Case Report
Concomitant lymphoplasmacytic lymphoma and plasma cell myeloma, a diagnostic challenge

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Abstract: Background: Lymphoplasmacytic lymphoma and plasma cell myeloma are two B cell lymphoproliferative neoplasms derived from mature B-lymphocytes in different differentiation stages. The coexistence of these two tumors in the same patient is exceedingly rare and can be difficult to diagnose. Case presentation: A 76-year-old male presented with a pathologic fracture after a fall. Radiography showed a lytic lesion in the pelvis. Serum immunofixation showed distinct IgM kappa and IgA kappa monoclonal protein bands. Bone marrow examination revealed aggregates of small, mature lymphoid cells with admixed plasma cells. Immunohistochemical studies and flow cytometric analysis showed the lymphoid cells were CD10-/CD5- kappa restricted monoclonal B cells. The plasma cells were monoclonal with kappa light chain restriction. The majority of plasma cells were positive for IgA and cyclin D1 with a few plasma cells positive for IgM. Additional studies showed the presence of both a positive MYD88 L265P mutation and a CCND1/IGH fusion. A diagnosis of concomitant lymphoplasmacytic lymphoma and plasma cell myeloma was rendered. Conclusion: Concomitant lymphoplasmacytic lymphoma and plasma cell myeloma can be rarely encountered and is diagnostic challenging. It is commonly associated with biclonal monoclonal proteins. This case demonstrates the importance of a comprehensive work-up in the diagnosis of this disease combination and highlights the diagnostic role of MYD88 mutation study.

Keywords: Lymphoplasmacytic lymphoma, plasma cell myeloma, MYD88

Introduction

Lymphoplasmacytic lymphoma (LPL) and plasma cell myeloma (PCM) are two B cell lymphoproliferative neoplasms that arise from mature B lymphocytes in different stages of differentiation. LPL is composed of neoplastic lymphocytes, plasmacytoid cells and plasma cells, and is usually associated with an IgM monoclonal paraprotein [1]. Waldenstrom macroglobulinemia (WM) is an IgM producing LPL involving bone marrow [2]. In the past, the diagnosis of LPL/WM was based on excluding other B cell lymphoproliferative disorders. The main differential includes other small mature B cell lymphomas with plasmacytic differentiation, primarily marginal zone lymphoma and plasma cell neoplasms in certain circumstances. Recently, the MYD88 L265P mutation was found to be a relatively sensitive and specific molecular abnormality in LPL/WM.

Plasma cell myelomas (PCM) and related plasma cell neoplasms are immunoglobulin producing terminally differentiated monoclonal B cells. PCM shows various cytogenetic abnormalities, such as translocation, hyperploidy and hypoploidy, which are often associated with different clinical and prognostic features. PCM can present with various clinical/laboratory abnormalities, including hypercalcemia, renal deficiency, anemia, bone lesions and increased M-protein in serum/urine. Plasma cell neoplasms producing IgG or IgA monoclonal proteins are relatively common whereas those producing IgM monoclonal proteins are rare. While the diagnosis of PCM is commonly straightforward, cases of PCM with atypical features may be difficult to distinguish from B cell lymphoma with plasmacytic differentiation, particularly LPL.

The coexistence of LPL and PCM in the same patient is extremely rare and has been previously reported in five patients only. The diagnosis can be very challenging due to many similarities between plasma cell neoplasms and LPL/WM at the histomorphologic level. We re-
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port a case of concomitant LPL and PCM that illustrates this diagnostic conundrum and the diagnostic role of ancillary studies.

Case presentation

The patient was a 76-year-old retired Caucasian male who presented with right hip pain after a trivial fall. X-ray showed an acetabular fracture of the right pelvis. Physical examination showed no lymphadenopathy or organomegaly. The patient’s past medical history was unremarkable.

Laboratory workup showed the following: (1) a mild normocytic anemia, 11.7 g/dL [reference interval, 13.4-17.0 g/dL], with normal white cell and platelet counts; (2) decreased total protein, 5.9 g/dL [reference interval, 6.3-8.2 g/dL] and albumin, 2.5 g/dL [reference interval, 3.5-5.0 g/dL]; (3) elevation of serum IgA, 728 mg/dL [reference interval, 60-400 mg/dL] and IgM, 904 mg/dL [reference interval, 60-300 mg/dL] with decreased serum IgG, 318 mg/dL [reference interval, 700-1500 mg/dL]. Immunoglobulin quantitation was performed on the Beckman Coulter Immage 800 (Brea, CA). Serum protein electrophoresis (SPEP) showed three distinct monoclonal protein bands (0.08 g/dL, 0.28 g/dL and 0.57 g/dL) in the gamma region. Serum immunofixation electrophoresis (IFE) confirmed three monoclonal protein bands: an IgM kappa monoclonal protein band and two IgA kappa monoclonal protein bands (Figure 3). Radiographs revealed one large lytic lesion within the right acetabulum and ischium with destruction of the medial wall of the acetabulum (Figure 2).

