



IgM myeloma: A multicenter retrospective study of 134 patients

Jorge J. Castillo¹  | Artur Jurczyszyn² | Lucie Brozova³ | Edvan Crusoe⁴ | Jacek Czepiel² | Julio Davila⁵ | Angela Dispenzieri⁶ | Marion Eveillard⁷ | Mark A. Fiala⁸ | Irene M. Ghobrial¹ | Alessandro Gozzetti⁹ | Joshua N. Gustine¹ | Roman Hajek¹⁰ | Vania Hungria¹¹ | Jiri Jarkovsky³ | David Jayabalan¹² | Jacob P. Laubach¹ | Barbara Lewicka² | Vladimir Maisnar¹³ | Elisabet E. Manasanch¹⁴ | Philippe Moreau⁶ | Elizabeth A. Morgan¹ | Hareth Nahi¹⁵ | Ruben Niesvizky¹² | Claudia Paba-Prada¹ | Tomas Pika¹⁶ | Ludek Pour¹⁷ | John L. Reagan¹⁸ | Paul G. Richardson¹ | Jatin Shah¹⁴ | Ivan Spicka¹⁹ | Ravi Vij⁸ | Anna Waszczuk-Gajda²⁰ | Morie A. Gertz⁶

¹Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ²Jagiellonian University Medical College, Krakow, Poland; ³Masaryk University, Brno, Czech Republic; ⁴Professor Edgar Santos University Hospital, Salvador, Brazil; ⁵University Hospital of Salamanca, Salamanca, Spain; ⁶Mayo Clinic, Rochester, Minnesota, USA; ⁷Nantes University Hospital, Nantes, France; ⁸Washington University School of Medicine, Saint Louis, Missouri, USA; ⁹Le Scotte Hospital, Siena, Italy; ¹⁰University of Ostrava and Faculty Hospital Ostrava, Ostrava, Czech Republic; ¹¹Santa Casa de Misericordia Hospital, Sao Paulo, Brazil; ¹²Weill Cornell Medical College, New York, New York, USA; ¹³Charles University Hospital, Hradec Kralove, Czech Republic; ¹⁴The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ¹⁵Karolinska University Hospital, Stockholm, Sweden; ¹⁶Palacky University Hospital, Olomouc, Czech Republic; ¹⁷University Hospital Brno, Brno, Czech Republic; ¹⁸Rhode Island Hospital, Alpert Medical School of Brown University, Providence, Rhode Island, USA; ¹⁹Charles University Hospital, Prague, Czech Republic; ²⁰Warsaw Medical University, Warsaw, Poland

Correspondence

Jorge J. Castillo, MD, 450 Brookline Ave, Mayer 221.

Email: jorgej_castillo@dfci.harvard.edu

Abstract

IgM myeloma is a rare hematologic malignancy for which the clinicopathological features and patient outcomes have not been extensively studied. We carried out a multicenter retrospective study in patients with diagnosis of IgM myeloma defined by >10% marrow involvement by monoclonal plasma cells, presence of an IgM monoclonal paraproteinemia of any size, and anemia, renal dysfunction, hypercalcemia, lytic lesions and/or t(11;14) identified by FISH. A total of 134 patients from 20 centers were included in this analysis. The median age at diagnosis was 65.5 years with a male predominance (68%). Anemia, renal dysfunction, elevated calcium and skeletal lytic lesions were found in 37, 43, 19, and 70%, respectively. The median serum IgM level was 2,895 mg dL⁻¹ with 19% of patients presenting with levels >6,000 mg dL⁻¹. International Staging System (ISS) stages 1, 2, and 3 were seen in 40 (33%), 54 (44%), and 29 (24%) of patients, respectively. The malignant cells expressed CD20 (58%) and cyclin D1 (67%), and t(11;14) was the most common cytogenetic finding (39%). The median overall survival (OS) was 61 months. Higher ISS score was associated with worse survival ($P = 0.02$). Patients with IgM myeloma present with similar characteristics and outcomes as patients with more common myeloma subtypes.

Jorge J. Castillo and Artur Jurczyszyn share first authorship.

