

A 35-year-old Male with Waldenstrom Macroglobulinemia

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Abstract:

Waldenstrom macroglobulinemia is one type of non-Hodgkin lymphoma that presents with a wide range of clinical features mainly due to secretion of the IgM paraprotein and infiltration of lymphoplasmacytic cells. Patients with Waldenstrom macroglobulinemia may experience fatigue, unexplained weight loss, enlarged lymph nodes, abdominal swelling, weakness, nose bleeding, blurring of vision etc. Waldenstrom macroglobulinemia is a disease of elderly individuals. The median age at diagnosis is 65 years, with a slight male predominance. We reported a case of a 35-year-old male who presented with fever, abdominal pain, loose motion and epistaxis. Examination revealed

cervical and inguinal lymphadenopathy with hepatosplenomegaly. Investigation revealed diffuse lymphocyte infiltration on bone marrow study. Protein electrophoresis showed monoclonal gammopathy with high serum IgM level. On the basis of clinical features and investigation reports finally we diagnosed that, this was a rare case of Waldenstrom macroglobulinemia in a young patient. The patient was transfused 5 units of whole blood and was treated following standard treatment protocol with dexamethasone, Bortezomib and G-CSF. Unfortunately, patient died 3 weeks after initiation of treatment.

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Introduction:

Waldenstrom macroglobulinemia (WM) is an uncommon B-cell lymphoproliferative neoplasm accounting for only 6% of all B-cell malignancies¹. Waldenstrom macroglobulinemia is a unique clinicopathologic entity with production of serum monoclonal immunoglobulin M (IgM) as well as lymphoplasmacytic bone marrow and tissue infiltration². However, 27% of patients diagnosed with WM are asymptomatic, presenting with an elevated IgM level (>3000 mg/dl) and lymphoplasmacytic

infiltration of the bone marrow only³. Waldenstrom macroglobulinemia (WM) is rare, with an incident rate of about 3 cases per million people per year in the United states⁴. WM is more common in men than women, and it is much more common among whites. The average age of people when they are diagnosed with WM is 70⁵.

Case report:

A 35-year-old non-diabetic, normotensive, farmer hailing from chitalmari, Bagerhat, Bangladesh admitted into medicine department of Shaheed Suhrawardy Medical College with low grade intermittent fever which was more marked in evening for one month. He also suffered from gradual onset, continuous, non-radiating dragging pain in left hypochondriac region which was associated with loss of appetite, nausea and abdominal fullness and occasional loose motion. At the same time, he noticed a lump in the left hypochondriac region, which was gradually increasing in size. He also noticed nodular swelling of variable size in both cervical and inguinal region. He had several episodes of spontaneous epistaxis which was not associated with nasal trauma, foreign body insertion or foul-smelling discharge per nose. He did not give any history of headache, visual difficulty, itching, purpuric spots anywhere in the body or significant weight loss. He did not suffer from TB or did not give any history of contact with known TB patient. He had history of working in an animal farm house for 3 months 4 years ago.

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On examination, the patient was moderately anemic, cervical and inguinal lymphadenopathy was present, largest one in cervical region was 1×.5 cm and in inguinal region was 2.5 × 2 cm. All lymph nodes were non-tender, firm, discrete, non-discharging, not adherent to the underlying structure or overlying skin. There was also huge hepatosplenomegaly but no ascites. Fundoscopy revealed the retinal blood vessels were dilated and there was huge retinal hemorrhage in both eyes which was related to hyper viscosity changes in retina.

Investigations revealed hemoglobin 7.7 gm/dl, neutrophil was 20%, lymphocyte 67% and platelet count was $115 \times 10^9/L$. Peripheral blood smear was suggestive of lymphocytosis with normocytic normochromic anemia with thrombocytopenia. Serum LDH was within normal limits. Liver function tests, renal function tests and blood sugar were within normal limits. Serum total protein was elevated 121gm/L (64-83gm/L). Ultrasonography of whole abdomen showed

