CASE REPORT

Primary cold agglutinin disease: A case report

Ramesh Thangatorai, MBBS, Koh Ewe Jin, MRCP(UK)

Department of Internal Medicine, Hospital Sultan Ismail, Johor Bahru, Johor

SUMMARY

Cold agglutinins are circulating autoantibodies directed against the i-antigen on red blood cells, causing complement-mediated extravascular haemolysis at a thermal amplitude of 3-4°C in vitro. Clinically, however, these autoantibodies may be active and cause haemolysis at higher temperatures such as in acral areas of the body. We report a 69-year-old Chinese man who presented to the emergency department with non-specific chest discomfort and acrocyanosis of his toes which was resolved with warming blankets. Interestingly, his routine blood investigation samples within the point of care were repeatedly rejected due to sample haemolysis. The constellation of clinical signs and laboratory findings prompted us to suspect the presence of cold agglutinins. He was ultimately diagnosed to have a primary cold agglutinin disease based on supporting biochemical, molecular, and histopathological evidence. As he did not have symptomatic anaemia nor any disabling cold-induced symptoms, no targeted B cell therapy was commenced. He is currently being managed supportively and is under our close follow-up. He remains well and asymptomatic to this date.

INTRODUCTION

Primary cold agglutinin disease is a rare cause of haemolytic anaemia. It accounts for 15-20% of autoimmune haemolytic anaemias (AIHAs) and refers to the presence of cold agglutinins, attributed to an indolent B cell lymphoproliferative disorder which is distinct from a classical non-Hodgkin's B cell lymphoma. Specifically, cold agglutinins are antibodies that recognise antigens on red blood cells at temperatures below normal core body temperature, leading to agglutination of red blood cells resulting in haemolysis via the complement-mediated pathway. Patients with cold agglutinin disease typically present with haemolysis and cold-induced symptoms such as the Raynaud phenomenon, acrocyanosis, and livedo reticularis. A thorough workup to rule out secondary causes of cold agglutinins is necessary before diagnosing a patient with primary cold agglutinin disease.

CASE REPORT

A 69-year-old man, chronic smoker with hypertension, presented with sudden onset of central chest pain for a day, pressing in nature associated with diaphoresis and shortness of breath. He was admitted and treated for unstable angina. During his admission to our cardiology ward, we noticed an incidental finding of a painless bluish discolouration on his toes. On further history, the patient mentioned that the bluish discolouration started on the day of admission, and he had never noticed any such changes before this. Apart from that he also complained of dark urine for two days and a non-productive mild cough for two days. He denied any symptoms to suggest a connective tissue disease, nor any constitutional symptoms such as fever, loss of weight, or night sweats. On examination, he was an average built Chinese man, with no palpable cervical, axillary, or inguinal lymph nodes. His cardiovascular examination was unremarkable, and he had no hepatosplenomegaly. His peripheral pulses were all present. He had no stigmata of peripheral vascular disease; however, he had persistent acrocyanosis, especially over his bilateral toes. His blood investigations agglutinated immediately after phlebotomy, thus making it difficult for the laboratory to process. The constellation of these symptoms and signs led to the suspicion of cold agglutinin disease.

His blood parameters on presentation are shown in Table I. His peripheral blood smear showed marked agglutination of red blood cells, with polycythaemia. Cold agglutinin titre of 1:1024 at 4°C confirmed our suspicion of cold agglutinin disease. Infectious screening for viral hepatitis, HIV, Epstein Barr virus (EBV), and cytomegalovirus (CMV) was negative. His serum mycoplasma serology was positive with a titre of 1:320. Autoimmune workup was negative. Serum protein electrophoresis showed IgM Kappa paraproteinemia in the gamma region. His bone marrow biopsy showed 15 small to medium sizes of paratrabecular lymphoid follicles, consisting of a mixture of B (C79a/CD20 positive cells) and T cells (CD3 and CD5 positive cells) that are negative to CD10 and CD38. There were no light chain restrictions noted in the trephine biopsy sample.

However, further Immunophenotyping of the marrow aspirate showed a mature B lymphoid population with increased kappa chain expression.

