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Case 6. 
No conflicts of interest to disclose.
Male 72 year old. Multiple pathological lymph nodes in the abdominal cavity and inguinal region. Mild hepatomegaly. LDH 65 U/L.
Histopathological differential diagnosis:

- Plasma cell type Castleman disease.
- Reactive Lymph node hyperplasia.
- Mantle cell lymphoma.
- Follicular B cell Lymphoma (diffuse Variant).
- Marginal Zone B cell Lymphoma.
- Lymphoplasmacytic Lymphoma.
Molecular results

- IgH clonally rearranged
- MYD88 L265P mutated

FR1 325 bp  FR2 259 bp  FR3 131 bp
Histopathology of the bone marrow

- Paratrabecular and nodular interstitial growth pattern.
- Small B cell infiltrate with plasmacytic differentiation.
- Scattered hystiocytes with some hemosiderin.
- Mast cell infiltration.
- Absence of intrasinusoidal infiltration. Absence of follicular dendritic cell meshworks with CD23.
M component 3.69 g/dL. IgG kappa

<table>
<thead>
<tr>
<th>Fracciones</th>
<th>%</th>
<th>Int. ref. %</th>
<th>g/dL</th>
<th>Int. ref. g/dL</th>
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<tbody>
<tr>
<td>Albumina</td>
<td>&gt;35,7</td>
<td>55,8 - 66,1</td>
<td>3,32</td>
<td>40,20 - 47,60</td>
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<tr>
<td>Alfa 1</td>
<td>3,4</td>
<td>2,9 - 4,9</td>
<td>0,32</td>
<td>2,10 - 3,50</td>
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<tr>
<td>Alfa 2</td>
<td>7,9</td>
<td>7,1 - 11,8</td>
<td>0,73</td>
<td>5,10 - 8,50</td>
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<td>Beta</td>
<td>&lt;7,2</td>
<td>8,4 - 13,1</td>
<td>0,67</td>
<td>6,00 - 9,40</td>
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<td>Gamma</td>
<td>&gt;45,8</td>
<td>11,1 - 18,8</td>
<td>4,26</td>
<td>8,00 - 13,50</td>
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</tbody>
</table>

CM:  
- 1: 39,7 g/dL

A/G: 0,56
P.T.: 9,3
• Proposed diagnosis:

• **Lymphoplasmacytic Lymphoma**

• MYD88 L265P mutated IgG producing small B cell lymphoma with lymphoplasmacytoid differentiation.
Diagnostic criteria for LPL. Waldestrom Macroglobulinemia.

- Lymphoplasmacytic lymphoma is a neoplasm of small B cell lymphocytes, plasmacytoid lymphocytes and plasma cells, usually involving the bone marrow and sometimes lymph node and spleen.
- The great majority (>90%) of LPL/WM have MYD88L265P mutation.
- It is usually associated with paraprotein of the IgM type. Diagnostic criteria for LPL/WM include the presence of lymphoplasmacytic lymphoma with bone marrow infiltration and IgM paraprotein of any concentration.
- Cases with <10% of lymphoplasmacytic infiltration in the marrow, <3 g/dL serum IgM monoclonal protein and absence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly or other end-organ damage related with the LPD are considered IgM-MGUS.
- Bone marrow aspiration and biopsy are essential for the diagnosis of WM, and should be evaluated by immunohistochemistry (and flow cytometry) as well as the presence of the MYD88 L265P gene mutation.
Bone marrow infiltration pattern in LPL/WM

• Bone marrow involvement is characterized by a **combined interstitial and paratrabecular pattern**.

• 39 bone marrow trephine biopsies from 30 patients from Hospital Universitario Marques de Valdecilla were reviewed. 26 patients were diagnosed as LPL/WM and 4 cases as IgM-MGUS.

• The majority of samples showed a **paratrabecular pattern** (21, 54%), **combined with either patchy (9, 23%) or nodular (7, 18%)** and less commonly diffuse (5, 13%) interstitial patterns. The presence of paratrabecular infiltrates is rare in SMZL. Intrasinusoidal infiltrates are uncommon in LPL&WM.

• 18 (46%) cases showed and **interstitial pattern without paratrabecular involvement**. In 9 (23%) cases it was patchy (4 IgM-MGUS cases and 5 LPL/WM), 4 cases (10%) showed a diffuse-solid pattern, 3 cases (7%) showed a nodular pattern and 2 cases (5%) a diffuse pattern.

• 3 additional non-IgM (2 IgA, 1 IgG) LPL: two cases with mixed paratrabecular and interstitial pattern and 1 case with diffuse interstitial pattern. All three cases were MYD88L265P mutated.
22 out of 26 patients with LPL/WM (84%) were positive for MYD88L265P mutation. Median Allele Frequency of the LPL/WM mutated cases was 11.2% (range 0.33-43.4%). One out of 4 IgM-MGUS cases was positive (25%) with an allele frequency of 0.45%.
Bone marrow infiltration . Morphology

• The bone marrow infiltrates include the presence of small B cell lymphocytes, plasmacytoid cells and plasma cells. **Clear cut plasmacytoid differentiation** is useful in the differential diagnosis with MZL. **Dutcher bodies are characteristic of LPL.**

• Increase in mast cells.

• **Uncommon presence of FDC using CD21/CD23.**

• Absence of lymphoid component and granulomatous reactions to pure monotypic plasma cell infiltrates can be seen after treatment.

• **AL amyloid deposition can be found associated to LPL infiltrates.**

Bassanova et al. Lymphoplasmacytic Lymphoma and Marginal Zone Lymphoma in the Bone Marrow. Am J Clin Pathol 2015
WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (revised 4th edition). IARC Lyon 2017
Non-IgM Lymphoplasmacytic Lymphoma

• The clinicopathological definition of WM should be confined to patients with lymphoplasmacytic lymphoma who have demonstrable IgM monoclonal gammopathy. Patients with IgG or IgA monoclonal proteins and those with non-secretory LPL exist and present with similar clinical problems to those seen in WM.

• Non-IgM LPL show clinical and pathological heterogeneity. Clinical features such as hyperviscosity related symptoms are uncommon.

• Differential diagnosis with multiple myeloma and MZL is critical for therapeutic reasons. MYD88L265P mutation testing is useful to rule out multiple mieloma. \( \approx 15\% \) of MZL (mostly SMZL) are MYD88L265P positive.

• MYD88L265P was found in 43% of non-IgM LPL cases in the larger series so far published (10/23 cases). No significant differences in clinical or pathological features were found between MYD88L265P mutated and unmutated cases.


Jimenez C et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenstrom’s macroglobulinemia Leukemia 2013

Martinez-Lopez et al. MYD88 (L265P) somatic mutation in marginal zone B cell lymphoma. AJSP 2015

Bassanova et al. Lymphoplasmacytic Lymphoma and Marginal Zone Lymphoma in the Bone Marrow. Am J Clin Pathol 2015

King et al. Lymphoplasmacytic Lymphoma with a non-IgM paraprotein shows clinical and pathologic heterogeneity and may harbor MYD88L265P mutations. Am J Clin Pathol 2016
Take Home Messages

• Lymphoplasmacytic Lymphoma mimics nodal MZL and other small B cell neoplasms in the lymph node.
• Bone marrow biopsy is useful providing key patterns for the diagnosis of LPL.
• Non-IgM LPL show overlapping histopathological and molecular features with IgM LPL/WM.
• Determination of MYD88L265P somatic mutation confirms the diagnosis in the proper clinicopathological context and is useful in cases in which the diagnosis is suspected but uncertain. A negative result however does not excludes the diagnosis.
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