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CASE REPORTS

IgM Myeloma or Waldenstrom's Macroglobulinemia Is the Big Question?

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ABSTRACT

Although critical from therapeutic and prognostic perspectives, differentiating IgM Myeloma (MM) from Waldenstrom's macroglobulinemia (WM) is fraught with failure. WM can usually be distinguished from IgM MM by the lymphoplasmacytic versus pure plasmacytic morphology, absent versus present lytic bone lesions, and immunophenotypic findings. However, all these features have their own limitations; hence, it requires constant vigilance and periodic re-evaluation. Here we describe a case of a 70-year-old woman initially diagnosed as smoldering IgM MM, who eventually turned out to have WM.

INTRODUCTION

Although critical from therapeutic and prognostic perspectives, differentiating IgM multiple myeloma (MM) and Waldenstrom's macroglobulinemia (WM) is fraught with failure (1). Here we describe a case of an elderly woman initially diagnosed as smoldering IgM MM, who eventually turned out to have WM. □

CASE REPORT

A 70-year-old woman was referred to hematology-oncology specialty clinic for increased total protein and anemia. The patient had a history of rheumatoid arthritis diagnosed one year back and complained of chronic back pain and multiple joint pains, otherwise she was asymptomatic. Past medical history was also significant for depression, irritable bowel disease, fatty liver, osteoporosis and hypothy-

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roidism. She had undergone 3 caesarean sections and skin cyst removal. Her medications included escitalopram, levothyroxine, combination of chlorthalidone and clidinium, ibandronate, calcium citrate and vitamin D. She was started on methotrexate, which was subsequently discontinued because of transiently elevated transaminases. Family history was significant for Parkinson's disease and breast cancer in mother; history of alcohol abuse in father, head and neck cancer in uncle and back tumor in aunt. Her recent mammogram and colonoscopy were normal. She had a history of 50 pack year smoking but denied drinking or recreational drug use.

On examination, she had blood pressure of 110/70 mmHg, heart rate of 80/minute, respiratory rate of 20/min and temperature of 99.7 F. Fine expiratory wheezes were noted on chest auscultation. She did not have any petechiae, bleeding from any site, lymphadenopathy, or hepatosplenomegaly. Rest of the examination was unremarkable.

Laboratory test results showed white count of 4600/ μ L, haemoglobin of 11.6 g/dl, platelet count of 137,000/ μ L, and lactate dehydrogenase of 149 U/L. She had albumin of 3.4 g/dL, normal glucose, calcium and electrolytes, and liver and renal function tests. Serum protein electrophoresis (SPEP) revealed elevated protein of 8.6 g/dl with M-spike of 1.71 g/dl; immunofixation confirmed IgM-kappa monoclonal protein. Further testing demonstrated: beta-2 microglobulin of 2.6 mcg/ml, serum free kappa light chain level of 72 mg/L, free lambda light chain level of 17.9 mg/L and free kappa/lambda ratio of 4.02, serum viscosity of 2 cP, serum IgM level of 2247 mg/dl, normal levels of IgA and IgG and collagen I C-terminal cross-linked telopeptide level of 154 pg/ml. Bone marrow biopsy examination highlighted normocellular marrow with unremarkable trilineage haematopoiesis and 12% plasma cells. Flow cytometry determined CD 45 +, CD5-, CD 10-, CD19-, CD 20-, CD 38+, CD 138+ plasma cells. Immunohistochemistry results illustrated kappa light chain restricted CD138 + plasma cells with small clusters. Karyotyping demonstrated a normal 46, XX pattern. Skeletal survey did not show any osteolytic lesion but showed osteopenic bones and osteoarthritic changes in cervical and lumbar spine. Magnetic resonance imaging (MRI) of thoracic and lumbar confirmed no osteolytic lesion, but mild

facet arthropathy within the lower lumbosacral spine. Computed tomography (CT) of abdomen and pelvis determined the absence of any organomegaly.

A diagnosis of smoldering IgM MM was considered primarily based on the bone marrow findings of CD138+ pure plasma cell dyscrasia and the absence of typical features of WM (such as lymphadenopathy, hepatosplenomegaly and hyperviscosity). However, given its rarity and the absence of osteolytic lesions on skeletal survey, Waldenstrom's macroglobulinemia was still considered as a possibility. Given the lack of end-organ dysfunction, the patient was closely monitored with regular clinical evaluation as well as monitoring of complete blood count, comprehensive metabolic panel, SPEP with immunofixation, LDH, serum IgM level, free light chain levels and viscosity. The patient's clinical and laboratory status remained to be stable, hence, it was decided not to start her on any chemotherapy.

