CASE REPORT

Concomitant Presence of Two Distinct Clones of Chronic Lymphocytic Leukemia and Plasma Cell Myeloma in a Patient

Sabina Langer · Meenal Mehta · Amrita Saraf ·
Aastha Gupta · Keyur Pipliya · Atul Kakar ·
Manorama Bhargava

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Abstract A 74 years old male patient, presented with history of generalized weakness, fatigue, loss of appetite and breathlessness on exertion for past one and a half months. On examination, he was found to have significant pallor and generalized lymphadenopathy (cervical, axillary and inguinal). The skeletal survey showed punched out lytic lesions in skull and pelvic bones. The peripheral smear examination showed lymphocytosis with absolute lymphocyte count of 25,000/ μ L. The bone marrow aspirates revealed a hypercellular marrow with 74 % lymphocytes & 14 % plasma cells, suggestive of chronic lymphoplasmacytic disorder. The bone marrow biopsy had two morphologically distinct populations of lymphocytes & plasma cells. The immunohistochemical markers on bone marrow biopsy showed that plasma cells were positive for CD138 with kappa light chain restriction. Flow cytometry showed B cell population with CD19/CD5 co expression, CD5/CD23 coexpression, were positive for CD22, CD20 and negative for FMC-7 and lambda light chain. In addition, plasma cells were also identified as

CD45 negative cells and showed CD38/CD138 co-expression with variable CD19 and CD56 positivity. Serum protein electrophoresis revealed M band, serum immunofixation electrophoresis corresponded to IgA -Kappa. The final diagnosis of chronic lymphocytic leukemia with concomitant presence of plasma cell myeloma was concluded. This case imparts an important message to look for presence of coexisting entities in a single specimen and highlights the benefits of testing both plasma cell and B-cell compartments when the clinical features are not entirely consistent. Flow cytometry together with protein electrophoresis can help to clinch difficult and rare dual diagnosis. These cases are rare and pose therapeutic challenge.

Keywords Multiple myeloma · Chronic lymphocytic leukemia · Flow cytometry

Introduction

Even though chronic lymphocytic leukemia (CLL) and multiple myeloma are individually quite common, there are very few published reports of concomitant presence of CLL and multiple myeloma in the same patient [1–6]. This diagnosis has to be carefully differentiated from small B cell lymphomas showing plasma cell differentiation, splenic marginal zone lymphoma with plasmacytic differentiation and chronic lymphocytic leukemia with plasmacytic differentiation [1]. The correct diagnosis rests on step wise and integrated approach in determining the immunophenotypic features of B lymphocytic cells and plasma cells. Both multiparametric flowcytometric immunophenotyping and immunohistochemical markers on the bone biopsy help in furnishing the correct diagnosis.

S. Langer (✉) · M. Mehta · A. Saraf · A. Gupta · M. Bhargava
Department of Hematology, Sir Ganga Ram Hospital, Rajinder
Nagar, New Delhi 110060, India
e-mail: sabinapost@yahoo.com

M. Mehta
e-mail: drmeenahmehta@gmail.com

A. Saraf
e-mail: amrita.saraf1@gmail.com

A. Gupta
e-mail: draashtagupta83@gmail.com

K. Pipliya · A. Kakar
Department of Medicine, Sir Ganga Ram Hospital, New Delhi,
India

This case report also emphasizes the need to routinely look for clonal plasma cells in cases of chronic lymphoproliferative disorders and clonal B lymphoid cells in cases of multiple myeloma. The multiparametric flow cytometry of the bone marrow specimen can give help in accurate and rapid diagnosis. Several pertinent questions have been raised in such cases as whether the B-cell chronic lymphocytic leukemia and multiple myeloma arise as a single clone or two separate clones presenting concomitantly. Previous studies have used various modalities, either FISH [3, 6] or immunoglobulin gene rearrangement analysis [7–9] to investigate into this. We present here a case which showed concomitant involvement by chronic lymphocytic leukaemia and plasma cell myeloma.

