

MYD88 p.L265P POSITIVITY IN FIVE CASES OF LYMPHOPLASMACYTIC LYMPHOMA/WALDENSTRÖM MACROGLOBULINAEMIA

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ABSTRACT

Background: Lymphoplasmacytic lymphoma (LPL), with its IgM-secreting form known as Waldenström macroglobulinaemia (WM), is a rare, indolent B-cell neoplasm whose diagnosis is increasingly anchored to the somatic MYD88 p.L265P mutation, present in 67–95% of cases across published series. We report a case series of five patients with LPL/WM, all found to harbour the MYD88 L265P mutation, and correlate their clinico-haematological profile with the existing literature. **Materials and Methods:** Clinical, haematological, biochemical, bone marrow morphological, immunophenotypic and molecular (MYD88 p.L265P, tested by next-generation sequencing [NGS]) data of five patients diagnosed with LPL/WM were reviewed and compared against eight primary reference articles and six supplementary publications identified through PubMed. **Result:** The cohort comprised four men and one woman (median age 55 years; range 48–63), all presenting with anaemia, hypoalbuminaemia with a reversed albumin:globulin ratio, and a serum IgM paraprotein with an M-spike (range 7,400–12,000 mg/dL). Peripheral smear showed mild rouleaux formation in all cases, with circulating plasma cells identified in three of five (range 2–3%). Bone marrow was hypercellular with lymphoplasmacytic infiltration in all cases, with a CD20+/CD19+/CD79a+/CD5-/CD10- immunophenotype and light-chain restriction (kappa in four, lambda in one). MYD88 p.L265P was positive in 5/5 (100%) cases — higher than the 67–96% reported in the reference literature. Two of five patients (40%) succumbed to disease; no single laboratory parameter clearly separated them from the three patients on treatment, though one had the highest bone-marrow plasma-cell fraction in the cohort and the other the highest IgM level and hepatomegaly. **Conclusion:** This series reinforces MYD88 p.L265P as a near-universal and highly reproducible diagnostic biomarker in LPL/WM, in keeping with the literature. The high mortality in this small cohort, and the absence of CXCR4 co-mutation testing and formal IPSS-WM risk stratification, highlight parameters that should be captured prospectively to place these outcomes in proper context.

INTRODUCTION

Lymphoplasmacytic lymphoma (LPL) is a neoplasm of small B-lymphocytes, plasmacytoid lymphocytes and plasma cells that most commonly involves the bone marrow. When bone marrow involvement by LPL is accompanied by an IgM monoclonal gammopathy of any concentration, the disorder is termed Waldenström macroglobulinaemia (WM) — together accounting for an annual incidence of approximately 3 cases per million persons and under

2% of non-Hodgkin lymphomas.^[1,2] LPL/WM typically pursues an indolent course with a median survival approaching a decade, but it remains incurable with conventional chemoimmunotherapy.^[1]

LPL/WM lacks a disease-defining immunophenotype: tumour cells characteristically express pan-B-cell markers (CD19, CD20, CD79a, PAX5) and are usually negative for CD5 and CD10, but this profile overlaps substantially with other small B-cell neoplasms showing plasmacytic

differentiation, such as splenic/nodal marginal zone lymphoma, chronic lymphocytic leukaemia and IgM-secreting multiple myeloma.^[2] This diagnostic overlap was transformed in 2012 when whole-genome sequencing identified a recurrent somatic mutation — MYD88 p.L265P (c.794T>C), a leucine-to-proline substitution in the Toll/interleukin-1 receptor (TIR) domain of MYD88 — in 91% of patients with WM and non-IgM LPL, but rarely in mimicking B-cell disorders.^[3] The mutation constitutively activates IRAK1/IRAK4- and BTK-mediated NF- κ B signalling, providing both a diagnostic biomarker and the mechanistic rationale for BTK-inhibitor therapy in this disease.^[1,3,4] Subsequent series have confirmed MYD88 L265P positivity rates of 67–96% in LPL/WM using techniques ranging from Sanger sequencing to allele-specific PCR and droplet digital PCR, the last of which offers the sensitivity required for minimal residual disease monitoring.^[2,5–7]

