Extramedullary Presentation of Biclonal IgG**k** and IgA**k** Multiple Myeloma

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ABSTRACT

Multiple myeloma is characterized by plasma cell infiltration of the bone marrow and the presence of a monoclonal protein in the plasma or the urine in 90% of cases. Major manifestations of the disease are bone pain, anemia, renal insufficiency and recurrent infections. Less frequent presentations are hepatic and splenic enlargement (5% of cases), lymphadenopathy (4%) and biclonal gammopathy (1%). In this report we describe a biclonal multiple myeloma presenting with cervical lymphadenopathy and sternal mass. The immunohistochemical study of the lymph node and the flow cytometric analysis of the bone marrow showed IgGk and IgAk biclonality. In this report the features of lymph node involvement and biclonality constitute a rare presentation of multiple myeloma.

Key Words: Multiple myeloma, Extramedullary myeloma, Lymphadenopathy, Biclonal gammopathy.

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INTRODUCTION

Multiple myeloma (MM) is a neoplastic clonal disease characterized morphologically by plasma cell infiltration of the medullary space and involvement of extraosseous tissues[1-3]. MM is an uncommon malignancy accounting for approximately 10% of haematological malignancies. Biclonal gammopathies are characterized by simultaneous appearance of different M-components[4]. The incidence is approximately 1% of monoclonal gammopathies[5]. The most common combination is IgG and IgA (33%) and followed by IgM and IgG combination (24%)[4,5]. Peripheral lymphadenopathy is a rare presentation observed in only 4% of cases at the diagnosis[6]. We report here a patient who presented with cervical lymphadenopathy and sternal mass. Further evaluation revealed a IgGk and IgAk biclonality in lymph node, bone marrow and peripheral blood. It is interesting that the two rare presentations occur simulta-

neously.

CASE REPORT

A 72 year old male was referred to the thoracic surgery department in 1999 for investigation of fatigue, sternal mass and cervical lymphadenopathy. Physical examination at presentation showed enlargement of the right cervical lymph nodes, 5 cm diameter mass on the sternum and 5 x 4 cm diameter nodule of the thyroid gland. Skin was wet, fine and thin. The remainder of the physical examination was normal.

Lymph node biopsy of the cervical node showed large cell immunoblastic lymphoma. Then the patient was referred to the haematology clinic with suspicion of malign lymphoma. The laboratory examination findings were as follows; haemoglobin 9.6-9/dL, the white cell count was 6.0 x 10^9/L, the erythrocyte sedimentation rate was 120 mm/h and globulin 44 g/L. Serum protein electrophoresis showed monoclonal band on the beta 41 g/L (7.5-18.8) and the gamma 22.9 g/L (9.0-20.0) region. Immunofixation of the serum revealed the presence of two monoclonal components which are IgGk and IgAk. Serum IgG was 2650 mg/dL (650-1600), IgA 5750 mg/dL (45-380), IgM 9 mg/dL (50-300), lambda light chain 30 mg/dL (350-900), kappa light chain 6860 mg/dL (500-1800). The analysis of urine showed kappa light chain paraproteinemia, 595.00 mg/dL (0-1.85). The liver and the kidney functions were normal. X-ray films of the bones revealed lytic areas in the skull, pelvis and the ribs. Bone marrow aspiration showed normal cellularity with 80% plasma cell infiltration.

The immunohistochemical analysis of lymph node was performed for differential diagnosis. Hemotoxilen eosine stained sections showed diffuse infiltration of atypical cells, with wide cytoplasm excentric nucleus with prominent nucleolus (Figures 1,2). Neoplastic cells were CD45 negative but positively stained by plasma cell antigen (PCA) (Figure 3). Heavy chains IgA and IgG were both positive in the cell cytoplasms. IgA positivity was stronger compared to IgG (Figures 4,5). IgM was negative. Kappa light chain was strongly positive while lambda was negative (Figure 6). Fine needle aspiration of the sternal mass revealed atypical plasma cell infiltration.

The flow cytometric analysis of the bone marrow could be done only after a cycle of chemotherapy. Plasma cell population was 10%. Cytoplasmic IgG and IgA were both expressed (Figure 7). Surface k and l monoclonality were not detected. After the third cycle of chemotherapy the flow cytometric analysis revealed the still existing biclonality.

