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Research paper

# The role of high serum CXCL13 level in Waldenström macroglobulinemia

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ABSTRACT

*Purpose:* To explore the value of elevated CXCL13 levels in Waldenström macroglobulinemia (WM).
*Methods:* We collected serum samples from 41 patients and bone marrow tissues from 14 patients with newly diagnosed symptomatic WM. Serum and bone marrow samples from patients with other indolent B-cell lymphomas and MGUS were also collected for comparison. Serum CXCL13 levels were measured by enzyme-linked immunosorbent assay, and bone marrow tissues were examined by immunohistochemistry.
*Results:* The median serum level of CXCL13 in patients with symptomatic WM was 2483.0 (range 36.8–5644.0) pg/ml, which was significantly higher than in patients with other indolent B-cell lymphomas with monoclonal IgM (median 380.9 pg/ml, range 23.8–5518.0 pg/ml) ($p = 0.01$). Serum CXCL13 > 3250 pg/ml and serum M-protein > 38 g/l diagnosed WM with a sensitivity of 98% and specificity of 85%. Serum CXCL13 was strongly correlated with hemoglobin levels ($\rho = -0.46$, $p = 0.002$), serum M-protein ($\rho = 0.47$, $p = 0.002$), and IgM levels ($\rho = 0.30$, $p = 0.05$) in patients with symptomatic WM. Immunohistochemistry analysis indicated that CXCL13 and activated mast cell levels were also higher in the bone marrow of WM patients compared to patients with IgM-MGUS or other indolent B-cell lymphomas with monoclonal IgM.
*Conclusions:* Serum CXCL13 levels were significantly elevated in patients with WM and correlated with tumor load. Detection of serum CXCL13 may therefore be helpful in the differential diagnosis of WM.

## 1. Introduction

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoma characterized by serum monoclonal immunoglobulin M (IgM) secreted by lymphoplasmacytic cells. Symptomatic anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and hyperviscosity caused by IgM are typical clinical manifestations of WM [1]. However, monoclonal IgM can also be present in other indolent B-cell lymphomas [2]. MYD88$^{L265P}$ has a 90% mutation rate in patients with WM and thus plays an important role in its diagnosis [3]. Over 30 different nonsense and frameshift mutations of CXCR4 have been reported in patients with WM. CXCR4$^{S338X}$ is the most common one according to reports as well as our previous study [4,5]. However, previous work found that the MYD88$^{L265P}$ mutation could also be detected in patients with diseases including diffuse large B-cell lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia (CLL), and monoclonal gammopathy with undetermined significance (MGUS) [5,6]. Sometimes the similar morphologies and immunophenotypes make it difficult to differentiate between WM and other indolent B-cell lymphomas, especially marginal zone lymphomas.

C-X-C motif chemokine ligand 13 (CXCL13), or B lymphocyte chemoattractant, is a chemokine expressed in the follicles of the spleen, Peyer's patches, and lymph nodes. CXCL13 is required for B lymphocyte migration to follicles in secondary lymphoid organs [7]. CXCL13 has been well-studied in many chronic inflammatory diseases, including rheumatoid arthritis and ulcerative colitis [8,9], and CXCL13 has demonstrated predictive diagnostic and prognostic values in hematologic malignancies, such as primary central nervous system lymphoma and CLL [10–12]. In 2017, Vos et al. reported that serum CXCL13 levels were elevated in patients with WM, and indicated its potential value for predicting response to ibrutinib treatment [13].

In our study, we analyzed serum CXCL13 levels in patients with WM as well as in patients with other indolent B-cell lymphomas with or without monoclonal IgM, and tried to provide insights into the differential diagnosis of WM. Also, we investigated CXCL13 level in the bone marrow, and studied the relationship between CXCL13 and tumor load in patients with WM.

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## 2. Materials and methods

### 2.1. Sample collection

We collected serum samples from 44 patients with newly diagnosed WM (including 41 patients with symptomatic WM and 3 patients with smoldering WM) at Peking Union Medical College Hospital from January 2015 to May 2018, and 22 serum samples from age- and sex-matched healthy donors were collected as well. Twenty-seven serum samples were collected from patients diagnosed with other indolent B-cell lymphomas for comparison, including 14 patients with simultaneous monoclonal IgM. Ten serum samples were also collected from patients with IgM-MGUS.

