



WALDENSTROMS MACROGLOBULINEMIA IN A PATIENT WITH DUODENAL PERFORATION

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<p>Article Info <i>Received 04/05/2015</i> <i>Revised 10/05/2015</i> <i>Accepted 16/05/2015</i></p> <p>Key words: Waldenstroms macroglobulinemia, Lymphoplasmacytic lymphoma, Perforation, Paraproteinemia, Immunoglobulin.</p>	<p>ABSTRACT Waldenstrom Macroglobulinemia is a lymphoproliferative disorder that is characterized by the production of a monoclonal immunoglobulin M (IgM) and lymphoplasmacytic bone marrow infiltrate. It is, one of the more infrequent subtypes of Non-Hodgkins lymphoma and defined by the World Health Organization classification as lymphoplasmacytic lymphoma associated with IgM monoclonal gammopathy. In this case report, we present a case of Waldenström's macroglobulinemia in a 68-year old male who was presented with duodenal perforation alone.</p>
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INTRODUCTION

Waldenström's macroglobulinemia is one of the malignant monoclonal gammopathies first discovered by Dr. Jan Gosta Waldenstrom in 1944. It is an indolent, lymphoproliferative disease, characterized by heterogeneous lymphoplasmacytic bone marrow infiltrate and high immunoglobulin M production [1]. Classic features include anemia, hepatosplenomegaly, lymphadenopathy, serum hyperviscosity. There may also be paraneoplastic manifestations like pleural and pulmonary amyloidosis. The pathologic designation of Waldenstroms macroglobulinemia is lymphoplasmacytic lymphoma because of its morphologic and immunophenotypic features. This case report is presented with Waldenström's macroglobulinemia in a 68-year old male who was presented with duodenal perforation alone .

CASE REPORT

A 68 -year- old male presented with complaints of chest pain following fall from his bed. History revealed no

manifestations of any other ailments. On examination, the air entry equal in both lung fields. There was abdominal tenderness and guarding in the epigastrium and right hypochondrium regions. Chest X-Ray showed fracture of # 6 and 7 ribs on left side and #5 and 6 ribs on the right side. X-ray of abdomen showed air under the diaphragm and a diagnosis of intestinal perforation was made. Patient was taken up for laparotomy. A 1 cm perforated duodenal ulcer in anterior wall of first part of duodenum and was repaired. Blood investigations showed hemoglobin: 5 %, platelet: 60,000/ microliter, total Leukocyte count: 5.3 (neutrophil: 66%, lymphocyte: 30%, eosinophil: 4%), erythrocyte sedimentation rate: 112, urea:31 mg/dl, creatinine: 2 mg/dl, total proteins:7.8 g/dl, albumin: 2.7 g/dl. prothrombin time: 21.4 sec. with international normalized ratio: 1.79, lactate dehydrogenase: 735 IU/L, calcium: 7.7 mg/dl and magnesium:1.9 mg/dl. Peripheral smear showed normocytic normochromic anaemia. Since post surgical thrombocytopenia and ecchymosis were evidenced, a



multiple myeloma work-up was done which include Bence-Jones protein in urine (negative), serum electrophoresis (showed M band in gamma region) (Figure 1). Serum beta 2 microglobulin: >4 mg/L (0.81-2.19 mg/L), Free kappa light chain: 75.31 mg/L (3.3-19.4 mg/L). Free lambda light chain: 25.08 mg/dl (5.71-26.30 mg/L), IgA: 40.9 mg/dl (70-400 mg/dl), IgG: 603.8 mg/dl (700-1600 mg/dl) and IgM: 2267.51 mg/dl (40-230 mg/dl). Bone marrows aspirate showed lymphocytoid and

plasmacytoid cells (Figure 2A) and bone marrow biopsy showed lymphoplasmacytoid infiltration with a few mature plasma cells (figure 2 B). In view of the elevated IgM paraproteinemia with lymphoplasmacytic lymphoma consistent with Waldenström's macroglobulinemia in the bone marrow aspiration diagnosis of Waldenström's macroglobulinemia was confirmed. During the follow-up, the patient was found recovered well from surgery. He was referred to the Oncology department for further treatment.