With a clinical suspicion of myeloma, bone marrow evaluation of the right posterior iliac crest was performed. Histomorphological examination (Figure 3) revealed a hypercellular bone marrow with frequent lymphoplasmacytic aggregates consisting small mature lymphocytes and lesser number of plasma cells (Figure 3A and 3B). Morphologically, the plasma cells have
two distinct cytologic appearances (Figure 3C and 3D). One group of plasma cells had the classical plasma cell morphology that makes them indistinguishable from the typical normal/reactive plasma cells. The other group of plasma cells showed ample homogeneous eosinophilic or clear cytoplasm with very dense nuclei, mimicking epithelioid histiocytes. These histiocytoid plasma cells were more abundant than those having a classical plasma cell appearance.

Immunohistochemical studies revealed the small lymphocytes within the aggregates were primarily CD20 (Figure 3E) and PAX-5 positive B cells. CD138 showed that plasma cells comprised about 5-10% of the cell population in the bone marrow (Figure 3F) and were kappa restricted (Figure 3G). The histiocytoid plasma cells were positive for IgA (Figure 3H); the plasma cells with classical morphology were positive for IgM (Figure 3I). Additional immunohistochemical stains indicated that the histiocytoid
plasma cells were positive for cyclin D1 (Figure 3J). Double immunohistochemical staining for IgA and cyclin D1 (Figure 3K) vs IgM and cyclin D1 (Figure 3L) demonstrated co-localization of IgA and cyclin D1, confirming that only the IgA positive histiocytoid plasma cells were expressing cyclin D1.

Flow cytometric analysis of bone marrow demonstrated a monoclonal B cell population with kappa light chain restriction. These B cells were positive for CD19 and CD20 and negative for CD5 and CD10 (Figure 4). CD23 was also negative. In addition, a monotypic plasma cell population positive for CD38, CD138 and cytoplasmic kappa light chain (Figure 5) was identified.

Karyotypic analysis performed on the bone marrow aspirates showed normal male karyotype. Fluorescence in situ hybridization (FISH) was positive for t(11;14) CCND1/IGH fusion gene (Figure 6). Sequencing study of myeloid differentiation primary response gene 88 (MYD88) was positive for the L265P mutation. The diagnosis of a kappa restricted lymphoplasmacytic lymphoma with concomitant kappa restricted plasma cell myeloma was rendered.

The patient responded well to a bortezomib based regimen and has since been in hematologic remission.

Discussion

LPL/WM is an uncommon lymphoproliferative disorder with an incidence of 3.4/10^6 among men and 1.7/10^6 among women [3]. LPL/WM generally has an indolent course with median survival of 5-10 years. The proposed cell of origin is a post-germinal center B-cell that lacks ongoing somatic mutation [4]. There is no specific immunophenotypic or cytogenetic abnormality in LPL/WM. Deletion of the long arm of chromosome 6 (6q-) is the most common abnormality, occurring in more than 40% of the cases [5]. LPL does not show translocation of CCND1, MALT1, BCL2 or BCL6 [1]. In 2012, Treon et al. [6] described a MYD88 L265P somatic mutation in LPL/WM patients. MYD88 functions as an adapter molecule that is used by most toll-like receptors (TLR) to facilitate signaling. Treon et al. [6] reported that the MYD88 L265P mutation was the most common gene mutation in LPL, identified in 91% of LPL patients. By contrast, PCM, including IgM producing myeloma, is negative for MYD88 L265P mutation. The majority of small mature B cell lymphomas are also negative for this mutation except for 10-15% of splenic marginal zone lymphoma cases and 4% of chronic lymphocytic leukemia cases. Notably, MYD88 L265P mutation is preferentially identified in non-germinal
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**Figure 5.** A monotypic CD38+, CD138+, dim CD45+ and cytoplasmic kappa light chain restricted plasma cell population.

center type diffuse large B cell lymphoma and is usually associated with poorer prognosis. These findings support the clinical utility of MYD88 L265P mutational analysis in the differential diagnosis of LPL, PCM and other low grade B cell lymphomas.