Additionally hyperthyroid status was found as fT3: 9.26 pg/mL (1.80-4.40), fT4: 3.83 ng/dL (0.90-1.70), TSH < 0.005 MIU/mL (0.27-4.20). Scintigraphic analysis of the thyroid gland revealed that right lobe of the gland was hyperplastic and nodules were hypoactive. Fine needle aspiration of the nodule was benign in nature, without a plasma cell infiltration.

The case was accepted as stage III A MM. He was put on melphalan, steroid combination with antithyroid drugs. Partial remission was obtained after six cycles of chemotherapy but the case is now out of medical follow up.

DISCUSSION

Biclonal gammopathy is associated with MM (16%), gammopathy of undetermined significance (65%) and the other lymphoproliferative disease-including lymphoma, macroglobulinemia, chronic lymphocytic leukaemia (19%)[5]. The distribution between various clinical entities, the clinical features of the patients as well as the prognosis seems to be similar to that of monoclonal gammopathies[5]. The incidence of biclonal gammopathy is approximately 1 percent of the incidence of monoclonal gammopathy contrast with 7 percent[5,7]. Biclonal gammopathy associated with MM may result either from a neoplastic transformation of a cell clone undergoing class switching or from independent transforming events yielding proliferation of unrelated plasma cell clones[8]. Two types of biclonal gammopathy can be distinguished:

a. Both homogeneous Ig components carry the same idiotype, suggesting a common precursor and therefore monoclonal in origin (apparent

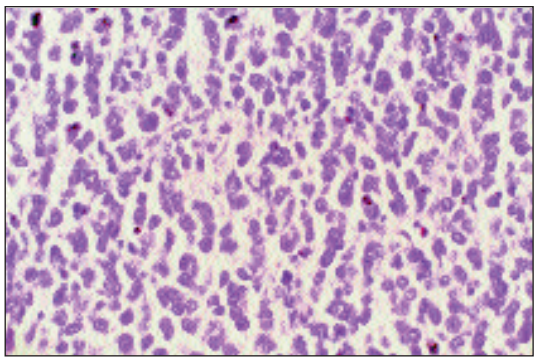

Figure 1. Diffuse atypical plasma cell infiltration in the lymph node (H & E, x 400).

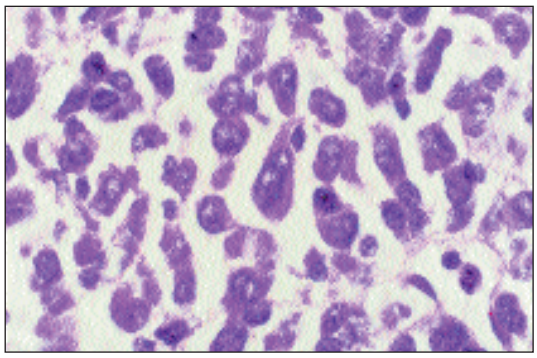

Figure 2. Atypical plasma cell infiltration in lymph node (H & E, x 1000).

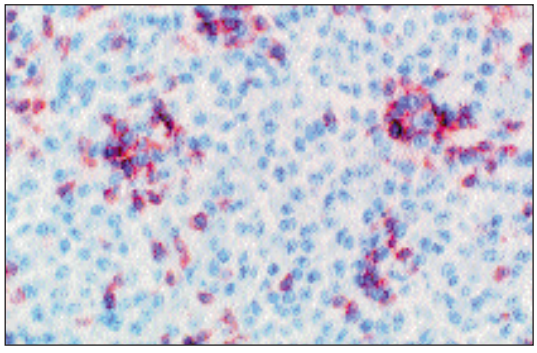

Figure 3. CD45 is negative on the atypical cells, (ABC-peroksidase, AEC), (x 400).

biclonal gammopathy) and

b. The idiotypes of the clones are different and both homogeneous Ig components are not related to each other (real biclonal gammopathy)[9]. Monoclonal immunoglobulins, even of different classes but of a common clonal origin should share variable (V) and joining (J) segments used in their light chains (L) and the same V, diversity (D) and J segments selected for their heavy chains (H) Thus, structural studies on the V_H and V_L regions of these homogenous proteins, should indicate the mono-or biclonality of the cell lineages[10]. In our study we were not able to discrimi-

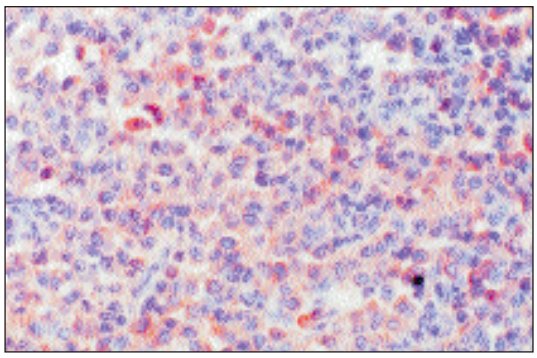

Figure 4. Cytoplasmic strong IgA positivity on the atypical plasma cells, (ABC-peroksidase, AEC), (x 400).