The chemokine receptor CXCR4 is the second most frequently mutated gene in LPL/WM (approximately 30–40% of MYD88-mutated cases), with WHIM-like nonsense and frameshift mutations that are associated with higher IgM levels, greater marrow disease burden, hyperviscosity, and blunted or delayed response to BTK-inhibitor therapy.^[4,8] A minority of LPL cases (approximately 5%) are non-IgM-secreting — producing IgG or IgA paraproteins, or none at all — and these non-WM-type LPLs harbour MYD88 mutations less frequently and behave somewhat differently in terms of extramedullary presentation, although overall survival appears comparable to classical WM.^[9,10]

We describe five patients diagnosed with LPL/WM, all of whom tested positive for MYD88 p.L265P, and compare their clinical, laboratory and immunophenotypic features against this body of published work, including an Indian cohort that is the most geographically relevant comparator available.^[2]

MATERIALS AND METHODS

This is a retrospective case series of five patients diagnosed with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. For each patient, the following were recorded: presenting complaints, general and systemic examination findings, complete blood counts, peripheral smear findings (rouleaux formation and circulating plasma cells), serum albumin/total protein/globulin with albumin:globulin (A:G) ratio, serum protein electrophoresis (for an M-spike), quantitative serum immunoglobulins (IgM, IgG, IgA), bone marrow aspirate cytology, trephine biopsy histology, immunophenotyping (LCA, CD20, CD19, CD79a, CD138, CD5, CD10, and kappa/lambda light-chain restriction), MYD88 p.L265P mutation status (assessed by next-generation sequencing [NGS]), and clinical outcome. Findings were compared against eight primary reference publications supplied for this

review and six supplementary publications retrieved from PubMed (National Library of Medicine) to provide additional context on CXCR4 co-mutation, non-IgM LPL, and BTK-inhibitor therapy outcomes.^[1–14]

RESULTS

Cohort overview: The cohort comprised four men and one woman (male:female ratio 4:1), with a median age of 55 years (range 48–63). All five patients presented with constitutional or cytopenia-related symptoms — fatigue, breathlessness, epistaxis, fever, headache with pedal oedema, or facial puffiness — and none had lymphadenopathy; one patient had hepatomegaly. All five had anaemia (haemoglobin range 6.2–10.0 g/dL), hypoalbuminaemia with a reversed A:G ratio, an M-spike on serum protein electrophoresis, and a markedly elevated serum IgM (range 7,400–12,000 mg/dL) with normal-range IgG and IgA. Peripheral blood smear showed mild rouleaux formation in all five cases; circulating plasma cells were demonstrable in three of five cases (range 2–3%) and absent in the remaining two. Bone marrow was hypercellular in all cases with a lymphoplasmacytic infiltrate (aspirate lymphocyte fraction 12–31%; plasma cells 4–15%), an LCA+/CD20+/CD19+/CD79a+ immunophenotype (focal CD79a positivity in two cases), negative CD5 and CD10, and light-chain restriction (kappa in four cases, lambda in one). All five patients (100%) were positive for the MYD88 p.L265P mutation. Two patients (40%) succumbed to their disease. No single laboratory parameter distinguished them cleanly from the three patients on treatment: they were not the most anaemic (haemoglobin 10.0 and 9.9 g/dL — the two highest values in the cohort), and while one had the highest IgM in the series (12,000 mg/dL) together with hepatomegaly and facial puffiness, the other had a mid-range IgM (8,500 mg/dL) but the highest bone-marrow plasma-cell fraction in the cohort (15%), presenting instead with headache and pedal oedema.

Individual case summaries:

Case 1

A 62-year-old male: A 62-year-old male presented with fatigue and breathlessness with body pain, 2 months. General examination revealed pallor present, with no organomegaly, and no lymphadenopathy. Haematological work-up showed anaemia (haemoglobin 6.2 g/dL) with a total leucocyte count of 1,910/ μ L and platelet count of 1,12,000/ μ L; peripheral smear showed rouleaux formation with circulating plasma cells (3%). Biochemistry revealed hypoalbuminaemia (3.3 (low) g/dL) with a raised globulin fraction (4.55 (high) g/dL) and a reversed albumin:globulin ratio (0.73 (reversed)), reflecting a monoclonal gammopathy; serum protein electrophoresis confirmed an M-spike. Immunoglobulin quantification showed a markedly

elevated serum IgM of 10,400 (high) mg/dL (IgG 1300 mg/dL, IgA 106 mg/dL).

