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Multimodal Imaging Characteristics and Risk Factors Analysis of Waldenström Macroglobulinemia Retinopathy

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Title: Multimodal Imaging Characteristics and Risk Factors Analysis of Waldenström Macroglobulinemia Retinopathy

Short title: Risk Factors of Waldenström Macroglobulinemia Retinopathy

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CRediT author statement

Huan Chen and Yuelin Wang: Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing - Original Draft, Project administration. **Zhengbo Xu:** Data Curation, Formal analysis, Visualization. **Donghui Li and Hong Du:** Investigation, Validation. **Youxin Chen and Jun Feng:** Conceptualization, Methodology, Writing – Review & Editing, Supervision.

TABLE OF CONTENTS STATEMENT

Waldenström macroglobulinemia (WM) is a rare indolent B cell non-Hodgkin's lymphoma. WM retinopathy was characterized by tortuous retinal vessels, extensive retinal hemorrhage, and distinctive shape of macular edema in multimodal images. The presence of WMR in WM patients was significantly correlated with M protein and serum IgM, with cut-off value of 26.2g/L and 51.0g/L. It is important to monitor WMR by ophthalmic exam and hematological parameters.

Abstract:

PURPOSE: To summarize the multimodal imaging features and analyze the risk factors of Waldenström macroglobulinemia retinopathy (WMR).

DESIGN: Retrospective, cross-sectional study.

METHODS: Patients diagnosed with Waldenström macroglobulinemia and underwent ophthalmic examination in Peking Union Medical College Hospital in the last decade were included. Multimodal imaging characteristics of WMR were summarized. Univariate and multivariate logistic regression analysis of

WMR and potential systemic and ocular factors was performed.

RESULTS: A total of 50 WM patients were included in this study, and 28 patients had WMR in at least one eye. WMR was found to have worse LogMAR visual acuity (VA) (0.52±0.54 vs. 0.21±0.18, $p=0.009$), and was characterized by tortuous retinal vessels, extensive retinal hemorrhage, and distinctive shape of macular edema, etc. In univariate analysis, the presence of WMR was significantly associated with the mean VA (LogMAR), serum RBC counts, serum PLT counts, HGB level, serum M protein, serum IgM level, and LDH (with $p<0.05$). In multivariate analysis, WMR was significantly correlated with M protein (adjusted OR=1.127, 95% CI 1.052-1.209, p= 0.001) and serum IgM (adjusted OR=1.059, 95% CI 1.023-1.095, p= 0.001) with the predicted AUC of 0.820 and 0.859, respectively. The optimal cut-off values were 26.2g/L for M protein, and 51.0g/L for IgM, which accounts for a sensitivity of 95.4% and 95.4%, and specificity of 64.3% and 60.7%.

CONCLUSIONS: Retinopathy of WM has specific characteristics in ophthalmic examinations. Serum IgM levels and M protein are good predictors of WMR, which could attach important value of fundus examinations for WM patients.

Keywords: Waldenström macroglobulinemia; Retinopathy; Multimodal imaging; Risk factor.

1. Introduction

Waldenström macroglobulinemia (WM) is a type of B cell non-Hodgkin's lymphoma characterized by lymphoplasmacytic infiltration of the bone marrow and elevated levels of monoclonal immunoglobulin (IgM) in serum and/or urine [1,2]. WM is a rare disease with an annual incidence rate of approximately 2.5–6.1 per million people [3]. The etiology and pathogenesis of WM remain unclear, although some studies have suggested that it may be related to chronic immune stimulation and autoimmune disorders [4,5]. M protein, also known as paraprotein, refer to the abnormal monoclonal immunoglobulins produced in large numbers by the malignant proliferation of plasma cells or B lymphocytes, which are key to the pathology of WM [6]. Somatic mutations and chromosomal abnormalities are observed in malignant B cells of WM patients, with most WM patients having a specific mutation in the myeloid differentiation pathway response 88 (MYD88) gene (MYD88 L265P) [7].

WM retinopathy (WMR) is one of the manifestations of hyperviscosity syndrome (HVS) caused by WM [8]. WMR has some typical manifestations, such as distortion of retinal vessels and retinal hemorrhage, etc., some of which can lead to impaired vision [9,10]. Early diagnosis and treatment of WMR are beneficial [9,11].

Due to the low incidence rate of WM, there have been few studies describing WM retinopathy and most of these have been case reports [12-14]. Research on the fundus characteristics and risk factors of WMR is limited, especially in terms of multimodal imaging analysis, nor have the associations between WMR, systemic, and ocular risk factors been analyzed. We, therefore, conducted this study to describe the fundus manifestations of WM patients and analyze the risk factors of WMR and aimed to provide some references for further study.

2. Methods

Ethics statement

This retrospective, cross-sectional, comparative study was performed according to the guidelines of the Declaration of Helsinki. The Medical Ethics Committee of the Peking Union Medical College Hospital approved the study protocol, and all participants were given their written informed consent.

