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Case Report

Internal Medicine Section

Successful Management of Rituximab Refractory Warm Autoimmune Haemolytic Anaemia with Splenectomy: A Case Report

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ABSTRACT

Autoimmune Haemolytic Anaemia (AIHA) is a rare haematological disorder characterised by autoantibodies directed against autologous red blood cells. It can be idiopathic or secondary and classified as Warm type AIHA (WAIHA), cold, or mixed. The primary treatment for WAIHA is a long course of steroid administration, which has an early response rate of 80-90%. However, up to 20-30% of patients require second-line therapy. In the last decade, rituximab has replaced splenectomy as the first-choice therapy for refractory WAIHA patients due to its efficacy and safety. There is a paucity of reported cases of WAIHA refractory to both steroids and rituximab that have responded to splenectomy. This is a case of a 35-year-old female with a history of jaundice and anaemia for the past two years. The patient was diagnosed with WAIHA with a Direct Antibody Test (DAT) positive, IgG positive, and C3d negative results, and massive splenomegaly that was initially refractory to steroids and rituximab but responded to splenectomy. Significant splenomegaly may be an indication for choosing splenectomy over rituximab as a second-line treatment in steroid-refractory WAIHA.

Keywords: Multisection computed tomography, Splenomegaly, Steroid

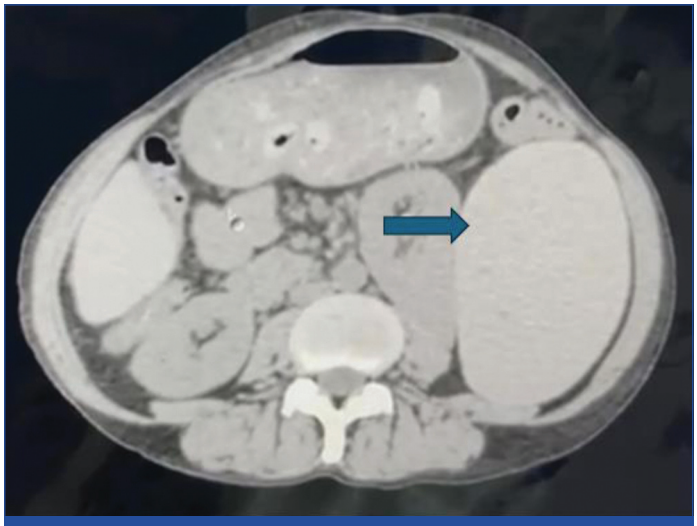
CASE REPORT

A 35-year-old female with no co-morbidities presented to us in September 2022 with chief complaints of breathlessness, jaundice, and mild dull pain in the left upper quadrant. Upon taking a detailed history and reviewing medical records, it was found that the patient was an established case of Warm AIHA with a history of onset of jaundice and anaemia in March 2020 when the patient's Haemoglobin (Hb) level dropped to 4.7 g/dL. The patient had previously sought care at a different tertiary care institute (Institute A) in June 2021, where the diagnosis of Warm AIHA was established based on Direct Antibody Test (DAT) positive, IgG positive, and C3d negative results. The patient was started on prednisolone 40 mg per day in January 2021 by Institute A; however, the Hb level remained between 5-7 g/dL during the steroid course over the next 15 months, indicating a lack of response to steroids.