1 | INTRODUCTION

Multiple myeloma accounts for 10% of all hematological malignancies and is characterized by the malignant proliferation and accumulation of monoclonal plasma cells in the bone marrow along with the presence of monoclonal immunoglobulin in the serum or urine.¹ IgM-secreting myeloma is rare and accounts for 0.5–1% of all myeloma cases.² The diagnosis of IgM myeloma has been defined, in a small case series, by the presence of an IgM monoclonal paraprotein in the serum and/or urine, >10% bone marrow clonal plasma cells or plasmacytomas, lytic bone lesions and/or identification of t(11;14) by fluorescent in situ hybridization (FISH).³

Distinguishing IgM myeloma from Waldenström macroglobulinemia (WM), also a rare lymphoproliferative disorder is important and often challenging due to the similar characteristics between these conditions. The cases of IgM myeloma described in the literature present with features typical of myeloma, including lytic bone lesions, hypercalcemia, renal failure, and decreased serum IgA and IgG levels.⁴ However, IgM myeloma patients can also present with WM-like features such as lymphadenopathy and hyperviscosity, and IgM myeloma cells can express CD20 and have lymphoplasmacytoid morphology.^{4,5}

Given its rarity, the characteristics and survival of patients with IgM myeloma have not been extensively studied. We carried out a multicenter retrospective study in patients with IgM myeloma. The purpose of this multi-institutional retrospective study was to gather clinical and pathological data on patients with IgM myeloma, as well as outcomes and prognostic factors for survival.

2 | PATIENTS AND METHODS

2.1 | Case selection

Patients with a diagnosis of IgM multiple myeloma (MM) were identified from the medical records at the participating institutions. Pathological reports and/or samples were reviewed by expert hematopathologists at each participating institution. Cases were defined by the presence of >10% monoclonal plasma cells in the bone marrow, and an IgM monoclonal gammopathy of any size identified by serum protein electrophoresis, presence of lytic lesions and/or identification of t(11;14) by FISH.¹ The study protocol was reviewed and approved by the Institutional Review Board of each participating institution.

2.2 | Data gathering

Clinical data were gathered and included year of diagnosis, age, sex, hemoglobin level, serum calcium level, serum lactate dehydrogenase (LDH) level, estimated glomerular filtration rate (GFR), presence lytic bone lesions, International Scoring System (ISS, stages 1, 2, and 3),⁶ cytogenetic abnormalities, type of and response to treatment, time from diagnosis to treatment, symptoms that prompted treatment, overall survival (OS) time, and cause of death. Overall survival was defined as the time in months from IgM MM diagnosis to last follow-up or death. Patients' response to first line therapy was divided into

complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR).⁷ For this analysis, CR includes stringent and near CR, and NR includes stable and progressive disease.

2.3 | Statistical analysis

The Chi-square and the rank-sum tests were used to compare categorical and continuous variables, respectively. The Kaplan–Meier method was used to estimate OS curves, which were compared using the log-rank test. The Cox proportional-hazard regression method was used to fit univariate and multivariate survival models, reported as hazard ratio (HR) with 95% confidence intervals (CI). All reported *P* values are two-sided, and were considered significant if <0.05. Calculations and graphics were obtained using the statistical software STATA version 13.1 (College Station, Texas).

3 | RESULTS

3.1 | Patients' characteristics

A total of 159 patients with IgM myeloma from 20 centers were submitted. Of these, 101 patients met all the criteria for inclusion (definitive cases). Of the remaining 58 patients, 33 patients met the pathological criteria, did not have lytic lesions or t(11;14) but presented with at least one of the CRAB criteria, and were included in this study (probable cases). Twenty-five patients were excluded, as they did not have lytic lesions, anemia, renal dysfunction or hypercalcemia. Our final analysis was performed in 134 patients with IgM myeloma (i.e., 101 definitive and 33 probable).

