Case Report

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Waldenstrom macroglobulinemia with 11q deletion: A rarely diagnosed entity with review of literature

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Abstract:

Waldenstrom macroglobulinemia (WM) is a rare, chronic, and indolent B-cell lymphoproliferative disorder characterized by bone marrow infiltration by small lymphocytes, lymphoplasmacytoid cells, and plasma cells along with the presence of a detectable monoclonal immunoglobulin M. It represents 1%–2% of hematological malignancies with an overall incidence of 3–4 cases/million persons/year. Some deletions are associated with a more aggressive IgM gammopathy and have a high probability of symptomatic transformation. 6q deletion, the most common cytogenetic abnormality, which is present in 42% of cases whereas 11q deletion is rare in WM and is present in only 8% of cases. We are presenting a case of a 70-year-old male patient diagnosed as WM with 11q deletion.

Keywords:

11q deletion, immunoglobulin M gammopathy, Waldenstrom macroglobulinemia

Introduction

Waldenstrom macroglobulinemia (WM) is a rare, chronic, and indolent B-cell lymphoproliferative disorder.[1] The 2016 revision of the WHO classification of lymphoid neoplasms has defined WM as bone marrow infiltration by small lymphocytes, lymphoplasmacytoid cells and plasma cells along with the presence of a detectable monoclonal immunoglobulin M (IgM).[2]

WM patients present mostly with nonspecific clinical symptoms such as weakness, anorexia, and weight loss.[3] Morphologically, it is a diagnostic dilemma as the bone marrow lymphoplasmacytoid cells can demonstrate a broad spectrum of findings that overlap with other B-cell lymphomas having plasmacytic differentiation. Hence, WM is a diagnosis of exclusion.[1,4]

The American Society of Hematology, in their annual meeting in 2011, stated that MYD88 (L265P) mutation is present in most cases of WM, thus changing the view of this disease remarkably.[5] This mutation is recognized now in >95% of cases, while 30%–40% of cases show CXCR4 mutations.[5]

Recent advances made in genomic profiling of these patients have impacted the diagnosis, presentation, treatment outcome, and survival overall. Some deletions are associated with a more aggressive IgM gammopathy and have a high probability of symptomatic transformation. 6q deletion, the most common cytogenetic abnormality, which is present in 42% of cases whereas 11q deletion is rare in WM and is present in only 8% of cases. 11q deletion and trisomy 4 adversely affect the clinical and biological parameters.[6]

Despite having an incurable disease course, median survival has improved from 5 to 8 years in patients with WM.[7] Here, this case report weighs in on the gravity of a

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thorough hematological workup which helps make an early diagnosis, prevents complications, and improves survival outcomes. As reviewed in the literature, cytogenetic studies, though not mandatory, determine the prognosis.[6]

Case Report

A 70-year-old male patient presented with weakness, generalized body aches, and shortness of breath on exertion for 4 months. On examination, there was pallor but no evidence of icterus, clubbing, cyanosis, or lymphadenopathy. The patient did not have hepatosplenomegaly. He was a known hypertensive. Complete blood count (CBC) showed normocytic normochromic anemia (hemoglobin 5.6 g/dl) and thrombocytopenia (total platelet count 1 lakh/µl). Total and differential leukocyte count was normal. The patient was admitted as a suspected case of multiple myeloma, 1 unit of PRBC was transfused, and the relevant investigations were advised.

Serum protein electrophoresis revealed hypoalbuminemia and a monoclonal gammopathy ("M" spike) seen in the beta-2 globulin region [Figure 1a]. Immunofixation electrophoresis identified the "M" spike as IgM and Kappa. An immunoglobulin profile was advised, which showed high serum IgM levels (>3300 mg/dl) [Figure 1b]. Free serum kappa light chain was increased (534 mg/dl) and kappa/lambda free light chain ratio (FLC) was 43.065 suggesting a monoclonal gammopathy. There was a significantly high serum beta 2 microglobulin level of 11874 ng/ml and a normal serum LDH level. The patient had low serum Vitamin B12 levels. The rest of the biochemical parameters were within normal limits.

