Differential Diagnosis of Suspected MYD88 Wild-Type Waldenstrom's Macroglobulinemia includes other malignant and non-malignant IgM secreting entities, including frequent cases of IgM Myeloma.

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Introduction

Molecular diagnostic testing for mutated MYD88 is increasingly being used to distinguish WM from other IgM secreting malignancies. IgM myeloma (IgM MM) shows no MYD88 mutations, while marginal zone lymphoma (MZL) and chronic lymphocytic leukaemia (CLL) express $MYD88^{MUT}$ but at very low frequencies (<10%). Despite this, diagnostic ambiguity often exists between $MYD88^{WT}$ WM and other $MYD88^{WT}$ IgM secreting entities. We therefore performed a systematic review of patients with suspected $MYD88^{WT}$ WM and examined their clinical, pathological and laboratory studies to establish their underlying clinicopathological diagnosis using World Health Organization (WHO) and WM consensus guidelines.

Patients and Methods

Sixty-four patients with suspected *MYD88^{WT}* WM were identified. All patients had a monoclonal IgM protein, and morphological and histopathological findings on a bone marrow biopsy that were suspicious for lymphoplasmacytic lymphoma. AS-PCR testing for *MYD88^{L265P}* mutation, and investigation for non-L265P MYD88 mutations in negative cases by Sanger sequencing was performed in all these cases to confirm *MYD88^{WT}* status utilizing CD19-selected and unselected BM mononuclear cells (Xu *et al*, 2013). A systematic review of clinical, pathological, and laboratory studies was undertaken for all *MYD88^{WT}* cases, and further studies were obtained as warranted that included additional immunohistochemistry, skeletal and CT imaging, and CXCR4 mutation determination (Xu *et al*, BJH 2016). World Health Organization (WHO) and WM consensus guidelines (*Owen* et al, 2003; *Swerdlow* et al, 2008) were used to establish definitive diagnosis.

Findings

Table 1 shows the **baseline characteristics and diagnosis determined by WHO and WM consensus criteria for 64 patients who presented with suspected $MYD88^{WT}$ WM.** Forty-six (71.8%) patients, 48% of whom were male, fulfilled the WHO and WM consensus criteria for WM. Their median BM involvement was 37.5% with a predominately interstitial pattern of diffuse B-cells, lymphoplasmacytic cells, and plasma cells. Flow cytometric analysis showed monotypic B-cells ($CD19^+CD20^+CD5^{+/-}CD10^-CD23^{+/-}$ $sIgM^+s\kappa/\lambda^+$) and plasma cells ($CD38^+CD138^+CD56^-cIgM^+c\kappa/\lambda^+$). The median serum IgM for these patients was 2,980 mg/dL, and hemoglobin was 11 g/dL. Sixteen (35%) and 13 (28%) had adenopathy and splenomegaly, respectively**.** Four (8.7%) patients had frameshift *CXCR4* mutations..

Results

At a median follow-up of 5.0 (range 0.8-17.9 years), 31 (67%) of $MYD88^{WT}$ WM patients required therapy. **Notably, 7 (15%) $MYD88^{WT}$ patients were also diagnosed with diffuse large B-cell lymphoma (DLBCL), three synchronous and four metachronous to their WM diagnosis**. **Eleven (24%) patients succumbed during the follow-up period that included 7 deaths due to WM, and 4 because of DLBCL.**

Table 1. Baseline characteristics and diagnosis determined by WHO and WM consensus criteria for 64 patients who presented with suspected $MYD88^{WT}$ WM.

Diagnosis	N=	Age (yrs)	Gender (% male)	BM (%)	sIgM (mg/dL)	Hb (g/dL)	Adenopathy (%)	Splenomegaly (%)
WM	46	58.5 (range 29-85)	48	37.5 (range 2.5-95)	2,980 (range 160-9,000)	11.0 (range 4.0-15.5)	35	28
IgM MM	7	59 (range 55-75)	71	60 (range 10-80)	8,375 (range 2,530-12,000)	9.0 (range 8.4-12.1)	14	14
MZL	6	64.5 (range 51-74)	0	10 (range 5-25)	1,642 (range 95-2,800)	11.3 (range 8.6-12.3)	67	33
IgM PC MGUS	3	62 (range 61-76)	33	5 (range 5-10)	1,846 (range 1,846-2,390)	13.9 (range 13.1-14.7)	0	0
CLL	1	83	0	5	1,822	13.2	0	0
DLBCL	1	76	0	5	355	9.5	0	100

Among the other $MYD88^{WT}$ patients, 7 (10%) had findings consistent with IgM MM. Their median BM disease involvement was 60% (range 10%-80%), with a predominant plasma cell infiltrate. In 3 (43%) patients, monotypic B-cells ($CD19^+CD20^+CD5^-CD10^-CD23^{+/-}sIgM^+s\kappa/\lambda^+$) and plasma cells ($CD38^+CD138^+CD56^-cIgM^+c\kappa/\lambda^+$) were detected, while only clonal plasma cells ($CD38^+CD138^+CD56^-cIgM^+c\kappa/\lambda^+$) were observed in 4 other patients. FISH testing of BM mononuclear cells showed t(11;14) in 5 patients; t(14;16) in one patient; and normal cytogenetics in one patient**. Lytic lesions were detected in three (43%) patients. The median serum IgM level was significantly higher at 8,375 mg/dL (p=0.016 versus $MYD88^{WT}$ WM patients).** One (14%) patient had both adenopathy and splenomegaly. With a median follow-up of 2.4 (range 0.4-7.4 years), all patients required treatment and one died of myeloma. No DLBCL events occurred.

Findings consistent with marginal zone lymphoma (MZL) were observed in 6 (9%) patients, all female. **Their median BM involvement was 10%, with paratrabecular and nodular predominant infiltrate of mainly small to medium sized lymphocytes and few mature plasma cells.** Three (50%) patients had monotypic B-cells ($CD19^+CD20^+$ $CD5^{+/-}CD10^-CD23^+CD45^+s\kappa/\lambda^+$) by flow cytometric analysis. Their median serum IgM level was 1,642 mg/dL, and not significantly different vs. $MYD88^{WT}$ WM patients. Adenopathy and splenomegaly were present in 4 (67%) and 2 (33%) patients. With a median follow-up of 3.8 (range 1.3-5.2 years), four (67%) required therapy, and are alive. No DLBCL events occurred in these patients.

For 3 patients, the findings favored a diagnosis of IgM MGUS with plasma cell infiltration. The median BM involvement for these patients was 5% (range 5-8%) with flow cytometric analysis demonstrating a clonal plasma cell population. The median serum IgM level for these patients was 1846 (range 1262-2390 mg/dL), and did not differ significantly versus $MYD88^{WT}$ WM patients. No DLBCL events were observed. Lastly, in one patient, the findings favored the diagnosis of CLL while another patient had intravascular DLBCL. The CLL patient remains alive without treatment and a DLBCL event, while the patient with DLBCL required therapy and remains alive.

Summary

- **Up to 30% of suspected $MYD88^{WT}$ WM cases had an alternative clinicopathological diagnosis that included both malignant and non-malignant entities.**
- **IgM MM was frequently present among suspected $MYD88^{WT}$ cases, and presented with high serum IgM levels and chr. 14 translocations.**
- **WM patients with *MYD88^{WT}* disease had a high incidence of associated DLBCL events that impacted survival.**