IgM multiple myeloma presenting with bleeding tendency: A case report with immunophenotype analysis

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Abstract. IgM multiple myeloma (MM) is an extremely rare lymphoproliferative disease associated with an aggressive clinical course. However, the diagnosis of IgM MM may be complicated by Waldenstrom's macroglobulinemia (WM), particularly when clinical manifestations and morphological features are not typical. It is crucial to distinguish between IgM MM and WM as their prognoses and treatment strategies are different. We report a case of IgM MM presenting with bleeding tendency and an immunophenotype analysis using flow cytometry and immunohistochemistry. Bone marrow cells exhibited a typical phenotype for plasma cells, expressing monoclonal cytoplasmatic IgL-λ, CD38 and CD138 instead of pan-B cell antigens CD19, CD20 and CD22, which are characteristic of the typical immunophenotype of WM. Therefore, the diagnosis of IgM MM was confirmed in this case, highlighting the significance of detailed immuno-phenotypic evaluation when clinical and morphological features are atypical.

Introduction

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in the bone marrow. MM accounts for approximately 10% of all hematologic malignancies (1,2). It is characterized by skeletal destruction, renal failure, hypercalcaemia and monoclonal immunoglobulin (M protein) accumulation in serum or urine. The IgG and IgA type M proteins are most commonly observed. The IgM type is extremely rare, accounting for 0.5% of patients with myeloma (3,4).

The distinction between IgM MM and Waldenstrom's macroglobulinemia (WM) is usually straightforward. The presence of an IgM monoclonal gammopathy with lymphadenopathy, hepatosplenomegaly, hyperviscosity syndrome and lymphoplasmacytoid cell infiltration is characteristic of WM. The possibility of IgM myeloma arises when a patient presents with monoclonal IgM protein, multiple lytic bone lesions and renal insufficiency, particularly in the absence of lymphadenopathy and hepatomegaly. However, it has been noted that typical clinical features, such as lytic bone lesions in IgM MM or organomegaly in WM, are not always present. Therefore, additional diagnostic tools are required for a definitive diagnosis of IgM MM. We present a case of IgM myeloma without multiple lytic bone lesions and renal insufficiency. The diagnosis was confirmed by immuno-phenotype analysis.

Case report

A 57-year-old male complained of repeated epistaxis for one week prior to admission. No organomegaly or lymphadenopathy was documented upon physical and abdominal ultrasound examination. Laboratory findings at diagnosis were: erythrocyte sedimentation rate 147 mm/h, white blood cells $5.07x10^9$/l, hemoglobin 72 g/l, platelets $219x10^{12}$/l, activated partial thromboplastin time 68.3 sec (reference range, 25.5-45.5 sec), creatinine 77.4 μmol/l (reference range, 52-102 μmol/l), blood urea nitrogen 7.48 μmol/l (reference range, 2.86-8.20 μmol/l) and calcium 2.46 μmol/l (reference range, 2.03-2.54 μmol/l). Other routine laboratory parameters were normal. Serum electrophoresis revealed a homogeneous spike in the gamma region identified as an IgM by immunofixation with the presence of IgL-λ in the serum. Nephelometry showed a higher IgM level of 106 g/l (reference range, 0.40-3.00 g/l), a higher IgL-λ level of 11.6 g/l (reference range, 0.9-2.1 g/l), a lower level of IgG 6.13 g/l (reference range, 7.0-16.0 g/l), and a normal level of IgA of 0.64 g/l (reference range, 0.5-4.00 g/l). The ß2-microglobulin level was 3.76 mg/l (reference range, 0.7-1.8 mg/l). Whole body bone scan and an X-ray of the skull and pelvis showed no evidence of osteolytic lesions. Bone marrow aspirate morphology showed a diffuse infiltration of 35% atypical plasma cells. The cells showed eccentrically placed nuclei, intracytoplasmic vacuoles, clumped chromatin and a prominent nucleolus (Fig. 1). Immunohistochemical staining of a bone marrow trephine biopsy specimen revealed CD38- and CD138-positive cell infiltration (Fig. 2). The cells were CD19-, CD20-, CD56- and CD117-negative. As shown in Fig. 3, the flow cytometric analysis of bone marrow cells revealed monoclonal cytoplasmatic IgL-λ. Abnormal cells were positive for CD38, CD138 and CD23. These cells did

