Lymphoplasmacytic lymphoma and marginal zone lymphoma involving bone marrow: A diagnostic dilemma. Useful clinicopathological features to accurate the diagnosis

Patricia García-Abellás¹ | Ana Ferrer Gómez¹ | Diego Bueno Sacristán¹ | Miguel Piris Villaespesa² | María Talavera Yagüe³ | María Eugenia Reguero Callejas¹ | Mónica García-Cosío⁴

¹Department of Pathology, Ramón y Cajal Universitary Hospital, Madrid, Spain
²Department of Hematology, Ramón y Cajal Universitary Hospital, Madrid, Spain
³Department of Genetics, Ramón y Cajal Universitary Hospital, Madrid, Spain
⁴Head of Hematopathology Department, Ramón y Cajal Universitary Hospital; Alcalá University, Madrid, Spain; Instituto Ramon y Cajal de Investigacion Sanitaria, Madrid, Spain; CIBERONC, Madrid, Spain

Correspondence
Mónica García-Cosío, Department of Pathology, Ramón y Cajal Universitary Hospital, Ctra. de Colmenar Viejo, km. 9,100, 28034, Madrid, Madrid, Spain.
Email: monica.garciacosio@salud.madrid.org

Abstract
Lymphoplasmacytic lymphoma (LPL) and marginal zone lymphoma (MZL) frequently infiltrate the bone marrow with similar histologic and immunohistochemical characteristics posing diagnostic problems. Bone marrow biopsy specimens from 25 LPL and 16 MZL have been studied, correlating with clinical, laboratory parameters and the MYD88_p.L265P mutation. Paratrabecular and interstitial infiltration pattern, serum IgM paraprotein levels, and MYD88_p.L265P mutation were significantly more frequent in LPL. Nodular or intrasinusoidal pattern with lymphocytosis and splenomegaly were associated with MZL diagnosis. Different clinical and histological parameters should be collected when LPL or MZL is suspected in bone marrow biopsy specimens.

KEYWORDS
bone marrow, diagnosis, lymphoplasmacytic lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia

1 | INTRODUCTION

Lymphoplasmacytic lymphoma (LPL) is a B-cell neoplasm composed of small lymphocytes, lymphoplasmacytoid, and plasma cells, usually involving the bone marrow. In a small subset of patients affects lymph nodes and spleen. Waldenström macroglobulinemia (WM) is defined as LPL with bone marrow involvement and IgM monoclonal gammapathy. Symptoms are usually related with bone marrow infiltration (anaemia, thrombocytopenia or leukopenia) and paraprotein deposition (cryoglobulinemia, neuropathy, diarrhoea, coagulopathy). Marginal zone lymphomas (MZL) are indolent B-cell lymphomas characterised by the proliferation of B cells from the marginal zone of B-cell follicles. This lymphoma includes three different entities, extranodal MZL of MALT type (EMZL), splenic lymphoma (SMZL), and nodal MZL (NMZL). Plasmacytic differentiation is frequent and differentiation from LPL may be challenging, especially in cases with paraproteinemia. Morphologic, immunophenotypic, and clinical features are necessary to make a certain diagnosis, since new pathogenic mechanisms and therapeutic strategies have been proposed [1, 2]. MYD88_p.L265P gene mutation, present in more than 90% of LPL, was described initially by Treon et al. as a useful tool to establish an accurate diagnosis [3]. Nevertheless, this mutation is not specific and has also been described in a small percentage of MZL[4–6].

As LPL and MZL can infiltrate the bone marrow with similar histologic and immunohistochemical characteristics, several studies...
defining the distinctive features of each neoplasia have been published with no matching results [7–10].

The aim of the present article is to study the clinical and bone marrow histological features from series of LPL and MZL cases, highlighting the distinctive features that could help in the differential diagnosis.

2 | MATERIAL AND METHODS

2.1 | Patient selection

A retrospective review of bone marrow biopsy specimens with the diagnosis of LPL and MZL from 2017 to 2021 from the Pathology Department files of Ramón y Cajal Universitary Hospital was performed. In total, 25 patients with LPL and 16 patients with MZL were included (eight SMZL and eight NMZL).

