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Original contribution

# IgM plasma cell myeloma in the era of novel therapy: a clinicopathological study of 17 cases☆

**Evgeniya A. Angelova MD, PhD, Shaoying Li MD, Wei Wang MD, PhD, Carlos Bueso-Ramos MD, PhD, Guilin Tang MD, PhD, L. Jeffrey Medeiros MD, Pei Lin MD***

*Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA*

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**Summary** IgM plasma cell myeloma (PCM) is a rare subtype of myeloma, and its response to novel therapies has not been fully characterized. We describe clinicopathological features and outcome of 17 patients with IgM PCM (11 men and 6 women) with a median age of 63 years. Patients presented with serum hyperviscosity (77%), bone lesions (71%), anemia (65%), renal dysfunction (53%), and hypercalcemia (35%). Median serum IgM level was 6.4 g/dL (0.7-12.1 g/dL). Bone marrow plasma cells (median, 80%; range, 20%-90%) were frequently of lymphoplasmacytic type (8/17; 47%). Immunophenotypically, the myeloma cells were positive for CD38, CD138, CD20 (5/16; 31%), CD56 (4/16; 25%), and CD117 (2/12; 17%); negative for CD19; and decreased or absent CD27 and CD81 in all cases. Seven (41%) patients had a complex karyotype, and fluorescence in situ hybridization showed *CCND1-IGH* (13/16; 81%), and deletions of 17p13/*TP53* (29%) and 13q14/*RB1* (38%). No *MYD88* L265P mutation was detected. Most patients (94%) received proteasome inhibitor with or without immunomodulatory drug, 62% of patients required multiple regimens because of refractory disease, and 11 (65%) of 17 patients underwent autologous stem cell transplant (ASCT). The median OS was 67 months. After a median follow-up of 38 months (range, 3-106 months), only 5 patients achieved complete remission, 5 had persistent disease, and 7 died (2 progressed to plasma cell leukemia and 1 to blastic variant). In summary, IgM PCM is highly associated with t(11;14) and lymphoplasmacytic morphology. Patients are refractory to novel therapy and progression to high-risk myeloma is common, suggesting a need for alternative novel therapies.


## 1. Introduction

IgM plasma cell myeloma (PCM) is a very rare and poorly characterized subtype that accounts for about 0.8% of all myeloma cases [1-3]. Most patients with IgM PCM present with lytic bone lesions, anemia, and renal failure, similar to other subtypes; however, hyperviscosity, lymphadenopathy, and hepatosplenomegaly have been reported to be more frequent in patients with IgM PCM [4-6]. Patients with IgM PCM

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* Corresponding author at: Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Box 72, 1515 Holcombe Blvd, Houston, TX 77030.
*E-mail address:* peilin@mdanderson.org (P. Lin).

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responded poorly to therapy before novel agents, such as proteasome inhibitors (PIs) and immune-modulating drugs, became available [7,8].

The diagnosis of IgM PCM is usually established based on the International Myeloma Working Group (IMWG) criteria [9,10]. This system integrates clinical, laboratory, and pathologic criteria: presence of IgM paraprotein of any size, at least 10% bone marrow monoclonal plasma cells (or plasmacytoma), and 1 or more myeloma-defining events, such as evidence of end-organ damage, free light-chain ratio, and lesions on magnetic resonance imaging (MRI). However, the definition of IgM PCM has been evolving in recent years, resulting in variable selection criteria in published series [11-14]. The scope of clinicopathological features and outcomes of patients with IgM PCM remain poorly characterized, in large part due to the rarity of the disease. A limited number of patient cohorts and case reports focused on IgM PCM have been documented in the literature. Although a few reports deal with the bone marrow findings in IgM PCM, these series are small or lack comprehensive data on cytogenetic findings, therapy, and follow-up. Many series included heterogeneous patients treated differently or when novel agents were not available [6,12,15,16].

In this study, we report our single-institution experience with 17 cases of IgM PCM to better characterize the clinicopathological features, including clinical and laboratory data, morphology, immunophenotype, and conventional cytogenetic and molecular studies with an emphasis on the clinical course and outcome of patients treated with novel therapies.

