Cold Agglutinin Disease:

A Rare Case Managed with Rituximab

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Background

Cold Agglutinin Disease (CAD) is a rare form of haemolytic anaemia with an incidence of 1 per million people per year and accounts for 15% of all autoimmune haemolytic anaemia cases[1-2]. It is more common in women, with 65 years being median age of onset of symptoms[1]. Most cases are presented with an underlying cause (e.g. lymphoproliferative, infection), while others are idiopathic[3].

The term ***cold*** in cold agglutinin refers to the autoantibody involved (usually IgM) reacting strongly with red cells at low temperatures; and little or none at 37°C[1,3]. In the body core, circulating IgM remains unbound from the red cell surface. However, as the blood cools in the peripheral vessels, IgM binds to the red cells and activates a cascade of events that results in extravascular haemolysis. The severity of haemolysis is dependent on thermal amplitude, rather than the concentration of IgM[3].

This case outlines the development of the disease, ongoing management and treatment, focusing on the use of rituximab.

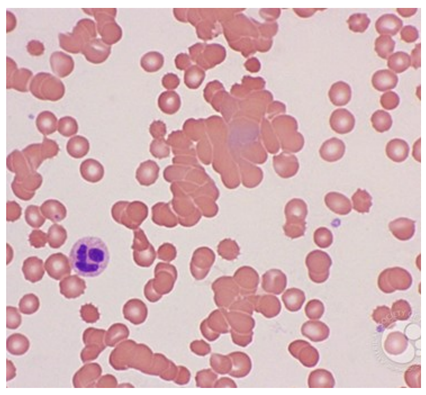

Figure 1: at high definition, blood film shows variable clumps of red blood cells at room temperature

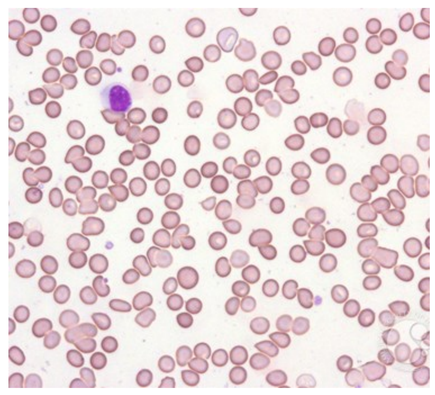

Figure 2: when blood sample is warmed to 37°

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A Man with Black Digits

This is a 68-year-old Caucasian man with congenital blindness and extensive comorbidities including poorly controlled diabetes, ischaemic heart disease and active Crohn's disease. Patient presented with sudden onset of pain and ischaemic digits of unknown aetiology. Physical examination and ultrasound revealed no arterial stenosis in the extremities. A series of laboratory tests were performed but no infective, lymphoproliferative or rheumatological causes were identified.

Patient was initially managed with iloprost infusion, therapeutic enoxaparin, corticosteroids and plasma exchange. Upon further investigation, patient was diagnosed with cold agglutinin disease based on extensive haemolysis of blood specimens, agglutination of blood films at room temperature, positive direct Coombs test and high cold agglutinin titre.

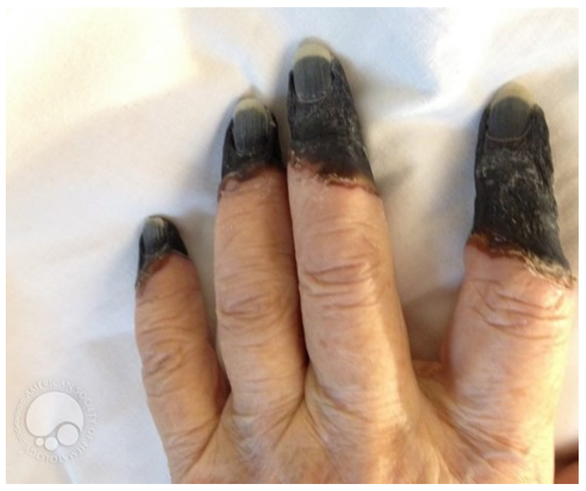

Figure 3: Necrotic fingers as a result of Cold Agglutinin Disease

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Treatment and Response with Rituximab

Single agent rituximab (375mg/m^2) was commenced as weekly infusions over four weeks after diagnosis was made. One month later, there was a stable increase in haemoglobin (80 to 125g/L) combined with a reduction of serum Immunoglobulin M (IgM) concentration (3.2 to 1.3g/L) and cold agglutinin titre (4096 to 512 at 4°C) (*see Table 1).* Patient's response was consistent with previously published cases[3-8]. He has been exacerbation free and no hospital admission since.