Patient selection

Patients who were diagnosed with WM and underwent fundus examination at Peking Union Medical College Hospital (PUMCH) from May 2012 to May 2022 were retrospectively and consecutively enrolled. The diagnostic criteria of WM [15] should meet (i) lymphoplasmacytic bone marrow involvement; (ii) any level of IgM paraprotein, and (iii) exclusion of other low-grade lymphomas. Patients were excluded if they (1) had not undergone ophthalmic examinations (including fundus examination); (2) were diagnosed with multiple myeloma, IgM monoclonal gammopathy of undetermined significance (MGUS), marginal zone lymphoma, chronic lymphocytic leukemia, amyloidosis, or mantle cell lymphoma.

All included WM patients were divided into two groups according to whether WMR was found in at least one eye. WMR was defined by the presence of dilated, segmented, and tortuous retinal veins, giving a "sausage link" appearance. The WMR category was determined based on: (1) fundus photography, if available; (2) clear diagnosis of WMR written in the consultation record, as assessed by two ophthalmologists of whom at least one was an attending doctor according to the requirements for consultant doctors in PUMCH; (3) records of inconsistent manifestation with primary disease (such as extensive hemorrhage with no obvious microaneurysms in diabetes mellitus (DM) patients, serous macular detachment without arteriolar constriction in hypertension patients, unexplainable tortuous vessels, and hemorrhages associated with other fundus diseases).

Data extraction

Data collection included: (1) basic information about patients (such as age and sex); (2) bone marrow biopsy results; (3) hematological data, including complete blood count (CBC), liver function tests, renal function tests, coagulation index, M protein, serum IgM, and mutations in the MYD88 and CXC chemokine receptor 4 (CXCR4) genes (tested by real-time allele-specific polymerase chain reaction (AS-PCR), AS-PCR, or Sanger sequencing); (3) ophthalmological examination mainly include visual acuity (VA), intraocular pressure (IOP), and slit lamp examination (including anterior segment and fundus examination with pupil dilatation). The VA test was performed using the Snellen chart (Tumbling E chart) with standard measurement procedures in PUMCH. The smallest row of letters that the patient could read accurately from a 5-m distance determined the visual acuity in each eye. Ultra-wide-field fundus photographs (UWF-FP), optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), fundus autofluorescence (FAF), and fundus fluorescein angiography (FFA) were also collected if available. The revised International Prognostic Scoring System for Waldenström Macroglobulinemia (rIPSS-WM) was calculated to predict the prognosis of WM

[16].

Statistical analysis

All statistical analyses were performed by SPSS 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8 (GraphPad Prism Software Inc., San Diego, CA, USA) software. The prevalence of WMR was calculated. The normality of the continuous parameters was tested with the Shapiro-Wilk test. Continuous data were reported as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) where applicable; categorical data were reported as numbers (percentages, %). Independent sample Student's *t*-test or the Wilcoxon Mann-Whitney test were used to evaluate differences between two groups. Categorical variables were tested with the χ2 test or Fisher's exact test. We performed both univariate and multivariate logistic regression analyses to assess associations with WMR, presenting results with 95% Confidence intervals (CI) and odds ratios (ORs). All P-values were two-sided and were considered statistically significant when the values were <0.05.

A p-value < 0.05 was considered significant.

3. Results

A total of 50 patients diagnosed with WM were included, with a mean age of 64.78±11.14 years old. WMR in at least one eye was detected in 28 patients, accounting for a prevalence of 56% in WM patients. Bilateral retinopathy was found in 27 out of the total 28 WMR patients (96.4%). **Table 1** summarizes the demographic characteristics of patients with WMR. The mean LogMAR VA was 0.52±0.54 (mean 0.3 in decimal) in WMR patients compared with 0.21±0.18 (0.62) in non-WMR patients (p=0.009). In terms of the symptoms of

WMR, “decreased vision”, “blurred vision”, and “metamorphopsia” were often described in the medical records and could be the chief complaints of some patients. Compared with WM patients without WMR, the serum red blood cell (RBC) counts, platelet (PLT) counts, serum hemoglobin (HGB), prothrombin time (PT), and international normalized ratio (INR) were significantly different from those of patients with WMR ($p<0.05$). In particular, serum M protein and serum IgM in WMR patients were significantly higher in comparison with WM patients without WMR ($p<0.001$). The MYD88 L265P and CXC chemokine receptor 4 (CXCR4) WHIM mutations were present in 68.4% and 14.3% of WMR patients, respectively, while 31.8%, 9.1%, and 12.5% of WMR patients had previously been diagnosed with hypertension, diabetes mellitus, and hepatitis B virus (HBV) infection, respectively.