Nine patients (7%) were diagnosed before 2000, 53 (40%) between 2000 and 2009, and 72 (54%) between 2010 and 2016. Seventy-eight patients (58%) were from the United States, 54 (40%) from Europe and 2 (1%) from Latin America. The median age at diagnosis was 65.5 years (range 37–86 years) with a male-to-female ratio of 1.9:1. The median serum IgM level was 2,895 mg dL⁻¹ (range 27–12,100 mg dL⁻¹) with 33 patients (25%) having a serum IgM level below 300 mg dL⁻¹ and 25 patients (19%) with serum IgM levels of 6,000 mg dL⁻¹ or higher. There were no differences between definitive and probable cases with regards to age, sex, serum IgM level and ISS stage (*P* > 0.05 for all comparisons). There were no differences between men and women with regards to age, serum IgM level and ISS stage (*P* > 0.05 for all comparisons). Selected categorized clinical characteristics are shown in Table 1.

Immunohistochemistry and/or flow cytometry data were limited. Plasma cell markers such as CD38 and/or CD138 were expressed in 27/27 (100%) patients evaluated. CD20 expression was seen in 15/26 (58%) and cyclin D1 expression in 10/15 (67%) patients evaluated. The most common cytogenetic abnormalities identified by FISH were t(11;14) in 26/67 (39%), del13q in 25/76 (33%) and del17p in 6/76 (8%) patients. There was no difference in the proportion of patients with poor risk cytogenetic abnormalities between definitive and probable cases (*P* = 0.72). There was also no difference in the proportion of poor risk cytogenetic abnormalities between men and women

TABLE 1 Categorized clinical characteristics of patients with IgM myeloma

Characteristic	Number positive/tested	Percentage
Age ≥ 70 years	35/134	26%
Male sex	88/134	66%
Hemoglobin < 10 g dL ⁻¹	49/131	37%
Estimated GFR < 60 mL min ⁻¹	56/130	43%
Elevated calcium level	24/129	19%
Skeletal lytic lesions	89/127	70%
Elevated LDH level	23/99	23%
Serum IgM $\geq 3,000$ mg dL ⁻¹	57/116	49%
Kappa restriction	75/128	58%
Lambda restriction	50/128	39%
ISS stage 1	40/123	33%
ISS stage 2	54/123	44%
ISS stage 3	29/123	24%

GFR: glomerular filtration rate; LDH: lactate dehydrogenase; ISS: International Staging System.

($P = 0.32$). However, women were more likely to carry the $t(14;16)$ than men (16% vs. 2%; $P = 0.03$). Polymerase chain reaction looking for the MYD88 L265P gene mutation was negative in 15/15 patients tested.

3.2 | Treatment and survival

One hundred and forty six patients (92%) received systemic therapy for IgM myeloma. Data on time from diagnosis to initiation of therapy were available in 77 patients, of which 55 (71%) began treatment within 1 month, 19 (24%) between 1 and 6 months, and 3 (4%) within 6 months and 5 years of diagnosis. Reasons for initiation of therapy were available in 78 patients, and included skeletal pain in 34 patients (44%), anemia in 25 (32%), renal dysfunction in 13 (17%), constitutional symptoms in 11 (14%), hyperviscosity in 7 (9%), acquired von Willebrand disease in 3 (4%) and neuropathy in 1 (1%). Frontline treatment modalities used for IgM myeloma are shown in Table 2. Data on autologous stem cell transplant (ASCT) were available in 80 patients, of which 23 (29%) underwent ASCT. Data on response to frontline treatment were available in 72 patients, of which 10 (14%), 18 (25%), 28 (39%) and 16 patients (22%) obtained CR, VGPR, PR, and NR, respectively. There were no differences in frontline treatments used, rate of ASCT and response to therapy between definitive and probable cases ($P > 0.05$ for all comparisons). There were no differences in frontline treatments used, rate of ASCT and response to therapy between men and women ($P > 0.05$ for all comparisons).

After a median follow-up of 47 months, 61 patients (46%) have died. The median OS was 61 months (95% CI 41–77 months) and the 5-year OS was 52% (95% CI 40–62%; Figure 1A). Cause of death was known in 38 patients, and the most common causes were myeloma