Bone marrow aspirate showed lymphocytes 21%, plasma cells 12%, and trephine biopsy was hypercellular with infiltration by lymphoplasmacytic cells. On immunohistochemistry, the infiltrate was LCA+, CD20+, CD19+ and CD79a positive, with CD138 showing occasional highlighting of an interstitial plasma-cell component (12% of cells); it was negative for CD5 and CD10, and showed kappa light-chain restriction. This constellation — small B-lymphocytes with plasmacytic differentiation, an IgM paraprotein and bone marrow involvement, in the absence of CD5/CD10 expression — was diagnostic of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. Molecular testing for the MYD88 p.L265P hotspot mutation by next-generation sequencing (NGS) was positive, supporting the diagnosis. The patient was started on treatment and remains on follow-up.

Case 2

A 48-year-old male: A 48-year-old male presented with epistaxis, 5 days. General examination revealed normal, with no organomegaly, and no lymphadenopathy. Haematological work-up showed anaemia (haemoglobin 9.0 g/dL) with a total leucocyte count of 6,500/ μ L and platelet count of 2,26,000/ μ L; peripheral smear showed rouleaux formation without circulating plasma cells. Biochemistry revealed hypoalbuminaemia (3.0 (low) g/dL) with a raised globulin fraction (5.12 (high) g/dL) and a reversed albumin:globulin ratio (0.59 (reversed)), reflecting a monoclonal gammopathy; serum protein electrophoresis confirmed an M-spike. Immunoglobulin quantification showed a markedly elevated serum IgM of 9,040 (high) mg/dL (IgG 1000 mg/dL, IgA 76 mg/dL).

Bone marrow aspirate showed lymphocytes 12%, plasma cells 4%, and trephine biopsy was hypercellular with infiltration by lymphoplasmacytic cells. On immunohistochemistry, the infiltrate was LCA+, CD20+, CD19+ and CD79a positive, with CD138 negative in the lymphoplasmacytic infiltrate; it was negative for CD5 and CD10, and showed kappa light-chain restriction. This constellation — small B-lymphocytes with plasmacytic differentiation, an IgM paraprotein and bone marrow involvement, in the absence of CD5/CD10 expression — was diagnostic of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. Molecular testing for the MYD88 p.L265P hotspot mutation by next-generation sequencing (NGS) was positive, supporting the diagnosis. The patient was started on treatment and remains on follow-up.

Case 3

A 51-year-old female: A 51-year-old female presented with easy fatigability with fever. General examination revealed pallor present, with no organomegaly, and no lymphadenopathy. Haematological work-up showed anaemia (haemoglobin 7.0 g/dL) with a total leucocyte count of 4,100/ μ L and platelet count of 1,45,000/ μ L;

peripheral smear showed rouleaux formation with circulating plasma cells (2%). Biochemistry revealed hypoalbuminaemia (2.9 (low) g/dL) with a raised globulin fraction (4.64 (high) g/dL) and a reversed albumin:globulin ratio (0.63 (reversed)), reflecting a monoclonal gammopathy; serum protein electrophoresis confirmed an M-spike. Immunoglobulin quantification showed a markedly elevated serum IgM of 7,400 (high) mg/dL (IgG 1210 mg/dL, IgA 216 mg/dL).

Bone marrow aspirate showed lymphocytes 31%, plasma cells 8%, and trephine biopsy was hypercellular with infiltration by lymphoplasmacytic cells. On immunohistochemistry, the infiltrate was LCA+, CD20+, CD19+ and CD79a focal positive, with CD138 negative in the lymphoplasmacytic infiltrate; it was negative for CD5 and CD10, and showed lambda light-chain restriction. This constellation — small B-lymphocytes with plasmacytic differentiation, an IgM paraprotein and bone marrow involvement, in the absence of CD5/CD10 expression — was diagnostic of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. Molecular testing for the MYD88 p.L265P hotspot mutation by next-generation sequencing (NGS) was positive, supporting the diagnosis. The patient was started on treatment and remains on follow-up.