WMR had specific manifestations in the fundus, and representative multimodal images of WMR are shown in **Figures 1 and 2**. Mild WMR was apparent merely as tortuous and dilated retinal vessels while in severe WMR, the retinal vessels showed increased dilation together with segmentation and beading, with a sausage-like appearance. Ultra-wide-field photographs showed extensive retinal hemorrhage, which manifested in a similar manner as retinal vein occlusion. Optic disc edema was sometimes accompanied by macular edema, and even serous macular detachment (SMD). In FAF, the main manifestation was autofluorescent blockage caused by hemorrhage, with some appearance of hyperautofluroescence in the posterior pole corresponding to chronic SMD. In FFA, tortuous dilated retinal vessels could be observed with blockage of fluorescence due to retinal hemorrhage. Capillary leakage and the hyperfluorescent dots of microaneurysms were usually apparent in the mid and peripheral retina on ultra-wide-field FFA. Hyperfluorescence of the optic disc and macula could sometimes be observed. On OCT, WMR showed the presence of macular edema, retinal thickening, intraretinal fluid, subretinal fluid, or even SMD. The morphology of macular edema often appeared as polycystic edema, and the deposition of irregular hyper-reflective particles could occasionally be observed. In addition, the cystoid macular edema was intended to appear in the outer nuclear layer. OCTA showed vascular tortuosity and capillary tortuosity in different layers.

In univariate analysis, the presence of WMR was significantly associated with mean VA (LogMAR) (p=0.018), serum RBC counts (p=0.012), PLT counts (p=0.006), HGB level (p=0.006), serum M protein (p=0.001), serum IgM level (p=0.001), and serum LDH (p=0.043). WMR was not significantly associated with the MYD88 L265P mutation (p=0.194), the CXCR4 WHIM mutation (p=0.522), serum WBC counts (p=0.062), serum lymphocyte counts (p=0.954), monocyte counts (p=0.235), coagulation indicators (p>0.05), serum albumin (p=0.129), β2-macroglobulin (β2MG) (p=0.419), IPSS-WM (p>0.05), or serum IgM light-chain type (p=0.141).

Multivariate logistic regression analysis was performed on variables with statistical significance in univariate analysis. Forward stepwise analysis was used. Considering that M protein and IgM were found to be strongly correlated (R^2 = 0.841, **Figure 3A**), these two variables were included separately in two multivariate logistic regression models. The model analysis confirmed that the odds of elevated serum M protein and serum IgM were significantly higher in WMR patients, even after adjustment of other significant variables (OR=1.127, 95% CI 1.052-1.209, P = 0.001; OR=1.059, 95% CI 1.023-1.095, P = 0.001).

(see **Table 2**) The two models achieved predicted areas under the curve (AUCs) of 0.859 and 0.820 for M protein and IgM, respectively. Receiver operating characteristic (ROC) curve analysis with Youden's J index method showed that the optimal cut-off values were 26.2 g/L for M protein, and 51.0 g/L for IgM. (**Figure 3B, 3C**) By simply grouping WM patients with the cut-off values of M protein and IgM, it was found that the sensitivity for predicting WMR was 95.4% and 95.4%, respectively, with specificities of 64.3% and 60.7%, respectively. (see **Figure 3D, 3E**)

4. Discussion

WM is a rare B-cell lymphoproliferative disease characterized by malignant lymphocytic plasma cell bone marrow infiltration and the presence of monoclonal IgM molecules. WM is more common in males[17], and the proportion of male WM patients in the present study was 67.3%. The clinical manifestations of WM mainly include non-specific systemic symptoms (such as fatigue and weight loss), lymphoma-related symptoms (such as anemia, hemorrhage, lymphadenopathy, and hepatosplenomegaly), and HVS. For HVS, mild cases may have symptoms of blurred vision, headache, dizziness, diplopia, tinnitus, and ataxia. However, in severe cases, confusion, dementia, and coma may occur[18]. Therefore, symptomatic HVS may develop into a medical emergency and deserves attention. The presence of WMR can easily be observed by a noninvasive physical examination in WM patients, and its incidence is about 34% as reported in the literature [2]. In our study, WMR was found in 56% of WM patients, which is higher than that observed in previous studies. This may be because the participants in this study were mainly hospitalized patients with relatively high levels of M protein (average 25.37±20.21 g/L).