progression in 28 (74%) and infectious in 3 (8%). Prognostic factors associated with worse OS were age ≥ 70 years (HR 1.83, 95% CI 1.03–3.25; $P = 0.04$) and ISS score (ISS stage 2: HR 1.43, 95% CI 0.83–2.48; $P = 0.10$, and ISS stage 3: HR 3.03, 95% CI 1.54–5.98; $P = 0.001$, using ISS stage 1 as reference group). The median OS for patients ≥ 70 years was 53 months (95% CI 19–NR months) while for patients younger than 70 was 63 months (95% CI 46–83 months; Figure 1B). The median OS for patients with ISS stage 1, 2, and 3 were 63 (95% CI 37–115 months), 61 (95% CI 39–79 months) and 30 months (95% CI 17–68 months), respectively (Figure 1C). Male sex was associated with a better OS than female (HR 0.39, 95% CI 0.23–0.67; $P < 0.001$). The median OS for men and women were 77 months (95% CI 58–91 months) and 30 months (95% CI 20–52 months), respectively (Figure 1D). Hemoglobin < 10 g dL⁻¹, elevated calcium level, estimated GFR < 60 mL min⁻¹, presence of skeletal lytic lesions and serum IgM levels $\geq 3,000$ mg dL⁻¹ or $\geq 6,000$ mg dL⁻¹ did not associate with a worse OS. There was no difference in survival between definitive and probable cases of IgM myeloma (HR 1.44, 95% CI 0.75–2.77; $P = 0.28$). In the multivariate analysis, male sex was associated with a better OS (HR 0.39, 95% CI 0.22–0.67; $P = 0.001$) and ISS with worse OS (ISS 2: HR 1.79, 95% CI 0.96–3.34; $P = 0.07$, and ISS 3: HR 2.60, 95% CI 1.22–5.55; $P = 0.01$, using ISS 1 as reference group) in patients with IgM myeloma.

4 | DISCUSSION

Because of the rare incidence of IgM myeloma, most of the current evidence relies on case reports and small case series.^{3–5,8–19} Herein, we present the clinicopathological characteristics, outcomes and prognostic factors identified in 159 IgM myeloma cases from 20 participating centers in Europe, United States and Latin America.

On the basis of our results, the median age at IgM myeloma diagnosis was 65 years with a 2:1 male predominance, which appear similar to the features in more common myeloma subtypes. Based on Surveillance Epidemiology and End Results (SEER) statistics, the median age

TABLE 2 Frontline treatment of IgM myeloma

Treatment	Number treated	Percentage
PI only	14/128	11%
IMiD only	18/128	14%
Chemotherapy only	31/128	24%
Chemotherapy + PI	20/128	16%
Chemotherapy + IMiD	8/128	6%
PI + IMiD	14/128	11%
Chemotherapy + PI + IMiD	6/128	5%
Rituximab-containing	9/128	7%
Steroids only	8/128	6%

PI: proteasome inhibitor; IMiD: immunomodulatory drugs. Chemotherapy includes bendamustine, cyclophosphamide, doxorubicin, and/or melphalan.