PCM and its related plasma cell neoplasms are composed of terminally differentiated B cells that secrete monoclonal immunoglobulins. However, monoclonal immunoglobulin can be also occasionally produced by B cell lymphoma. If bone marrow evaluation demonstrates a monoclonal plasma cell population with polyclonal B cells, a diagnosis of plasma cell neoplasm is indicated. If a monoclonal B cell population with polyclonal plasma cell population is detected, a diagnosis of B cell lymphoma rather than plasma cell neoplasm is entertained. If both a monoclonal B cell population and a monoclonal plasma cell population with the same light chain restriction are identified, a diagnosis of B cell lymphoma with plasma- cytic differentiation is most likely to be rendered. In such cases, however, exclusion of a coexisting but separate plasma cell neoplasm based solely on morphologic evaluation is essentially impossible.

The metachronous or synchronous coexistence of LPL/WM with other hematolymphoid malignancies is rare. In a study performed on 924 patients with WM [7], only 17 patients (2.8%) were found to have concomitant hematologic malignancies. Out of these 17 patients, 13 patients had diffuse large B cell lymphoma and the remaining 4 patients had therapy related acute myeloid leukemia. Reports in the litera-
The diagnosis of current case was very challenging. The presence of both monoclonal B cell population and plasma cell population with same light chain restriction suggests a diagnosis of either B cell lymphoma with plasma cell differentiation or B cell lymphoma with coexisting plasma cell neoplasm. The B cells in the bone marrow are small and mature by morphology and CD5-/CD10- by immunophenotyping. The main differential diagnosis includes marginal zone lymphoma and LPL/WM. In the past, a more descriptive diagnosis of small B cell lymphoma with plasmacytic differentiation would have been rendered due to the diagnostic difficulty of further differentiating between marginal zone lymphoma and LPL/WM. Positive MYD88 L265P mutation result in the current case allowed us to give specific diagnosis of LPL/WM. However, an additional question was raised: is the monoclonal plasma cell population in the bone marrow part of LPL/WM spectrum or a separate plasma cell neoplasm? Lytic bone lesions, as seen in the current case, is not typical for LPL/WM. Additionally, the presence of two paraproteins (IgM and IgA) in the serum, raises suspicion for biclonality. Further morphologic and immunohistochemical evaluation demonstrated two distinct plasma cell morphologies. The histiocytoid plasma cells express IgA and the plasma cells with classical morphology express IgM, in line with two disease processes. Finally, the presence of t(11;14) detected by FISH and positivity for cyclin D1 by immunohistochemical stain clinched the diagnosis of a concomitant plasma cell myeloma.

**Conclusion**

Concomitant LPL and PCM is rarely encountered and is associated with biclonal monoclonal protein. To arrive at the correct diagnosis, the integration of the clinical, morphologic, immunophenotypic and cytogenetic work-up is necessary. When LPL is being considered in the differential diagnosis, the MYD88 mutational assay is of value.
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Table 1. Clinicopathologic features of concomitant plasma cell neoplasm and lymphoplasmacytic lymphoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>LAD</th>
<th>Organomegaly</th>
<th>Lytic bone lesions</th>
<th>Monoclonal proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine et al. [11]</td>
<td>73</td>
<td>F</td>
<td>Fatigue, back pain</td>
<td>Y</td>
<td>Hepatomegaly</td>
<td>Y</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>Wang et al. [12]</td>
<td>73</td>
<td>M</td>
<td>Mild pancytopenia</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>IgM/IgA</td>
</tr>
<tr>
<td>Carruli et al. [13]</td>
<td>75</td>
<td>F</td>
<td>Anemia</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>McNutt et al. [14]</td>
<td>54</td>
<td>M</td>
<td>Fatigue, bleeding</td>
<td>Y</td>
<td>Hepatomegaly</td>
<td>N</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>Sanders et al. [15]</td>
<td>42</td>
<td>F</td>
<td>Bronchitis, oral mass</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>IgM/IgG</td>
</tr>
<tr>
<td>Current case</td>
<td>76</td>
<td>M</td>
<td>Back pain, fracture</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>IgM/IgA</td>
</tr>
</tbody>
</table>

References


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