Case 4

A 55-year-old male: A 55-year-old male presented with headache with pedal oedema. General examination revealed normal, with no organomegaly, and no lymphadenopathy. Haematological work-up showed anaemia (haemoglobin 10.0 g/dL) with a total leucocyte count of 3,200/ μ L and platelet count of 1,12,000/ μ L; peripheral smear showed rouleaux formation with circulating plasma cells (3%). Biochemistry revealed hypoalbuminaemia (3.3 (low) g/dL) with a raised globulin fraction (4.98 (high) g/dL) and a reversed albumin:globulin ratio (0.66 (reversed)), reflecting a monoclonal gammopathy; serum protein electrophoresis confirmed an M-spike. Immunoglobulin quantification showed a markedly elevated serum IgM of 8,500 (high) mg/dL (IgG 930 mg/dL, IgA 108 mg/dL).

Bone marrow aspirate showed lymphocytes 29%, plasma cells 15%, and trephine biopsy was hypercellular with infiltration by lymphoplasmacytic cells. On immunohistochemistry, the infiltrate was LCA+, CD20+, CD19+ and CD79a positive, with CD138 showing occasional highlighting of an interstitial plasma-cell component (19% of cells); it was negative for CD5 and CD10, and showed kappa light-chain restriction. This constellation — small B-lymphocytes with plasmacytic differentiation, an IgM paraprotein and bone marrow involvement, in the absence of CD5/CD10 expression — was diagnostic of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. Molecular testing for the MYD88 p.L265P hotspot mutation by next-generation sequencing (NGS) was positive, supporting the diagnosis. The patient was

started on treatment but subsequently succumbed to the disease.

Case 5

A 63-year-old male: A 63-year-old male presented with facial puffiness with fever. General examination revealed facial puffiness, with hepatomegaly, and no lymphadenopathy. Haematological work-up showed anaemia (haemoglobin 9.9 g/dL) with a total leucocyte count of 6,500/ μ L and platelet count of 1,67,000/ μ L; peripheral smear showed rouleaux formation without circulating plasma cells. Biochemistry revealed hypoalbuminaemia (2.6 (low) g/dL) with a raised globulin fraction (5.38 (high) g/dL) and a reversed albumin:globulin ratio (0.48 (reversed)), reflecting a monoclonal gammopathy; serum protein electrophoresis confirmed an M-spike. Immunoglobulin quantification showed a markedly elevated serum IgM of 12,000 (high) mg/dL (IgG 1240 mg/dL, IgA 112 mg/dL).

Bone marrow aspirate showed lymphocytes 22%, plasma cells 8%, and trephine biopsy was hypercellular with infiltration by lymphoplasmacytic cells. On immunohistochemistry, the infiltrate was LCA+, CD20+, CD19+ and CD79a focal positive, with CD138 showing occasional highlighting of an interstitial plasma-cell component (10% of cells); it was negative for CD5 and CD10, and showed kappa light-chain restriction. This constellation — small B-lymphocytes with plasmacytic differentiation, an IgM paraprotein and bone marrow involvement, in the absence of CD5/CD10 expression — was diagnostic of lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia. Molecular testing for the MYD88 p.L265P hotspot mutation by next-generation sequencing (NGS) was positive, supporting the diagnosis. The patient was started on treatment but subsequently succumbed to the disease.

Table 1: Demographic and clinical features

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	62	48	51	55	63
Sex	Male	Male	Female	Male	Male
Presenting complaint	Fatigue and breathlessness with body pain, 2 months	Epistaxis, 5 days	Easy fatigability with fever	Headache with pedal oedema	Facial puffiness with fever
General examination	Pallor present	Normal	Pallor present	Normal	Facial puffiness
Organomegaly	Absent	Absent	Absent	Absent	Hepatomegaly
Lymphadenopathy	Absent	Absent	Absent	Absent	Absent
Outcome	On treatment	On treatment	On treatment	Succumbed	Succumbed

Abbreviation: A:G, albumin:globulin.

Table 2: Haematological, biochemical and immunoglobulin profile

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Haemoglobin (g/dL)	6.2	9.0	7.0	10.0	9.9
Total leucocyte count (/ μ L)	1,910	6,500	4,100	3,200	6,500
Platelet count (/ μ L)	1,12,000	2,26,000	1,45,000	1,12,000	1,67,000
Rouleaux formation	Present	Present	Present	Present	Present
Circulating plasma cells	3%	0%	2%	3%	0%
Serum albumin (g/dL)	3.3 (low)	3.0 (low)	2.9 (low)	3.3 (low)	2.6 (low)
Total protein (g/dL)	7.85	8.12	7.54	8.28	7.98
Globulin (g/dL)	4.55 (high)	5.12 (high)	4.64 (high)	4.98 (high)	5.38 (high)
A:G ratio	0.73 (reversed)	0.59 (reversed)	0.63 (reversed)	0.66 (reversed)	0.48 (reversed)
Serum M-spike	Present	Present	Present	Present	Present
Serum IgM (mg/dL)	10,400 (high)	9,040 (high)	7,400 (high)	8,500 (high)	12,000 (high)
Serum IgG (mg/dL)	1300	1000	1210	930	1240
Serum IgA (mg/dL)	106	76	216	108	112

All values as recorded at diagnosis. Platelet and leucocyte counts expressed per μ L.