Paraffin-embedded bone marrow tissues were collected from patients with newly diagnosed WM (n = 14) and control patients with other indolent B-cell lymphomas with monoclonal IgM (n = 2) and IgM-MGUS (n = 3). The tissues were sectioned for immunohistochemistry analysis.

### 2.2. Patients and diagnostic criteria

All patients with WM were required to meet the following diagnostic criteria: (i) lymphoplasmacytic bone marrow involvement; (ii) any level of IgM paraprotein, and (iii) exclusion of other low-grade lymphoma. Symptomatic WM was defined as the presence of constitutional symptoms (weakness, fatigue, recurrent fever, night sweats, or weight loss), cytopenia, bulky and/or symptomatic lymphadenopathy, splenomegaly or hepatomegaly, symptomatic hyperviscosity syndrome, or IgM-related symptoms. Smoldering WM was defined as for WM, but without the related clinical symptoms [14].

Patients with symptomatic WM were classified into low-, intermediate-, and high-risk groups according to the International Prognostic Scoring system for symptomatic Waldenström macroglobulinemia (IPSS-WM). Low risk was defined by the presence of not more than one adverse characteristic and age ≤65 years; high risk was defined by the presence of at least three adverse characteristics; and the remaining patients were classified as intermediate risk [15].

IgM-MGUS was diagnosed by the presence of serum IgM monoclonal protein without morphological evidence of bone marrow infiltration by lymphoplasmacytic lymphoma, and no clinical symptoms attributed to monoclonal IgM protein [14].

Other indolent B-cell non-Hodgkin lymphoma was diagnosed according to the World Health Organization classification [16].

Monoclonal IgM was confirmed by immunofixation electrophoresis. Patients with other indolent B-cell lymphomas were described as other indolent B-cell lymphoma with or without monoclonal IgM, respectively.

### 2.3. Data collection

Information on sex, age at diagnosis, and baseline laboratory test results including hemoglobin level, platelet count, serum protein electrophoresis, IgG/IgA/IgM level, serum β2-microglobulin, bone marrow pathology, and $MYD88^{L265P}$ and $CXCR4^{S338X}$ mutation statuses was collected. $MYD88^{L265P}$ and $CXCR4^{S338X}$ were detected by real-time allele-specific oligonucleotide polymerase chain reaction using unsorted bone marrow samples [5]. In our study, symptomatic WM patients were treated immediately after the diagnosis. Thus information and baseline laboratory test results were used for IPSS-WM risk stratification accordingly.

All patients signed informed consent for participation in the study. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital in accordance with the Declaration of Helsinki.

### 2.4. Experimental methods

Serum concentrations of CXCL13 were measured by enzyme-linked immunosorbent assay, according to manufacturer's instructions (Quantikine ELISA; R&D Systems, MN, USA).

Immunohistochemistry was performed using the DAB peroxidase method with anti-human CXCL13 antibody (dilution 1:100; rabbit polyclonal; Proteintech, IL, USA), anti-human CD117 antibody (dilution 1:400; rabbit polyclonal; Proteintech), and anti-human mast cell tryptase antibody (dilution 1:200; rabbit monoclonal; Abcam, USA). All antibodies were treated and used according to the manufacturer's instructions. Semi-quantitative analysis of anti-human CD117 and anti-human mast cell tryptase antibodies was performed manually by counting the absolute number of immunoreactive cells in 10 non-overlapping high-power fields (HPFs) (40×), and the mean number of positive cells was calculated.

### 2.5. Statistical analysis

Categorical variables are presented as percentages, and quantitative data are presented as mean ± standard deviation or median (range). Categorical variables were compared by $\chi^2$ tests and numerical variables were compared by Mann–Whitney tests because of the non-parametric data distribution. Covariate analysis was performed using Spearman's rank correlation coefficient (ρ). Through square root transformation, numerical variables including serum CXCL13 level, hemoglobin level, serum IgM and M-protein levels were converted to normal distribution, and then univariate and multivariate linear regression analysis were applied to evaluate association between these variables. A $p$ value $< 0.05$ was deemed statistically significant. Diagnostic performance was evaluated by receiver operating characteristic (ROC) curve analysis (SPSS Inc., IL, USA).