## 2. Materials and methods

### 2.1. Study group

We searched the database of the Department of Hematopathology at The University of Texas MD Anderson Cancer Center from January 1, 2002, to January 31, 2018, for cases diagnosed as "plasma cell myeloma", "plasma cell neoplasm" or "multiple myeloma" with serum IgM monoclonal protein (regardless of size). We identified 17 cases meeting the current diagnostic criteria for PCM, defined by IMWG [10] and included in the World Health Organization classification [17]: presence of monoclonal bone marrow plasma cells of at least 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the myeloma defining events: (1) evidence of end-organ damage (CRAB: Anemia, Renal dysfunction, elevated Calcium, and lytic Bone lesions), (2) clonal bone marrow plasma cell percentage of at least 60%, (3) involved/uninvolved serum free light-chain ratio of at least 100, and (4) more than 1 focal lesion on MRI studies. Cases with a clonal B-cell lymphocytic component defined by morphology, immunohistochemistry, or flow cytometry as well as cases with a second non-IgM paraprotein were excluded from the study cohort.

Medical records were reviewed for all relevant clinical and laboratory data, such as stage of diseases, therapy, and clinical outcome. We also reviewed imaging studies for evidence of lytic bone lesions, focal lesions by MRI, organomegaly, or lymphadenopathy. The study was conducted under an MDACC institutional review board–approved protocol.

### 2.2. Histologic examination and immunophenotypic analysis

Hematoxylin and eosin–stained slides of bone marrow core and/or clot specimens, with corresponding Wright-Giemsa–stained aspirate smears and/or touch imprints and available peripheral blood smears, were evaluated in all cases. Hematoxylin and eosin–stained slides of extramedullary tissue involved were also reviewed.

Immunohistochemical analysis was performed using formalin-fixed, paraffin-embedded tissue sections of bone marrow aspirate clot and/or biopsy specimens. Monoclonal antibodies to assess the following antigens were used: CD20, CD138, cyclin D1, and κ and λ (Dako, Carpinteria, CA), and PAX5 (BD Biosciences, San Jose, CA).

For all the cases, multicolor flow cytometric immunophenotypic analysis was performed using bone marrow aspirate or fine needle aspiration of involved tissue. In all cases, a 4-color or 8-color analysis was performed and plasma cells were identified by bright CD38/CD138 expression. Assessment of other markers including CD19, CD20, CD27, CD28, CD56, CD81, and CD117 was performed for most cases. Expression of κ/λ light chains was assessed simultaneously on lymphocytes to determine B-cell clonality, and cases of B-cell lymphoma with monotypic plasma cells were excluded. In our institution, specimens were analyzed using FACSCalibur or FACSCanto II (BD Biosciences, Mountain View, CA), with all antibodies obtained from Becton-Dickinson Biosciences.

### 2.3. Cytogenetic, fluorescence in situ hybridization, and molecular analyses

Conventional chromosome analysis was performed on unstimulated 24-hour and lipopolysaccharide-stimulated 72-hour bone marrow aspirate cultures following standard procedures as has been described previously [18]. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (2016).

Interphase fluorescence in situ hybridization (FISH) studies were conducted on cultured bone marrow cells using 4 sets of dual-color FISH probes targeting *CDKN2C/CKS1B*, *MYEOV/CCND1-IGH*, *RB1*/13q34, and *TP53*/CEN17 (Abbott, Des Plaines, IL, USA) according to the manufacturer's instructions and laboratory procedures. At least 200 cells were assessed for each probe set.

Molecular testing was performed in a subset of patients to exclude the presence of *MYD88*$^{L265P}$ mutation by pyrosequencing assay as has been described [19].

### 2.4. Statistical analysis

Statistical analyses were performed using GraphPad Prism 6 software (GraphPad Software, La Jolla, CA) and the IBM SPSS Statistics Version 24.0 (SPSS, Chicago, IL). For continuous variables, data were reported as median and range. For nominal variables, data were reported as the number of patients unless otherwise specified. The follow-up interval and overall survival (OS) were calculated from the time of initial diagnosis until time of last follow-up or death. Distribution of OS was estimated using the Kaplan-Meier curves. A *P* value of less than .05 was considered statistically significant.

## 3. Results

### 3.1. Clinical characteristics and laboratory findings

The study group consisted of 11 men and 6 women (1.8:1) with a median age of 63 years (range, 42-79 years) at the time of initial diagnosis; 53% of patients were younger than 65 years. The clinical and laboratory features are summarized in Table 1. A history of IgM monoclonal gammopathy of undetermined significance (IgM MGUS) was documented in 2 (11.7%) patients. One patient (case 8) had a history of mantle cell lymphoma in tonsil, was treated, and was in complete remission for 2 years before the diagnosis of IgM PCM. At the time of IgM PCM diagnosis, a full lymphoma panel was done and the myeloma cells did not express CD5. No lymphadenopathy or monoclonal B cells were detected on multiple follow-up occasions in this patient.