2.2 | Histological and immunohistochemical study

Bone marrow trephine biopsies were reviewed by two pathologists (M.G.C and P.G.A). Histopathological infiltration patterns in the bone marrow were categorised as intrasinusoidal, diffuse, paratrabecular, nodular, and interstitial. A neoplastic infiltrate was considered paratrabecular when the contact surface of the infiltrate with the trabecular bone was larger than the maximum diameter perpendicular to the bone; interstitial if solitary or groups of the neoplastic cells were intermingled with normal bone marrow cellularity; nodular when clearly defined focal infiltrates were found in an inter trabecular location and diffuse when confluent areas of infiltration with a loss of hematopoietic elements and fat spaces are observed. Percentage of each pattern, immunophenotype profile, quantification of mast cells, plasma cells, or the presence of immunoglobulin light chain restriction was also recorded. Immunohistochemical analysis was performed with the following monoclonal antibodies: CD20 (clone L26, Agilent), CD3 (polyclonal, Agilent) CD79 (clone JBC117, Agilent), CD138 (clone MI15, Agilent), tryptase (clone AA1, Agilent), k light chains (polyclonal, Agilent), l light chains (polyclonal, Agilent), CD25 (clone 4C9, Leica biosystems), and CD5 (clone 4C7, Agilent). All of them were done on an OMNIS (Agilent) automated stainer, except for CD25, which was performed on the BOND III systems (Leica Biosystem), according to the manufacturer’s instructions. Appropriate external positive controls were used.

The cut-off value for defining lymphoma with plasmacytic differentiation was CD138 expression in the neoplastic cells higher than 10% [7]. We considered an arbitrary cut-off value for defining overexpression of mast cells as 10% or higher of the global bone marrow cellularity.

2.3 | Clinical data

Clinical and laboratory parameters such as age, gender, the presence of lymphocytosis (≥5 × 10^9/L), lymphadenopathy, splenomegaly, and elevated serum IgM paraprotein were collected from electronic clinical records.

2.4 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation and qualitative variables were expressed as number and percentage. Continuous variables were compared using Student’s t test or the Mann–Whitney U test according to their distribution, and categorical variables were compared using the chi-squared test or the Fisher’s exact test as appropriate.

2.5 | Molecular analysis

MYD88_p.L265P mutation status was determined using real-time allele-specific polymerase chain reaction and Sanger DNA sequencing from diagnostic bone marrow aspirates and/or peripheral blood.

3 | RESULTS

Clinical, histological and laboratory parameters are described in Table 1. A summary of the clinical and pathological features of lymphoplasmacytic lymphoma and marginal zone lymphoma with statistical significance is defined in Table 2.

Median percentage of bone marrow infiltration was quite similar in both entities: 36% in LPL and 33.1% in MZL. Paratrabecular and interstitial patterns of infiltration of the bone marrow were significantly more frequent in LPL (p = 0.035 and p = 0.008, respectively) whereas MZL showed more frequent intrasinusoidal and nodular involvement (p = 0.006 and p = 0.003, respectively). Plasmacytic differentiation was observed in 12.2% of LPL and in 5.6% of MZL cases. The percentage of cells with light chain restriction was higher in LPL compared to MZL cases (84% vs. 38%, respectively) (p = 0.006) (Figure 1). CD5 was expressed on B cells in three of the 25 (12%) LPL cases and in one of the 16 (6%) MZL cases. No significant differences were found. In four samples of LPL (16%), mast cells comprised ≥10% of the bone marrow cellularity. None of the MZL cases presented increasing number of mast cells.

Elevated serum monoclonal IgM component was detected in 88% LPL and in 30% MZL cases (p = 0.001). Interestingly, none of the MZL cases had an IgM higher than 1000 mg/dL. Lymphocytosis was presented in 63% of MZL and 20% of LPL cases (p = 0.009) and splenomegaly in 32% of LPL and 75% of MZL cases (p = 0.011). Otherwise, lymphadenopathy was present in 44% of LPL cases and in 38% of MZL cases, showing no statistically significant difference.