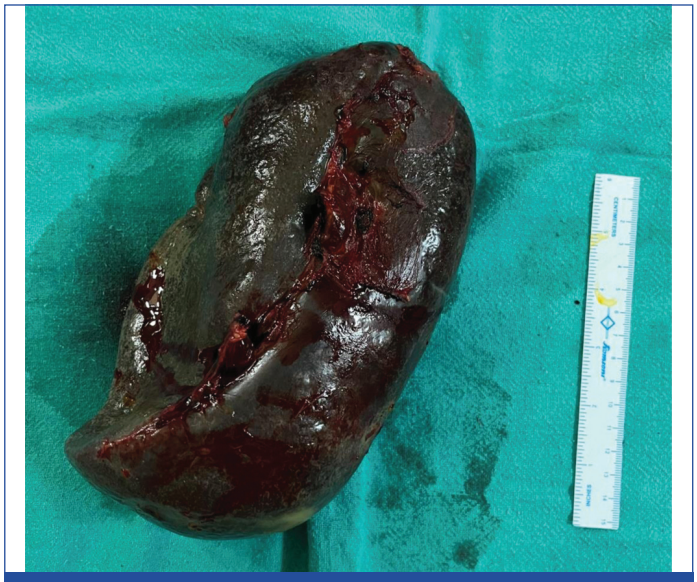
At the time of presentation to us, the patient had a pulse rate of 105/min, blood pressure of 106/66 mmHg, oxygen saturation on room air of 93%, height of 155 cm, weight of 43 kg, and a body mass index of 17.9 kg/m^2. A physical examination of the patient revealed anaemia and jaundice. Abdominal examination revealed Hackett's Grade IV splenomegaly and mild hepatomegaly. Laboratory findings revealed Hb of 5.9 g/dL, White Blood Cells (WBC) of 9.3×10^3/µL, platelet count of 127×10^3/µL, total/indirect bilirubin of 7.7/6.5 mg/dL, Lactate Dehydrogenase (LDH) of 732 µ/L, and Alkaline Phosphatase of 527 µ/L. Computed Tomography (CT) revealed a spleen length of 22.5 cm and a liver length of 17.4 cm in craniocaudal length [Table/Fig-1]. The patient was taking tablet prednisolone 40 mg per day at the time of presentation.

Injection Rituximab 100 mg weekly for four cycles was started in October 2022, and the patient was followed for the next eight weeks to evaluate the response. The patient did not show significant improvement after rituximab therapy, and the Hb levels remained between 5-7 g/dL, indicating non responsiveness to rituximab.

Laparotomy and splenectomy were performed on the 1st of January 2023. The operative time was 130 minutes, and blood loss was 150 mL. No blood transfusion was required during surgery. The spleen weighed 2400 grams [Table/Fig-2]. Gross pathological examination



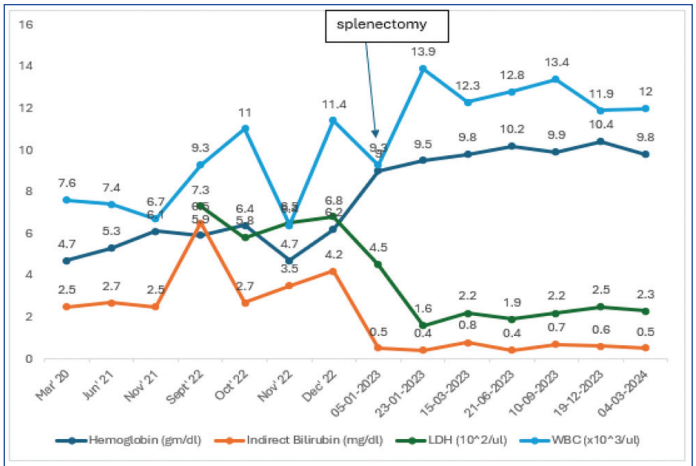
[Table/Fig-1]: Non-contrast CT scan showing massive splenomegaly.



[Table/Fig-2]: Resected specimen of spleen.

revealed no obvious mass. Histopathological examination revealed no evidence of lymphoma. The postoperative period was uneventful.

By postoperative day 7, the Hb level reached 9 g/dL, and the indirect bilirubin level was reduced to 0.3 mg/dL. The patient was discharged on postoperative day 12. Prophylactic aspirin was given for three months because of postsplenectomy thrombocytosis as per institute protocol. Hb levels remained between 9-11 g/dL during three monthly follow-ups. The steroid dose was tapered down over four months after surgery. At the 15-month follow-up, the Hb was 10 g/dL, and the indirect bilirubin was 0.7 mg/dL, signifying a complete response after splenectomy [Table/Fig-3].



[Table/Fig-3]: Clinical course of disease before and after surgery.