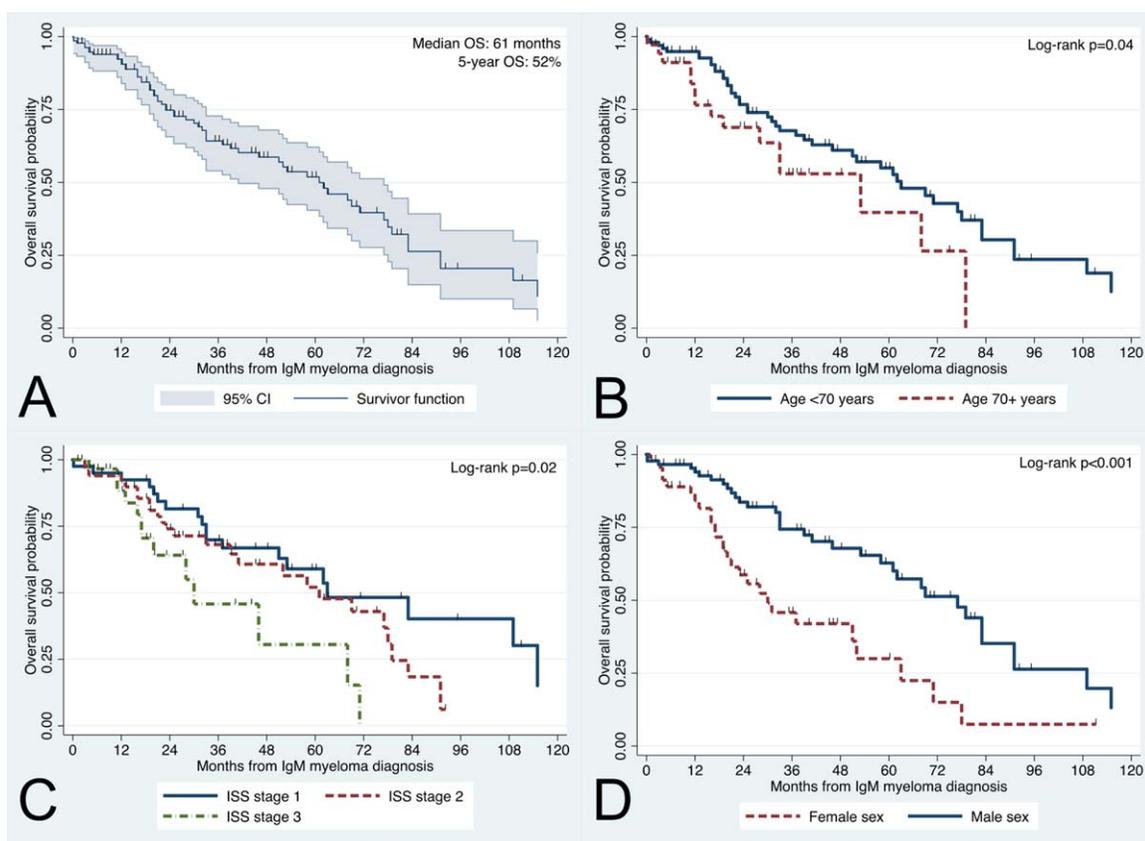


FIGURE 1 Overall survival estimates for the entire group (A), and by age (B), international staging system (C), and sex (D) [Color figure can be viewed at wileyonlinelibrary.com]

at myeloma diagnosis is 69 years with a 1.6:1 male to female ratio. The clinical features of anemia, renal disease and lytic lesions are as common in IgM myeloma as they are in non-IgM myeloma. However, hyperviscosity might be a more common feature of IgM myeloma given the higher molecular mass of IgM at ~950 kDa versus ~380 kDa of IgA and ~150 kDa of IgG. On the other hand, about a quarter of patients in our series had normal serum IgM levels despite having an identifiable monoclonal IgM paraprotein. Acquired von Willebrand disease (vWD) can also be a relatively common presentation of IgM myeloma, which can be induced by increased von Willebrand factor clearance from the plasma (associated with high levels of immunoglobulins) or the presence of autoantibodies (associated with normal or low levels of immunoglobulins).²⁰ The ISS stage distribution in our cohort was relatively well balanced, as would be expected in more common myeloma subtypes.⁶

Based on the pathological features of the patients in our series, IgM myeloma cells can express CD20 and cyclin D1. CD20 expression can be seen in 5–20% of myeloma cases,^{21,22} and appears to be expressed in IgM myeloma with expression rates ranging between 5–80%.^{5,14} Our study reports positive expression of CD20 in 58% of the evaluated cases. Similarly, cyclin D1 expression is reported in about two thirds of cases in our series. Previous reports have cyclin D1 expression in myeloma at rates ranging from 20 to 70%.^{23,24} Furthermore, cyclin D1 overexpression has been closely related with the presence of *t(11;14)*, which was identified in 40% of our cases, and has

been previously reported with a high prevalence (60–80%) in IgM myeloma.^{3,5,10}

At present, there are no specific treatment guidelines for IgM myeloma. Our study findings support that patients with IgM myeloma are treated similarly and have similar response and survival rates than patients with more common myeloma subtypes. As expected, over 80% of our patients began therapy within 3 months of diagnosis, and approximately two thirds of patients in our cohort received novel agents. ASCT was performed in about one third of our patients as consolidation in the frontline setting. Also, the overall response rate to frontline treatment ~80%. Although not a comparative study, the frontline treatment options, the use of ASCT and response to therapy appear similar to what would be expected in patients with more common myelomas. Our numbers, however, did not allow for a formal comparative analysis between treatment options in patients with IgM myeloma. Of interest is the potential use of rituximab in IgM myeloma given the positive CD20 expression in some cases. Rituximab was used in 10 patients with IgM myeloma in our series, usually in combination with other agents. The sample, however, is too small to draw any conclusion. We are aware of only one previous case reported on the use of rituximab in a patients with IgM plasma cell leukemia.²⁵

