Case report

A case report of cold autoimmune haemolyticanaemia in pulmonary tuberculosis

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Abstract

Autoimmune hemolyticanemia (AIHA) can be caused by a variety of etiologies. Approximately one-half of warm AIHAs are idiopathic, while the nonidiopathicetiologies include lymphoproliferative disorders, autoimmune disease, and infection-induced AIHA. AIHA may be frequently challenged by infectious complications, mainly as a result of immunosuppressive treatments administered. Here we reported an extraordinary case of *Mycobacterium* tuberculosis infection presented with high titer cold-agglutinin autoimmune hemolysis in an immunocompetent patient. Although being risk factors for mortality, infections are an underestimated issue in AIHA. No antecedent case of pulmonary tuberculosis associated with cold agglutinin disease has been reported from Malaysia.

Keywords: Cold AIHA; Pulmonary tuberculosis; Cold agglutinin syndrome

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Introduction

AIHA is a group of uncommon disorders characterized by hemolysis due to autoantibodies against red blood cell surface antigens. Each of these types of AIHA may be sub-classified based on the presence or absence of underlying diseases. In the absence of an underlying disease, the AIHA is termed primary or idiopathic. When AIHA occurs as a manifestation or complication of another disease, the term secondary AIHA is used [1].

Cold reactive type probably accounts for about 25% of all AIHA cases[2]. It was then further characterized into cold hemagglutinin disease (CHAD) and paroxysmal cold hemoglobinuria whereby, CHAD is rare, accounting for 15% of AIHA cases with an incidence of 1 per million people per year[3].

It is important to diagnose the subtype of AIHA as the approach to treatment differs. Here we reported

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an extraordinary case of *Mycobacterium* tuberculosis presented with high titer cold-agglutinin autoimmune hemolysis in an immunocompetent patient. No antecedent case of pulmonary tuberculosis associated with cold agglutinin disease has been reported from Malaysia.

Case Report

This a case of a 68-year-old Malay man who had underlying diabetes mellitus, presented with fever, cough, and worsening progressive dyspnea. Clinically, he was pale, jaundice, and tachycardia. He had reduced breath sounds over the left upper lobe of the lungs. There was mild hepatosplenomegaly with no lymphadenopathy.

His peripheral blood count showed anaemia with leucocytosis (Table 1). His full blood picture showed improvement of the red blood cell agglutination using pre-warm sample (Figure 1).

Table 1: Peripheral blood count and bone marrow aspirate, trephine result

Parameters	Value
Total White Cell Count	17.44 x 10^9/L
Haemoglobin	4.7 g/dL
Mean Corpuscular Volume (MCV)	85.4 fL
Mean Corpuscular Haemoglobin Concentration (MCH)	32.6 pg
Haematocrit (HCT)	12.3 %
Reticulocytes (%)	9.11
Platelet	308 x 10^9/L
Bone marrow aspirate and trephine	Reactive marrow with no evidence of tumor infiltration.

His biochemical investigations showed evidence of ongoing haemolysis with cold agglutinin titre of 1 in 2048 (positive with anti I specificities). Other investigations were also done. (Table 2)

Table 2: Biochemical and other investigation results

Parameters	Value
Lactate dehydrogenase	1061 U/L
Total bilirubin	69 µmol/L
Indirect bilirubin	39 µmol/L
Albumin	32 g/L
Alkaline phosphatase	266 U/L
Direct coombs test	IgG (Negative), C3d 3+
Cold agglutinin titre	1 in 2048 (positive with anti I specificities)
Chest Xray	Heterogeneous opacities over the left upper zone
Sputum culture	Mycobacterium tuberculosis complex
ANA, Rheumatoid Factor	Not detected
Thyroid function test	Normal
Infective screening	
Hepatitis B surface antigen (HBsAg)	Non reactive
(Anti-HCV)	
Human Immunodeficiency Virus (HIV ag/ab)	

He was started on oral drugs ie: Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide. Intravenous immunoglobulin (IVIG) with a dose of 400mg/day was given for 5 days and 2 cycles of plasma exchanged have opted for him. Unfortunately, he succumbed to death despite improving hemolytic parameters and aggressive treatment for his pulmonary tuberculosis.

Discussion

AIHA which can be classified into warm and cold is a decompensated acquired haemolysis caused by the host's immune system acting against its own red cell antigens. Cold AIHA describes as a reaction of autoantibodies known as cold agglutinins at a temperature < 37°C with an optimum of 0-4°C (2). It is a relatively uncommon disorder with an estimated incidence in adults of 0.8–3 per 10^5/year, a prevalence of 17:100,000[4]. However, there is limited data on the prevalence of AIHA among the Asian population.

