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(Article begins on next page)

**Jorge J Castillo** 

## **IgM Myeloma: A Multicenter Retrospective Study of 134 Patients**

**Short title:** IgM myeloma

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## 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 with 19% of patients presenting with levels >6,000 mg/dl. 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.

## Keywords:

IgM; multiple myeloma; CD20; cyclin D1; t(11;14); survival

## 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.

## **Patients and Methods**

### **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 institutions. 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.

### **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.

### 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 less than 0.05. Calculations and graphics were obtained using the statistical software STATA version 13.1 (College Station, Texas, USA).

## Results

### 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 (range 27-12,100 mg/dl) with 33 patients (25%) having a serum IgM level below 300 mg/dl and 25 patients (19%) with serum IgM levels of 6,000 mg/dl 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 ( $p=0.32$ ). 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.

### 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  $\geq 70$  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  $\geq 70$  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, elevated calcium level, estimated GFR  $<60$  ml/min, presence of skeletal lytic lesions and serum IgM levels  $\geq 3,000$  mg/dl or  $\geq 6,000$  mg/dl 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.

## Discussion

Due to 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.

Based on 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 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 20-70% [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 approximated 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 approximately 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 differences 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.

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### **Authors' 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.

## **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.

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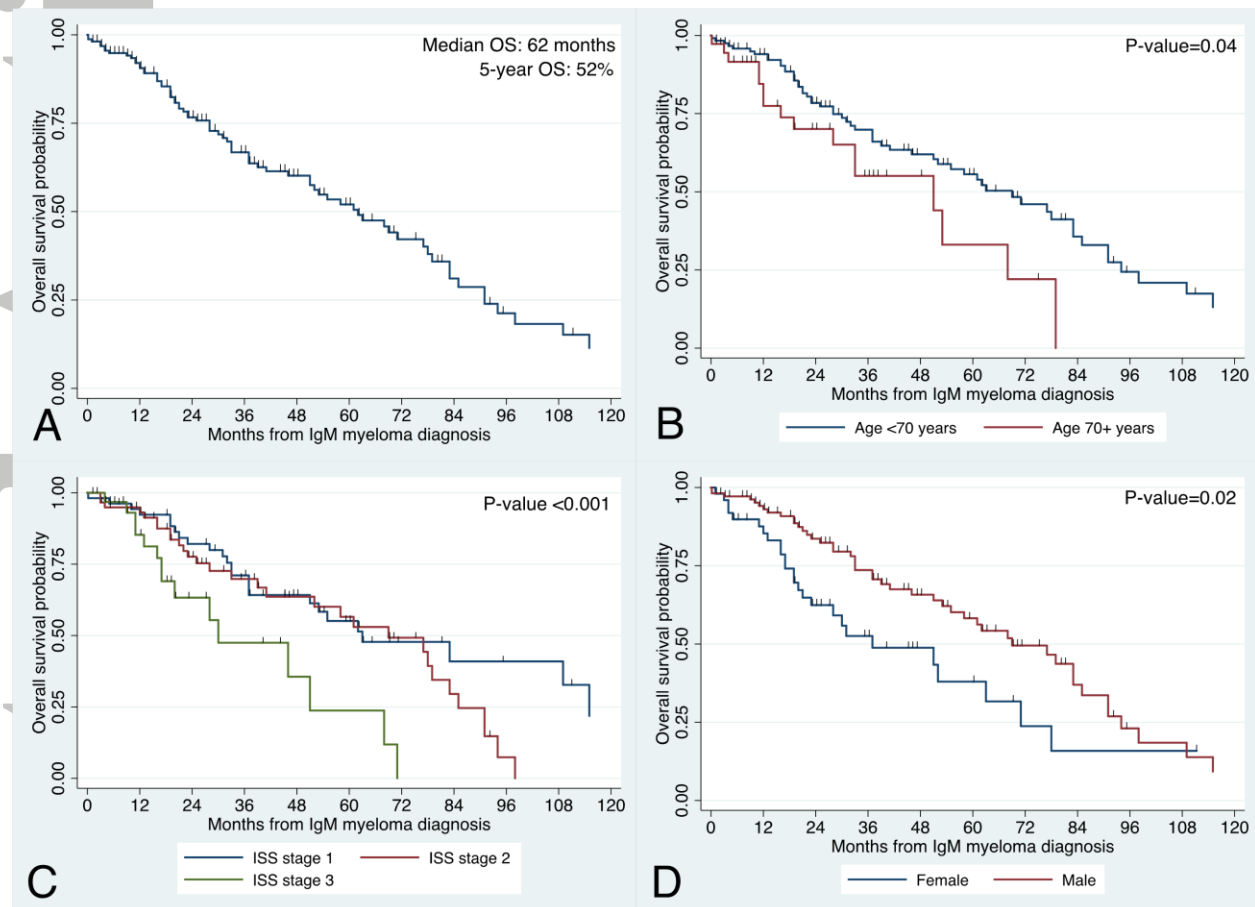
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## Figure legends

Figure 1. Overall survival estimates for the entire group (A), and by age (B), International Staging System (C), and sex (D)



**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      | 49/131                 | 37%        |
| Estimated GFR <60 ml/min | 56/130                 | 43%        |
| Elevated calcium level   | 24/129                 | 19%        |
| Skeletal lytic lesions   | 89/127                 | 70%        |
| Elevated LDH level       | 23/99                  | 23%        |
| Serum IgM ≥3000 mg/dl    | 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

**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