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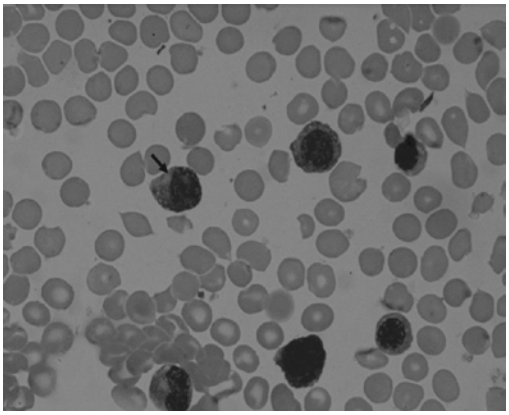

Figure 1. Bone marrow aspirate showing an atypical plasma cell (arrow), with eccentrically placed nuclei, intracytoplasmic vacuoles, clumped chromatin and a prominent nucleolus (Wright-Giemsa; magnification, x1000).

not express B-cell markers, such as CD19, CD20, CD22, nor other markers, such as CD5, CD10, CD25, CD27, CD49e, CD56 and CD117.

The diagnosis of IgM myeloma was made, and the patient was treated with a combination chemotherapy of cyclophosphamide, methylprednisolone and thalidomide. Currently, the patient is free of epistaxis and has shown signs of improvement during the eight months following initial diagnosis.

Discussion

IgM MM is a rare lymphoproliferative disease accounting for approximately 0.5% of MM cases (3,4). Few cases of IgM MM have been reported in the medical literature thus far (5). In 2006, Annibali *et al* (6) reported 4 cases of IgM MM and reviewed another 9 cases published as case reports since 1998.

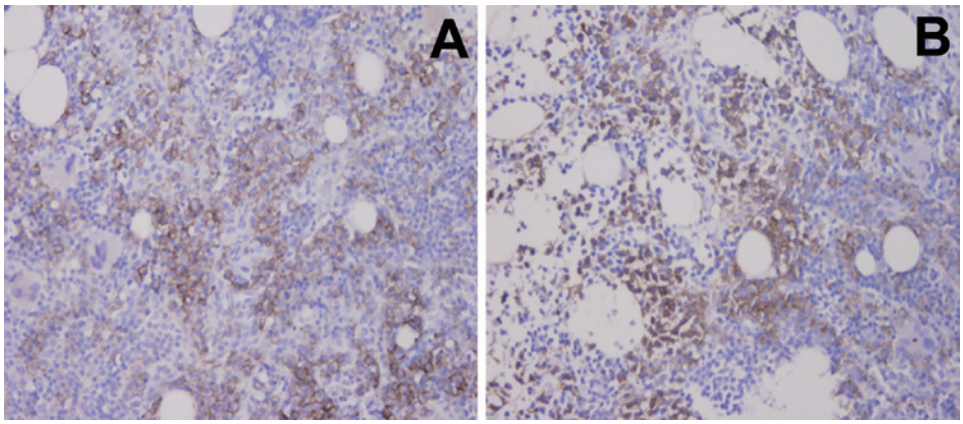

Figure 2. Immunohistochemical staining of a bone marrow trephine biopsy specimen. (A) Positive for CD138 (magnification, x100), (B) positive for CD38 (magnification, x100).

