

## CASE REPORT

## Autoimmune Haemolytic Anaemia Treated by Therapeutic Plasma Exchange and Rituximab: A Case Report

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### Abstract

Autoimmune haemolytic anaemia (AIHA) is an uncommon disorder characterized by shortened red blood cell (RBC) survival and the presence of autoantibodies directed against autologous RBCs.<sup>1</sup> It presents with anaemia, jaundice, and splenomegaly with reticulocytosis, unconjugated hyperbilirubinaemia, and direct antiglobulin test (DAT) positivity.<sup>2</sup> AIHA has an estimated incidence of 1–3 cases per 100,000 subjects per year, a prevalence of 17:100,000 and a mortality rate of 11%.<sup>3–5</sup> AIHA is classified as warm AIHA (75.0% of all AIHA cases), cold AIHA (about 15.0%), and mixed type AIHA (less than 5.0%), based on the thermal range of autoantibodies involved in the pathogenesis.<sup>6</sup> It can be idiopathic (50.0%) or secondary to lymphoproliferative syndromes (20.0%), autoimmune diseases (20.0%), infections, tumors and drugs.<sup>7</sup> The laboratory diagnosis of AIHA depends on the result of direct antiglobulin test (DAT) which shows positivity with anti-IgG (usually in warm AIHA) and/or anti-C3d (usually in cold AIHA) antisera, and also the presence of laboratory findings supporting hemolysis such as increase of serum lactate dehydrogenase (LDH), reticulocytosis and spherocytosis in peripheral blood smears.<sup>8</sup> The treatment of AIHA is still not evidence-based. The first-line therapy for warm AIHA is corticosteroids, which are effective in 70.0–85.0% of patients and should be slowly tapered over a time period of 6–12 months. For refractory/relapsed cases, the current sequence of second-line therapy is splenectomy (effective approx. in 2 out of 3 cases but with a presumed cure rate of up to 20.0%), rituximab (effective in approx. 80.0–90.0% of cases), and thereafter any of the immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporin, mycophenolate mofetil). Additional therapies are intravenous immunoglobulins, danazol, plasma-exchange, and alemtuzumab and high-dose cyclophosphamide as last resort option.<sup>4</sup> Most of the immunosuppressive drugs have many deleterious side-effects and the onset of action is slow. Splenectomy carries the risk of an overwhelming post splenectomy sepsis.<sup>8</sup> Rituximab (so called “medical splenectomy”) is an effective second-line therapy, can work quickly with lasting effects, providing high initial response rates up to 87.0% and prolonged disease free survivals of 56.0% up to 2 years with reduced adverse reactions.<sup>8–10</sup> For warm AIHA, rituximab therapy is considered as a second line option as monotherapy or combined therapy. It can also be used as a first line therapy in combination with steroids for newly diagnosed patients.<sup>11</sup> Another option, with less supportive evidence in the literature, is the use of therapeutic plasma exchange (TPE) to quickly reduce the pathologic antibody titer in patients with an overwhelming hemolysis.<sup>12</sup> TPE has been performed in a relatively small number of severely affected warm AIHA patients in whom the anemia could not be stabilized with steroids and transfusion therapy alone, as a temporizing measure which seemed to stabilize the disease and increase the efficiency of blood transfusions.<sup>4</sup> Current indication categories endorsed by the American Association of Blood Banks (AABB) and the American Society for Apheresis, TPE for AIHA is considered as a category III indication, i.e. an application representing “heroic or last-ditch efforts on behalf of a patient”.<sup>13</sup> Decision to transfuse RBC in AIHA should be based on the clinical condition of the patient. No critical patient should be denied blood transfusion due to serological incompatibility and “the least incompatible” RBC should be transfused in this situation.<sup>4,8,14,15</sup> Severe AIHA cases sometimes misdiagnosed or lately diagnosed. Early diagnosis and appropriate emergency interventions can save the life of these patients. In this case, we demonstrate the concomitant use of TPE and rituximab in the treatment of life-threatening warm AIHA.

**Keywords:** Autoimmune haemolytic anaemia, Corticosteroid, Therapeutic plasma exchange, Rituximab

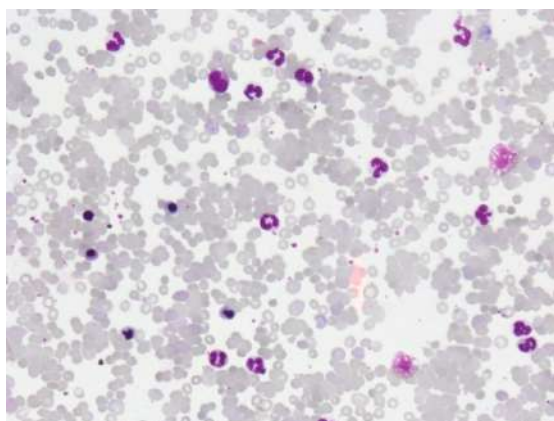
### The case

Aminul Haque, 67-year-old man, known case of DM, admitted in Lab one hospital, Dhaka on the 3<sup>rd</sup> December 2017, with 7 days history of

weakness, bodyache, fever, dizziness, fatigue and progressive shortness of breath. He denied any history of trauma, evidence of GIT bleeding, drug ingestion, previous history of anaemia, haemoglobinopathy or kidney disease. On physical examination, the patient was febrile, tachycardic, severely anaemic, mildly icteric and