## 3. Results

### 3.1. Baseline characteristics

The baseline characteristics of the 41 patients with symptomatic WM are shown in Table 1. Among the 14 patients with other indolent B-cell lymphomas with monoclonal IgM, two were diagnosed with spleen marginal zone lymphoma, one with mantle cell lymphoma, one with mucosa-associated lymphoid tissue, four with follicular lymphoma, and six with CLL. IgM-κ M-protein was found in 11/14 (78.6%) patients, while IgM-λ M-protein was found in 3/14 (21.4%) patients. The median marrow lymphoplasmacytic infiltrate was 4.6% (1–23.5%). The baseline characteristics of these 14 patients are also shown in Table 1. There were no significant differences in most parameters between patients with other indolent B-cell lymphomas with monoclonal IgM and patients with WM, except that M-protein and IgM levels were significantly lower in patients with other indolent B-cell lymphomas with monoclonal IgM (both $p < 0.001$), and the incidence of $MYD88^{L265P}$ mutation was also significantly lower ($p = 0.04$).

### 3.2. Serum CXCL13 level at diagnosis

The median serum CXCL13 level in patients with symptomatic WM was 2483.0 (range 36.8–5644.0) pg/ml, which was significantly higher than that in patients with smoldering WM (median 35.6 pg/ml, range 27.7–549.6 pg/ml) ($p = 0.0176$), IgM-MGUS (median 33.5 pg/ml, range 20.8–873.3 pg/ml) ($p < 0.0001$), or healthy donors (median 26.6 pg/ml, range 14.0–98.3 pg/ml) ($p < 0.0001$) (Fig. 1).

Serum CXCL13 levels were also elevated in patients with other indolent B-cell lymphomas, either with monoclonal IgM (median 380.9 pg/ml, range 23.8–5518.0 pg/ml) ($p < 0.0001$) or without monoclonal IgM (median 213.5 pg/ml, range 24.3–2747.0 pg/ml) ($p < 0.0001$), compared with healthy donors. There was no significant

**Table 1**
Clinical characteristics of patients with symptomatic WM and other indolent B-cell lymphomas with monoclonal IgM.

| Baseline characteristics | Symptomatic WM (n = 41) | Other indolent B cell lymphoma with monoclonal IgM (n = 14) | *p* value |
|---|---|---|---|
| Median age, years | 62 (33–81) | 68.5 (39–85) | 0.39 |
| Male-to-female ratio | 1.9:1 (27:14) | 3.7:1 (11:3) | 0.58 |
| Median hemoglobin, g/L | 87 (50–145) | 110 (60–159) | 0.08 |
| Median platelet count, ×10 [9] /L | 204 (78–581) | 174 (40–688) | 0.68 |
| Median β2-microglobulin, mg/L | 5.35 (2.40–12.80) | 4.73 (2.31–7.34) | 0.35 |
| Median M protein, g/L | 21.6 (0.2–56.3) | 0.7 (0.0–20.9) | < 0.0001* |
| Median IgM, g/L | 30.8 (0.9–85.0) | 2.6 (0.8–34.1) | < 0.0001* |
| Median marrow lymphoplasmacytic infiltrate | 4.6% (1–23.5%) | 0.0% (0.0–0.0%) | – |
| Mutation status | | | |
| $MYD88^{L265P}$ | 31/35 (88.6%) | 2/5 (40.0%) | 0.04* |
| $CXCR4^{S338X}$ | 4/35 (11.4%) | 0/5 (0.0%) | – |
| International Prognostic Scoring system | | | |
| Low | 9/41 (22.0%) | NA | |
| Intermediate | 19/41 (46.3%) | NA | |
| High | 13/41(31.7%) | NA | |

* $p < 0.05$ was defined as significant.