Table 3: Bone marrow, immunophenotype and molecular findings

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Bone marrow aspirate	Lymphocytes 21%, plasma cells 12%	Lymphocytes 12%, plasma cells 4%	Lymphocytes 31%, plasma cells 8%	Lymphocytes 29%, plasma cells 15%	Lymphocytes 22%, plasma cells 8%
Bone marrow biopsy	Hypercellular	Hypercellular	Hypercellular	Hypercellular	Hypercellular
LCA	+	+	+	+	+
CD20	+	+	+	+	+
CD19	+	+	+	+	+
CD79a	Positive	Positive	Focal Positive	Positive	Focal Positive
CD138	Occasional (12%)	Negative	Negative	Occasional (19%)	Occasional (10%)
CD5	–	–	–	–	–
CD10	–	–	–	–	–
Kappa light chain	Restricted	Restricted	–	Restricted	Restricted
Lambda light chain	–	–	Restricted	–	–
MYD88 p.L265P	Positive	Positive	Positive	Positive	Positive

Abbreviations: LCA, leucocyte common antigen; NGS, next-generation sequencing. MYD88 p.L265P mutation status was assessed by NGS in all cases.

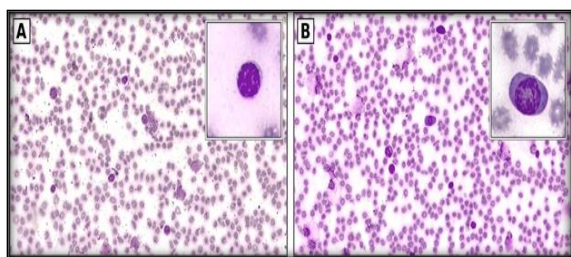


Figure 1: Peripheral blood smear (Leishman stain, ×40). (A) Mild rouleaux formation with atypical lymphoid cells (inset); these cells are small, round to oval, with scant cytoplasm, coarse “soccer-ball” chromatin, and inconspicuous 0–1 nucleoli. (B) A circulating plasma cell (inset), reflecting marrow disease spilling into the peripheral blood.

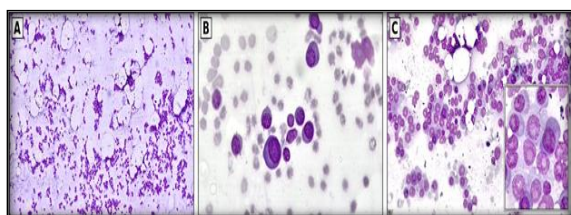


Figure 2: Bone marrow aspirate smear (Leishman stain). (A) Scanner view (×4) showing marrow elements with occasional megakaryocytes and interspersed fat spaces. (B) ×100 view showing plasma cells admixed with atypical lymphoid cells. (C) ×40 view showing plasma cells with intranuclear inclusions, i.e., Dutcher bodies (inset) — accumulations of immunoglobulin within the nuclear envelope, a recognised feature of lymphoplasmacytic differentiation.

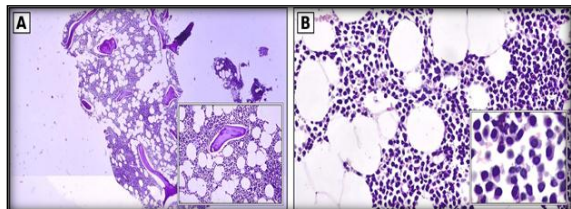


Figure 3: Bone marrow biopsy (H&E stain). (A) ×4 view showing a single core of tissue with five intertrabecular spaces, satisfactory for evaluation; the paratrabecular space shows plasma cells arranged in diffuse sheets (inset). (B) ×40 view showing plasma cells with eccentrically placed nuclei; inset highlights cells bearing intranuclear inclusions.