Fig 1. Serum electrophoresis showing M band in gamma region

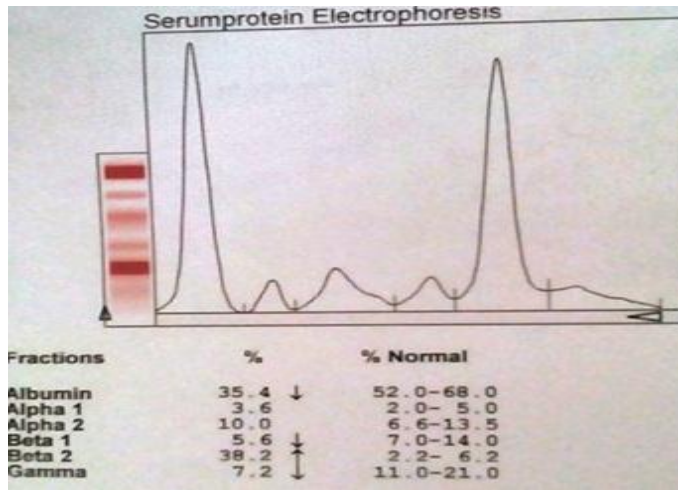
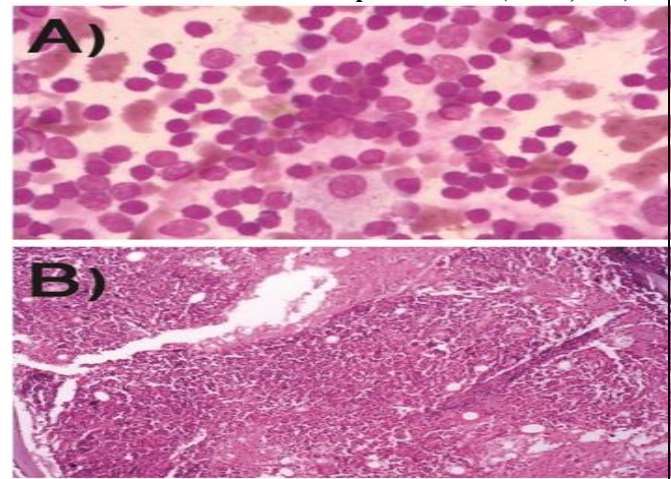


Fig 2. Photomicrographs of A) Bone marrows aspirate showing lymphocytoid and plasmacytoid cells and B) Bone marrow biopsy showing lymphoplasmacytoid infiltration with a few mature plasma cells (H&E; x20)



DISCUSSION

Waldenström's macroglobulinemia is a B-cell lymphoplasmacytic lymphoma characterized by monoclonal immunoglobulin M protein in the serum with lymphoplasmacytic cells infiltration bone marrow [2]. The incidence is high in males, in Caucasians and increases with age [3]. It occurs among elder individuals (in the seventh or eighth decade of life), with a median age of 60s at diagnosis [4]. The age of male patient presented in this case was 68 years.

The pathogenesis of the disease is not fully known. A genetic predisposition has been suggested for the familial cases [5,6]. No such familial predisposition could evidence in this case. The existence of somatic hypermutation in Waldenstrom Macroglobulinemia indicates a role for antigenic stimulation in its development. The IgH variable region genes are commonly mutated and the VH3 gene is often used, suggesting antigen exposure and selection. Studies have shown that clonal IgH and IgL gene rearrangements. The IgH variable region is commonly mutated in Waldenström's macroglobulinemia, but intraclonal variation is usually absent and IgH switching usually does not occur [7]. The clonal proliferation in the bone marrow leading to anemia and the paraproteinemia is responsible for the development of the hyper viscosity syndrome.