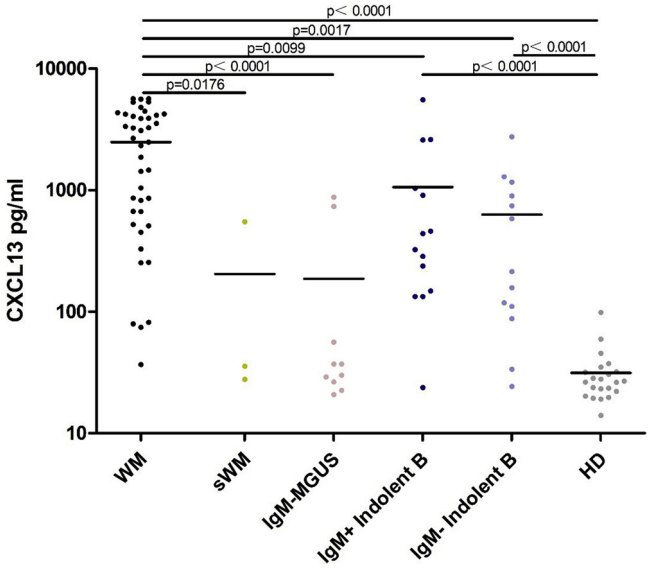


**Fig. 1. Serum CXCL13 levels in patients with WM, IgM-MGUS, and other indolent B-cell lymphomas.** Indolent B: other indolent B-cell lymphoma; HD: healthy donors; IgM+: with monoclonal IgM; IgM-: without monoclonal IgM.

difference in serum CXCL13 levels between patients with other indolent B-cell lymphomas with or without monoclonal IgM. Notably, the median serum CXCL13 level in patients with other indolent B-cell lymphomas with monoclonal IgM was 380.9 (23.8–5518.0) pg/ml, which was significantly lower than that in patients with WM ($p = 0.0099$) (Fig. 1).

We evaluated the value of serum CXCL13 in the diagnosis of WM by ROC curve analysis. Forty-one patients with symptomatic WM and 14 patients diagnosed with other indolent B-cell lymphomas with monoclonal IgM were analyzed. The area under the ROC curve was 0.715 for serum CXCL13 levels > 3250 pg/ml, with a sensitivity and specificity for diagnosing WM of 81% and 64%, respectively. Combining serum CXCL13 and serum M-protein levels, a serum level of CXCL13 > 3250 pg/ml and serum M-protein level > 38 g/l produced an area under the ROC curve of 0.935, with a sensitivity and specificity for diagnosing WM was 98% and 85%, respectively (Fig. 2).

### 3.3. Serum CXCL13 level and tumor load

We classified symptomatic WM patients into low-, intermediate-, and high-risk groups and showed that the median serum CXCL13 level was significantly lower in the low-risk group (median 327.5 pg/ml, range 79.2–3249.0 pg/ml) compared with the intermediate-risk (median 3248.0 pg/ml, range 36.8–5606.0 pg/ml) ($p = 0.0059$) and high-risk groups (median 3535.0 pg/ml, range 521.1–5644.0 pg/ml) ($p = 0.0007$). Among patients with newly diagnosed WM, serum CXCL13 level was strongly correlated with hemoglobin level (correlation coefficient of -0.46, $p = 0.0016$), and with serum IgM and serum M-protein levels (correlation coefficients of 0.30 and 0.47, $p = 0.0494$ and $p = 0.0021$, respectively) (Fig. 3). In univariate linear regression model, serum CXCL13 was also significantly related to hemoglobin level ($\beta = -0.603$, $p < 0.0001$), serum IgM ($\beta = 0.33$, $p = 0.019$) and serum M-protein levels ($\beta = 0.415$, $p = 0.004$). Results of multivariate linear regression model revealed that only hemoglobin level was negatively significantly related to serum CXCL13 level in patients with WM ($\beta = -0.528$, $p < 0.0001$). No correlation between MYD88 or CXCR4 mutation status and serum CXCL13 level was found.

### 3.4. Immunohistochemical staining

We further analyzed the origin of the high CXCL13 levels in relation to the tumor microenvironment by immunohistochemical staining of bone marrow trephine biopsies from 14 patients with newly diagnosed WM. CXCL13 staining was significantly higher in bone marrow from patients with WM compared with other indolent B-cell lymphomas with monoclonal IgM or IgM-MGUS (Fig. 4A–D). We also found more CD117-positive mast cells and tryptase-positive activated mast cells in the bone marrow of WM patients (Fig. 4E–H). Semi-quantitative analysis showed that the median CD117-positive cell counts per HPF were 12.9 (2.4–43.6) in WM patients, 0.2 (0.0–1.7) in patients with IgM-MGUS, and 0.15 (0.0–0.3) in patients diagnosed with other indolent lymphomas with monoclonal IgM. The equivalent median tryptase-positive cell counts/HPF were 2.3 (0.0–38.3), 0.0 (0.0–0.0), and 0.8 (0.0–1.5), respectively.

## 4. Discussion

Cytokines are involved in many biological processes, including cell growth, survival, inflammation, and differentiation [17]. In malignancies, cytokines can affect tumor cells either directly or by acting on the surrounding environment [18]. Previous studies reported that CXCL13 gene expression and serum levels were elevated in patients with WM [13,19]. We therefore further investigated CXCL13 levels in serum and bone marrow from WM patients, and studied its elevation and correlation with tumor load in WM.