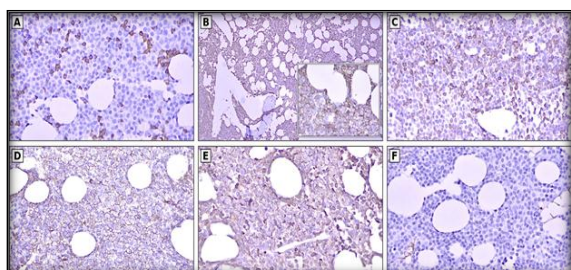


Figure 4: Immunohistochemistry — lineage and diagnostic markers. (A) LCA positive, confirming the infiltrate is of leucocytic (lymphoid) lineage. (B) CD20 positive (inset), confirming a mature B-cell phenotype. (C) CD79a positive in the lymphoid infiltrate, supporting B-cell lineage. (D) CD138 positive in plasma

cells, highlighting the plasmacytic component of the infiltrate. (E) Kappa light chain positive, showing light-chain restriction consistent with a clonal plasma-cell population. (F) Lambda light chain negative, in keeping with kappa light-chain restriction.

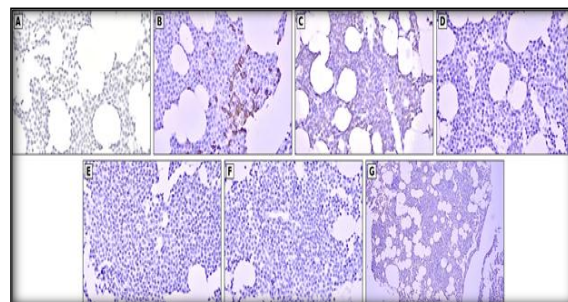


Figure 5: Immunohistochemistry — differential/exclusionary markers. (A) CD5 negative, a finding used to help exclude CLL/SLL and mantle cell lymphoma. (B) MPO positive in scattered reactive myeloid cells, a background finding rather than a feature of the lymphoid infiltrate. (C) CD117 positive in myeloid precursors, again reflecting the reactive myeloid background. (D) CD10 negative, a finding used to help exclude follicular and Burkitt lymphoma. (E) PAX5 negative. (F) TdT negative, arguing against a precursor (lymphoblastic) process. (G) CD34 negative, arguing against a blastic/precursor population.

DISCUSSION

MYD88 L265P positivity: higher than the pooled literature range: Every patient in this series (5/5, 100%) was MYD88 p.L265P–positive by NGS. This exceeds the rates reported in every comparator series reviewed: 91% in the original whole-genome-sequencing cohort.^[3] 84.8% by allele-specific PCR in the largest Indian series to date (Vinarkar et al., n=33).^[2] 75% by MEMO-PCR in a Korean cohort (Shin et al., n=28).^[5] 96% by PCR-based testing on decalcified, formalin-fixed marrow in a German cohort (Schmidt et al., n=51).^[7] and 95.3% on unsorted baseline bone marrow using droplet digital PCR, the most sensitive platform available (Drandi et al.).^[6] A comparative summary is presented in [Table 4]. The 100% positivity here most plausibly reflects the small sample size and a degree of pre-test selection — all five patients already had a hypercellular, lymphoplasmacytic marrow with an IgM paraprotein before molecular testing was requested, i.e., a cohort enriched for a high pre-test probability of LPL/WM, rather than an unselected screening population. It nonetheless reinforces the point made across the literature that MYD88 p.L265P is a near-universal, highly reproducible lesion in morphologically and immunophenotypically typical LPL/WM, and a valuable adjunct where the differential includes marginal zone lymphoma, CLL with plasmacytic differentiation, or IgM myeloma — entities in which the mutation is rare or absent.^[1,3,7]

Table 4: This series compared with published cohorts

Series (reference)	N	Age (y)*	M:F	MYD88 L265P +ve	Method
This case series	5	55 (median)	4:1	100% (5/5)	NGS
Vinarkar et al., India, 2019 [2]	33	64 (median)	2.3:1	84.8% (AS-PCR)	AS-PCR / Sanger
Shin et al., Korea, 2016 [5]	28	65 (mean)	1.8:1	75%	MEMO-PCR
Treon et al. (NEJM), 2012 [3]	57 (LPL total)	n/r	n/r	91%	WGS / Sanger
Schmidt et al., Germany, 2015 [7]	51	n/r	n/r	96%	PCR-based (FFPE)
Drandi et al. (ddPCR), 2018 [6]	128 (BM, baseline)	67 (median)†	~1.9:1†	95.3% (BM)	Droplet digital PCR

n/r = not reported for the LPL/WM subgroup in the cited source. Bracketed numbers refer to the reference list.

