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Case Reports

Cold Agglutinin Disease Secondary to Multiple Myeloma in a Psoriatic Patient

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Abstract:

Cold agglutinin disease (CAD) is a chronic compensated hemolytic anemia. We report a case of cold agglutinin disease secondary to multiple myeloma (MM) in a patient of erythrodermic psoriasis. The patient presented with acral cyanosis, progressive weakness and generalized desquamating scaly lesions. After confirming the diagnosis (80-90% plasma cells in bone marrow, M- spike in serum protein electrophoresis, G-λ restriction pattern in immune electrophoresis) he was given chemotherapy with CTD (cyclophosphamide, thalidomide and dexamethasone) protocol. His clinical symptoms improved and he has now completed 4 cycles of chemotherapy. The interim follow up showed achievement of PR (partial response).

Key words: *Cold agglutinin disease, multiple myeloma, psoriasis*

Introduction:

Cold agglutinin disease (CAD) is a chronic immune haemolytic anaemia due to agglutination of red blood cells (RBC) within microvasculature by cold agglutinins (CA) which reacts best at 4°c. CAD is usually secondary to Waldenstörm's macroglobulinaemia (WM), chronic lymphocytic leukaemia (CLL), angioimmunoblastic lymphoma, T-large granular cell lymphoma, multiple myeloma and IgM-myeloma and rarely, viral and bacterial infections.[1,2,3] On exposure to cold, antigen –antibody complex activates complement generating C3b. In warm central circulation, the CA falls off the RBCs while the bound C3b causes their preferential destruction in liver. Intravascular haemolysis can occur but hepatic destruction is the principal mechanism of haemolysis in CAD the degree depending on thermal amplitude and titre of cold agglutinins.

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Mild chronic haemolytic anaemia, acrocyanosis, livedo reticularis and very rarely digital gangrene can occur when it is associated with cryoglobulin.[2] Hepatosplenomegaly and/or lymphadenopathy can be found in secondary CAD. 50% patients are transfusion dependant at some point of the disease course.[4] Large masses of agglutinated red cells are seen in the blood film. Reticulocyte count, serum bilirubin and lactate dehydrogenase level are elevated. Because the CA dissociates, the DAT with anti-Ig can be negative, but by definition, is positive with anti-C3dg.

Treatment options include single or combination chemotherapy with alkylating agent, immunotherapy, avoidance of cold and red cell transfusion through in-line blood warmer when required. Corticosteroids and splenectomy are ineffective.[1] Combination of Rituximab and fludarabine has been successfully used in primary CAD patients. Eculizumab and bortezomib have been used to treat Rituximab-refractory CAD patients.[5,6,7]

Case report:

A-50-year old male, diagnosed of erythrodermic psoriasis by skin biopsy since July 2011, presented to our hospital in October 2011 with acrocyanosis for 4 years, progressive weakness for 1 year. Acrocyanosis was unrelated to fever or sore throat and involved ear helices, tip of nose and tips of fingers and toes with a characteristic sequential change of pallor, blue discoloration followed by redness on warming. Central cyanosis, peripheral neuropathy and digital gangrene were absent as were bone pain and old fractures. He did not have jaundice, haematuria and never received blood transfusion. Examination was remarkable for severe pallor,

raised JVP, bilateral pedal oedema and generalized desquamating lesions including in the soles of feet and onycholysis. Lymphadenopathy was absent. He had hepatomegaly (4cm) without splenomegaly. Ophthalmoscopy revealed bilateral retinal haemorrhage. Other systems were unremarkable.