Our study revealed that CXCL13 levels were significantly elevated in WM compared with other indolent lymphomas with monoclonal IgM. At the beginning, we assumed that elevated serum CXCL13 level was

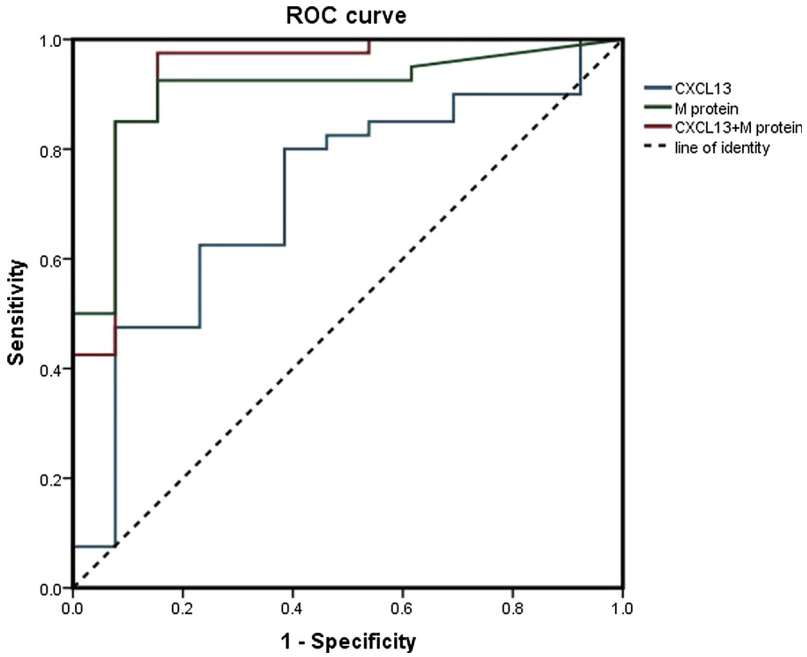


**Fig. 2.** ROC curves evaluating efficacies of serum CXCL13 and M-protein levels for diagnosing WM.

associated with monoclonal IgM. However, through comparing of serum CXCL13 level in patients diagnosed with indolent B-cell lymphomas with or without monoclonal IgM, we haven't found any relation between monoclonal IgM and elevated CXCL13. This finding indicated that elevated serum CXCL13 level was not associated with monoclonal IgM but was related to disease entity. $MYD88^{L265P}$ mutation which was regarded as a diagnostic marker of WM, was detected in 88.6% of patients with WM in our study. In our center, marrow lymphoplasmacytic infiltration was measured by marrow smear, which might be the reason for the relatively low median marrow infiltrate. But as we verified in previous study, testing of MYD88 and CXCR4 mutation was not affected by the marrow infiltrate result [5]. However, we previously identified a mutation rate of 34.1% for $MYD88^{L265P}$ in patients with non-Hodgkin lymphomas with monoclonal IgM, including diffuse large B-cell lymphoma, marginal zone lymphoma, and CLL [5], suggesting that $MYD88^{L265P}$ mutation is not only present in WM. Our results showed a significant elevation of CXCL13 could act as an assistant biomarker especially helpful in the differential diagnosis of WM and other indolent B cell lymphomas with $MYD88^{L265P}$ mutation.

We also noted marked correlations between serum CXCL13 and hemoglobin levels in WM patients, which paralleled the findings of Vos et al. [13], as well as correlations between serum CXCL13 and serum M-protein, IgM levels, and IPSS-WM. Serum monoclonal IgM were secreted by lymphoplasmacytic cells, and serum IgM level was used as a marker for the treatment assessment in patients with WM. Our novel findings of the correlation between serum CXCL13 and IgM levels further implied that serum CXCL13 may be a marker of tumor load. These results warrant further studies to determine the use of serum CXCL13 as a marker for treatment assessment in patients with WM.