*Age statistic type (median/mean) as reported by the source; not all sources report the same statistic. †Drandi et al. reported age and sex distribution for the full baseline cohort (n=148: 133 WM, 10 IgG-LPL, 4 IgM-MGUS, 1 IgM-LPL amyloid), of whom 128 had a baseline bone marrow sample tested; the M:F ratio (34% female) is derived from that full cohort, not the 128-patient bone marrow subset specifically.

Demographics: a younger cohort with a comparable male predominance: The median age of 55 years in this series is notably younger than the 62–67-year medians reported in comparable cohorts, including the geographically closest comparator, Vinarkar et al.'s Indian series (median 64 years).^[2] and Shin et al.'s Korean series (mean 65 years).^[5] The male predominance (4:1) is consistent with, if somewhat more pronounced than, the 1.8:1 to 3:1 ratios reported elsewhere.^[2,5] Given the small sample size, the younger age at presentation here should be regarded as a descriptive observation rather than a definitive departure from the literature, but it would be worth confirming in a larger regional cohort.

Immunophenotype and laboratory profile: a textbook LPL/WM signature: All five cases displayed the immunophenotype classically described for LPL/WM — CD20+/CD19+/CD79a+ with negative CD5 and CD10 — which is the combination used across the literature to exclude CLL/SLL (typically CD5+) and follicular/Burkitt lymphoma (typically CD10+).^[1,2,11] CD79a positivity was focal rather than diffuse in two of the five cases, but this is consistent with the pan-B-cell marker being expressed at variable intensity across the lymphoplasmacytic-to-plasmacytic spectrum.^[2] The presence of an interstitial CD138+ plasma-cell component (occasional, comprising 10–19% of cells where present, to negative across cases) is in keeping with the lymphoplasmacytic-to-plasmacytic morphological spectrum described in the ASH reference case and in Rossi's review.^[1,11] Mild rouleaux formation, seen in all five cases, and circulating plasma cells, seen in three of five cases, on peripheral smear are non-specific but expected peripheral-blood correlates of a marrow driving a monoclonal IgM paraprotein. The universally reversed A:G ratio and elevated total protein reflect the hypergammaglobulinaemia driven by monoclonal IgM, and the markedly elevated IgM levels (7,400–12,000 mg/dL) in every case place all five patients above the threshold typically associated with symptomatic disease and, in some published cohorts, with hyperviscosity risk.^[2,8] Notably, all five cases in this series were IgM-secreting (WM-type);

none corresponded to the rarer non-IgM (IgG- or IgA-secreting) LPL variants described by Isaksen et al. and Castillo et al., which together comprise only about 5% of LPL and tend to harbour MYD88 mutations less frequently than IgM-type disease.^[9,10]

CXCR4 status: a notable gap relative to the literature: None of the five cases in this dataset were tested for CXCR4 mutations. This is a meaningful gap: CXCR4 WHIM-type mutations co-occur with MYD88 L265P in roughly 30–40% of WM/LPL cases, and patients with MYD88L265P/CXCR4WHIM genotypes present with significantly higher bone marrow disease burden, higher serum IgM, and a greater incidence of symptomatic hyperviscosity than MYD88L265P/CXCR4wild-type patients.^[2,7,8] CXCR4 mutation status also has direct treatment relevance: response rates to the BTK inhibitor ibrutinib are highest in patients with MYD88L265P/CXCR4wild-type disease (100% overall response in the pivotal trial) and lower/slower in those with CXCR4WHIM mutations.^[4,12] Given that two of the five patients in this series died, and that the literature specifically associates the WHIM-type CXCR4 genotype with higher IgM, greater tumour burden and inferior early outcomes, CXCR4 testing on stored or future samples would materially sharpen the interpretation of this series and any subsequent treatment decisions, particularly if BTK-inhibitor therapy is being considered for the three patients still on treatment.^[8,12]

