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Walderström Macroglobulinemia – presented as Cold Agglutinin Disease – a rare phenomenon – a case report

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ABSTRACT
Cold agglutinin disease usually develops as a result of the production of a specific immunoglobulin M auto-antibody directed against the I/i and H antigens, precursors of the ABH and Lewis blood group substances, on red blood cells. Waldenström macroglobulinemia is a distinct clinicopathological entity defined as a B-cell neoplasm characterized by lymphoplasmacytic infiltration of the bone marrow associated with IgM paraproteinemia. We report a case of 70 years old man presented as cold agglutinin disease later diagnosed as Waldenström macroglobulinemia.

Key Words: Waldenström macroglobulinemia, Cold agglutinin disease.

I. INTRODUCTION

Waldenström macroglobulinemia is a distinct clinicopathological entity defined as a B-cell neoplasm characterized by lymphoplasmacytic infiltration of the bone marrow. It is associated with IgM paraproteinemia.[1] It is a rare and slowly progressive disorder, a variant of lymphoplasmacytic lymphoma (LPL), characterized by high levels of monoclonal immunoglobulin M (IgM) protein in the blood. Clinical features include anemia, thrombocytopenia, hepato-spleenomegaly, lymphadenopathy, and rarely hyperviscosity syndrome. Presence of IgM monoclonal protein associated with more than 10% clonal lymphoplasmacytic in bone marrow confirms the diagnosis.[2]Cold agglutinin disease (CAD) is characterized by an auto-antibody which is able to agglutinate red blood cells (RBCs) at temperatures lower than that of the body, and subsequently to activate the complement system responsible for lysis of RBCs. Patients show haemolyticanaemia of varying degrees of severity, as well as episodes of hemoglobinuria and acrocyanosis, which arise or worsen upon exposure to low temperatures.[3]CAD manifests as either a primary disease, that is, chronic CAD, or secondary to Waldenström macroglobulinemia (WM) or B-cell type malignant lymphoma.[4,5] Secondary CAD also occurs in association with systemic lupus erythematosus or transiently upon Epstein-Barr virus or mycoplasma pneumoniae infection. Cold agglutinins, which are specific for the I-antigen expressed on the surface of red blood cells, belong to the IgM subclass and, in the majority of patients with primary CAD, are monoclonal IgM-kappa antibodies. Primary CAD is most often seen in elderly patients (median age at onset is 67 years (range 30–92 years)) and the incidence rate is 1 per 1 million people per year.[6] Primary CAD may develop in association with various hematological/immunological diseases, including pernicious anemia and common variable immunodeficiency.[7]

Here we present a case report of cold agglutinin disease diagnosed as Waldenström macroglobulinemia.

II. CASE REPORT

A 70 years old man presented with fatigue and weight loss for last four months. He was non diabetic non hypertensive. On examination, he was moderately pale with generalized lymphadenopathy and 4 cm enlarged liver. On collection of blood after venipuncture it was immediately coagulated in room temperature. Initial blood investigation was done after putting it on hot water bath after collection. It was revealed haemoglobin level 7.6 gm/dl, peripheral smear shows clumped of RBCs [Fig 1]. RDW was high. Serum ferritin was normal and the reticulocyte count was 0.77%. No haemoglobinopathy was detected on high-performance liquid chromatography (HPLC). The direct antiglobulin test was negative. The ESR was 116mm/1st hour. His renal and liver functions were normal. Bone marrow aspiration revealed diffuse infiltration by small to medium sized lymphocytes, plasma cells and lymphoplasmacytoid cells noted in 70% of the biopsy area [Fig 2]. Serum protein

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electrophoresis revealed a monoclonal band in the gamma region [Fig 3] and immunofixation revealed IgM, kappa light chain bands [Fig 4], suggestive of Waldenström Macroglobulinemia. Criteria to diagnose Waldenström Macroglobulinemia were fulfilled by the demonstration of an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by clonal lymphoplasmacytic cells.