Details of the investigations are shown in Table II.

DISCUSSION

Cold agglutinins are autoantibodies that are usually of the IgM type with kappa light chain restriction, while IgG and IgA lambda light chain phenotypes are rarer occurrences. A population-based retrospective study conducted in 2006 in 86 patients with cold agglutinin disease in Norway revealed that monoclonal IgM was detected in 90%; IgG and IgA in 3.5% each; with kappa light chains in 94%.[1] The binding of multiple RBCs by the pentameric IgM molecule is the basis for agglutination and haemolysis by these antibodies. Even a small amount of antibodies, perhaps as few as 25 per RBC, can produce obvious agglutination.[2]

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Corresponding Author: Ramesh Thangatorai
Email: ramesh.thangatorai@outlook.com

Table I: Initial blood investigations

	19 Sept 2021	20 Sept 2021	22 Sep 2021	4th Oct 2021
White blood cell ($\times 10^3$)	8.9	9.0	5.8	5.5
Haemoglobin (g/dl)	18.6	20.2	18.3	16.5
Mean cell volume (fl)	96	96.4	96.3	97
Mean cell Hgb concentration (g/dl)	35	36.8	36.9	38.7
Reticulocytes ($\times 10^3$/ul)	147	134	128	
Platelets ($\times 10^3$)	222	186	197	246
Lactate dehydrogenase(u/l)	-	571	621	
Total bilirubin (umol/l)	73	90	59.7	25.2
Direct bilirubin(umol/l)	14.3	20	17.2	
Indirect bilirubin(umol/l)	59	70	43	
Direct antiglobulin test				
i)Anticomplement	i) 2+			
ii)IgG	ii) Negative			
Mycoplasma antibody titre	1:320			Equivocal

Table II: Details for further tests

Date	Test	Results
22nd September 2021	Cold Agglutinin titre	@ 37°C : 1:2 @ 20°C : 1:8 @ 4°C: 1:1024
22nd September 2021	Serum electrophoresis	Total protein (serum): 63.81g/L Paraprotein (serum): 2.68g/L SPE shows IgM Kappa paraproteinaemia at the gamma region.
22nd September 2021	Urine electrophoresis	Total protein (urine) 0.04g/L Paraprotein (urine) Absent
22nd September 2021	Bone marrow immunophenotype	17.1% lymphoid population gated at CD45 positive andlow side scattered region, with the presence of 10.0% T cells and 4.3% B cells. The B-cells are positive for CD19, CD20, CD200, CD23 (heterogenous), CD79b and are negative for CD5, CD10, CD38, CD43, CD3. Kappa:Lambda ratio is 4.1:1 (increased kappa light chain expression). **Conclusion** Presence of 4.3% mature B-lymphoid population with increased kappa light chain expression.
	Workup for Polycythaemia vera	JAK2 Mutation not detected Mutation of Calreticulin gene(Exon9) is not detected.
24th Feb 2022	CT thorax/abdomen/pelvis.	No evidence of solid organ malignancy

There are primary and secondary causes of cold agglutinins. Secondary causes of cold agglutinins are due to viral/bacterial infections, autoimmune disorders, and overt lymphoid malignancies. This entity is known as secondary cold agglutinin syndrome. For the purposes of this report, only primary CAD will be discussed in more detail.

In the past, primary CAD was once believed to be due to a classical B cell lymphoma. However in a study by Randen et al.,[3] done between 1995 and 2012, they postulated that by restudying the bone marrow of 54 of patients diagnosed to have cold agglutinin disease, there is reason to believe that there are unique pathological and genetic features that distinguish the disease from the classical well-characterised B-cell lymphoma type such as marginal zone lymphomas and lymphoplasmacytic lymphomas.

The bone marrow findings in our patient are consistent with a primary cold agglutinin disease as the bone marrow aspirate, and trephine biopsy did not reveal any classical features of a B cell lymphoma.