IgM myeloma has been associated with a shorter survival than more common myeloma subtypes, although these findings have not been consistent.^{3,26,27} Our study showed a median OS of ~5 years in patients with IgM myeloma, which is consistent with the survival of

patients with more common myeloma subtypes in the era of novel agents. Limited data are available on the prognostic factors of survival in IgM myeloma. Our study suggests older age, female sex and higher ISS staging as adverse prognostic factors in these patients. Specifically, patients with ISS stage 3 had a median survival of 30 months while patients with ISS stages 1 and 2 had a median survival of over 60 months. Other studies have also identified older age and female sex as adverse prognostic factors in patients with myeloma.^{28,29} In one study, the worse outcome seen in women with myeloma was associated with a higher rate of poor risk cytogenetics, such as t(4;14) and t(14;16), when compared to men.²⁹ Our study suggests a higher proportion of women with myeloma than men carrying the t(14;16); however, it is difficult to ascertain if this factor alone is sufficient to explain the worse outcome seen in women.

IgM myeloma is, in some instances, difficult to distinguish from the more prevalent WM. According to the WHO classification, WM is classified as an IgM-secreting lymphoplasmacytic lymphoma.³⁰ IgM myeloma and WM might share clinical features but differ widely in therapy and prognosis, warranting appropriate diagnostic evaluations. In contrast to myeloma, for example, patients with WM have a median OS that approximates a decade.³¹ Clinically, the presence of lytic lesions, renal dysfunction and hypercalcemia might favor an IgM myeloma, as these are rare in WM.^{32,33} Pathologically, WM can be distinguished from IgM myeloma by the lymphoplasmatic versus pure plasmacytic morphology of the malignant cells, although lymphoplasmacytic morphology has been described in IgM myeloma.⁵ To further complicate the differential diagnosis, IgM myeloma cells can express CD20. However, the presence of mast cells in the marrow should point towards a diagnosis of WM, and the expression of cyclin D1 and/or identification of t(11;14) should direct our diagnostic suspicion to IgM myeloma, as these have not been reported in WM.³⁴ Other common abnormalities seen in myeloma such as del11q, del13q and del17p are less sensitive as they have also been described in WM.³⁴ The MYD88 L265P mutation, which is present in about 90% of patients with WM,³⁵ might also be of help differentiating these conditions when routine clinicopathological features are not definitive. The MYD88 L265P mutation has not been identified in IgM myeloma.^{36,37}

Our study however, is not without biases. The retrospective design, the presence of missing data, and treatment modalities that were heterogeneous among patients could have resulted in the introduction of selection bias as well as under or overestimation of some of our results. We believe that the sample size, the multicentricity of the study and the low likelihood that prospective studies will be performed in such a rare disease could have helped, up to some degree, balancing out some of these weaknesses.

In conclusion, we present the results of the largest series of patients with IgM myeloma. IgM can present with clinical features between myeloma (i.e., lytic lesions, renal dysfunction, and hypercalcemia) and WM (i.e., hyperviscosity and acquired vWD). Our study suggests the definition of IgM myeloma could be extended to include patients with any of the CRAB criteria, as probable cases did not seem to have clinical, cytogenetic, treatment, response, or survival differen-

ces when compared with definitive cases of IgM myeloma. The expression of cyclin D1 and the presence of t(11;14), as well as the absence of the MYD88 L265P gene mutation, can help differentiate IgM myeloma from WM. Based on our results, as response and survival rates appear equivalent to non-IgM myeloma, the management of IgM myeloma should not differ from more common myeloma subtypes.

ACKNOWLEDGMENTS

Portions of this research were presented at the 58th American Society of Hematology Annual Meeting and Exposition in San Diego, CA, USA.