In the current study, WMR was observed to have specific manifestations, which may be presumed to be related to the pathogenesis of the disease. First, the most commonly observed manifestations were tortuosity and dilation of retinal vessels, which may be related to the high intravascular viscosity caused by WM. Intravascular hyperviscosity can lead to venous stasis and increased blood flow turbulence, causing venous occlusion at an arteriovenous crossing[13]. Second, retinal hemorrhage and ischemic changes are usually seen in the mid-and peripheral fundus. This may be due to the elevated levels of monoclonal IgM that can cause vascular occlusion, leading to increased intravascular pressure and damage to the capillary vessels and resulting in retinal hemorrhage and ischemia. In addition, WM patients often show accompanying anemia and thrombocytopenia, which also aggravate retinal hemorrhage and ischemia. Furthermore, macular edema can be seen on OCT, characterized by intraretinal and subretinal fluid, often accompanied by SMD. The pathological mechanism of edema and SMD may be[19]: (1) Disruption of the blood-RPE barrier due to hypoxia and the deposition of IgM in Bruch's membrane and choriocapillaris, resulting in the leakage of fluid into the macula through the RPE defect; (2) Increased colloid osmotic pressure caused by the entry of IgM into the retina, leading to fluid entry into the retina and subsequent edema. Moreover, we found a tendency toward the appearance of cystoid macular edema in the outer nuclear layer. A similar finding was reported by Baker et al[20], who observed a complete disruption of the outer retina within the detachment and proposed that these focal outer retinal defects slowly progress over time, eventually allowing a so-called track for intraretinal IgM. In support of this hypothesis, immunofluorescent-labeled IgM paraprotein was found within the cystoid spaces of the outer nuclear or plexiform layers in patients with WM. Furthermore, the loose tissue structure between the outer plexiform and the outer nuclear layers may also have the accumulation of liquid in the macula.

This study found that the concentrations of serum M protein and IgM were significantly associated with the presence of WMR, and both M protein and IgM were found to be independent risk factors. M protein refers to monoclonal immunoglobulins or immunoglobulin fragments produced by the monoclonal malignant proliferation of plasma cells or B lymphocytes. In WM, the main component of M protein is IgM. IgM has a high molecular weight and presents as a pentamer in vessels. These IgM-type M proteins tend to self-aggregate and encapsulate platelets or red blood cells, leading to their aggregation and subsequent obstruction of vessels, particularly through the blocking of choriocapillaris, resulting in retinal vein occlusion-like manifestations[21]. IgM has also been detected by immune-electrophoresis in the subretinal fluid and cystoid spaces of the outer plexiform layer, in the superficial retina, and around photoreceptors in WM patients[22,23].

Our study found that M protein levels of 51.0 g/L or IgM levels of 26.2 g/L were important cut-off points for predicting WMR. When these two conditions were met, the sensitivity of WMR detection reached over 95%, although the specificity was not very high. However, it is more important to screen patients for the presence of WMR in case of progression, and ophthalmological intervention should be carried out in time. Indeed, timely intervention in WMR may be beneficial. Xu et al [24] reported a case where both eyes were treated with intravitreal bevacizumab, resulting in a significant reduction in intraretinal fluid and improvements in vision from 20/100 to 20/60 in the left eye and from 20/50 to 20/60 in the right eye. Besides, plasmapheresis can also rapidly reduce serum IgM levels by 30-60%, which helps reverse WMR after 2–3 sessions[25]. On the contrary, if macular edema, retinal ischemia, and retinal hemorrhage are not detected in time and there is a delay in treating WMR, long-term fundus impairment could result in permanent retinal cell necrosis and the development of proliferative membranes, leading to severe vision loss or even blindness. In particular, in some remote areas where there are no ophthalmology specialists to evaluate the condition of the fundus, patients may miss their chances of early diagnosis and treatment. Besides, due to the reliability and reproducibility of the total IgM measurement, if both IgM and M protein levels can be obtained, the total IgM is the preferred reference.

In assessing the relationship between M protein (or IgM) and WMR, previous case studies have provided some clues. Willerslev et al. [26] found decreases in venous tortuosity and the disappearance of retinal hemorrhages and cotton wool spots after a reduction of the total IgM to < 17 g/L in WM. Menke et al.[25] reported a significant increase in retinal venous blood speed accompanied by decreased vessel diameters in WMR after a significant reduction in serum IgM by plasmapheresis. Schatz et al.[10] analyzed the OCTA of a WM patient and found a decrease in both retinal capillary and large vessel density following plasmapheresis. In terms of risk factor analysis, although a few previous studies have focused on the symptoms of hyperviscosity syndrome, which include headache, vertigo, dizziness, nystagmus, deafness, and slow mentation, none have focused specifically on WMR. Gustine et al[27] reported that a serum IgM level of 60 g/L was likely to be associated with the manifestations of hyperviscosity, including epistaxis, new-onset headaches, new-onset blurry vision, and slowed mentation. Abeykoon et al.[18] found that a serum IgM of >28 g/L is an important boundary point that predicts systemic hyperviscosity in the dataset of symptoms containing 67% fatigue and 59% epistaxis but only 21% retinal hemorrhage. In our study, the cut-off value of serum IgM was 26.2 g/L, which perhaps means a lower threshold is required for the occurrence of WMR.

However, it is still difficult to predict WM merely by fundus characteristics as similar manifestations occur in other systematic and ophthalmic diseases. While there is good evidence to support that Waldenström macroglobulinemia can cause retinopathy, the available evidence does not allow the definition of levels of IgM or M protein that definitely refute or confirm the diagnosis. Thus, the response to treatment, if undertaken, is also going to be of value for the final assessment of the diagnosis. We recommend that patients who have bilateral onset of symptoms such as extensive hemorrhage and tortuous vessels should receive blood examinations, including the assessment of the complete blood count, glucose, coagulation, and immunoglobulin test, amongst others, to determine the presence of WM.