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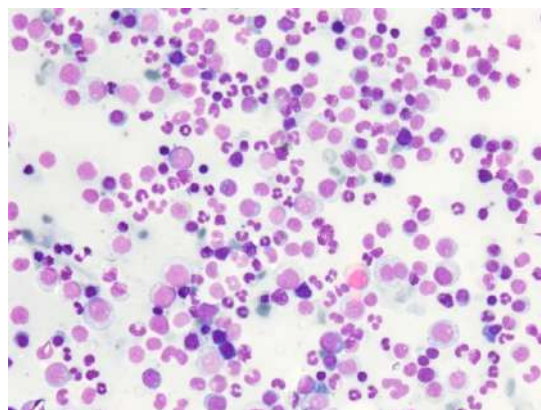
just palpable splenomegaly. Laboratory findings showed: Haemoglobin 5.7 g/dl; ESR 140 mm in 1<sup>st</sup> hour ; WBC: TC  $18.5 \times 10^9/L$ , Neutrophil 80%, Lymphocyte 15%; Platelet  $295 \times 10^9/L$  ; PBF : RBC showed spherocytosis, clumping & frequent nRBC; Total S. bilirubin (total) 5.8 mg/dl; S. LDH markedly raised (2749 U/L); ALT 46 U/L; AST 92U/L; S. Alkaline phosphatase 299 U/L; Renal function was normal; RBS: 18mmol/l; USG: mild splenomegaly; DAT: strongly positive; IAT: weakly positive; S. protein electrophoresis: polyclonal gammopathy; Bone marrow study: Dimorphic erythroid hyperplasia.



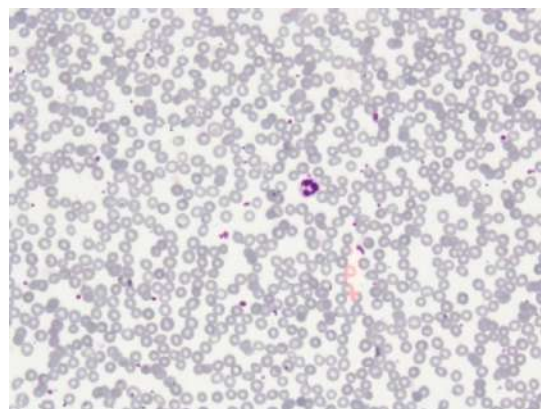
**Figure 1:** PBF showing spherocytosis, clumping, frequent nRBC & neutrophilic leukocytosis

With these findings, the patient was diagnosed as a case of warm AIHA. Treatment was started with high dose corticosteroid (Dexamethasone 5mg i/v 8hourly). Out of 10 donors, only 1 was found least incompatible and thus only 1 unit of RCC can be transfused to the patient. A further decrease in hemoglobin was observed on day 3 of corticosteroid therapy and blood glucose level was rising despite of insulin therapy. Further RCC transfusion was not possible because of donor incompatibility. The patient's clinical condition was gradually becoming worsened significantly. TPE was therefore started under intensive care monitoring on day 4. TPE was performed on every alternate day for 5 times. The patient was in better clinical condition after the procedures. There after 2 units of RCC was transfused. After that he was haemodynamically stable and has not shown any further hemolytic phenomena. Then azathioprine (50mg b.d) was added and tapering of dexamethasone had to be started because of uncontrolled DM. But few days later, haemoglobin was again gradually decreasing and ESR was rising. Then Inj. Rituximab (375mg/m<sup>2</sup> weekly for 4 weeks) was started along

with azathioprine. After the 1<sup>st</sup> dose of rituximab, he was gradually improving and successfully completed remaining 3 doses, without any major adverse reactions with further improvement of clinical conditions. Since then, no further transfusion support was required and the patient was then on azathioprine only.



**Figure 2:** Bone marrow showing Dimorphic erythroid hyperplasia



**Figure 3:** Normal PBF findings after completion of treatment

## Discussion

Plasma exchange has been used in the therapy of a wide variety of disorders, particularly those associated with a well-documented or suspected immunologic pathogenesis. It sounded rationale to use plasma exchange to remove antibodies as a supportive treatment to sustain the vital functions of the patient, until immunosuppressive therapy became effective. The American Society for Apheresis suggests the usage of TPE in AIHA as an emergency measure. TPE can be used to maintain acceptable haemoglobin levels, remove free haemoglobin, reduce the titre of auto-antibodies and sustain cardiopulmonary functions.<sup>13</sup> Rituximab therapy is considered as a second line option as monotherapy or combined

therapy. It can also be used as a first line therapy in combination with steroids for newly diagnosed patients. Therapy with rituximab is well tolerated, effective and has a shorter time of onset compared to the other immunosuppressive agents and provides a prolonged remission with a relatively short course of steroid therapy.

The patient had severe disease, manifested by the rapid development of anemia in less than 96h, minimal reticulocytosis, haemoglobinuria and a poor response to conventional therapy. It was TPE as an emergency measure which controlled the overwhelming hemolysis. Then rituximab therapy provided the sustained response.

### Conclusion

In summary, the patient presented with a severe, life-threatening AIHA not responsive to conventional therapy. TPE was initiated on emergency basis to quickly and temporarily reduce the over whelming titre of pathologic antibody. This was demonstrated by an improved reticulocytosis and a reduction in the net change in hemoglobin following TPE. Rituximab was added as an immunosuppressant that provided prolonged remission from the overwhelming haemolysis. The combination of all the modalities resulted in the successful management of this severe case of AIHA.

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