DISCUSSION

The AIHA is a relatively uncommon disorder caused by autoantibodies directed against self-red blood cells. The disease may be primary (idiopathic) or secondary to autoimmune diseases (20%), lymphoproliferative syndromes (20%), tumours, and infections [1]. The disease course is greatly unpredictable, ranging from cases developing gradually or fully compensated to patients with rapid onset of life-threatening anaemia. Diagnosis is based on haemolytic anaemia and serological evidence of antierythrocyte antibodies, detectable by the DAT [1].

Two serological types of the disease, WAIHA, and Cold Agglutinin Disease (CAD), are recognised based on the thermal range of the autoantibodies. In WAIHA, the DAT usually shows positive results with anti-IgG antisera like in the present case, and in CAD, the DAT shows positive results with anti-C3d antisera, indicating the presence of high-titre cold agglutinins. In rare cases, there is the co-existence of high-titre cold agglutinins and warm antibodies, which are designated as mixed-type AIHA. The DAT can demonstrate negative results in 10% of AIHA cases designated as atypical AIHA [1].

For many years, the standard first-line therapy has been glucocorticoids, which are effective in 80-90% of patients [2]. Prednisolone is usually started at a dose of 0.5-1.5 mg/kg for 1-3 weeks until haemoglobin levels greater than 10 g/dL are reached. The response mainly occurs during the second week, and if no or minimal improvement is observed in the third week, this therapy is assumed to be ineffective [3,4]. However, 10-20% of patients are either refractory to steroid therapy or relapse after an early response and need additional second-line therapies, which consist of various immunosuppressive agents such as azathioprine, cyclosporin, mycophenolate mofetil, rituximab, and splenectomy, which are reported to provide a 40%-75% response rate [5]. However, high clinical heterogeneity in the disease, encompassing both presentation and treatment response, necessitates an empirical approach to second-line therapy selection due to a lack of well-established guidelines. Currently, no reliable prognostic factors are available to guide treatment decisions. Traditionally, after initial steroid treatment, splenectomy was the established second-line intervention. However, in recent years, rituximab has emerged as the preferred strategy. This shift likely reflects the advantages of rituximab, including its minimally invasive nature compared to surgery and the preservation of essential splenic function [2,6].

Recent American [7] and United Kingdom [1] guidelines have also recommended rituximab. In a meta-analysis, the overall response rate of WAIHA to rituximab was 79% [8]. In a recent multicentre retrospective study, the time to respond to rituximab was one month in 87.5% and three months in 12.5% of patients [9]. Therefore, authors waited for eight weeks after completing rituximab therapy before deciding on splenectomy in the present case. Low-dose rituximab (100 mg fixed weekly dose for four weeks) has been reported to be as effective as the conventional dose (375 mg/m^2 weekly for four weeks) in WAIHA [10], and that was the basis of using low-dose rituximab in the present case. The long-term response of splenectomy in medically refractory AIHA has been reported as 70-80% [11,12]. Authors still do not have a clear answer as to why some patients respond and others do not respond to steroids or other medical therapy. The course of the disease and treatment outcome remain largely unpredictable. There is also a lack of research on the predictive factors that may help in choosing appropriate therapy from the beginning, which could potentially reduce the incidence of refractory cases. In the present case, authors hypothesise that the inadequate response to rituximab and steroids was partly due to the massive size of the spleen, which becomes the dominant factor for haemolysis because extravascular haemolysis in WAIHA occurs mainly in the spleen due to the action of Immunoglobulin G, and the adequate response could have been achieved only after splenectomy. However, because of the lack of data in the literature, especially on the role of spleen size in disease outcome and treatment planning, this hypothesis requires validation in prospective or randomised larger studies.

CONCLUSION(S)

The treatment outcomes of AIHA are mostly unpredictable, with high rates of primary treatment failure often requiring second or third-line treatments. Authors hypothesise that the size of the spleen should be considered before selecting a treatment option for WAIHA. The presence of significant splenomegaly in patients with WAIHA may serve as a useful indicator for choosing splenectomy over rituximab as second-line therapy in cases of WAIHA that are refractory to steroids, in selected cases.

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