There are several limitations to this study. First, WM is a rare disease, and thus a limited number of patients were included in the study. Second, this study was retrospective, and thus selection bias may have occurred. However, for a rare disease, it is difficult to conduct prospective studies. Third, serum viscosity (SV) was not measured in this study, because in actual clinical practice, serum

M protein or IgM is more commonly measured to assess the need for treatment to reduce M protein levels, and the SV is not required. Besides, according to the Task Form from the 8th International Workshop on WM [28], SV levels are slow to be reported, not reproducible, and may lack correlation with serum IgM levels, while serum IgM levels are more expedient and reliable.

5. Conclusion

In conclusion, WMR is a specific manifestation of WM, which is characterized by retinal vessel tortuosity, retinal hemorrhage, and macular edema due to the hyperviscosity caused by serum monoclonal IgM. Our study demonstrated that both serum IgM and M protein levels are risk factors for WMR with good predictive value. It is recommended that patients with WM should undergo fundus examinations if their IgM or M protein levels reach 26.2 g/L or 51.0 g/L, respectively.

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All authors attest that they meet the current ICMJE criteria for authorship.

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Figure Captions:

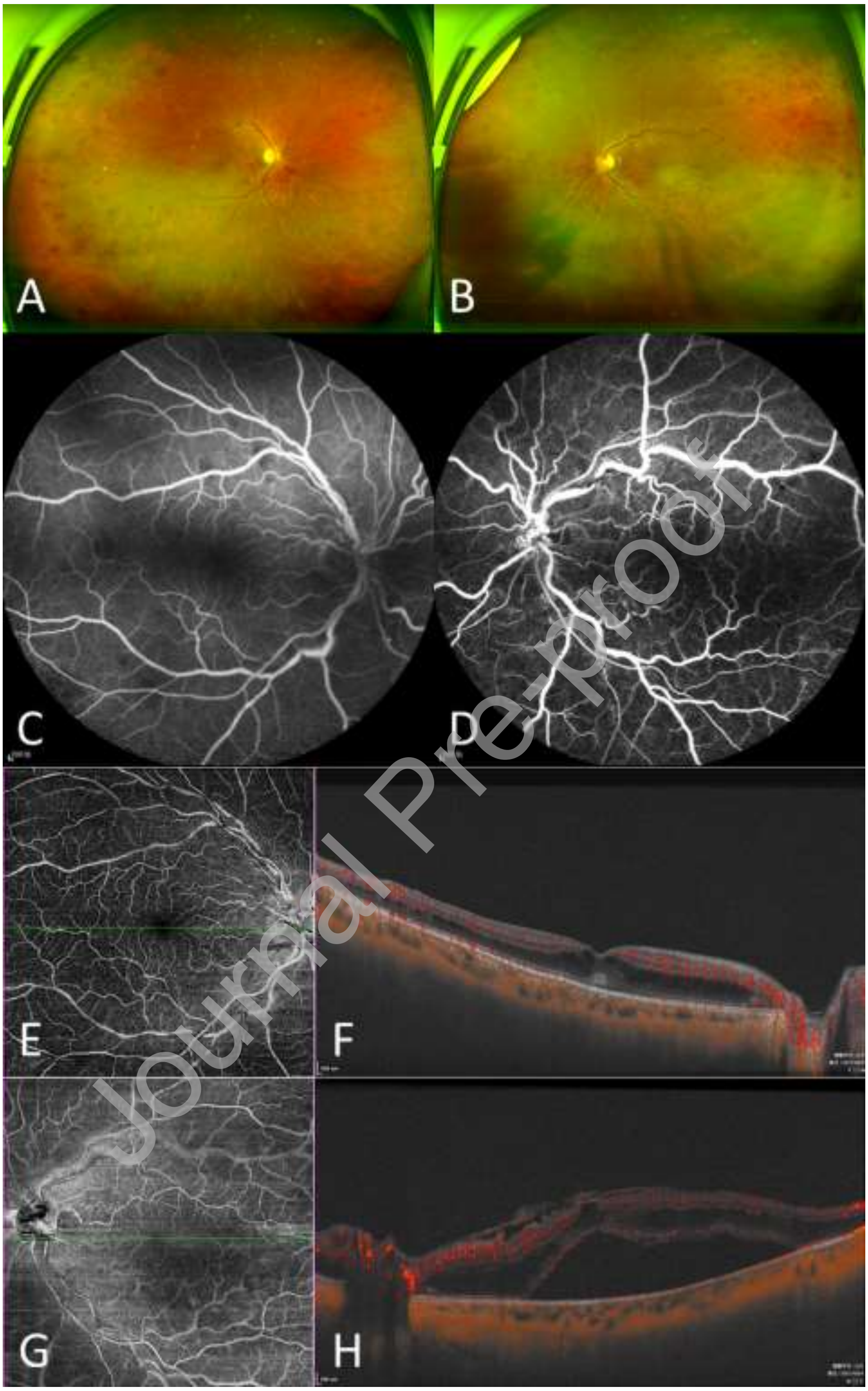

Figure 1 Multimodal images of a 74-year-old female WMR patient. Her serum M protein was 78 g/L and the serum IgM level was 85 g/L. Ultra-wide-field fundus photographs (UWF-FP) on initial presentation of the

