ and platelets $169 \times 10^9/L$. The peripheral blood film showed dimorphic picture with polychromasia, nucleated RBCs and spherocytes. Direct antiglobulin test was strongly positive. Total bilirubin levels were 2.3mg/dl with a direct fraction of 0.4mg/dl. His malarial parasite (MP) and MP-ICT were negative. The results of antinuclear antibody (ANA), ASMA, AMA and anti-dioxyribonucleic acid (anti-DNA) were negative. Serum C3 was mildly low 0.74 g/dl (Normal range 0.79-1.52 g/dl). Serology for CMV, HIV, EBV and Mycoplasma pneumonia were negative. Urine detail report (DR) showed trace haemoglobinuria. He was given the least incompatible packed red cell volume transfusion and was started on intravenous (IV) Methylprednisolone 4mg/kg/day. In 72 hours, he became afebrile and maintained Hb of 9.5g/dl. He was switched to oral Prednisolone 2mg/kg/day for 5 days. In follow-up, his Prednisolone was tapered off successfully over a period of 3 weeks and he maintained Hb/Hct in the range of 10-12g/dl in his fortnight clinic follow-up.

He remained well for the following 3 months, but then again developed fever and his Hb dropped to around 7g/dl. He was restarted on Prednisolone for 3 days and then tapered off over 3 weeks. Again after 4 months of the second episode of the illness, he became profoundly anaemic with a febrile illness and Hb dropped to 4.5g/dl. He was re-started on IV Methylprednisolone for 3 days and then oral Prednisolone, but he continued to haemolyse for about a week. On 10th day of admission, he was started on IV Rituximab 375mg/m² as he was not responding early on steroids this time. The other option was IVIG but its response is usually short-lived and is costly as well, so his family agreed on IV Rituximab after understanding the risk of increased infection. He received a total of 4 doses of Rituximab once a week for 4 weeks. Thereafter, he is being followed up in clinic initially weekly and then monthly. Post-Rituximab, in the last 12 months, he has maintained Hb in the range of 10-12g/dl despite a few febrile episodes of upper respiratory tract infection.

Discussion

B- or T-lymphocyte-mediated autoimmune disorders may lead to clinical disease characterised by low blood cell counts. The term autoimmune cytopenias has been collectively applied to this heterogeneous group of disorders. Most autoimmune cytopenias are rare diseases, making it difficult to perform randomised trials. The literature on Rituximab therapy for autoimmune cytopenias is growing rapidly. Nevertheless, the low prevalence and incidence rate of most of these diseases makes it difficult to perform large, prospective studies that can underpin evidence-based guidelines.¹⁰

Rituximab, IVIG, immunosuppressive drugs and danazol have been shown to be effective in refractory AIHA and in poor surgical candidates for splenectomy.¹¹ The use of Rituximab is currently limited in non-Hodgkin Lymphoma and in autoimmune haematological disorders, partly because it is not an approved indication for the usage and also because of the cost. However, based on the encouraging results from various recent studies, rituximab has been successfully used in an off-label setting in a wide range of clinical disorders.¹²

Conclusion

As a single agent, Rituximab was effective and safe in the context of a life-threatening and fulminant warm antibody AHIA that had been resistant to glucocorticoids. With the use of Rituximab, the more aggressive modes of treatment, such as splenectomy and the use of cytotoxic drugs, could be avoided.

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