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RITUXIMAB in Lupus Related Autoimmune Haemolytic Anemia

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Abstract: ***The treatment of choice of warm antibody Autoimmune Hemolytic Anemia is still corticosteroids. While many centres have now adopted rituximab as the 2nd line agent over splenectomy, there is also data on upfront use of rituximab in Autoimmune Hemolytic Anemia / Idiopathic Thrombocytopenic Purpura. We report a case for the role of Rituximab in a patient of adult autoimmune haemolytic anaemia who was refractory to the conventional corticosteroid therapy. We have used rituximab early on in our patient with good response.***

Keywords: Rituximab, Lupus, Autoimmune Haemolytic Anemia

1. Introduction

Rituximab is a B cell depleting agent used in a variety of rheumatological and immunological disorders like Systemic Lupus Erythematosus, Rheumatoid Arthritis, Sjogren's Syndrome and inflammatory eye diseases. It is usually given as a second line therapy for refractory cases, or used as a steroid sparing agent.

Autoimmune Hemolytic Anemia (AIHA) is a rare, but serious haematological disorder. AIHA should be suspected in the setting of laboratory abnormalities of anaemia associated with increased serum unconjugated bilirubin, increased lactate dehydrogenase, increased reticulocyte count and reduced haptoglobin. The direct Coomb's test is typically positive and usually is mediated by warm-reacting IgG anti-erythrocyte antibodies. There are studies that have reported an association between AIHA and the presence of anti-cardiolipin antibodies [1]. AIHA can be the first presenting manifestation of SLE, and may predate other manifestations by years [2].

This report describes the case of a 20 year-old girl presenting with severe anaemia. On, further evaluation she was found to have SLE related AIHA. AIHA is the most common haematological manifestation of paediatric SLE [3]. This was an unusual case of AIHA where rituximab was used early on.

2. Case Report

A 20 year-old lady was admitted with the complaints of easy fatiguability, dyspnea on exertion (NYHA grade 3) and palpitation, which were insidious in onset, but progressive in nature over a period of 7-8 months. These were associated with off and on mild grade fever and yellowish discolouration of eyes and urine since the last one month. On examination, she had severe pallor (grade 3), mild pedal edema with facial puffiness, lemon-yellow sclera, and ejection systolic murmur on cardiovascular examination.

Table 1: Showing lab investigations on admission

Hemoglobin	2.1gm%
Total bilirubin (<0.8mg/dl)	3.1mg%
Unconjugated bilirubin (0.2-0.8mg/dl)	2.1mg%
LDH (140-280U/L)	334
Reticulocyte count (<2.5%)	16%
DCT	+ve
ICT	+ve
Urea (7-30mg/dl)	23mg%
Creatinine (0.6-1.1mg/dl)	0.9mg%
Urine routine / micro	No RBC, no proteinuria / casts
ANA by IIF	3+ speckled with SSA pattern
ANA blot	Anti dsDNA+, Anti-Sm+, Anti-histone+
Peripheral smear	Tear-drop cells & polychromasia

Her ANA blot was suggestive of connective tissue disease - SLE most likely, and was referred to Rheumatology department for further management with a working diagnosis of SLE with AIHA.