MYD88_p.L265P mutation was detected in 19 of 22 (86.36%) LPL studied cases and none of the 7 MZL studied cases (p = 0.000). In 18 of the 19 LPL cases in which MYD88_p.L265P mutation resulted positive, there was a serum IgM monoclonal component (94.73%). There was only one case nonsecretory. By contrast, in the MYD88_p.L265P
| Case | Gender | Age | Diagnosis | Lymphadenopaties | Splenomegaly | Lymphocytosis | IgM (mg/dl) | MYD88 | % B.M | % PT | % D | % N | % IS | % I | % CD138 | LCR | % tryp | CD25 | CD5 |
|------|--------|-----|-----------|------------------|--------------|---------------|-------------|--------|-------|------|-----|-----|------|-----|--------|------|--------|------|-----|
| 1    | F      | 74  | LPL       | Yes              | No           | No            | 1350        | pos    | 60    | 50   | 30  | 20  | 0    | 0   | 12     | nr   | 12     | No   | No  |
| 2    | M      | 50  | LPL       | No               | Yes          | No            | 2450        | pos    | 60    | 0    | 0   | 10  | 5    | 0   | 1     | 0    | 20     | K    | 7    |
| 3    | M      | 78  | LPL       | Yes              | No           | No            | 3230        | pos    | 30    | 30   | 0   | 10  | 0    | 0   | 60     | 12   | K      | 5    | No  |
| 4    | F      | 57  | LPL       | Yes              | No           | No            | 1040        | pos    | 20    | 40   | 0   | 20  | 0    | 0   | 40     | 6    | nr     | 2    | No  |
| 5    | M      | 64  | LPL       | No               | No           | No            | 1680        | pos    | 30    | 0    | 0   | 70  | 0    | 30  | 5     | K    | 2     | Yes  | No  |
| 6    | M      | 74  | LPL       | Yes              | No           | No            | 1590        | pos    | 90    | 0    | 80  | 0   | 0    | 20  | 20    | K    | 2     | No   | No  |
| 7    | M      | 38  | MZL       | No               | Yes          | Yes           | nd          | nd     | nd    | 15   | 0   | 90  | 0    | 10  | 5     | nr   | 1     | No   | No  |
| 8    | M      | 76  | MZL       | No               | Yes          | Yes           | nd          | nd     | nd    | 50   | 0   | 10  | 10   | 0   | 80     | 4    | nr     | 2    | No  |
| 9    | F      | 81  | MZL       | Yes              | Yes          | Yes           | 340         | nd     | nd    | 70   | 0   | 100 | 0    | 0   | 0      | 5    | nr     | 2    | No  |
| 10   | M      | 57  | LPL       | Yes              | No           | No            | 96          | pos    | 30    | 10  | 80  | 0   | 0    | 10  | 18    | K    | 10    | Yes  | No  |
| 11   | M      | 71  | LPL       | Yes              | No           | No            | 958         | pos    | 30    | 20  | 0   | 0   | 0    | 80  | 10    | K    | 15    | No   | No  |
| 12   | F      | 78  | LPL       | Yes              | No           | No            | 1600        | pos    | 10    | 0   | 0   | 0   | 100  | 3    | K     | nr   | 1     | No   | No  |
| 13   | M      | 76  | MZL       | Yes              | No           | No            | 177         | neg    | 25    | 10  | 0   | 10  | 70   | 5    | K     | 5    | No    | No   | No  |
| 14   | M      | 73  | MZL       | No               | Yes          | Yes           | nd*IgG       | neg    | 80    | 0   | 10  | 80  | 0    | 10  | 7     | K    | 5     | No   | No  |
| 15   | F      | 69  | MZL       | No               | Yes          | Yes           | 59          | neg    | 80    | 0   | 0   | 90  | 5    | 5    | 10    | L    | 5     | No   | No  |
| 16   | M      | 52  | MZL       | Yes              | Yes          | Yes           | 7           | neg    | 90    | 0   | 0   | 0   | 100  | 3    | nr    | 1    | 1     | No   | No  |
| 17   | F      | 83  | MZL       | Yes              | Yes          | Yes           | 22          | nd     | 7     | 0   | 0   | 90  | 5    | 5    | 5     | K    | 3     | No   | No  |
| 18   | M      | 70  | MZL       | No               | Yes          | Yes           | nd          | nd     | 15    | 0   | 0   | 0   | 100  | 0    | 1     | nr   | 1     | No   | No  |
| 19   | F      | 87  | MZL       | No               | Yes          | Yes           | 461*IgA     | neg    | 5     | 20  | 0   | 0   | 30   | 50  | 15    | L    | 3     | No   | No  |
| 20   | F      | 82  | MZL       | No               | Yes          | No            | 29          | nd     | 15    | 0   | 10  | 60  | 15   | 10   | 10    | nr   | 5     | No   | No  |
| 21   | M      | 72  | LPL       | No               | No           | No            | 274         | nd     | 70    | 20  | 0   | 0   | 20   | 60   | 70    | L    | 5     | No   | No  |