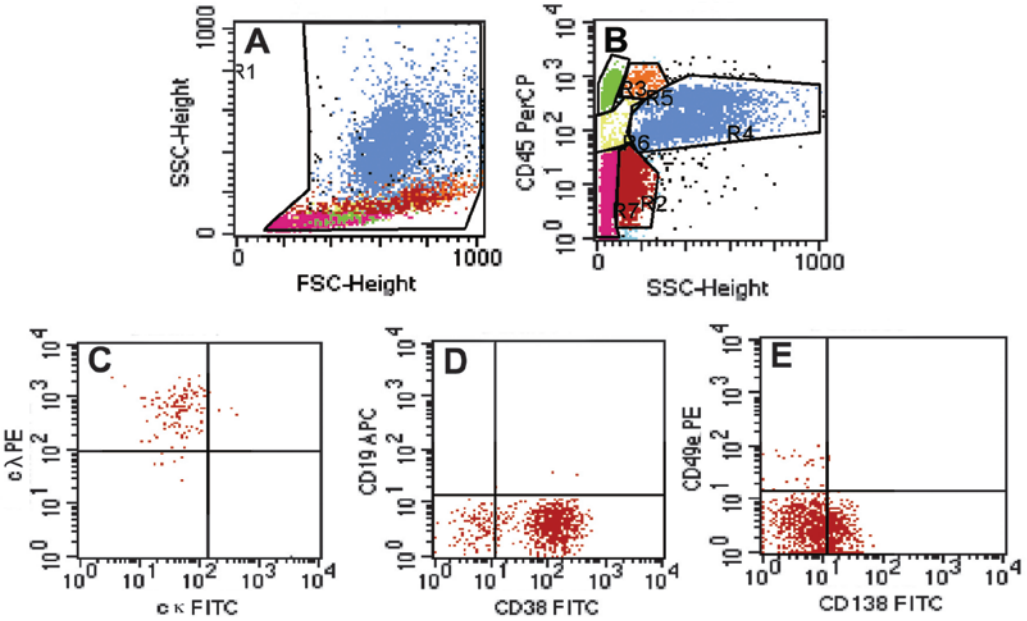

Figure 3. Flow cytometric plots showing (A) the cell population of interest selected in gate R1 on a forward scatter/side scatter (FSC/SSC) dot-plot; (B) the different bone marrow cell populations identified in six gates on a CD45/SSC dot-plot: R2 (abnormal cells 18%), R3 (lymphocytes 11%), R4 (granulocytes 45%), R5 (monocytes 3%), R6 (blast cells 1%) and R7 (nucleated red cells 22%); (C) expression of cytoplasmatic IgL-κ and IgL-λ; (D) expression of CD38 and CD19; and (E) expression of CD138 and CD49e.

Among these 13 patients only 1 patient survived more than 36 months, suggesting that IgM MM is more aggressive than WM which is associated with a median survival of 60 months (7). Therefore, accurate differentiation of these conditions is vital as they run different courses and require different therapeutic approaches.

Regarding the differential diagnosis between IgM MM and WM, the presence of multiple lytic bone lesions with bone marrow plasma cell infiltration supports a diagnosis of myeloma while lymphadenopathy or hepatosplenomegaly with lymphoplasmacytoid bone marrow proliferation favors WM (8). Therefore, certain authors consider lytic bone lesions to be an indicator for differentiating IgM MM from WM (7,9). However, clinical features are not always helpful in differentiating IgM MM from WM. Notably, lytic bone lesions may not be present in IgM MM patients (6), limiting the diagnostic potential. Therefore, the correct diagnosis of IgM MM should be based on plasma cells with >15% nucleated bone marrow cells. Berman (10) recommended morphologic criteria as an ideal way to distinguish between IgM MM and WM. When infiltrated cells do not exhibit typical plasma cell morphology, an accurate immunophenotype characterization is required. However, limited data are available in the literature relating specifically to the phenotype of IgM MM (9,11).

The clinical manifestation of our patient was atypical. He presented with bleeding tendency rather than bone pain or renal failure. No lymphadenopathy or hepatomegaly was documented. The distinction between lymphoid cells with plasmacytoid features and atypical plasma cells was difficult under light microscopy. However, the immunophenotype was suggestive of MM as these cells were uniformly positive for cytoplasmatic IgL-λ and expressed CD38 and CD138, both of which are typical for plasma cells, but absent in WM. Pan-B-cell surface markers, CD19, CD20 and CD22, which are characteristic of the typical immunophenotype of WM, were negative. In addition, the expression of CD5, CD10, CD25, CD27, CD56 and CD117 was negative, disproving the diagnosis of WM (7). The pattern of immunohistochemical staining for the bone marrow trephine biopsy specimen also supported a diagnosis of IgM MM.

In conclusion, our case of IgM MM confirmed the existence of this rare subtype of MM. Given the more aggressive clinical course of patients with IgM MM, detailed immunophenotype evaluation is critical when clinical and morphological features are atypical.

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