Previous studies suggested that follicular dendritic cells may be a source of CXCL13 in normal and inflammatory lymphoid tissues [7], while CXCL13 can also be secreted by malignant B cells in malignancies such as follicular or primary central nervous system lymphomas [10,11]. We analyzed bone marrow biopsies from patients with WM and found that, in accordance with serum levels, CXCL13 levels were also markedly elevated in the bone marrow. However, we were unable to identify the cellular origin of CXCL13 because numerous cells in the bone marrow stained positive. Moreover, previous studies suggested that excessive mast cell infiltration was a feature of WM [20,21], and these mast cells could provide growth and survival signals to tumor cells through tumor necrosis factor family ligands and CD27–CD70 interactions [22,23]. Co-culturing mast cells with lymphoplasmacytic cells resulted in mast cell dose-dependent tumor-colony formation and proliferation through CD154/CD40 signaling [24]. Inflammatory cytokines secreted by activated mast cells can also contribute to tumor cell survival in WM [22]. The role of CXCL13 in tumorigenesis has been studied in other lymphomas, such as angioimmunoblastic T-cell lymphoma, in which CXCL13 was able to attract mast cells to the bone

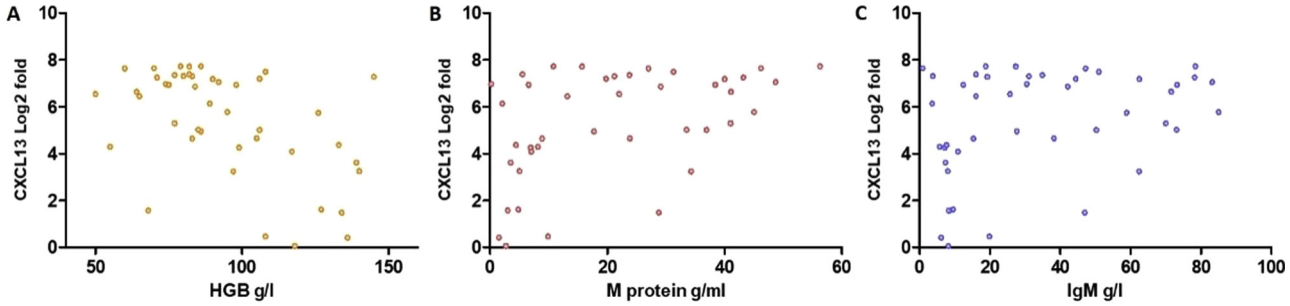


**Fig. 3. Correlations of serum CXCL13 with hemoglobin, M-protein, and IgM.** Serum CXCL13 correlated with hemoglobin level ($\rho = -0.46$, $p = 0.0016$) (A), serum M protein level ($\rho = 0.47$, $p = 0.0021$) (B), and serum IgM level ($\rho = 0.30$, $p = 0.0494$) (C). Serum CXCL13 was expressed as fold-change relative to healthy donors.