right **(A)** and left eye **(B)** demonstrated extensive retinal hemorrhages. Fundus fluorescein angiography (FFA) of the right **(C)** and left eye **(D)** showed venous dilation and tortuosity with peripheral capillary nonperfusion. Wide-field OCTA of the retinal layer demonstrated apparent tortuous vessels in the right **(E)** and left eye **(G)**. B-scan OCT showed macular edema with intraretinal and subretinal fluid in both eyes **(F, H)**.

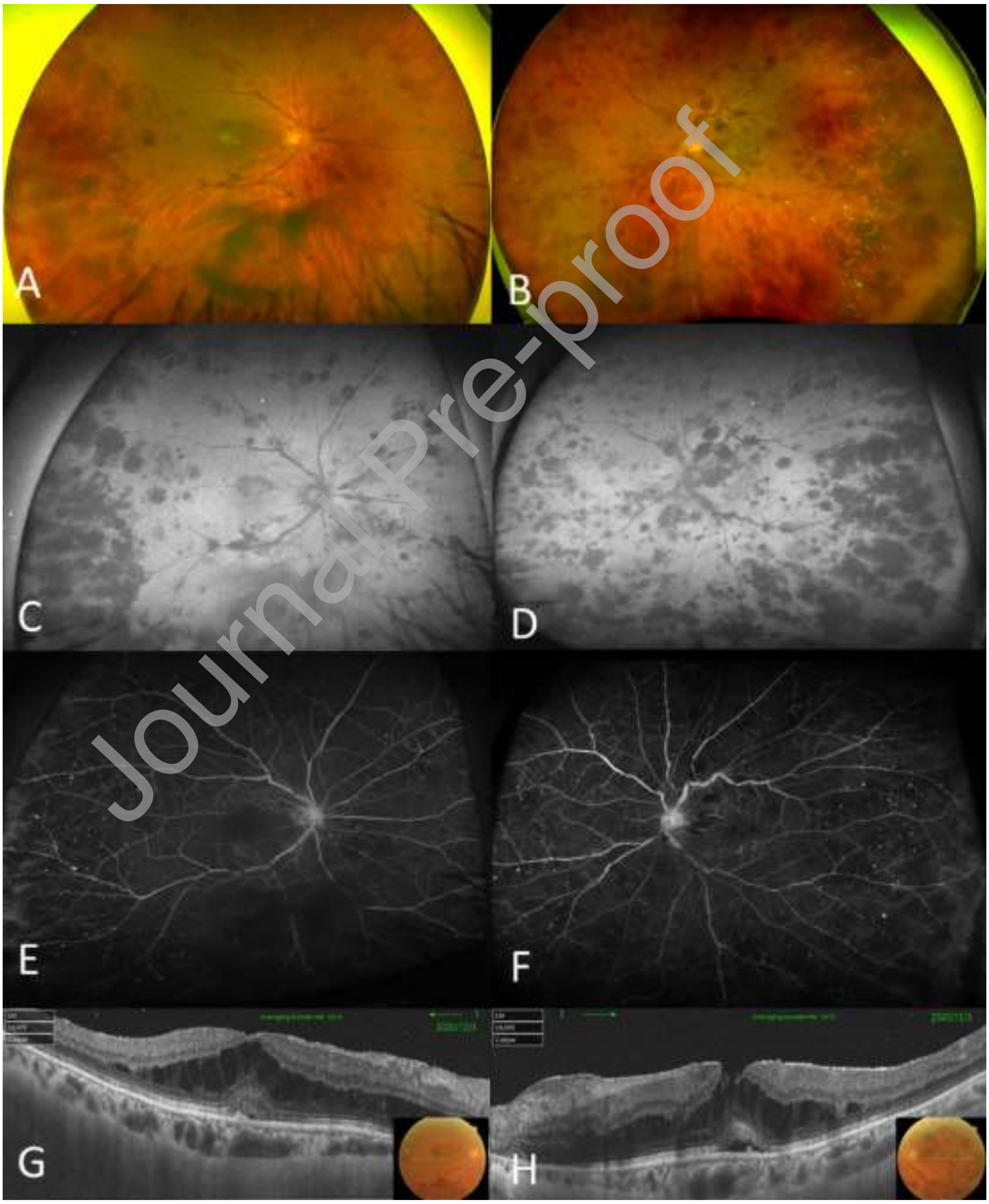

Figure 2. Multimodal images of a 74-year-old male WM patient. The patient was admitted to hospital for fatigue lasting for four months and decreased vision for two months. His M protein level was 75.7 g/L and the IgM level was 104.71 g/L. UWF-FP showed retinal hemorrhages and dilated, segmented vessels of the right **(A)** and left eye **(B)**. UWF-AF showed blocked autofluorescence of hemorrhage **(C, D)**. UWF-FA angiography showed “sausage-link” like retinal vessels staining, peripheral capillary leakage, and microaneurysms **(E, F)**. OCT showed diffuse cystoid macular edema with intraretinal and subretinal fluid.