The clinical and radiologic features including stage of diseases are summarized in Table 2. Lytic bone lesions were present in 12 (71%) patients. Mild splenomegaly was observed in 2 (12.5%) patients, detected only by computed tomographic imaging studies. In 2 (12.5%) patients, lymphadenopathy was identified on imaging studies. Biopsy-confirmed extramedullary involvement in one patient and the other patient was not biopsied.

The median serum IgM level was 6.4 g/dL (range, 0.7-12.1 g/dL). Serum IgM levels were greater than 3.0 g/dL in 14 (82.4%) of patients and at least 6 g/dL in 9 (53%) patients. The median level of M-protein was 4.5 g/dL (range, 0.5-7.1 g/dL), that of κ was 7 (41.2%), and that of λ was 10 (58.8%). Serum levels of IgG and IgA were decreased in 14 (82%) and 13 (77%) patients, respectively. Hyperviscosity was detected in 13 (77%) patients. The median serum creatinine level was 1.5 mg/dL (range, 0.7-5.9 mg/dL), and 3 (17.7%) patients had a creatinine level of greater than 2 mg/dL.

### 3.2. Morphologic findings

The morphologic findings are summarized in Table 3. In the bone marrow biopsy specimen, cellularity ranged from 30% to 90% and plasma cells ranged from 20% to 95% of cellularity with a median tumor load of 80% (Fig. 1). The cytology of the neoplastic cells varied (Fig. 2). A "lymphoplasmacytic" appearance was most common in 8 (47%) cases. In other cases, the plasma cells were of mature Marschalko type in 4 (24%) cases or were more immature asynchronous forms in 5 (29.4%) cases. In patient 1, the initial sample showed predominantly asynchronous type with prominent nucleoli admixed with more well-differentiated plasma cells. At the follow-up 65 months later, however, the asynchronous type of cells was admixed with plasmablasts with frequent mitoses, multinucleated and pleomorphic forms (Fig. 2G). A concurrent femoral lesion biopsy specimen showed infiltrate of plasmablasts with extensive necrosis.

Circulating plasma cells were noted in 4 patients, ranging from 1% up to 75%. In 2 patients (cases 5 and 16), the circulating plasma cells were noted at initial presentation (1% and 15%, respectively). Two patients (cases 3 and 15) progressed to plasma cell leukemia during the course of disease, with plasma cells exceeding 20% of peripheral blood elements (24%-75% and 60%, respectively). Notably, all patients with circulating plasma cells showed lymphoplasmacytic morphology (Fig. 2A). Rouleaux formation in peripheral blood smears ranged from mild to marked and was seen in 9 (90%) of 10 patients.

### 3.3. Immunophenotypic findings

The results of immunophenotypic studies are summarized in Fig. 3A. The plasma cells were positive for CD138 (100%) and cyclin D1 (n = 9) in all cases assessed, CD20 in 3 (38%) of 8 cases, and PAX-5 in 1 (12.5%) of 8 cases.

By flow cytometry, the neoplastic cells were positive for CD38 (bright), CD138, and bright monotypic cytoplasmic immunoglobulin light chains in all cases (κ in 7 and λ in 10). CD20 was positive (partial and dim) in 5 cases (31%), and CD45 was dimly expressed in 5 (31%) of 16 cases. Histograms of a representative case are shown in Fig. 3B. CD19 was partially positive in on1 case only. Aberrant expression of CD56 and CD117 was observed in only 4 (25%) of 16 and 2 (17%) of 12 cases, respectively. Decreased or negative expression of CD27 and CD81 was observed in all tested cases (n = 6). Seven cases were analyzed for CD28, and all were negative. All cases were negative for CD5. In 15 patients, where immunophenotype was assessed at multiple time points, the phenotype was stable, except for the loss of CD38 expression in patients who received Daratumumab as part of their therapy.