Onset is insidious and nonspecific. Many patients are asymptomatic at presentation and are diagnosed incidentally from routine blood work. Weakness, anorexia and weight loss are the most common symptoms. Merlini et al. reported the frequency of presenting features such as weakness (66%), anorexia (25%), peripheral neuropathy (24%), weight loss (17%), fever (15%) and Raynaud phenomenon (11%) [8]. Patients may also present with a history of abnormal bleeding. The patients in this study had no such features at the time of admission except for the abdominal pain due to the intestinal perforation. This may probably ascribed to the hyperviscosity state caused by antigen-antibody reactions triggered by the paraprotein. The laboratory results showed neutropenia hypoalbuminemia and thrombocytopenia with elevated ESR, LDH and creatinine. Later blood test found creatinine as normal. Findings on peripheral blood smear revealed normochromic, normocytic anemia and marked rouleaux formation. Significantly increased free light chain production and an abnormal kappa/lambda ratio (normal ~ 0.26 to 1.65) indicate poorer prognosis as well as increased risk of disease progression.

The laboratory diagnosis of Waldenström macroglobulinemia is contingent on demonstrating a significant monoclonal IgM spike and identifying malignant cells consistent with Waldenström macroglobulinemia (usually found in bone marrow biopsy



samples) [9]. Both manifestations in this case could make the diagnosis. However, differential diagnoses required for chronic lymphocytic leukemia, Non-Hodgkins lymphoma, monoclonal gammopathies of uncertain origin, and also Multiple Myeloma. The image in the Computed tomography scan of the chest, abdomen, and pelvis may show evidence of adenopathy, hepatosplenomegaly, or both. No such evidences were manifested in this case. The bone marrow infiltrate consists of a heterogeneous population of post-germinal center (hypermutated), mature B cells, ranging from small B lymphocytes (CD19+, CD20+) to completely differentiated plasma cells (CD138+), half of which may have visible cytoplasmic inclusions, known as Dutcher's Bodies [10]

Based on prognosis in symptomatic patients, International prognostic scoring system for Waldenstrom macroglobulinemia has developed a treatment guide using multivariate analysis. Five variables were identified which were associated with adverse outcomes: age >65 years, hemoglobin 11.5 %, platelet 100 000/microliter, β_2 -microglobulin >3 mg/L and serum monoclonal protein concentration >70 g/L. The low-risk group is defined as having no more than one of these characteristics, excluding age >65, and is associated of an average 5-year survival of 87%. Intermediate risk patients have two of the above characteristics or age >65, and is associated with 5-year survival of 68% on average. Finally, the high-risk group has three or more adverse characteristics, with a 5-year survival of 36% [11]. Another biological factor found to be associated with prognosis was the von Willebrand factor which showed increased levels in cases of poor prognosis. In addition, von Willebrand factor concentration was associated with the existence of a microenvironment that stimulates the growth and survival of tumor cells [12].

Treatment recommendations based on individual patient and disease characteristics [13]. Combinations of

rituximab with cyclophosphamide/dexamethasone, bendamustine, or bortezomib/dexamethasone provide durable responses and are indicated for most patients. New monoclonal antibodies (ofatumumab), second-generation proteasome inhibitors (carfilzomib), mammalian target of rapamycin inhibitors and Bruton's tyrosine kinase inhibitors are promising. However, different regimen is typically recommended for relapsed or refractory disease, although reuse of a prior effective regimen may be appropriate in selected patients with relapsed disease after long-lasting remission. In young patients with chemosensitive disease and in newly diagnosed patients with very-high-risk features, autologous stem cell transplantation may be considered.

CONCLUSION

This case report concluded that patient with Waldenstrom macroglobulinemia may present with gastrointestinal symptoms without weakness, anemia, or any other manifestations indicative of the disease. Complete haemogram with Patho-radiological studies, if necessary, are required for the correct diagnosis.

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DECLARATION OF INTEREST

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the performance or presentation of the work described in this manuscript.

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