CASE REPORT

Cold Agglutinins in Low-Grade B-Cell Lymphoma

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Summary

The presence of serum cold agglutinin can be the initial presentation of lymphoproliferative diseases. Conditions with persistent cold agglutinins are a spectrum of diseases that vary from benigh lymphoproliferation of the "autoimmune-like chronic cold agglutinin disease" to malignant lymphoma. We report a case of a 72-year-old woman who presented with severe anaemia, hepatosplenomegaly and episodes of peripheral haemagglutination precipitated by cold exposure. The haemoglobin was 5.6g/dL with a cold agglutinin titer of 1:256 at 4°C and 1:8 at room temperature (30°C). The cold agglutinin showed anti-I specificity and kappa light chain restriction. Peripheral blood showed atypical lymphoid cells with a B-cell immunophenotype. Immunoglobulin gene rearrangement study by polymerase chain reaction (PCR) showed an amplified band at 100bp, consistent with a clonal proliferation of B-lymphocytes. We believe that our patient had cold antibody haemolytic anaemia as the initial presentation of a low-grade non-Hodgkin's lymphoma. The association of cold antibody haemolytic anaemia with low-grade B-cell lymphoma is unusual.

Key Words: Cold agglutinins, Immunoglobulin gene rearrangement, PCR, Low-grade B-cell lymphoma

Introduction

Cold agglutinins are complement fixing IgM antibodies that react with the Ii antigen system on red cells. Normal individuals have low titers of cold agglutinins (less than 1:16 at 4°C) that have low thermal amplitude and do not bind to red cells at 20° to 37°C. In cold agglutinin disease, the antibody titers measured at 4°C are greatly increased (up to 1:1 x 10^6) and the thermal amplitude of the antibody is increased so that the antibody binds to the surface of red cells at temperatures as high as 28° to 32°C. Cold agglutinins associated with lymphoproliferative diseases are usually monoclonal. Cold agglutinins as the initial presentation of low-grade non-Hodgkin's lymphoma are a rare occurrence.

Case Report

A 72-year-old Chinese woman presented with a 3-month history of extreme fatigue, exertional dyspnoea, low-grade fever and marked weight loss. There were episodes of bluish discoloration and numbness of the fingertips and toes that were precipitated by exposure to the cold. On examination there were marked pallor, jaundice and moderate hepatosplenomegaly. The peripheral lymph nodes were not enlarged. The blood count showed haemoglobin of 5.6 g/dL with normal leucocyte and platelet counts. Microscopic examination of the peripheral blood revealed marked erythrocyte agglutination, reticulocytosis of 5% and abnormal and immature lymphoid cells (Fig. 1). Bone marrow showed marked erythroid hyperplasia and the erythrocyte maturation was megaloblastic, and dysplastic. Atypical and immature lymphoid cells constituted 5% of the total nucleated cells in the bone marrow. The mononuclear cells expressed CD19, HLA-DR and kappa light chain markers and but not CD5 marker. Immunoglobulin gene rearrangement study by polymerase chain reaction showed an amplified band at 100bp, consistent with a clonal proliferation of B-lymphocyte (Fig. 2). The cold agglutinin titer was 1:256 at 4°C and 1:8 at room temperature (30°C). The cold agglutinin that was IgM

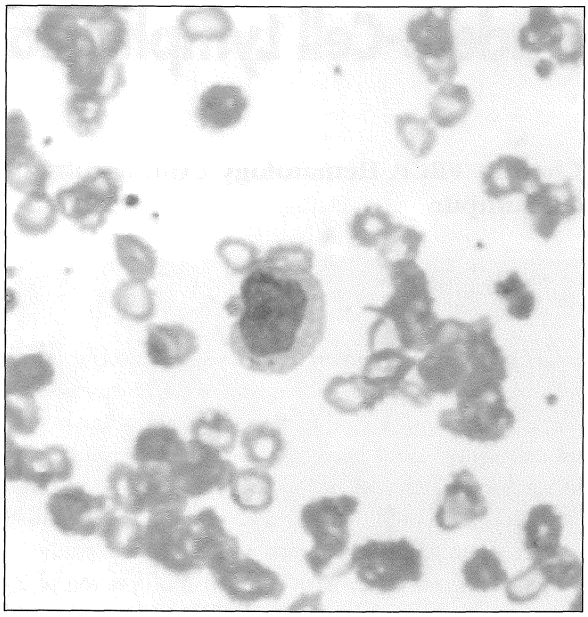

Fig. 1: Microscopic examination of the peripheral blood revealed marked erythrocyte agglutination, hypochromic and microcytic erythrocytes, abnormal and immature lymphoid cells.

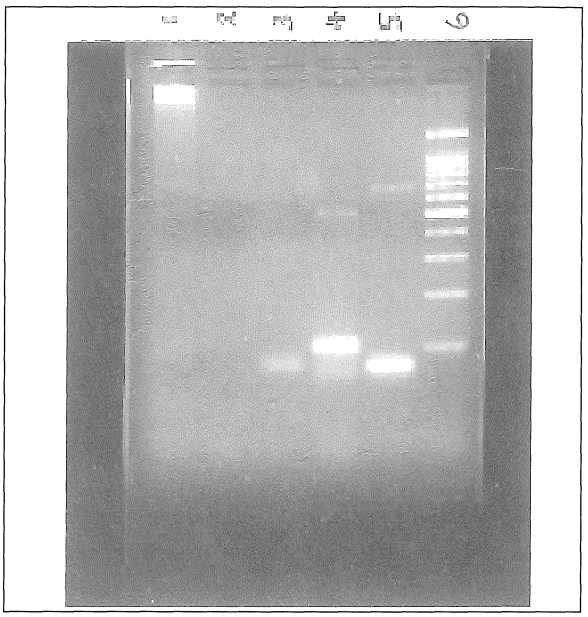

Fig. 2: Immunoglobulin gene rearrangement study by polymerase chain reaction. Presence of an amplified band at 100bp in the 4th lane.