All tests were done after warming the syringes and slides. Blood count revealed macrocytic anaemia with Hb 4.6 g/dL (MCV 100 fL) and reticulocytosis (7%). Film was leukoerythroblastic and showed schistocytes, nucleated RBC and marked rouleaux formation (Figure 1). LDH was 980 u/L and serum bilirubin was normal. Urine for haemosiderin was negative. Direct Coomb's test was positive (2 on a scale of 4). Cryoglobulin demonstration test was negative and serum showed haemolysis after incubation at 8°c. Viral markers and connective tissue screen were negative for association with cryoglobulinaemia. Bone marrow aspiration was complicated by instantaneous clotting of particles even in EDTA. Marrow was infiltrated by plasma cells comprising 80-90% of the nucleated cells (Figure 2). Serum protein electrophoresis revealed monoclonal band (conc.14.46 g/L) in gamma region and immunoelectrophoresis showed IgG β restriction pattern (Figures 3,4). Bony lesions were absent and corrected calcium level was 10.8 g/dL. The patient was then labeled as a case of IgG myeloma ISS stage IIA (serum albumin 2.95 g/dL and β2 microglobulin was 4.02 mg/L).[8] He was given five units of whole blood transfusion and folate supplements. For MM he was treated with chemotherapy CTD (cyclophosphamide 500mg/d on days 1,8,15, thalidomide 100 mg/d days 1-21 and dexamethasone 40 mg/d on days 1-4 & 12-15). After 4 cycles of CTD, interim follow up showed partial response (PR) with 75.10% reduction in M protein and 5-6% of plamsa cells in the bone marrow. His haemoglobin was 11.5 g/dL without transfusion.β2 microglobulin was 2.05 mg/L.

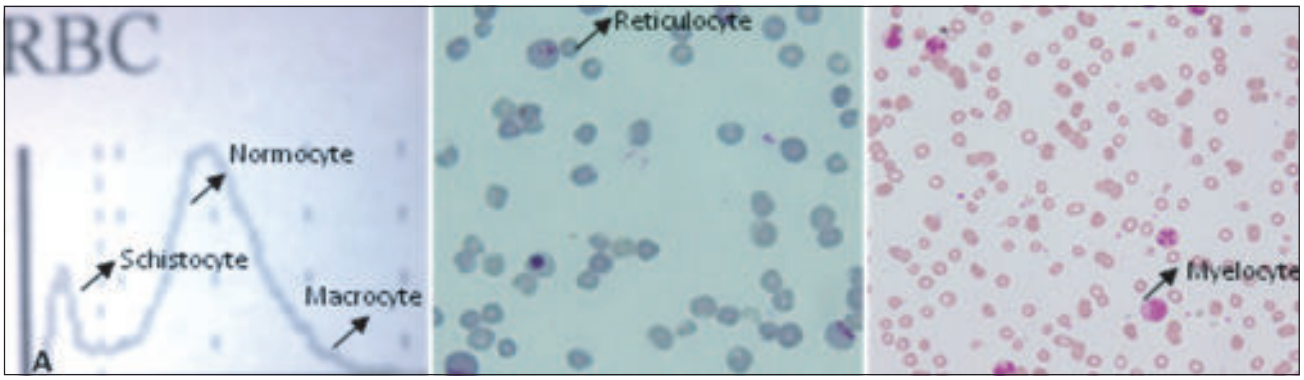

Fig.-1: *Evidence of haemolysis. (A) Red cell histogram showing three different populations of cells schistocyte, macrocytes and normocytes. (B) Reticulocyte count. Reticulocytes with filamentous material are increased in number. New methylene blue stain. Oil immersion objective. (C) Leishman stained blood film (×40 objective) shows rouleaux formation and myelocytes.*