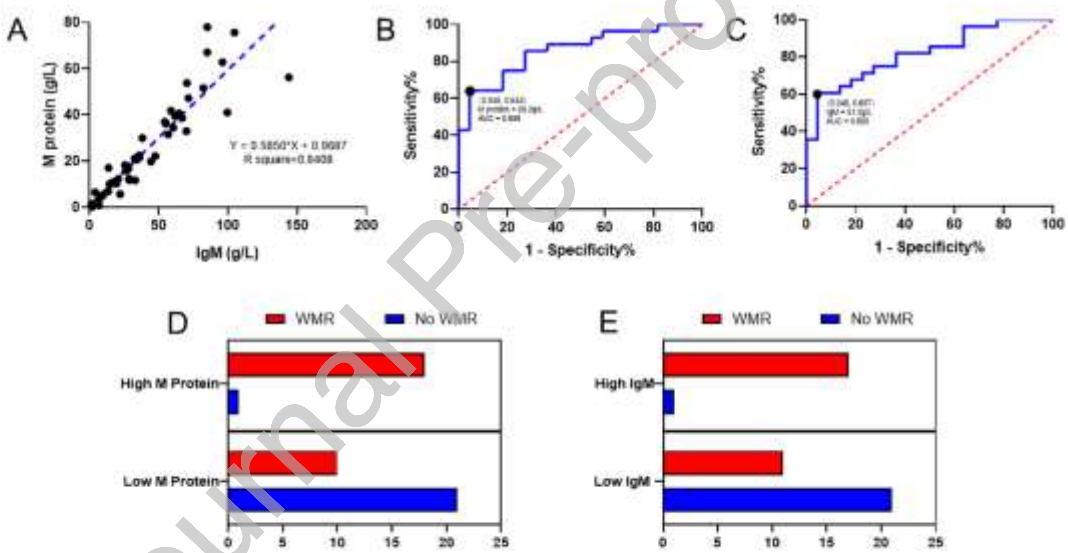

Figure 3. Analysis of serum M protein and IgM in WM patients. (A) Correlations between serum IgM and M protein. **(B-C)** ROC curve and cut-off value analysis using the Youden Index method. (the black dot represents the best critical point). **(D-E)** Prediction of WMR or no WMR by the M protein or IgM levels.

Table 1 Demographic characteristics of patients with WM

Variable [a]	Patients with WMR (n=28)	Patients without WMR (n=22)	p value
Age (y)	65.00 [60.00-72.75]	65.00 [62.75-70.00]	0.747
Sex (Female, %)	21(75)	12(54.5)	0.130
Mean VA (LogMAR)	0.52±0.54	0.21±0.18	0.009 [c]
Mean IOP (mmHg) [Ref: 10-21]	12.50 [11.04-14.94]	13.70 [12.33-16.13]	0.116
MYD88 L265P (Mutation, %)[b]	13(68.4)	14(87.5)	0.181
CXCR4 WHIM (Mutation, %) [b]	1(14.3)	2(28.6)	1.000
RBC counts (×10^12/L) [Ref: 4.00-5.50]	3.14±0.90	3.81±0.71	0.006 [c]
WBC counts (×10^9/L) [Ref.:3.50-9.50]	4.78±2.43	6.26±2.87	0.054
LY counts (×10^9/L) [Ref.:0.80-4.00]	1.75 [1.07-2.05]	1.50 [1.01-2.76]	0.961
MONO counts (×10^9/L) [Ref.:0.12-0.80]	0.35 [0.16-0.52]	0.43 [0.26-0.58]	0.229
PLT counts (×10^9/L) [Ref.:100-350]	167.42±88.84	239.77±117.72	0.017 [c]
HGB (g/L) [Ref.:120-160]	92.29±24.73	113.64±22.12	0.003 [c]