(Continues)
### Table 1 (Continued)

| Case | Gender | Age | Diagnosis | Lymphadenopaties | Splenomegaly | Lymphocytosis | IgM (mg/dl) | MYD88 | % B.M. | % PT | % D | % N | % IS | % I | % CD138 | LCR | % tryp | CD25 | CD5 |
|------|--------|-----|-----------|------------------|--------------|---------------|-------------|--------|--------|------|-----|-----|------|-----|--------|------|--------|------|-----|
| 22 F | 81     | LPL | No        | No               | No           | 300           | nd          | 10     | 0      | 0    | 0   | 10  | 0    | 90 | 10     | K    | 1      | No   | No |
| 23 F | 75     | LPL | No        | Yes              | Yes          | 244           | pos         | 30     | 0      | 0    | 0   | 0   | 0    | 100| 5      | K    | 3      | Yes  | No |
| 24 M | 68     | LPL | Yes       | No               | No           | 3600          | pos         | 7      | 0      | 0    | 10  | 0   | 90   | 12 | K      | 5    | No     | No   | No |
| 25 M | 68     | LPL | No        | No               | Yes          | 346           | pos         | 10     | 0      | 0    | 0   | 10  | 0    | 100| 5      | K    | 1      | No   | No |
| 26 F | 86     | LPL | No        | No               | No           | 282*lgG1730   | neg         | 20     | 30     | 0    | 30  | 10  | 30   | 100| K      | 6    | Yes    | No   | No |
| 27 M | 62     | LPL | No        | Yes              | No           | 4500          | pos         | 60     | 10     | 0    | 0   | 0   | 0    | 90 | 5      | K    | 1      | No   | No |
| 28 M | 76     | LPL | Yes       | No               | No           | 3760          | pos         | 70     | 40     | 40   | 20  | 0   | 0    | 20 | K      | 7    | No     | No   | No |
| 29 M | 51     | LPL | No        | Yes              | No           | 2450          | pos         | 10     | 10     | 0    | 80  | 0   | 10   | 2  | K      | 1    | Yes    | No   | No |
| 30 F | 67     | MZL | No        | No               | No           | 91            | neg         | 10     | 0      | 0    | 40  | 0   | 40   | 2  | K      | 1    | Yes    | No   | No |
| 31 F | 70     | LPL | No        | Yes              | No           | 1660          | pos         | 20     | 40     | 40   | 20  | 0   | 20   | 8  | K      | 5    | No     | Yes  | No |
| 32 M | 81     | LPL | No        | No               | No           | 672           | nd          | 70     | 0      | 0    | 0   | 0   | 100  | 20 | L      | 10   | Yes    | Yes  | No |
| 33 M | 69     | LPL | Yes       | No               | No           | 336           | pos         | 70     | 0      | 20   | 0   | 0   | 80   | 5  | K      | 7    | Yes    | Yes  | No |
| 34 F | 77     | LPL | Yes       | Yes              | Yes          | 49            | neg         | 60     | 0      | 0    | 0   | 0   | 100  | 2  | nr     | 2    | No     | No   | No |
| 35 F | 56     | MZL | No        | Yes              | No           | 343           | neg         | 15     | 0      | 0    | 20  | 0   | 60   | 20 | nr     | 2    | No     | No   | No |
| 36 F | 69     | MZL | Yes       | No               | No           | nd            | nd          | 7      | 0      | 0    | 90  | 10  | 0    | 5  | nr     | 5    | Yes    | Yes  | No |
| 37 F | 82     | MZL | No        | Yes              | No           | 17            | nd          | 20     | 10     | 0    | 60  | 0   | 30   | 7  | nr     | 3    | Yes    | No   | No |
| 38 F | 58     | MZL | Yes       | No               | No           | nd            | nd          | 30     | 0      | 0    | 95  | 0   | 5    | 2  | nr     | 1    | No     | No   | No |
| 39 M | 78     | LPL | Yes       | No               | No           | 282*lgG3400   | neg         | 5      | 100    | 0    | 0   | 0   | 7    | K  | 2      | Yes  | No     | No   | No |
| 40 F | 77     | LPL | No        | No               | No           | 2160          | pos         | 10     | 10     | 0    | 0   | 0   | 90   | 10 | K      | 1    | No     | No   | No |
| 41 F | 71     | LPL | No        | Yes              | No           | 1260          | pos         | 20     | 10     | 0    | 0   | 0   | 90   | 7  | K      | 5    | No     | No   | No |