A further four doses at a three monthly interval was given as maintenance therapy. Patient's haemoglobin has been persistently above 110g/L during the 12 months period (*Figure 5).*

Reference Range	0	0	< 4	< 32
Temperature / Date	37°C	30°C	22°C	4°C
27/06/2016	16	128	1024	> 2048
04/07/2016	< 2	< 2	256	4096
12/07/2016	2	8	128	2048
18/08/2016	4	8	128	512
15/09/2016	< 2	4	8	1024

Table 1: Patient's cold agglutinin titre at the time of diagnosis (27/06/17) and during the course of initial rituximab treatment

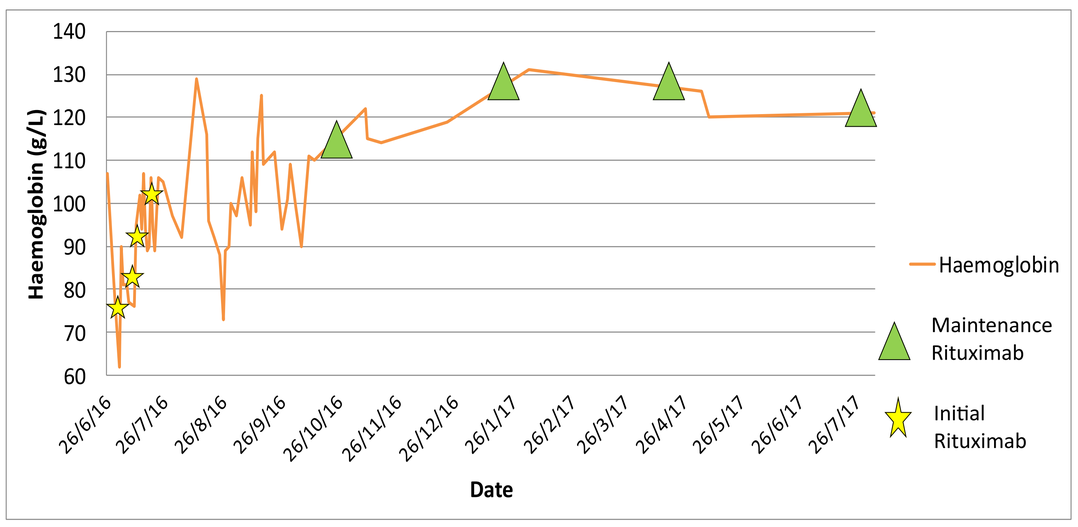

Figure 5: Trend of haemoglobin before and after maintenance rituximab treatment

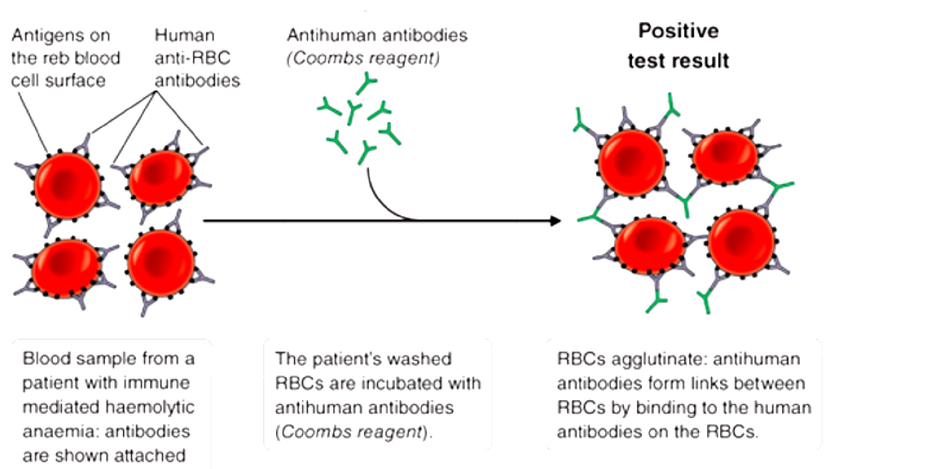

Figure 4: Process of Coombs test

Source: Transfusion Biology and Therapy, Harrison's Principles of Internal Medicine, 19e

Conclusion

Rituximab is a useful and tolerable treatment in CAD. Due to the rarity of this condition, large-scale robust studies are impossible to conduct to establish the optimal frequency and treatment duration of this agent. Treatment outcome of this patient could potentially add value to current body of evidence and the role of maintenance rituximab.

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