Bone marrow aspiration and biopsy revealed a hypercellular marrow. Erythroid, myeloid, and megakaryocyte hematopoiesis were markedly suppressed and replaced by sheets of atypical cells present in an intertrabecular pattern. The cells were small to medium sized, having scanty cytoplasm and coarse clumped chromatin to some with vesicular chromatin and prominent nucleoli [Figure 2a]. These mature and immature lymphoid cells comprised 70% of marrow elements with 50% immature forms. Few plasmacytoid cells were seen [Figure 2b], suspecting a hematolymphoid neoplasm and immunohistochemistry (IHC) was done. On IHC, the lymphoid cells and plasmacytoid lymphocytes showed strong membranous positivity for CD-45 and CD-20 [Figure 2c]. Focal scattered positivity for CD-38 [Figure 2h] and CD-138 in the plasma cells. IHC was negative for CD-3, CD-5, CD-10, and CD-23 [Figure 2d-g] excluding other small B-cell lymphomas. Thus, considering the clinical findings, serum electrophoresis, immunofixation electrophoresis, bone marrow aspiration, and biopsy findings, the diagnosis of Waldenstrom macroglobulinemia was rendered.

Interestingly, fluorescence *in situ* hybridization (FISH) revealed 11q deletion in 50% of interphase cells studied. The cytogenetic study complied with it, showing a deletion in the long arm of chromosome 11 [Figure 1c], found in 43% of the metaphases studied. However, FISH did not reveal any translocation related to the IGH gene. MYD88$^{L[265]P}$ mutation was noted by polymerase chain reaction (PCR). Positron emission tomography–computed tomography (PET-CT) reported the presence of fludeoxyglucose uptake in supradiaphragmatic and infradiaphragmatic nodes, suspicious for a low-grade

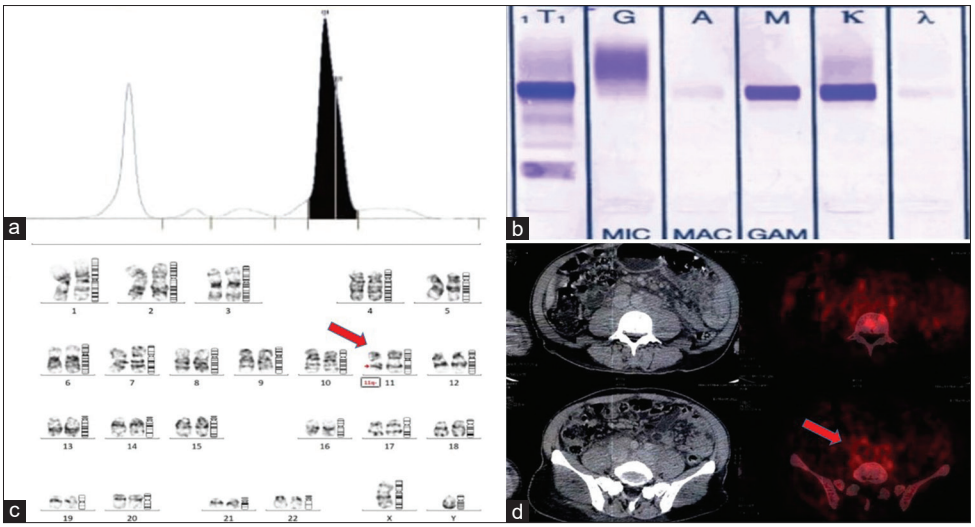

Figure 1: (a) Serum protein electrophoresis revealed hypoalbuminemia and a monoclonal gammopathy ("M" spike) seen in the beta-2 globulin region. (b) Immunofixation electrophoresis identified the "M" spike as IgM and Kappa. (c) The cytogenetic study complied with it, showing a deletion in the long arm of chromosome 11. (d) Positron emission tomography–computed tomography reported the presence of fludeoxyglucose uptake in supradiaphragmatic and infradiaphragmatic nodes, suspicious for a low-grade lymphoma