**Table 1** Clinical and laboratory characteristics and treatment outcome of patients with IgM myeloma

| Patient no. | Age (y) | Sex | M-protein SPEP (g/dL) | Serum IgM (g/dL) | Light chain | Lytic bone lesions | HGB (g/dL) | Calcium (mg/dL) | Cr (mg/dL) | GFR (mL/min/1.73 $m^2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 53 | M | 6.2 | 6.4 | λ | Yes | 9.9 | 12.8 | 1.6 | 51 |
| 2 | 68 | M | 4.6 | 6.5 | λ | Yes | 11.1 | 9.8 | 1.1 | 71 |
| 3 | 65 | M | 5.3 | 8.1 | λ | Yes | 5.3 | 12.3 | 1.5 | 50 |
| 4 | 56 | F | 6.5 | 10.4 | κ | Yes | 6.2 | 12.6 | 3.3 | 20 |
| 5 | 66 | M | 7.1 | 8.4 | κ | Yes | 10.5 | 10.5 | 0.9 | 88 |
| 6 | 73 | M | 0.5 | 0.7 | κ | No | 11.7 | 9.8 | 1.6 | 45 |
| 7 | 72 | F | 4.6 | 5.2 | λ | Yes | 11.4 | 11.7 | 1.01 | 54 |
| 8 | 62 | F | 3 | 6.2 | λ | No | 11.2 | 9.7 | 1.5 | 68 |
| 9 | 57 | M | 6.69 | 12.1 | λ | Yes | 9.2 | 11 | 1.4 | 69 |
| 10 | 56 | M | 6.4 | 8.9 | κ | No | 7.6 | 11.9 | 2.11 | 33 |
| 11 | 76 | F | 3.5 | 5.5 | κ | No | 9.1 | 10.6 | 1.45 | 35 |
| 12 | 63 | M | 0.7 | 4 | κ | No | 10 | 9.8 | 1.65 | 46 |
| 13 | 53 | M | 3.8 | 8.4 | λ | Yes | 8 | 10.4 | 1.36 | 73 |
| 14 | 50 | F | 0.9 | 2.8 | λ | Yes | 9.4 | 13.1 | 1.5 | 78 |
| 15 | 79 | M | 4.5 | 6.4 | κ | Yes | 6.5 | 10.6 | 5.87 | 9 |
| 16 | 42 | F | 2.1 | 2.7 | λ | Yes | 8.3 | 10 | 0.7 | 130 |
| 17 | 72 | M | 3.36 | 3.7 | λ | Yes | 9.4 | 16 | 1.6 | 60 |

**Table 1** (*continued*)

| LDH (U/L) | Viscosity (cP) | B2M (mg/L) | SM | LAD | RISS stage | Therapy | ASCT | FU (mo) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 636 | 2.4 | 2.4 | No | No | II | Multiple, including thalidimide + dexamethasone, VD + thalidomide; DT-PACE Hyper-CVAD | Yes, ×2 | 67 | DOD |
| 446 | 7.9 | 3 | No | No | II | Cyclophosphamide + Rtx Hyper-CVAD | No | 30 | DOD |
| 1026 | 4 | 5.8 | Mild [a] | Yes | III | Rituximab Bortezomib Hyper-CVAD | Yes | 12 | DOD |
| 582 | NA | 10.8 | No | Yes PCN [b] | III | CyBor Revlimid | Yes | 106 | Alive, PD |
| 308 | 2.7 | 4.5 | No | No | II | Multiple, including CyBorD; VRD; VDT-PACE | No | 102 | DOD |
| 423 | 1.1 | 4.2 | No | No | II | VD-Rtx | No | 36 | DOC, colon cancer IgMM PD |
| 466 | 1.5 | 2.7 | No | No | I | NA | Yes | 48 | Alive, CR |
| 673 | NA | 2.2 | No | No | I | VRD Carfilzomib + dexamethasone | Yes | 58 | Alive, CR |
| 301 | 6.5 | 2.6 | No | No | III | Multiple, including CyBorD, bendamustine + Rtx, CPD Ibrutinib Daratumunab Vaccine therapy | No | 38 | DOD |
| 398 | 4.3 | 6 | Mild [a] | No | III | Multiple, including VRD, CyBorD, elotuzumab + RD Ixazomib + pomalidomide + Dex | Yes, ×2 | 60 | Alive, PD |
| 294 | 2.4 | 6.4 | No | No | III | VRD + Rtx Lost to FU | No | 26 | Alive, CR |
| 368 | 14 | 9.5 | No | No | III | Multiple, including bendamustine, VD-Rtx, ibrutinib, crafilzomib + RD, VDT-PACE | Yes | 45 | Alive, PD |
| 431 | 4.8 | 1.9 | NA | NA | II | Multiple, including VRD, carfilzomib + DT-PACE, dendamustine CAR-T Daratumumab | Yes | 47 | Alive, PD |
| NA | NA | 2.2 | No | No | II | VRD | Yes | 16 | Alive, CR |
| 492 | 2.2 | 20.7 | No | No | III | VD CyBorD | No | 3 | DOD |
| 472 | NA | 4.63 | No | No | II | Carfilzomib + RD | Yes | 3 | Alive, CR |
| 387 | 1.5 | 2.3 | No | No | I | CyBorD | Yes | 6 | Alive, PD |