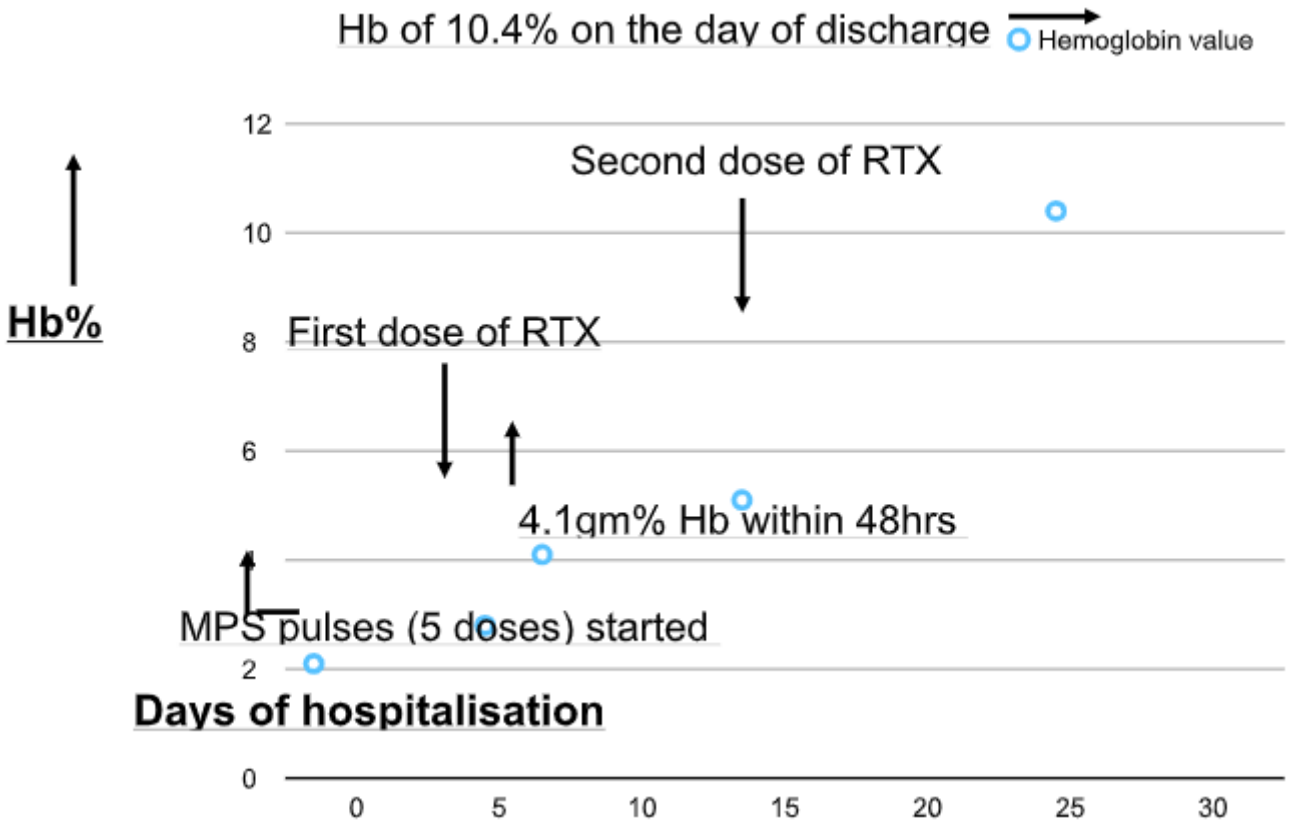

Figure 1: Showing the progress of Hb% with treatment during hospitalisation.

Over the next 5 days, 5 doses of methylprednisolone (500mg) were given, but her haemoglobin did not improve significantly (rose to only 2.8 mg%). She was considered for Rituximab (500mg). 48hrs after the first dose of RTX, her haemoglobin rose to 4.1gm%.

One week later, 2nd dose of RTX (500mg) was given and she was discharged the following day with a haemoglobin of 5.1gm%. She was discharged on oral prednisolone 40mg/day and Azathioprine 50mg BID. She was followed up in the OPD on day 19th from the 1st dose of RTX with a haemoglobin count of 10.4gm%. At this visit, her prednisolone dose was reduced to 20mg/day (and we planned to stop oral steroids within a month) and azathioprine was stopped. At last follow up, almost 6 months after the RTX infusions, she has been maintaining remission on only Hydroxychloroquine.

3. Discussion

For the diagnosis of AIHA, the initial approach should be the same as that of any other haemolytic anaemia i.e. elevated haptoglobin, lactate dehydrogenase and indirect bilirubin, together with finding of reticulocytosis on peripheral smear examination. Coomb's test should be used to determine the cause of hemolysis as autoimmunity, although one should keep in mind that a positive result may be seen in warm antibody positive individual without hemolysis, so always order the test after the diagnosis of hemolysis has been established. Identification of the type of antibody responsible for haemolysis must be done ideally, i.e. whether it is warm-acting-AIHA or cold-acting-AIHA based on the optimal temperature of antigen-antibody reactivity.