DISCLOSURES

JJC has received honoraria and/or research funding from Abbvie, Biogen, Celgene, Gilead, Janssen, Millennium and Pharmacyclics. AJ has received honoraria and/or research funding from Amgen, Janssen and Karyopharma. AD has received honoraria and/or research funding from Alnylam, Celgene, Janssen, Pfizer, Prothena, and Takeda. JPL has received honoraria and/or research funding from Celgene, Janssen, Millennium, Novartis and Onyx. JLR has received honoraria and/or research funding from Alexion and Teva. RH has received honoraria and/or research funding from Amgen, Bristol-Myers Squibb, Celgene and Takeda. RN received honoraria from Celgene, Millennium and Onyx. IS has received honoraria and/or research funding from Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda. RV has received honoraria and/or research funding from Abbvie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Karyopharma and Takeda. MAG has received honoraria from Amgen, Celgene, Ionis, Prothena and Sandoz. LB, ED, JC, JDV, ME, MAF, IMG, AG, JG, VH, JJ, DJ, BL, EEM, PM, EAM, HN, CPP, TP, LP, PGR, JS and AWG have no conflict of interests to disclose.

AUTHOR CONTRIBUTIONS

JJC and AJ designed the study, analyzed the data and drafted the initial manuscript. JJC performed the statistical analysis. All authors provided patients, critically reviewed the initial manuscript and approved the final version of the manuscript.

REFERENCES

- [1] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15:e538–e548.
- [2] Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78:21–33.
- [3] Schuster SR, Rajkumar SV, Dispenzieri A, et al. IgM multiple myeloma: disease definition, prognosis, and differentiation from Waldenstrom's macroglobulinemia. *Am J Hematol*. 2010;85:853–855.
- [4] Zarrabi MH, Stark RS, Kane P, Dannaher CL, Chandor S. IgM myeloma, a distinct entity in the spectrum of B-cell neoplasia. *Am J Clin Pathol*. 1981;75:1–10.
- [5] King RL, Howard MT, Hodnefield JM, Morice WG. IgM multiple myeloma: pathologic evaluation of a rare entity. *Am J Clin Pathol*. 2013;140:519–524.