Two years later, the patient underwent resection of 0.6 cm intramammary lymph node which revealed a low grade CD 20 + B-cell marginal zone lymphoma with fragment of lymphoid infiltrate with large germinal centers and increased number of small to intermediate B-cells, positive for a clonal immunoglobulin heavy chain (IgH) gene rearrangement. Subsequently, the patient was also found to have a palpable splenomegaly. CT chest, abdomen and pelvis showed splenomegaly without enlargement of liver or lymph nodes. Repeat skeletal survey was negative. A repeat bone marrow biopsy done 4 years from the initial visit showed 5-20% of CD20+/CD138+ small lymphocytes with plasmacytic features with over-expression of kappa light chains scattered through the marrow with some areas of island formation. The patient subsequently also developed marginal zone lymphoma over her right paranasal area. Thus, a diagnosis of slowly progressing WM (lymphoplasmacytic lymphoma) was established and the patient was treated with Rituximab. One year after the initiation of Rituximab, the patient is doing well and remains on maintenance therapy. \square

DISCUSSION

IgM MM is extremely rare and accounts for <0.5% of all MM (2). A large series of patients with IgM paraprotein had shown that WM was

the most common cause accounting for nearly 60% of cases whereas MM was not diagnosed even in a single patient (3). Being such a rare disease, there is a lack of large-scale studies of IgM MM with a gap in knowledge about the sensitive and specific case definition.

The diagnosis of IgM MM currently requires the presence of IgM monoclonal gammopathy, $\geq 10\%$ plasma cells on bone marrow biopsy and lytic bone lesions and/or translocation t (11;14) (4, 5). This strict definition lacks sensitivity and fails to diagnose a subset of patients with IgM monoclonal gammopathy with immunophenotypic features suggestive of MM (5). The diagnosis of WM requires the presence of IgM monoclonal gammopathy, bone marrow infiltration by small lymphocytes, plasmacytoid cells and plasma cells, diffuse, interstitial or nodular pattern of bone infiltration and surface Ig+, CD5-, CD10-, CD19+, CD20+, CD23-immunophenotype. It is accepted that WM can be distinguished clinically from IgM myeloma by the lymphoplasmacytic versus pure plasmacytic morphology, absent versus present bone involvement, and immunophenotypic findings (6).

Pure plasmacytic morphology has been considered a differentiating feature (6); however, its presence in a single bone marrow biopsy may not always be reliable as demonstrated by this case. Although unilateral biopsy has been shown to be false-negative in significant percentage of patients with solid tumor, this is not the case for MM (7) and currently National Comprehensive Cancer Network guideline recommends unilateral biopsy for both MM and WM (8). Although it cannot be said with certainty, in retrospect it is possible that the presence of only pure plasma cells in the first bone marrow biopsy could have been the result of the sampling error. Therefore, in cases such as ours, we suggest that repeat or bilateral bone marrow biopsy be considered. Transformation

of WM to MM (9) or extramedullary plasmacytoma (10) have been described, however, to our knowledge, there has not been any case report of transformation of MM to WM and this seems very unlikely.

The presence of lytic bone lesions and/or translocation t (11;14) can differentiate between IgM MM and WM, however, these features may be absent in 20 % of cases (11). Myeloma plasma cells are characterized by loss of CD19, CD27, CD45 along with aberrant expression of CD56, CD20, CD117 and cyclin D1 (12, 13), although IgM MM is associated with lower incidence of CD56 expression (13) and there could be immunophenotypic heterogeneity (14). Even though useful, immunophenotyping of IgM MM and WM can have significant overlap (15). Thus the suggested differentiating features have limitations.

In our patient, subsequent development of marginal zone lymphoma and splenomegaly indicated the possibility of WM, which was confirmed with repeat bone marrow biopsy. This case highlights that differentiating IgM MM from WM can be quite challenging and requires close follow-up and re-assessment. \square

CONCLUSION

Although critical from therapeutic and prognostic perspectives, differentiating IgM MM from WM is fraught with failure. WM can usually be distinguished from IgM MM by the lymphoplasmacytic versus pure plasmacytic morphology, absent versus present bone involvement, and immunophenotypic findings. However, all these features have their own limitations; hence, it often requires constant vigilance and periodic re-evaluation to confirm the diagnosis.

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