Case Report

A 74 years old male patient, known case of bradycardia on pacemaker, presented with history of generalized weakness, fatigue, loss of appetite and breathlessness on exertion for past one and a half months. On examination, he was found to have significant pallor, generalized lymphadenopathy (cervical, axillary and inguinal). Cardiovascular examination revealed systolic flow murmur in mitral area. There was no sternal tenderness. Fundus examination was suggestive of chorioretinal degeneration. Complete blood count (CBC) revealed leukocytosis, total leukocyte count: 35,700/ μ L, haemoglobin: 6.4 g/dL, platelet count: 1,20,000/ μ L with raised erythrocyte sedimentation rate (ESR): 140 mm/h. The biochemical reports had shown hypoalbuminemia (albumin 2.1 g/dL, globulin 4.9 g/dL) with A/G ratio reversal and hypercalcemia with corrected calcium of 12.2 mg/dL and elevated serum creatinine. The

skeletal survey showed punched out lytic lesions in skull (Fig. 1) and pelvic bones.

The peripheral smear examination showed lymphocytosis $\sim 70\%$, along with presence of smudge cells and rouleaux formation. The absolute lymphocyte count was 25,000/ μ L. Bone marrow aspiration and biopsy were carried out. The bone marrow aspirates revealed a hypercellular marrow with 74 % lymphocytes & 14 % plasma cells, suggestive of chronic lymphoplasmacytic disorder (Fig. 2a). The bone marrow biopsy had two morphologically distinct populations of lymphocytes & plasma cells. Many plasma cells were immature, some were showing Dutcher bodies (Fig. 2b). The immunohistochemical markers on bone marrow biopsy showed that plasma cells were positive for CD138 with kappa light chain restriction (Fig. 2c, d).

The flow cytometric immunophenotyping of the bone marrow specimen revealed increase in total lymphocytes which were 65 % of total acquired events of which the B cells were about 90 %, an absolute B cell count of approximately 19,000/ μ L (Fig. 3). These B cells were showing surface lambda light chain restriction with CD19/CD5 co expression. These cells also expressed CD23, heterogeneous CD 20, CD 22, and CD 25 along with CD 11c. A small cell population of about 3–4 % plasma cells were showing CD 38/CD138 co expression with CD 56 positivity and lack of CD 45 and CD 19 expression (Fig. 4). However, cytoplasmic kappa and lambda staining on flow cytometry could not be performed due to insufficient sample submitted.

The flow cytometric findings were consistent with a B-cell chronic lymphoproliferative disorder showing CLL phenotype with a small coexisting plasma cell clone. The serum protein electrophoresis revealed M protein band in gamma region which on immunofixation corresponded to Ig A—Kappa.

There was a prominent M protein band on serum protein electrophoresis which was found to be Ig-A kappa on serum immunofixation electrophoresis. The increase in plasma cells on the bone marrow aspirate ($>10\%$) and bone biopsy together with anemia, hypercalcemia, renal failure and lytic lesions in skull and pelvic bones were consistent with a diagnosis of multiple myeloma. Moreover the flow cytometry and immunohistochemical markers demonstrated the clonal nature of these plasma cells. On the other hand the leukocytosis with absolute lymphocytosis, smudge cells along with the flowcytometric immunophenotyping showing monoclonal B cells ($>5,000/\mu$ l) established the diagnosis of CLL. Therefore a diagnosis of concomitant co-existence of CLL and multiple myeloma was finally confirmed.