- [6] Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23:3412–3420.
- [7] Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467–1473.
- [8] Ackroyd S, O'Connor SJ, Rawstron AC, Owen RG. IgM myeloma with t(4;14)(p16;q32). *Cancer Genet Cytogenet*. 2005;162:183–184.
- [9] Annibaldi O, Petrucci MT, Del Bianco P, et al. IgM multiple myeloma: report of four cases and review of the literature. *Leuk Lymphoma*. 2006;47:1565–1569.
- [10] Avet-Loiseau H, Garand R, Lode L, Harousseau JL, Bataille R, Inter-groupe Francophone Du M. Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. *Blood*. 2003;101:1570–1571.
- [11] Chehal A, Taher A, Shamseddine A. IgM myeloma and Waldenstrom's macroglobulinemia: a distinct clinical feature, histology, immunophenotype, and chromosomal abnormality. *Clin Lab Haematol*. 2003;25:187–190.
- [12] De Gramont A, Grosbois B, Michaux JL, et al. IgM myeloma: 6 cases and a review of the literature. *Rev Med Interne*. 1990;11:13–18.
- [13] Dierlamm T, Laack E, Dierlamm J, Fiedler W, Hossfeld DK. IgM myeloma: a report of four cases. *Ann Hematol*. 2002;81:136–139.
- [14] Feyler S, O'Connor SJ, Rawstron AC, et al. IgM myeloma: a rare entity characterized by a CD20-CD56-CD117-immunophenotype and the t(11;14). *Br J Haematol*. 2008;140:547–551.
- [15] Kondo H, Yokoyama K. IgM myeloma: different features from multiple myeloma and macroglobulinaemia. *Eur J Haematol*. 1999;63:366–368.
- [16] Masanes F, Pedrol E, Blade J, et al. IgM myeloma: a report of 2 cases. *Med Clin (Barc)*. 1991;96:777–779.
- [17] Willenbacher E, Erdel M, Strasser U, et al. IgM myeloma: more on a rare entity. *Br J Haematol*. 2008;143:146–148.
- [18] Xu Z, Van Der Jagt R, Faught C, Beaulieu Bergeron M. A rare IgM multiple myeloma with aberrant PAX5 expression mimicking lymphoplasmacytic lymphoma. *Ann Hematol*. 2014;93:1251–1252.
- [19] Zheng L, Zeng Z, Lin J, Chen J. IgM multiple myeloma presenting with bleeding tendency: a case report with immunophenotype analysis. *Oncol Lett*. 2011;2:55–57.
- [20] Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117:6777–6785.
- [21] Kapoor P, Greipp PT, Morice WG, Rajkumar SV, Witzig TE, Greipp PR. Anti-CD20 monoclonal antibody therapy in multiple myeloma. *Br J Haematol*. 2008;141:135–148.
- [22] Robillard N, Avet-Loiseau H, Garand R, et al. CD20 is associated with a small mature plasma cell morphology and t(11;14) in multiple myeloma. *Blood*. 2003;102:1070–1071.
- [23] Athanasiou E, Kaloutsi V, Kotoula V, et al. Cyclin D1 overexpression in multiple myeloma. A morphologic, immunohistochemical, and in situ hybridization study of 71 paraffin-embedded bone marrow biopsy specimens. *Am J Clin Pathol*. 2001;116:535–542.
- [24] Soverini S, Cavo M, Cellini C, et al. Cyclin D1 overexpression is a favorable prognostic variable for newly diagnosed multiple myeloma patients treated with high-dose chemotherapy and single or double autologous transplantation. *Blood*. 2003;102:1588–1594.
- [25] Oka S, Yokote T, Akioka T, et al. Successful treatment of multi-agent chemotherapy with rituximab for IgM plasma cell leukemia. *Leuk Res*. 2006;30:1581–1583.
- [26] Reece DE, Vesole DH, Shrestha S, et al. Outcome of patients with IgD and IgM multiple myeloma undergoing autologous hematopoietic stem cell transplantation: a retrospective CIBMTR study. *Clin Lymphoma Myeloma Leuk*. 2010;10:458–463.
- [27] Morris C, Drake M, Apperley J, et al. Efficacy and outcome of autologous transplantation in rare myelomas. *Haematologica*. 2010;95:2126–2133.
- [28] Ailawadhi S, Aldoss IT, Yang D, et al. Outcome disparities in multiple myeloma: a SEER-based comparative analysis of ethnic subgroups. *Br J Haematol*. 2012;158:91–98.
- [29] Boyd KD, Ross FM, Chiecchio L, et al. Gender disparities in the tumor genetics and clinical outcome of multiple myeloma. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1703–1707.
- [30] Swerdlow SH, Berger F, Pileri SA, Harris NL, Jaffe ES, Stein H. Lymphoplasmacytic lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008:194–195.
- [31] Castillo JJ, Olszewski AJ, Kanan S, Meid K, Hunter ZR, Treon SP. Overall survival and competing risks of death in patients with Waldenstrom macroglobulinaemia: an analysis of the surveillance, epidemiology and end results database. *Br J Haematol*. 2015;169:81–89.
- [32] Dimopoulos MA, Alexanian R. Waldenstrom's macroglobulinemia. *Blood*. 1994;83:1452–1459.
- [33] Dimopoulos MA, Panayiotidis P, Mouloupoulos LA, Sfikakis P, Dalakas M. Waldenstrom's macroglobulinemia: clinical features, complications, and management. *J Clin Oncol*. 2000;18:214–226.
- [34] Nguyen-Khac F, Lambert J, Chapiro E, et al. Chromosomal aberrations and their prognostic value in a series of 174 untreated patients with Waldenstrom's macroglobulinemia. *Haematologica*. 2013;98:649–654.
- [35] Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2012;367:826–833.
- [36] Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood*. 2013;121:2051–2058.
- [37] Willenbacher W, Willenbacher E, Brunner A, Manzl C. Improved accuracy of discrimination between IgM multiple myeloma and Waldenstrom macroglobulinaemia by testing for MYD88 L265P mutations. *Br J Haematol*. 2013;161:902–904.

How to cite this article: Castillo JJ, Jurczynsyzyn A, Brozova L, et al. IgM myeloma: A multicenter retrospective study of 134 patients. *Am J Hematol*. 2017;00:1–6. <https://doi.org/10.1002/ajh.24753>