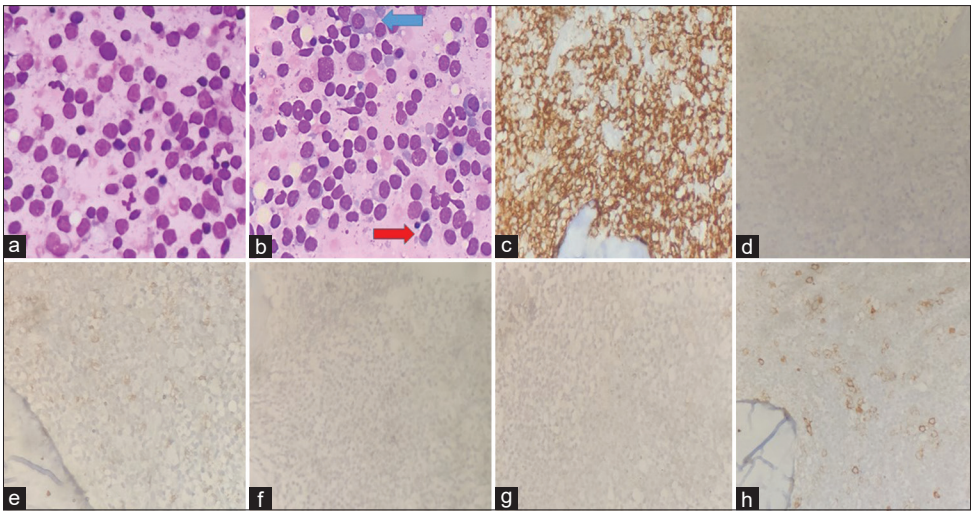

Figure 2: (a) Bone marrow aspiration smears show small to medium sized cells having scanty cytoplasm and coarse clumped to vesicular chromatin and prominent nucleoli admixed with mature lymphocytes (H and E, ×200); (b) Few plasma cells (blue arrow) along with few plasmacytoid cells (red arrow). (H and E, ×200); (c) Strong membranous positivity in >95% of tumor cells (IHC, ×200); (d-g) Negative for CD3, CD5, CD10, and CD23, respectively, (IHC, ×200); (h) scattered positivity for CD38 (IHC, ×200)

lymphoma [Figure 1d], and mild splenomegaly which appeared metastatic and metastasis in soft tissue of presacral and mesenteric region. There was no osteoporosis or any evidence of active disease elsewhere in the body.

Based on his age, comorbidities, and performance status, the patient was not eligible for intensive chemotherapy. After explaining to him the risks and benefits, 4 cycles of rituximab (375 mg/m^2) with acalabrutinib (100 mg) BD were given. His symptoms improved significantly and CBC parameters were normalized. Repeat PET-CT was in complete remission. After 6 months of chemotherapy, a repeat bone marrow aspiration and biopsy to check for remission suggested a residual infiltrate of a similar morphology constituting 60% of marrow nucleated cells. The patient did not give consent for a repeat IHC.

Discussion

WM was first described in 1944 by a Swedish physician, Jan Gosta Waldenstrom, who reported 6 cases of bleeding from the nose and mouth, anemia, hypofibrinogenemia, and enlarged lymph nodes. He found proliferating plasma cells in their bone marrow and the increased amount of macroglobulin made their blood sticky.[8] WM is a rare mature B-cell lymphoma representing 1%–2% of hematological malignancies with an overall incidence of 3–4 cases/million persons/year.[6] The incidence is higher in men with a median age of presentation in the seventh decade.[6]

The Mayo Clinic Criteria for WM diagnosis recommends the presence of monoclonal serum IgM of any concentration and at least 10% bone marrow lymphoplasmacytic infiltration.[9] The patient, in this case report, had fulfilled the said criteria. WM is a sporadic disease with a possible role of antigenic stimulation in its development due to the existence of somatic hypermutation in the B-cell clone.[1,10]

These patients were frequently present with nonspecific symptoms such as weakness, anorexia, and easy fatigability. The physical findings in WM result from infiltration into the BM by the malignant clone, causing cytopenias and progressive anemia or into extramedullary tissues such as lymph nodes, liver, and spleen causing organomegaly. The hyperviscosity state and derangement of hemostasis by the elevated monoclonal IgM paraprotein concentration and its antigen-antibody reactions result in abnormalities in bleeding and coagulation, Raynaud's phenomenon, headache, and visual and hearing problems.[3,11] In this case, the serum IgM levels were significantly high, but the patient did not have related symptoms. Moreover, serum FLC is higher in symptomatic patients and is associated with increased beta-2 microglobulin, hypoalbuminemia, and anemia, as is seen in this case.[10]