APTT (s) [Ref.:23.3-32.5]	33.80 [26.73-39.68]	30.40 [27.05-33.80]	0.304
PT (s) [Ref.:10.4-12.6]	13.25 [12.03-14.88]	12.40 [12.00-13.20]	0.049 [c]
D-Dimer (mg/L FEU) [b] [Ref.:0-0.55]	0.79 [0.36-1.09]	0.58 [0.16-1.07]	0.265
INR [Ref.:0.86-1.14]	1.19 [1.08-1.26]	1.08 [1.01-1.15]	0.008 [c]
M protein (g/L) [Ref.:0-0]	36.04±20.15	11.80±9.33	<0.001 [c]
Serum IgM (g/L) [Ref.:0.4-2.3]	56.73±32.72	22.60±16.87	<0.001 [c]
LDH (U/L) [Ref.:0-250]	138.89±36.32	170.35±55.17	0.026 [c]
Alb (g/L) [b] [Ref.:35-52 g/L]	31.00 [27.00-36.00]	34.50 [32.00-36.00]	0.076
β2MG (mg/L) [Ref.:0.7-1.8]	4.33 [3.60-5.63]	3.68 [2.52-5.58]	0.156
IPSS-WM (%) [b]			0.539
Very Low Risk	3(12.5)	2(12.5)	
Low Risk	6(25.0)	5(31.3)	
Intermediate Risk	8(33.3)	6(37.5)	
High Risk	5(20.8)	3(18.8)	
Very High risk	2(8.3)	0(0)	
Serum IgM light chain type (κ,%)	22(78.6)	13(59.1)	0.136
History of Hypertension (%)	7(25.0)	7(31.8)	0.594

History of Diabetes (%)	2(7.1)	2(9.1)	0.801
History of HBV infection (%)[b]	3(12.5)	3(20)	0.528

[a] Continuous data was reported as mean±SD or median [IQR] where applicable; categorical data was reported as number (percentages, %). Normal/reference range of laboratory values was described in the bracket.

[b] Partial patient data is incomplete.

[c] $p < 0.05$ was defined as significant difference.

Abbreviations: VA = visual acuity, IOP = intraocular pressure, WMR = Waldenström Macroglobulinemia Retinopathy, RBC = red blood cell, WBC= white blood cell, LY = lymphocyte, MONO = monocyte, PLT= platelet, HGB = hemoglobin, APTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, LDH = lactic dehydrogenase, Alb = albumin, β2MG = β2-microglobulin, IPSS-WM = International Prognostic Staging System for WM.

Table 2 Univariate and multivariate binary logistic regression analysis of factors associated with WMR

Factor	OR	95% CI	p value[a]	Adjusted OR[b]	95% CI	p value[a]
Age (y)	0.985	0.935-1.038	0.576			

Sex			
Male	Ref		
Female	2.5	0.754-8.256	0.134
Mean VA (LogMAR)	18.805	1.670-211.696	0.018[a]
Mean IOP (mmHg)	0.984	0.875-1.108	0.794
MYD88 L265P Mutation			
No	Ref		
Yes	0.310	0.053-1.816	0.194
CXCR4 WHIM Mutation			
No	Ref		
Yes	0.417	0.029-6.064	0.522
RBC counts (×10^12/L)	0.344	0.15-0.793	0.012[a]
WBC counts (×10^9/L)	0.803	0.637-1.011	0.062
LY counts (×10^9/L)	0.989	0.676-1.447	0.954
MONO counts	0.190	0.012-2.93	0.235

(×10^9/L)		6				
PLT counts (×10^9/L)	0.993	0.987-0.999	0.006[a]			
HGB (g/L)	0.962	0.935-0.989	0.006[a]			
APTT (s)	1.047	0.971-1.129	0.235			
PT (s)	0.992	0.879-1.121	0.901			
D-Dimer (mg/L FEU)	0.975	0.604-1.575	0.918			
INR	1.415	0.434-4.614	0.565			
Serum IgM (g/L)	1.059	1.023-1.095	0.001[a]	1.059	1.023-1.095	0.001[a]
M protein (g/L)	1.127	1.052-1.209	0.001[a]	1.127	1.052-1.209	0.001[a]
LDH (U/L)	0.983	0.968-0.999	0.043[a]			
Alb (g/L)	0.906	0.797-1.029	0.129			
β2MG (mg/L)	1.104	0.868-1.403	0.419			
IPSS-WM						
Very Low Risk	Ref					

Low Risk	0.800	0.093-6.848	0.839
Intermediate Risk	0.889	0.111-7.107	0.912
High Risk	1.111	0.112-10.986	0.928
Very High risk	No convergence	-	0.999
Serum IgM type			
λ	Ref		
K	2.538	0.735-8.770	0.141
History of Hypertension			
No	Ref		
Yes	0.714	0.207-2.467	0.595
History of Diabetes			
No	Ref		
Yes	0.769	0.100-5.944	0.801
History of HBV infection			
No	Ref		
Yes	0.571	0.099-3.29	0.531

0

[a] $p < 0.05$

[b] After adjusted mean VA, RBC counts, PLT counts, HGB, and LDH.

Abbreviations: VA = visual acuity, IOP = intraocular pressure, WMR = Waldenström macroglobulinemia retinopathy, RBC = red blood cell, WBC= white blood cell, LY = lymphocyte, MONO = monocyte, PLT= platelet, HGB = hemoglobin, APTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, LDH = lactic dehydrogenase, Alb = albumin, β2MG = β2-microglobulin, IPSS-WM = International Prognostic Staging System for WM.