Abbreviations: B.M., bone marrow; D, diffuse; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; N, nodular; PT, paratrabecular; I, interstitial; IS, intrasinusoidal; LCR, light chain restriction; nd, not determined; nr, no light chain restriction.

*Monoclonal component not IgM. Normal levels (mg/dl): IgM 40–230; IgG 700–1600; IgA 70–400.
TABLE 2  Summary of the clinical and pathological features of lymphoplasmacytic lymphoma and marginal zone lymphoma cases with statistical significance

| Variable                        | MZL n = 16 | LPL n = 25 | p-Value |
|---------------------------------|------------|------------|---------|
| Gender                          | 10 (63%)   | 10 (40%)   | 0.226   |
| Age, mean (SD)                  | 69.9 (13.3)| 71.2 (9.6) | 0.363   |
| Lymphocytosis                   | 10 (63%)   | 5 (20%)    | 0.009   |
| Splenomegaly                    | 12 (75%)   | 8 (32%)    | 0.011   |
| Lymphadenopathy                 | 6 (38%)    | 11 (44%)   | 0.549   |
| IgM paraprotein                 | 3 (30%)    | 22 (88%)   | 0.001   |
| MYD88p.L265P                    | 0 (0%)     | 19 (86.36%)| 0.000   |
| Infiltration, mean (SD)         | 33.1 (30.3)| 36.1 (26.0)| 0.367   |
| Paratrabecular, mean (SD)       | 3.8 (7.2)  | 17.0 (23.5)| 0.035   |
| Diffuse, mean (SD)              | 8.1 (24.8) | 10.0 (23.5)| 0.404   |
| Nodular, mean (SD)              | 43.4 (41.2)| 12.8 (21.7)| 0.003   |
| Intrasinusoidal, mean (SD)      | 17.8 (27.8)| 1.4 (4.5)  | 0.006   |
| Interstitial, mean (SD)         | 26.9 (32.2)| 58.8 (38.1)| 0.008   |
| CD138+, mean (SD)               | 5.6 (3.6)  | 12.2 (13.4)| 0.062   |
| Light chain                     |            |            | 0.094   |
| K                               | 4 (67%)    | 19 (90%)   |         |
| L                               | 2 (33%)    | 2 (10%)    |         |
| Light chain restriction         | 6 (38%)    | 21 (84%)   | 0.006   |
| Mast cells triptase, mean (SD)  | 2.8 (1.7)  | 4.7 (3.8)  | 0.070   |
| CD25                            | 3 (19%)    | 8 (32%)    | 0.551   |
| CD5                             | 1 (6%)     | 3 (12%)    | 0.584   |

Abbreviations: LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma.

Discussion

B-cell lymphoproliferative disorders with plasmacytic differentiation involving bone marrow represent a diagnostic challenge. Traditionally, it has been proposed that the presence of serum IgM paraprotein is useful for LPL diagnosis and could help in the differential diagnosis of MZL [11, 12]. However, IgM paraprotein can be seen in MZL in other B cell neoplasms.