Clinically, patients with SLE-related AIHA must also be observed for the development of thrombocytopenia to rule out Evan's syndrome [4].

The ACR and SLICC criteria recognise AIHA with reticulocytosis as one of the criteria for the classification of SLE, while the SLICC criteria also include a positive Coombs test as a criterion. Antierythrocyte antibodies in SLE are mainly warm-type IgG. Anti-phospholipid antibodies associate with Coombs-positive haemolytic anaemia in patients with SLE [5]. Anticardiolipin antibodies, IgG and IgM, are more common in patients with SLE with AIHA [6]. Comparative study, provided evidence delineating the role of aCL antibody in AIHA [7]. Other antibodies like antiband 3 IgG antibodies are believed to be involved in removal of aging erythrocytes from the circulation in healthy individuals [8]. But it remains to be proven if these have any association with AIHA or/and in patients with SLE and the antigen specificity of these also is not known.

Another observation is that there is an under expression of CD55 and CD59 on the erythrocytes of patients with SLE - related AIHA [9]. These membrane proteins protect the erythrocytes against complement-induced cell lysis. Similarly other associations have been found, but still no conclusions can be drawn regarding antigen specificity of anti erythrocyte antibodies.

Corticosteroids remain the first line of therapy [10, 11], effective in 70-80% of patients. According to Roumier, et al [11], about 63% of patients remain steroid dependent. This leads to cumulative toxic side effects of corticosteroids like obesity, cardio-vascular morbidities, osteoporosis and osteonecrosis in a majority of patients. Splenectomy was considered as the preferred second line of treatment before the era of B-cell depleting agents like rituximab. But as experience with rituximab increases, it is replacing splenectomy as the preferred second line therapy in view of lesser side effects like sepsis and venous thromboses [11].

Other immunosuppressive agents which have been tried in the past are azathioprine [12], mycophenolate mofetil [13], more commonly than cyclophosphamide [14] which is usually kept as 3rd or 4th line of therapy only in non-responders to any other immunosuppressive agents.

We searched literature for the clinical trials done for rituximab in AIHA. The two relevant RCTs have been enlisted in table 1.

Table 1

First author; (year of publication)	Arms of the study	Number of patients in each study group	Response rate
Michel M, et al; (2017) [15]	RTX v/s placebo	16 (RTX) v/s 11 (placebo)	75% v/s 45%
Birgens H, et al; (2013) [16]	RTX + prednisolone v/s Prednisolone (monotherapy)	32 v/s 32	75% v/s 36%

In RAIHA trial [15], patients received 1000mg of RTX, 2 weeks apart, who had previously received corticosteroids for <6 weeks (at least 2 weeks), at a dose of 1mg/kg/day. Response rate seen was 75%. Birgens H, et al (2013) [16] showed similar response rates (75%) in another phase III RCT by comparing combination therapy of RTX and prednisolone with mono-therapy of prednisolone (RR-36%) in patients with AIHA.

We also reviewed other studies done for evaluating the role of RTX in AIHA. The relevant studies are enlisted in table 2.

Table 2

First author; (year of publication)	Type of study	Number of patients	Response rate
Barcellini, et al; (2014) [10]	Retrospective observational study	55	80%
Roumier, et al; (2014) [11]	Prospective Cohort study	19	87%
Penalver, et al; (2010) [17]	Retrospective observational study	36	77%
D'Arena, et al; (2007) [18]	Retrospective observational study	11	100%

The patient had received glucocorticoid elsewhere before coming to us but we could not confirm the doses and exact duration of the same. IV gamma globulin was another option but our patient could not afford it. Since rituximab may have shorter periods of remission, especially with lower doses like the one we've used, she will need to be closely followed up for a relapse.

4. Conclusion

To conclude, this case report highlights the efficacy of rituximab as a second line therapeutic agent in adult AIHA, after the failure of conventional mono therapy with glucocorticoids. More studies will be needed to justify its use early on and even upfront to avoid or minimise the use of glucocorticoids.

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