Primary CAD usually presents in the seventh decade of life and predominantly affects women. The median age of onset is 66-72 years old, with a male to female ratio of 0.55.[4] It has a prevalence of 5-20 cases per million and an incidence of 0.5-1.9 cases per million per year, showing considerable variation with climate. CAD accounts for 15-30% of AIHAs.[5] Delays in diagnosis are common, owing to the rarity of the disease and insufficient recognition. The most common presenting symptoms are cold-induced circulatory symptoms such as acrocyanosis, Raynaud's phenomenon, distal ulcers, and livedo reticularis, occurring in 90% of patients in cold countries. Haemolysis is also common, its severity ranging



Fig. 1: Acrocyanosis of patient's toes

from compensated haemolysis without anaemia to severe haemolytic anaemia requiring transfusion. Mean haemoglobin is 9.3g/dL; however, there are patients who present with normal haemoglobin, indicating compensated haemolysis.[5]

In contrast with many other case reports on Cold agglutinin disease, our patient presented with macrocytic hyperchromic red blood cells, and polycythaemia. RBC agglutination in cold agglutinin disease can spuriously cause macrocytosis; however, polycythaemia is a rare finding in cold agglutinin disease. From our literature search, there is no reported case of Cold agglutinin disease presenting with polycythaemia. In our patient, we postulate that he has underlying chronic secondary polycythaemia due to his chronic smoking habit.

It is important to note that not all patients require definitive chemotherapy with B cell-reducing agents. Many patients are advised for lifestyle modifications like avoiding cold climates for an example. Chemotherapy is indicated only if the patient has disabling symptomatic anaemia or disabling cold-induced symptoms. The rationale of B cell-reducing agents such as Rituximab derives from the fact that the primary cause of CAD is a B cell lymphoproliferative disorder. There are also second-line treatment options such as the complement C1 inhibitor, sutimlimab. Of particular relevance for general physicians is to note that corticosteroids should not be used, as it only achieves remission in <20% of patients, and in responders, an unacceptably high maintenance dose is required to maintain remission.[6]

This patient is currently being treated conservatively as he does not have disabling anaemia or disabling cold-induced symptoms and is followed up as an outpatient.

CONCLUSION

To the best of our knowledge in Malaysia, there has only been one case report on primary cold agglutinin disease published in 1999. The authors from Universiti Kebangsaan Malaysia postulated that their patient had a low-grade non-Hodgkin's lymphoma. However, they also acknowledged that the patient did not fulfil the classical diagnosis of the more well-defined lymphomas.[7] To date there has also not been any population-based studies in Malaysia published. The majority of the data quoted in this report are based on population-based retrospective reviews of patients in Scandinavia. This is perhaps due to the fact that Malaysia has a tropical climate, and therefore the cold agglutinin disease may go unrecognised, especially in patients who are not exposed to cold environments.

However, it is a disease that should be recognised owing to the potential for transformation to an aggressive lymphoma and also the possibility of disabling symptoms such as anaemia and cold-induced symptoms.

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REFERENCES

1. Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, Ghanima W, et al. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. Haematologica 2006; 91(4): 460-6.
2. Rosse WF. The detection of small amounts of antibody on the red cell in autoimmune hemolytic anemia. Ser Haematol 1974; 7(3): 358-66.
3. Randen U, Trøen G, Tierens A, Steen C, Warsame A, Beiske K, et al. Primary cold agglutinin-associated lymphoproliferative disease: a B-cell lymphoma of the bone marrow distinct from lymphoplasmacytic lymphoma. Haematologica 2014; 99(3): 497-504.
4. Go RS, Serck SL, Davis JJ, Bottner WA, Cole CE, Farnen JP, et al. Long-term follow up of patients with cold agglutinin disease. Blood. 2005;106(11): 3710.
5. Berentsen S, Barcellini W, D'Sa S, Randen U, Tvedt THA, Fattizzo B, et al. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. Blood 2020; 136(4): 480-8.
6. Berentsen S. How I treat cold agglutinin disease. Blood 2021; 137(10): 1295-303.
7. Fadilah SA, Hamidah AB, Cheong SK. Cold agglutinins in low-grade B-cell lymphoma. Med J Malaysia 1999; 54(3): 383-5.