For a diagnosis, BM biopsy is crucial to assess the extent and pattern of infiltration and morphology of the neoplastic cells. There is an intertrabecular pattern of infiltration by a polymorphic population of small lymphocytes, plasma cells and lymphoplasmacytoid cells and often increased mast cells.[6,12] IHC and flow cytometry should be performed for diagnosis and to exclude other B-cell malignancies with plasmacytic differentiation such as marginal zone lymphoma, chronic lymphocytic leukemia, follicular lymphoma, and mantle cell lymphoma.

Based on IHC and flow cytometry, the lymphocytes and lymphoplasmacytic cells in WM express light chain restricted sIgM, pan B-cell markers such as CD19, CD20, CD22, and CD79a and are typically negative for CD5, CD10, CD103, CD23 and BCL6. There is frequent expression of CD25 and CD38. The plasma cells are CD138, CD45, and CD19 positive, unlike plasma cell myeloma and also show light chain restriction.[6,12] Correlating the clinical features, increased levels of serum IgM, bone marrow findings and IHC, a diagnosis of WM was given.

It has been hypothesized that clonal cells of WM arise from postgerminal B-cells that undergo somatic mutations in a chronic immunologically activated environment.[10] Strikingly, a mutation detected by PCR, leading to leucine to proline substitution in the myeloid differentiation primary response 88 genes, $MYD88^{L[265]P}$ is present in >90% of WM patients though it is not diagnostic.[6,10] Its low prevalence in IgM-MGUS suggests that it is associated with disease progression. This mutation also provides a potential target for treatment.[7,10,13]

FISH identifies a pattern of chromosomal abnormalities that help in diagnosis and prognostication and differentiating WM from other B-cell lymphomas. 6q deletion, the most common cytogenetic abnormality, is present in 42% of cases and is associated with an adverse prognosis. It is not observed in IgM-MGUS. Other abnormalities such as 11q and trisomy 4 adversely affect the clinical and biological parameters.[6,13-15] 11q deletion is rare in WM and is present in only 8% of cases. However, it is shared with other low-grade B-cell neoplasms.[6,13-15] IgH translocations involving heavy immunoglobulin locus are seen in only 3% of cases of WM. It was absent in this case.[10,15]

WM is a distinct lymphoproliferative neoplasm with unique cell surface characteristics and genetics.[13] Kastritis *et al*. recommended a Revised International Prognostic Scoring System for WM (rIPSSWM), which is used only for symptomatic patients of WM. It categorizes patients based on age (<65 years scored 0, 66–75 years scored 1, and >75 years scored 2) and beta 2 microglobulin >4 mg/l, LDH >250 IU/L, serum albumin <3.5 g/dl each given a score of 1. According to the cumulative scores, 5 prognostic groups (Score 0 = Very low risk, 1 = Low risk, 2 = Intermediate risk, 3 = High risk, and 4 or 5 = Very high risk) were identified with a 3-year WM-related death rate of 0%, 10%, 14%, 38%, and 48% and 10-year survival rate of 84%, 59%, 37%, 19%, and 9%.[6,16] However, RIPSSWM does not consider molecular or genetic characteristics.[16] This case falls into the high-risk category.

An asymptomatic WM patient without end-organ damage is carefully observed. For nonbulky disease in symptomatic cases, rituximab monotherapy is given, while those with bulky symptomatic disease require combination regimens such as chemotherapy. Ibrutinib monotherapy is effective in rituximab-resistant cases, especially in those with MYD88 mutations. Emergency plasmapheresis is required in hyperviscosity syndrome. In select cases, autologous stem cell transplantation is considered.[17]

Conclusion

WM is a rare neoplasm. The presence of 11q deletion in WM is infrequent too. Although indolent and incurable, there are improved survival outcomes if appropriately diagnosed and treated. Therefore, awareness about this disease and a thorough hematological workup is essential as the patients mostly present with nonspecific symptoms. There is clear evidence of a relationship between genetic factors such as $MYD88^{L[265]P}$ mutation and 11q deletion with the development and progression of WM. Hence, they can be used in the development of potential therapeutic targets.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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