In our study, the presence of elevated serum IgM monoclonal component was significantly more frequent in LPL than MZL. On the other hand, MZL presented significantly more blood lymphocytosis and splenomegaly. Lymphadenopathy was seen in both cases.

The histological patterns of bone marrow infiltration in each entity have been described by some authors as a very useful feature, with no concordant results. Bassarova et al. [8] have proposed the paratrabecular infiltration as the most characteristic architectural feature of LPL, although other authors have described intrasinusoidal and paratrabecular infiltration as characteristic of MZL[9, 10]. In accordance with other publications [13, 14], in our study, paratrabecular and interstitial patterns of infiltration were significantly higher in LPL, whereas intrasinusoidal or nodular infiltration was distinctive features of MZL.

It has been suggested that LPL and MZL also differ in the percentage of plasmacytic cells in the neoplastic infiltrate suggesting that a percentage of plasma cells higher than 10% could support LPL diagnosis [7]. In our cases, plasma cells were more abundant in LPL, without statistically significant difference. Moreover, according to Morice et al. [15], the percentage of cells with light chain restriction was significantly higher in LPL; hence we propose light chain restriction as a feature of LPL in bone marrow biopsies. Differentiating lymphomas with marked plasmacytic differentiation from plasma cell neoplasms can sometimes be a diagnostic challenge. Detection of CD19 and CD45 expression in neoplastic plasma cells of LPL and MZL can be useful [16].

Different publications remark that the immunophenotype of LPL and MZL is not very distinctive. Classically, LPL cells are negative for CD5 with frequent CD25 expression. However, some authors have described in some series the expression of CD5 in 43% of LPL cases [15]. In our series, no significant differences were found in the expression of CD5 or CD25.

Regarding the higher percentage of mast cells that have been described in LPL [17], our results conclude that this feature is relatively nonspecific and does not help in the differential diagnosis.
MYD88_p.L265P gene mutation was described in 2012 by Treon et al. as a useful tool to accurate the diagnosis of LPL [3]. However, the mutation that has been described in more than 90% of LPL cases has also been demonstrated less frequently in chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and particularly in MZL [18]. Our study, in accordance with others, suggests that the presence of MYD88_p.L265P gene mutation could be an additional tool to provide a certain diagnosis. Interestingly, we found that only in the LPL cases in which MYD88_p.L265P mutation resulted positive, there was a serum IgM monoclonal component higher than 1000 mg/dl, suggesting a lower rate of the mutation in IgM cases with low monoclonal component and non-IgM cases [19, 20].

The World Health Organization Classification of Haematolymphoid Tumours, in previous editions, suggested that “A small B-cell lymphoid neoplasm with plasmacytic differentiation should be diagnosed when the distinction between LPL and MZL, is not always clear-cut.” The results from the present study confirm that different clinical and histological parameters should be collected when LPL or MZL is suspected in bone marrow biopsy specimens, as it is suggested in the upcoming 5th edition of World Health Organization Classification of Haematolymphoid Tumours [21]. The recognition of paratrabecular and interstitial patterns of infiltration, the presence of plasmacytoid and lymphoplasmacytoid cells with light chain restriction, the presence of serum IgM monoclonal component higher than 1000 mg/dl, and the presence of MYD88_p.L265P mutation are findings that support LPL diagnosis. By contrast, blood lymphocytosis, splenomegaly, intrasinusoidal, and nodular pattern of bone marrow infiltration favor MZL diagnosis.

AUTHOR CONTRIBUTIONS
Patricia García Abellás and Ana Ferrer Gómez performed the research. Mónica García-Cosio designed the research study. Miguel Piris Villae-spesa and María Talavera Yagüe contributed with the clinical information and the molecular analysis. Patricia García Abellás and Diego Bueno Sacristán analyzed the data. Patricia García Abellás and Mónica Garcia-Cosío Pique wrote the paper.

CONFLICT OF INTEREST
There is no conflict of interest of any of the authors with the results of this study.

DATA AVAILABILITY STATEMENT
The data that supports the findings of this study are available in the references of this article.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICS STATEMENT
This study was approved by the Ramón y Cajal Universitary Hospital ethic committee and was conducted in accordance with the
Declarations of Helsinki. Informed consent was obtained from all included patients.

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