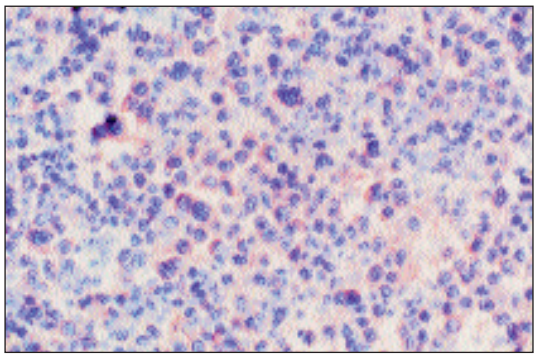

Figure 5. Cytoplasmic IgG staining is weaker than IgA, (ABC-peroksidase, AEC), (x 400).

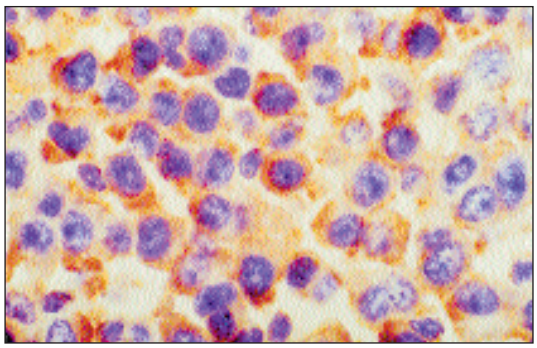

Figure 6. Cytoplasmic monoclonal Kappa light chain positivity in the plasma cells, (ABC-peroksidase, AEC), (x 1000).

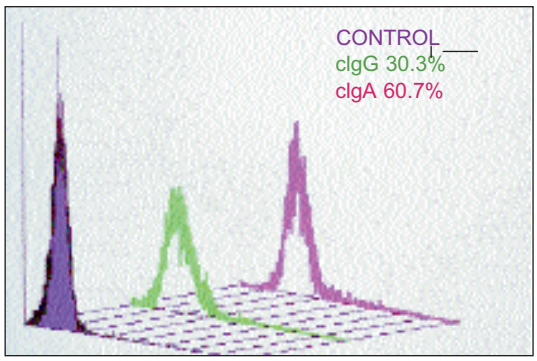

Figure 7. Flow cytometric analysis of the bone marrow, Cytoplasmic high level of IgA and IgG both expressed.

nate between apparent and real biclonality. Thus, most data speak in favour of the notion that, in the majority of biclonal gammopathies, the two M-components originate from the same clone[1,4].

Organ enlargement or infiltration is an uncommon presenting feature of myeloma, being present in approximately 5% of patients[11]. Peripheral lymphadenopathy is an even rarer finding, found in only 4% of cases at diagnosis, and most of these are secondary to amyloid infiltration[11]. There have been many cases of primary plasmacytoma of the lymph nodes in the literature but these cases were not associated with other diagnostic features of MM, specifically the presence of a serum M-band or marrow involvement[11]. MM can present clinically as lymphoma and it could be mistakenly diagnosed as immunoblastic lymphoma[2,11,12]. Although myeloma simulating lymphoma is a rare variant of myeloma it is important to recognise the disorder as it may be highly chemosensitive and potentially curable[11]. This case has been presented with cervical lymphadenopathy from which it was diagnosed as immunoblastic lymphoma. Thus the MM diagnosis was done after the analysis of bone marrow, serum protein electrophoresis and immunofixation. By the immunohistochemical analysis of the lymph node plasma cell infiltration could be demonsrated. Additionally biclonality has been shown in peripheral blood, bone marrow and lymph node.

In summary, as a clinician we must rule out MM in the patients who were diagnosed as immunoblastic lymphoma by only histologic evaluation. Immunohistochemical analysis should be done to confirm the diagnosis. Most of the biclonal gammopathy cases are asymptomatic and as biclonality is seen 60% in monoclonal gammopathy of undetermined significance; immunofixation should be done to all these cases not to miss biclonality.

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