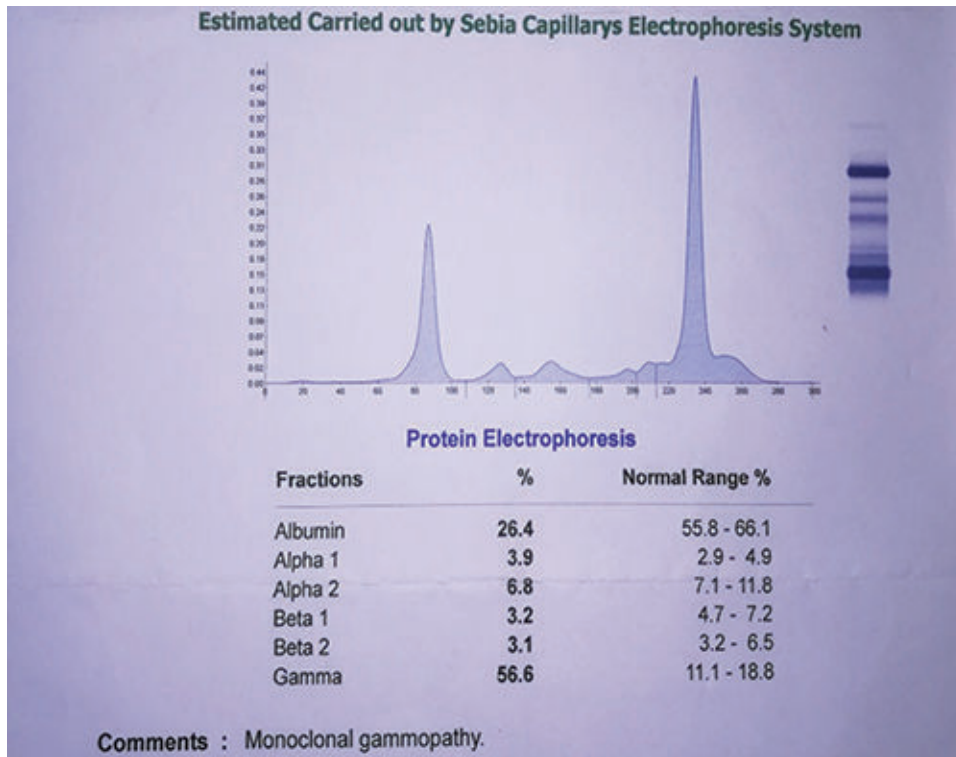


Fig.-1: Serum Protein Electrophoresis

Sample : Blood
 Method : Estimated by Nephelometric System
 Instrument : BN ProSpec, SIEMENS, USA

Test Name	Result	Reference Value
IgG	14.0 g/l	7 - 16 g/l
IgM	66.6 g/l	0.4 - 2.3 g/l
IgA	2.05 g/l	0.7- 4.0 g/l

Fig.-2: Serum Immunoglobulin

hepatosplenomegaly. Bone marrow study revealed hypercellular marrow with diffuse lymphocyte infiltration. Protein electrophoresis showed monoclonal gammopathy with elevated serum IgM level 66.6 g/L.

On the basis of clinical features and investigation reports a final diagnosis of Waldenstrom macroglobulinemia was made in a 35-year-old male. The patient was started on dexamethasone, bortezomib and G-CSF according to standard treatment protocol. Unfortunately, patient died after starting treatment.

Discussion:

Waldenstrom macroglobulinemia (WM) is an IgM-associated lymphoplasmacytic lymphoma, first described over seven decades ago by Jan G Waldenstrom. Although WM is typically a disease of the elderly, with a median age at diagnosis of 67 years, approximately 10% of patients are <50 years of age at diagnosis. Data for young patients are sparse⁶. Our reported case is only 35 years old.

Symptoms in WM are caused by tissue infiltration and the production of immunoglobulin M. Patients usually present at a median age of 63 years usually with constitutional symptoms such as fatigue (66%), fever (15%), anorexia (25%) and weight loss (17%) which are caused by tumor infiltration and clonal expansion⁷.

Infiltration of the liver, spleen and lymph nodes leads to hepatomegaly in 20% of patients, splenomegaly in 19% and lymphadenopathy in 15%. Involvement of other organs such as the lung, kidney, gut and skin are rare^{7,8}.

The circulation, tissue deposition, and autoimmune properties of IgM monoclonal proteins are responsible for an array of clinical manifestations in WM⁹. The most characteristics of these is hyper viscosity syndrome which is caused by the increasing serum concentrations of IgM, resulting in aggregation of red cells and increased serum viscosity. It is seen in 15% of WM patients at diagnosis and is clinically characterized by oronasal hemorrhage, visual defects, and multiple neurological abnormalities^{10,11}. Although younger patients are more likely to present with lymphadenopathy and splenomegaly, have higher IgM levels and hyperviscosity symptoms¹². The reported case here described Waldenstrom Macroglobulinemia presenting with generalized lymphadenopathy with huge splenomegaly.

Anemia (hemoglobin <12 g/dl) is the most common finding in patients with symptomatic WM (63%). It is generally caused by bone marrow infiltration, which less frequently can lead to thrombocytopenia (16%) and leukopenia (4%)^{7,8}. Our case was moderately anemic 7.7 gm/dl with neutropenia and thrombocytopenia.

In case of WM approximately three years is required for the elevation of serum IgM level upto 6000 mg/dl. From this median time, symptomatic hyper viscosity occurred within 3 months, which was revealed in a recent retrospective study on 825 newly diagnosed WM patients¹³. So, in an otherwise asymptomatic WM patient serum IgM level > 6000 mg/dl can be used as a criterion for therapy initiation. Even in absence of clinical manifestations early micro circular damage may be found in fundoscopic examination in a patient with serum IgM level >3000 mg/dl¹⁴.

Serum immunoglobulin M level of our patient was 6600 mg/dl. Our patient also had features of hyperviscosity syndrome such as epistaxis and retinal hemorrhage in both eyes.

Therapy of WM can be initiated on the basis of symptoms such as recurrent fever, night sweats, fatigue, anemia and weight loss rather than on the serum IgM levels. In addition, therapy can also be initiated if features of hyperviscosity syndrome, renal insufficiency, cryoglobulinemia, amyloidosis, sensorimotor peripheral neuropathy present¹⁵. Though plasmapheresis is effective in reducing serum viscosity and serum IgM level in the management of hyperviscosity¹⁶, chemotherapy with a combination of rituximab and 2-chloro-2'-deoxyadenosine (2-CDA), or of rituximab and bendamustine, is also effective for WM¹⁷⁻¹⁹. Recently some novel and promising agents such as atumumab, lenalidomide, bortezomib and the BTK inhibitor ibrutinib²⁰ etc. have been recommended for treatment of WM in the international consensus paper. Though bortezomib, dexamethasone and G-CSF were started according to standard treatment protocol, our case was died soon after starting treatment.

Conclusion:

Waldenstrom macroglobulinemia is a very rare entity in 35 years of age. Good clinical suspicion with proper investigation facilities can make diagnosis earlier and easier.

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