type had anti-I specificity and showed kappa light chain restriction. Direct antiglobulin test was positive and serum indirect bilirubin and lactate dehydrogenase levels were elevated. The patient's serum did not contain cryoglobulin. The results of the Ham's test and investigation for *Mycoplasma pneumoniae* infection and infectious mononucleosis were negative. A computerised tomography (CT Scan) examination disclosed hypodense lesions in the spleen but no enlarged lymph nodes in the thorax, abdomen or pelvis. Clinical and laboratory examinations did not show features of chronic lymphocyte leukaemia (CLL) hairy cell leukaemia, multiple myeloma or Waldenstrom macroglobulinaemia. A diagnosis of cold agglutinin disease with an underlying low-grade B-cell lymphoma was made and the patient was transfused washed red cells. Daily oral prednisolone of 40mg was administered for 6 weeks with no reduction in the cold agglutinin titer or improvement of her anaemia. The patient was lost to further follow-up.

Discussion

We describe an unusual case of low-grade non Hodgkin's lymphoma (NHL) presenting as severe anaemia due to cold agglutinins with anti-I specificity and IgM-kappa monoclonal protein. Cold agglutinins arise in two clinical settings: (1) monoclonal antibodies as a product of lymphocytic neoplasm and (2) polyclonal antibodies in response to infection. In most cases, cold antibody haemolytic anaemia is a primary disorder (chronic cold agglutinin disease/CAD) that typically becomes apparent after approximately 50 to 60 years of age.

Lymphocyte neoplasms can originate from cells that are at a stage prior to T- or B-lymphocyte differentiation from a primitive stem cell or from cells at various stages of maturation after stem cell differentiation. Variability in expression of a lymphopoietic stem cell disorder may result in the spectrum of lymphocytic diseases such as CLL, hairly cell leukaemia, multiple myeloma or Waldenstrom

macroglobulinaemia. We believe our patient may have low-grade B-cell lymphoma, as there were no clinical, haematological or immunological features in favor of the other disorders that constitute the spectrum of benign lymphoproliferative diseases. Although B-cell follicular lymphoma comprises 80% of the total low-grade NHL, the exact subtype of lymphoma in our patient could not be ascertained in the absence of lymph node biopsy. Among 78 patients with persistent cold agglutinins studied by Crisp *et al*[1], 31 had lymphoma (the subtypes not specified, 13 had Waldenstrom macroglubulinaemia, 6 had CLL and 28 had chronic CAD. Patients with chronic CAD had more haemolytic crises and less hepatosplenomegaly or lymphadenopathy. The specificity of the *cold-reactive antibodies* may be of value. Cold agglutinins reacting more strongly with adult cells than fetal (cord) cells are called *anti-I*; these antibodies that were detected in our patient are otherwise typically seen in benign lymphoproliferative states. On the contrary, those reacting more strongly with cord cells are called *anti-i*; these antibodies are seen in aggressive lymphomas. Crisp *et al*[1] noted that *anti-I* were common in chronic CAD (74%) and rare in other groups (32 - 33%) while *anti-i* and other cold agglutinins were rare in chronic CAD and common in lymphoma and Waldenstrom macroglobulinaemia. In chronic CAD and Waldenstrom macroglobulinaemia cold agglutinins usually had kappa light chains (92% and 71% respectively) whereas in lymphoma 71% of cold agglutinins had lambda light chains.

The severity of the anaemia is directly correlated with the thermal amplitude of the autoantibody. The higher the temperature at which the cold agglutinin can react with the red cell, the more rapid the destruction of the cell. Extravascular haemolysis occurs because membrane receptors for C3b on hepatic macrophages allow binding and ingestion of C3b coated red cells.

No treatment is usually required for the self-limited episodes associated with this disease except avoidance of cold. If the patient requires transfusion of red cells, the cross-match must be done at 37°C to find compatible units of blood. The blood must be warmed to body temperature before transfusion. Therapy with chlorambucil or cyclophosphamide[2] may be helpful for patients with chronic CAD of greater severity. These agents are sometimes used to reduce cold agglutinin titers in patients with B cell malignancies. Prednisolone[2] is usually not useful in treatment because corticosteroids do not impair macrophages binding of C3b coated red cells. Splenectomy[2] is usually not beneficial because hepatic clearance of red cells predominates. Although the results of prednisolone or glucocorticoids have generally been disappointing, exceptions have been reported[3]. Cold agglutinin disease tends to be chronic and unremitting. The underlying lymphoproliferative disease dominates the overall prognosis, if present. Patients with idiopathic CAD often have a relatively benigh course and survive for many years. Occasionally, death results from infection or, in the case of secondary CAD, from an underlying lymphoproliferative process. In one study[1], survival time from diagnosis was on average 2 years in lymphoma, 2.5 years in Waldenstrom macroglobulinaemia, more than 6 years in CLL and more than 5 years in chronic CAD. Low-grade non-Hodgkin's lymphoma is usually an indolent condition; an effective initial management policy for most patients is simply to observe them closely. Treatment is indicated if the disease is aggressive, involving vital structures (e.g. the liver), or is causing significant symptoms. The major controversy is whether any treatment can induce long-term disease free survival and alter the natural course of the disease. Whether improvement in the cold antibody haemolytic anaemia parallels the control of the underlying lymphoproliferative process remains uncertain.

References

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