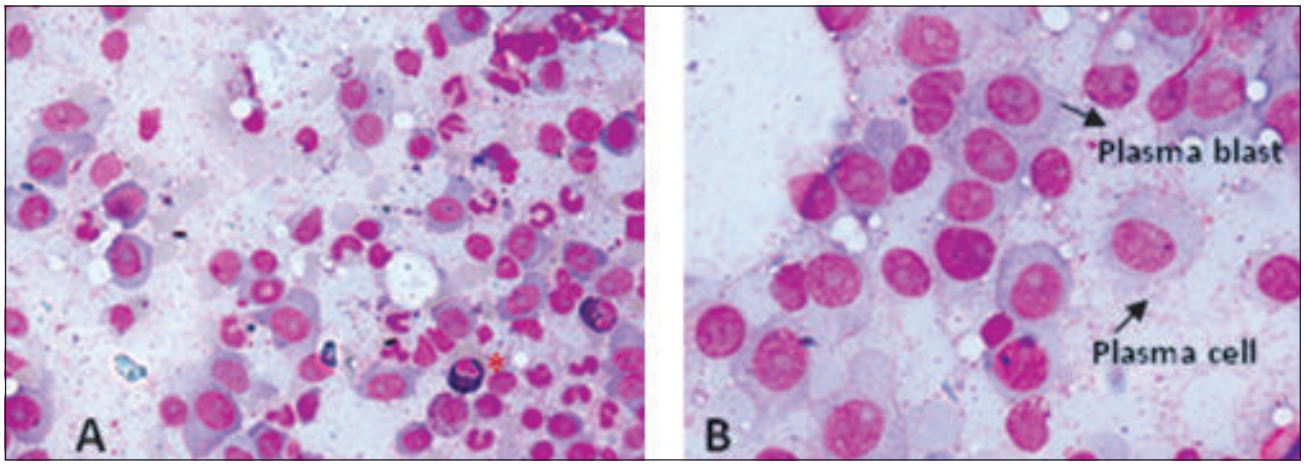

Fig.-2: *Plasma cell infiltrate in bone marrow. Plasma cells constitute 80-90% of non erythroid cells of the bone marrow.). (A)Marrow aspirate showing plasma cells, plasmablasts, mature neutrophils,eosinophilic myelocytes(*) and some band forms.(×10 objective, Leishman stain).(B) Both plasma cells and plasma blasts infiltrate the marrow. Plasmablasts have nucleoli. (×40 objective, Leishman stain).*

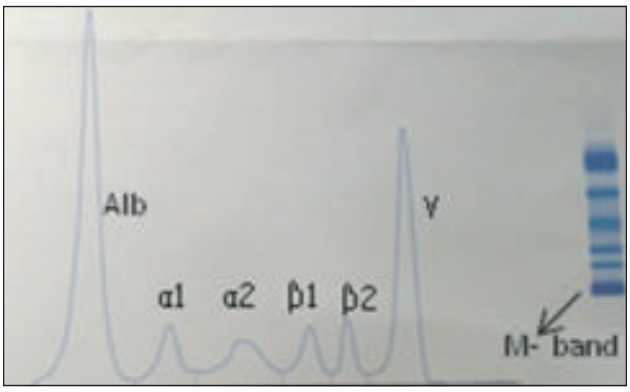

Fig.-3. *Serum protein electrophoresis. Shows monoclonal band at the gamma region (*) having broad base and sharp peak. Alkaline pH.650v. Stain acid blue and destain acetic acid.*

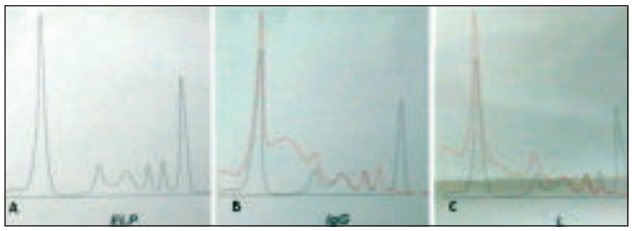

Fig.-4: *Evidence of clonality. Serum protein electrophoresis (A), Immunoelectrophoresis shows gamma heavy chain (B) and lambda light chain (C) restriction pattern.*

Discussion:

The anaemia in CAD is usually mild and haemoglobin (Hb) rarely falls to 5-6 g/dl. Persistent haemolysis and failure of compensatory erythroid hyperplasia by the plasma cell infiltrated bone marrow contributed to unusually severe anaemia in this patient. Liver is the principal site of complement mediated haemolysis in CAD explaining hepatomegaly in the absence of splenomegaly. Normal bilirubin despite haemolysis was from compensatory activity by liver. High LDH could be due to both active haemolysis and multiple myeloma.CA is monoclonal IgMκ (90% cases) but can rarely be IgG, IgA and mixed IgM-IgG. In our case it was IgG and β2**.**

Since CAD was secondary to MM, we recommended anti-myeloma therapy by CTD. After intensive online research no report of association of psoriasis was found with CAD, hence, it is regarded as another unrelated primary disease.

Conflict of interest: None.

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