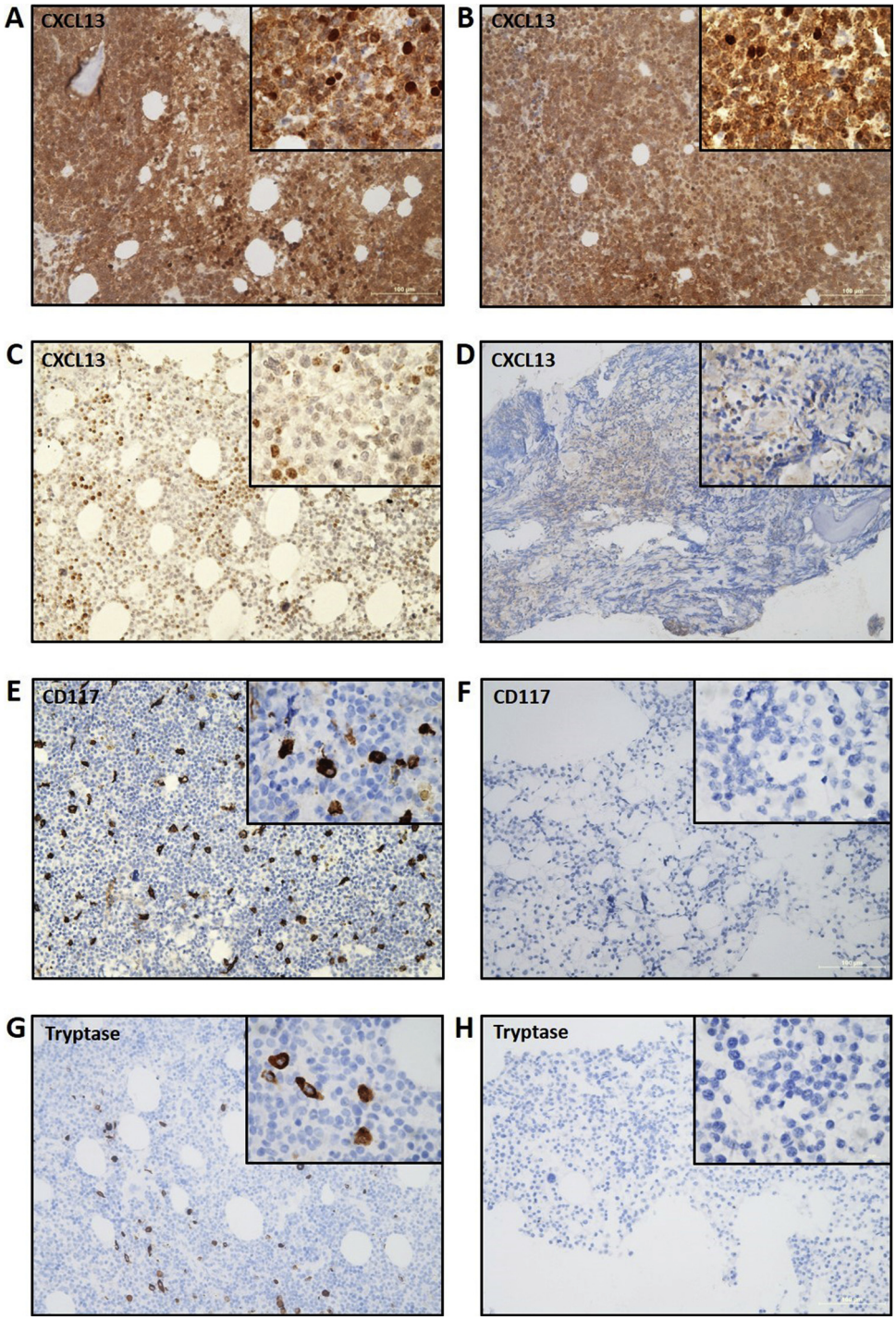


**Fig. 4. Bone marrow immunohistochemistry using anti-human CXCL13, anti-human CD117, and anti-human mast cell tryptase.** (A, B) Immunostaining of CXCL13 in two patients with WM patients; (C) immunostaining of CXCL13 in a patients with CLL with monoclonal IgM; (D) immunostaining of CXCL13 in a patient with IgM-MGUS; (E) immunostaining of CD117 in a patients with WM; (F) immunostaining of CD117 in a patient with IgM-MGUS; (G) immunostaining of tryptase in a patient with WM; (H) immunostaining of tryptase in a patient with IgM-MGUS.

marrow [25]. CXCL13 was also shown to cause tumor cell adhesion in CLL, and to promote the survival and proliferation of CLL cells through activation of the p44/42 mitogen-activated protein kinase pathway [26]. In the current study, we applied CD117 and tryptase as markers for mast cells and activated mast cells, respectively, and noted excessive infiltration of both of these in the bone marrow of patients with WM. We assume that excessive CXCL13 attracted mast cells to the bone marrow, and activated mast cells promoted growth and proliferation of tumor cells by both direct and indirect methods (inflammatory cytokine secretion) in WM. However, ex vivo and in vivo experiments should be carried out to verify our assumption, and the underlying disease biology of WM still needs further analysis.

The study had several limitations. First, the number of patients included was limited, especially patients diagnosed with other indolent B-cell lymphomas with monoclonal IgM, and patients with smoldering WM. An expanded sample size was required for further analysis. Given that serum CXCL13 levels parallel tumor load, further studies are needed to explore the efficacy of serum CXCL13 as a biological marker

for the assessment of WM. Second, the role of CXCL13 and mast cells in the pathogenesis of WM was merely assumption. Further studies are needed to clarify the underlying mechanisms, and to explore the potential therapeutic effect of CXCL13 in WM.

In conclusion, CXCL13 levels were significantly elevated in the serum and bone marrow of patients with WM, and were correlated with tumor load. Detection of serum CXCL13 may thus aid the differential diagnosis of WM.

## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical approval

This study was performed in accordance with the ethical standards of the Institutional Ethics Committee of Peking Union Medical College Hospital at the Chinese Academy of Medical Sciences & Peking Union Medical College, and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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