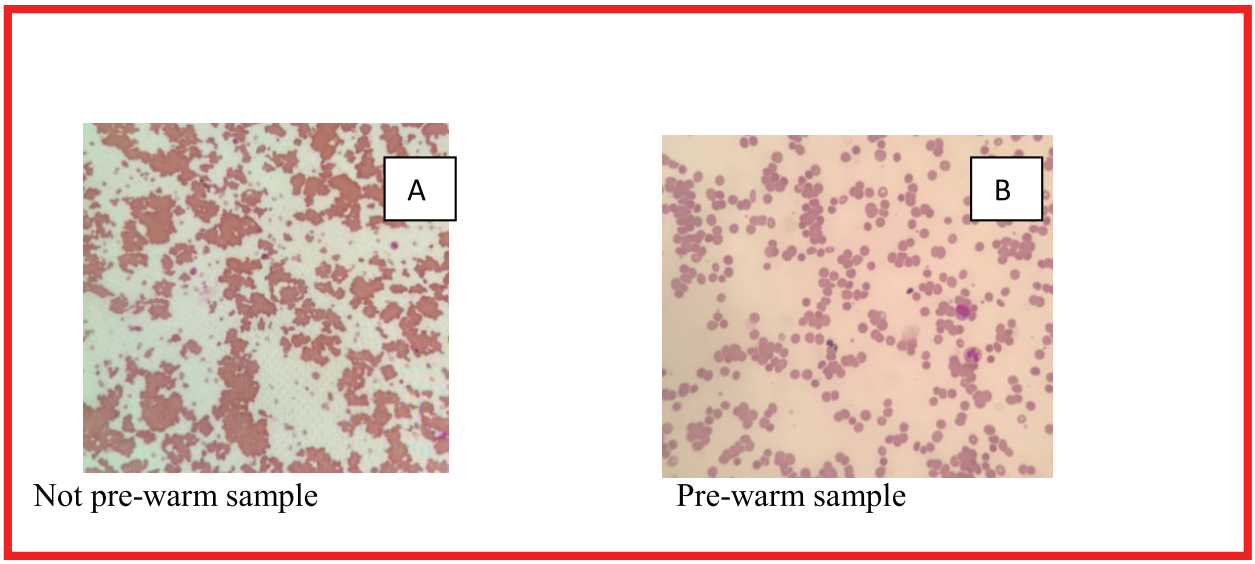

Figure 1: His full blood picture showed improvement of the red blood cell agglutination using pre-warm sample.

Clinically, the majority of cold AIHA presented with cold-induced circulatory symptoms like acrocyanosis or Raynaud phenomena. Whereas, others may be presented with exacerbating anaemia induced by an infection which was illustrated in our case. In term of laboratory investigations, there is no classical or standard laboratory method to diagnosed AIHA. However, they rely on positive direct antiglobulin test (DAT) and anti-C3d typically in cold AIHA antisera. Otherwise, others were reinforced by other hemolytic parameters i.e. increase of serum lactate dehydrogenase (LDH), reticulocytosis and red blood cells agglutinations in peripheral blood smears [5].

Cold agglutinins can be dictate based on semi-quantitative measurement of titer. Screening of cold agglutinin has shown that a high proportion of cold agglutinin titer is seen in normal healthy serum without evidence of hemolysis. These are usually polyclonal with the titer below 64[6].

The causes are commonly due to CHAD and rarely paroxysmal cold hemoglobinuria (PCH). For the CHAD, the definitions proposed by the consensus group defined as AIHA with monospecific strong Cd3 and negative or weekly positive IgG with a cold agglutinin titer of 64 or greater at 4°[7]. The causes of CHAD can be divided into primary and secondary. The majority are secondary and the causes include infections especially Mycoplasma pneumonia, malignancy mainly lymphoproliferative disorders, or viral causes like human immunodeficiency virus or *Epstein Barr Virus* (EBV) rarely cases with listeria, toxoplasma, tuberculosis, leishmaniosis, influenza viruses, and adenovirus have also been mentioned[8]. Amusingly, cold agglutinin syndrome with anti-I was also reported in a patient infected with the influenza A H1N1[9]. However, anti-I antibodies have not been associated with mycobacterium complex to our knowledge.

Usually, hematological changes in tuberculosis include nutritional deficiency, malabsorption syndrome, marrow suppression, and failure of iron utilization. To complicate things, there has been a report that anti-tuberculosis drugs rifampicin, streptomycin, and para-aminosalicylic aid may induce hemolyticanemia[10].

Based on the latest British Jurnal of Haematology guideline, the main approach to the management of this disease is to avoid cold exposure to treat the underlying causes. The details for starting treatment are if the patient had symptomatic anemia or anemia<10g/dL, severe circulatory symptoms, or transfusion dependence. It may give a brief benefit in terms of transfusion in AIHA due to the presence of autoantibodies that may result in rapid in vivo destruction. As observed in our case, he received multiple pints of pack cells however, his hemoglobin still showed a further reduction. Given that, clinicians started him on IVIg and plasma exchange.

Plasma exchanges are one of the rescue therapy in emergencies, which might reduce the level of IgM in the plasma[8].

Conclusion

Tuberculosis should be regarded as one of the differential secondary AIHA especially in an Asian country. Although the etiology of this patient's AIHA remains unclear, we hope that our paper can highlight the development of AIHA, as well as its potentially devastating complication of pulmonary tuberculosis infection.

Ethical consideration

Ethics clearance to conduct the study was provided by the Hospital Research and Ethical Committee School of medical sciences, University Sains Malaysia.

Conflict of interest

The authors declare that there is no conflict of interest.

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Authors Contribution

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