Immediate management of the patient included correcting hypercalcemia [calcitonin, fluid, diuretics] and

Fig. 1 X-ray lateral view skull showing punched out lytic lesions

Fig. 2 **a** Bone marrow aspirate showing hypercellular marrow with 74 % lymphocytes & 14 % plasma cells, suggestive of chronic lymphoplasmacytic disorder ($\times 400$). **b** Bone biopsy showing two morphologically distinct populations of lymphocytes & plasma cells, many immature and showing Dutcher bodies ($\times 400$). **c** Immunohistochemical stain on bone biopsy showing plasma cells positive for CD138 ($\times 400$). **d** Plasma cells positive for kappa light chains with unstained lymphoid nodule ($\times 400$)

packed red cell transfusions. Subsequently the patient was started on chemotherapy in the form of Inj. Bortezomib along with melphalan and prednisolone. The Total Leukocyte count had reduced from 35,700/ μL to 14,000/ μL and absolute lymphocyte count had come down from 21,000/ μL to 8000/ μL . A total of nine cycles of chemotherapy were given and the patient responded well. Follow up after 3 months showed the CBC, serum calcium and creatinine in the normal range.

Discussion

The synchronous presence of CLL and multiple myeloma in a patient is very rare. To the best of our knowledge less than 100 cases have been described in the literature so far [1, 3, 6, 8, 10–20].

One of the questions to be resolved in coming to the diagnosis of the presence of a dual malignancy would be whether the abnormal plasma cells in question belong to the same clone as CLL or have evolved as a distinct new clone. Some case studies have provided evidence that both arise from a single clone [8, 15]. On the other hand, some authors have concluded that chronic lymphocytic leukemia

and multiple myeloma occurring concomitantly in a single patient arise from two separate clones [5, 7, 9, 13]. The techniques applied by various authors include sequencing and study of heavy chain gene rearrangement in both the populations of lymphocytes and plasma cells or study of interphase FISH for clonal chromosomal abnormalities [3, 6, 10]. In the absence of such facilities the study of light chains expressed by B cells and plasma cells is helpful. In cases where the light chain expressed by plasma cells and B cells are same it becomes pertinent to demonstrate Cyclin D1 or CD56 expression on plasma cells [1].

In the present case the flowcytometric immunophenotyping on the bone marrow gave the first clue to the presence of plasma cells with aberrant expressions. Although the bone marrow sample submitted for flowcytometry was haemodilute, which is often the case, yet it was possible to evaluate a small population of clonal plasma cells. Two separate clones were identified as plasma cells were demonstrated to show kappa light chain restriction with Ig heavy chains on serum immunofixation electrophoresis and immunohistochemistry. The lambda light chain restriction on B lymphocytes was demonstrated by flow cytometric immunophenotyping. Expression of different light chains on plasma cells and lymphocytes

Fig. 3 Using SSC CD19 gating B-cell population were gated also showing CD19/CD5 co expression, CD5/CD23 co expression, CD20 positive (heterogenous), CD10 negative, CD22 positive, FMC-7 negative with lambda light chain restriction

Fig. 4 Plasma cells were gated using CD38 and CD138 coexpression. The abnormal plasma cells were demonstrated to be CD45 and CD19 negative with aberrant expression of CD56

helped towards identification of two separate clones. The Immunoglobulin gene rearrangement or FISH analysis could not be performed to confirm the above findings.

Clinically the patient presented with features of multiple myeloma such as hypercalcemia, elevated serum creatinine, and A/G reversal and punched out lytic lesions. In spite of having a coexistent clone of CLL, the patient responded well to myeloma specific therapy. The total leukocyte count had reduced from 35,700/ μ L to 14,000/ μ L and absolute lymphocyte count had come down from 21,000/ μ L to 8000/ μ L. There was improvement in clinical and biochemical parameters. This case highlighted the benefits of testing both plasma cell and B-cell compartments when the clinical features are not entirely consistent (e.g. IgM paraprotein with lytic lesions, or in this case IgA paraprotein with lymphocytosis). It is rare to detect a lymphoplasmacytic disorder with an IgA paraprotein and in such situations both B-cell and plasma cell flow cytometry are likely to inform the diagnosis. The plasma cells of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia express both CD19 and CD45 whereas primary plasma cell neoplasms are CD19 or CD45 negative, thus helps in differentiating [21].

Conflict of interest There is no potential conflict of interest.

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