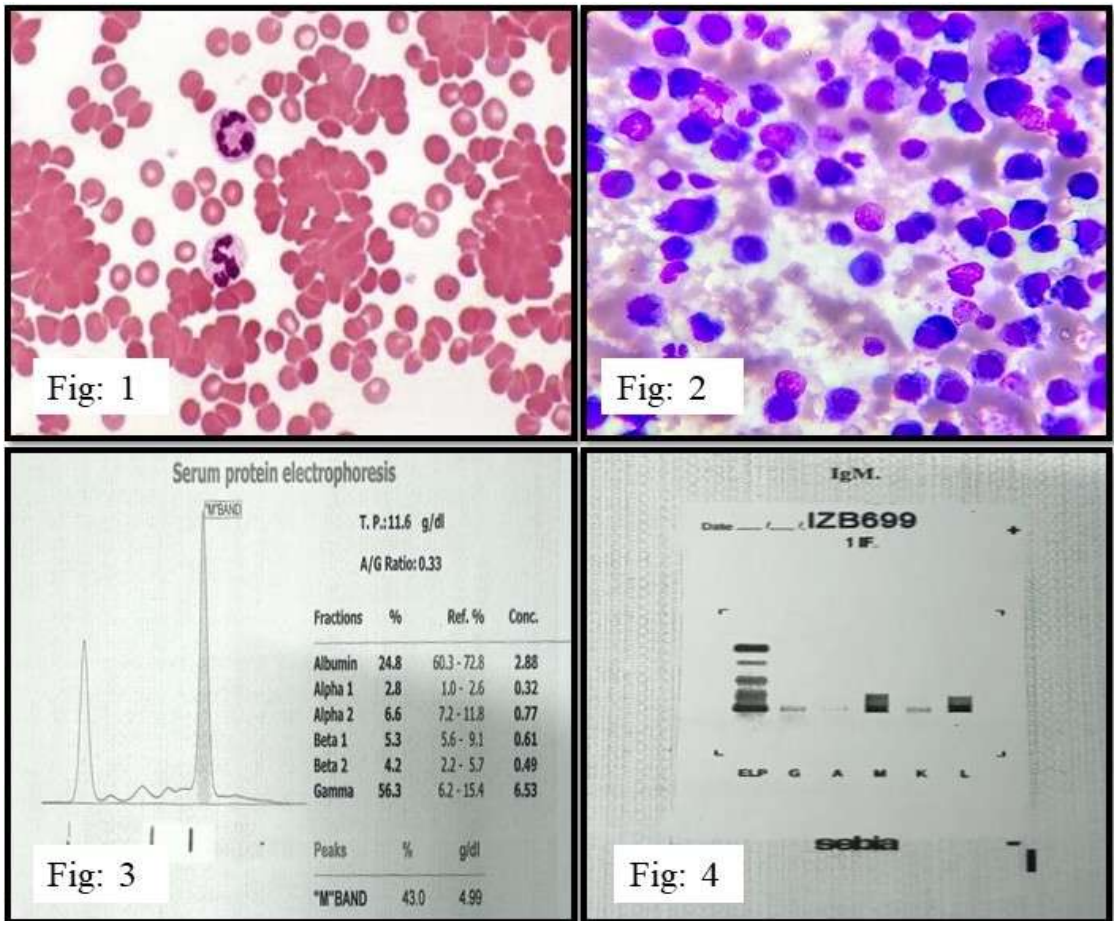

Fig 1: Peripheral blood shows clumps of RBCs. (L&G, 1000x). Fig 2: Lymphoplasmacytic cells in bone marrow aspiration (L&G, 1000x). Fig 3: Serum electrophoresis shows presence of M band in gama globulin region and hypoalbuminemia. Fig 4: Serum immunofixation electrophoresis shows two monoclonal IgM paraprotein.

III. DISCUSSION

Cold agglutinin antibodies are mainly specific for the I/i and H RBCs membrane systems[8], and their production can be stimulated by Mycoplasma pneumoniae or infection by the Epstein-Barr virus, as well as by lymphoproliferative disorders such as Waldenström's macroglobulinemia. The auto-antibody involved is usually an IgM, less frequently an IgA or IgG, which is able to agglutinate RBCs at temperatures of between 0 and 5°C. Complement activation generally occurs between 20 and 25°C, but is also possible at normal body temperature. It is also important to note that agglutination is not necessary for complement activation, especially in patients with high levels of auto-antibodies (wide thermal range of cold agglutinins).[9]

Waldenström macroglobulinemia is a mature B-cell lymphoid neoplasm composed of small B-lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and, very rarely, the spleen, which does not fulfill the criteria for the other small B-cell lymphoid neoplasms.[10] It is a diagnosis of exclusion and when associated with IgM monoclonal gammopathy, it is termed Waldenström macroglobulinemia.

The aetiology of Waldenströmmacroglobulinaemia is unclear, and no specific environmental or occupational exposure, including smoking, has been linked to this entity.

In most of the cases, it appears to be sporadic; however, there have been reports of familial clustering. Waldenströmmacroglobulinaemia can involve various organs, such as the skin, gastrointestinal tract, kidney, liver, adnexae, minor salivary gland, central nervous system, and retina. Features relating to monoclonal gammopathy, including hyperviscosity, cryoglobulinaemia and amyloidosis, may be observed. The symptoms and signs are mainly due to lymphocytic infiltration of marrow leading to cytopenias, especially anaemia, which commonly manifests as fatigue and constitutional symptoms such as fever, night sweats or weight loss.

Waldenströmmacroglobulinaemia is less uncommon than CAD. The occurrence of CA-mediated AIHA in occasional patients with Waldenströmmacroglobulinaemia has been recognized for decades. In 172 consecutive patients with serum monoclonal IgM, including Waldenströmmacroglobulinaemia, monoclonal gammopathy of undetermined significance (MGUS) and IgM-related disorders (IgM-RD), CA activity was detected in 10 (8.5%), all of whom had signs of AIHA. [11] In a series of 122 patients with Waldenströmmacroglobulinaemia requiring therapy, 3% had CAD.[12]

IV. CONCLUSION

The association and overlap between CAD and WM should lead to further studies in order to explore whether recently established or investigational therapies for WM will be effective in CAD.[13] It might be worthwhile to undertake prospective trials using proteasome inhibitors or immune modulatory drugs, alone or in combination with monoclonal antibodies.

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