Outcome: a higher-than-expected mortality in a small cohort: Two of five patients (40%) succumbed to disease. This is notably higher than would be expected for LPL/WM, which is generally described as an indolent lymphoma with a median survival approaching ten years.^[1,2] Contrary to a simple high-tumour-burden narrative, however, no single laboratory parameter in this dataset cleanly separated the two fatal cases from the three patients on treatment. The two who died were not the most anaemic in the cohort — their haemoglobin values (10.0 and 9.9 g/dL) were in fact the two highest recorded — and, as a pair, they were not the two highest for serum IgM either: one had the highest

IgM in the series (12,000 mg/dL, with hepatomegaly and facial puffiness), but the other had a comparatively mid-range IgM of 8,500 mg/dL (the second-highest IgM in the cohort, 10,400 mg/dL, was in a patient currently on treatment) and instead had the highest bone-marrow plasma-cell fraction recorded (15%), presenting with headache and pedal oedema. Taken individually, hepatomegaly, facial puffiness, headache and oedema are each compatible with a hyperviscosity-type or high-tumour-burden presentation, and it remains plausible that CXCR4 co-mutation status — not assessed here — differed between the fatal and non-fatal cases in a way that IgM level alone did not capture, consistent with the literature linking CXCR4 co-mutation, rather than IgM level in isolation, to more aggressive disease biology and inferior early outcomes.^[2,8] Given the small sample size, however, these observations should be read as descriptive rather than as an established predictor of outcome. Formal risk stratification with the International Prognostic Scoring System for WM (IPSS-WM).^[2] which incorporates age, haemoglobin, platelet count, β 2-microglobulin and serum monoclonal protein concentration — was not derivable from the dataset available, since β 2-microglobulin and lactate dehydrogenase values, cause and timing of death, and treatment regimens were not recorded; these would be valuable additions for interpreting mortality in this cohort with confidence.

Therapeutic and monitoring implications: For the three patients currently on treatment, the literature reviewed here offers two practical points. First, bortezomib-dexamethasone-rituximab (BDR) has been used successfully as first-line therapy in comparable MYD88-mutated LPL/WM cases, including in atypical (non-IgM) presentations, and was specifically favoured over a bendamustine-rituximab alternative in one such case because it is considered less myelosuppressive when bone marrow failure is the indication for treatment.^[9,13] Second, ibrutinib (alone or combined with rituximab) produces high and durable response rates in MYD88-mutated WM, particularly where CXCR4 is wild-type, and is now a standard option in the relapsed/refractory setting and, per the iNOVATE trial, in combination with rituximab regardless of prior treatment status.^[12,14] Should relapse or progression occur, CXCR4 testing prior to selecting a BTK inhibitor would align management with current evidence.^[4,8,12] For future follow-up, highly sensitive MYD88 p.L265P assays such as droplet digital PCR — validated for minimal residual disease monitoring on unsorted bone marrow, peripheral blood, and even cell-free plasma DNA — could offer a practical, minimally invasive way to track response in these patients over time.^[6]

Limitations

- Small sample size (n=5) drawn from a single dataset, limiting statistical comparison with larger published cohorts.

- CXCR4 mutation status was not tested, precluding assessment of WHIM-type co-mutations known to influence presentation, prognosis and ibrutinib response.
- β 2-microglobulin, LDH and formal IPSS-WM risk scores were not available, limiting prognostic contextualisation of the two fatal outcomes.
- Treatment regimens, duration of follow-up, and cause of death were not specified in the source data.

CONCLUSION

This series of five LPL/WM patients demonstrates a classical clinical, morphological and immunophenotypic picture, with universal (5/5) positivity for the MYD88 p.L265P mutation — consistent with, and at the upper end of, the 67–96% positivity rates reported across the international and Indian literature reviewed here. The findings support MYD88 p.L265P testing as a robust, near-universal diagnostic adjunct in morphologically typical LPL/WM. The unexpectedly high mortality (40%) in this small cohort was not explained by any single laboratory parameter captured here — notably, the two fatal cases were not the two with the highest IgM, nor the most anaemic. This underscores the literature's emphasis on CXCR4 co-mutation, IgM level and formal IPSS-WM risk stratification as joint, rather than singular, determinants of outcome in LPL/WM, and argues for prospective CXCR4 testing and structured outcome/follow-up data collection in any expansion of this case series.

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