Abbreviations: B2M, $\beta_2$-macroglobulin; cP, centipoise; CPD, carfilzomib, pomalidomide, and dexamethasone; CR, complete remission; Cr, creatinine; CyBorD, cyclophosphamide, bortezomib (velcade), and dexamethasone; DOC, dead of other cause; DOD, dead of disease; F, female; FU, follow-up; GFR, estimated glomerular filtration rate; HGB, hemoglobin; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; PD, persistent disease; κ, kappa immunoglobulin light chain; λ, λ immunoglobulin light chain; LAD, lymphadenopathy; LDH, lactate dehydrogenase; M, male; NA, not available; PCN, plasma cell neoplasm; RISS, revised International Staging System for Myeloma; RD, revlimida and dexamethasone; Rtx, rituximab; SPEP, serum protein electrophoresis; SM, splenomegaly; VDT-PACE, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VRD, bortezomib, revlimid and dexamethasone.

[a] Mild splenomegaly determined by computed tomographic scan imaging.

[b] Biopsy-proven diagnosis.

**Table 2** Clinical and laboratory parameters in 17 patients with IgM myeloma

| Parameter | Median (range) | Category | No. of positive/tested cases | Percentage |
|---|---|---|---|---|
| Age (y) | 63 (42-79) | Age ≥70 y | 5/17 | 29.4 |
| Sex (M/F) | 11:6 (1.8:1) | Male sex | 11/17 | 64.7 |
| Serum IgM (g/dL) | 6.4 (0.7-12.1) | Serum IgM ≥3.0 g/dL | 14/17 | 82.4 |
| Clonal BM PC (%) | 80 (20-95) | Clonal BM PC ≥60% | 11/17 | 64.7 |
| Bone lytic lesions | 12 yes/5 no | Bone lytic lesions | 12/17 | 70.6 |
| HGB (g/dL) | 9.25 (5.3-11.7) | HGB <10 g/dL | 11/17 | 64.7 |
| Estimated GFR (mL/min/1.73 $m^2$) | 54 (9-130) | Estimated GFR <60 mL/min/1.73 $m^2$ | 9/17 | 52.9 |
| Calcium (mg/dL) | 10.6 (9.7-16.0) | Elevated calcium >11 mg/dL | 6/17 | 35.3 |
| $\beta_2$-Microglobulin (mg/L) | 4.2 (1.9-20.7) | $\beta_2$-microglobulin ≥5.5 mg/L | 6/17 | 35.3 |
| LDH (U/L) | 433 (294-1026) | Elevated LDH level | 3/16 | 18.8 |
| Viscosity (cP) | 2.7 (1.1-14.0) | Hyperviscosity >1.5 cP | 10/13 | 76.9 |
| | | t(11;14) by FISH | 13/16 | 81.3 |
| | | High-risk cytogenetics [del(17p), t(4;14) or t(14;16)] | 6/17 | 35.3 |
| | | RISS stage I | 3/17 | 17.6 |
| | | RISS stage II | 7/17 | 41.2 |
| | | RISS stage III | 7/17 | 41.2 |

Abbreviations: BM, bone marrow; cP, centipoise (unit for viscosity); GFR, glomerular filtration rate by Modification of Diet in Renal Disease formula (the current recommendation for the evaluation of CrCl); HGB, hemoglobin; LDH, lactate dehydrogenase; PC, plasma cells; RISS, revised International Staging System for Myeloma [10].

## 3.4. Cytogenetic and molecular findings

Conventional karyotypes performed on bone marrow aspirates were available in all 17 patients (Table 3). Eight (47%) patients had an abnormal karyotype. A complex karyotype, defined here as 3 or more chromosomal aberrations, was present in 7 (41.2%) patients. Recurrent aberrations (noted in >1 case) included t(11;14)/*IGH-CCND1* rearrangement (n = 6),

**Table 3** Bone marrow and cytogenetic findings in 17 patients with IgM myeloma

| Case | Specimens | BM PC (%) | PC morphology | Karyotype |
|---|---|---|---|---|
| 1 | BM<br>Bone | 80 | Atypical | 45,XY,del(6)(q13q23),add(7)(q36),t(11;14)(q13;q32),−13[10]/46,XY[10] |
| 2 | BM | 85 | Mature, CPC | 46,XY,t(2;18)(q23;q22),add(6)(q12),add(9)(p24),<br>t(11;14)(q13;q32)[12]/46,XY[8] |
| 3 | BM<br>PB 24%-75% PC | 80 | Mature, LP | 42,XY,t(1;16)(q12;p11.2),−6,t(11;14)(q13;q32),−13,<br>del(14)(q12q21),−17, add(19)(p13.3),−20[3]/42,idem,<br>add(12)(q24.3)[5]/39-44,idem,add(9)(p24),−15,+20[cp3]/46, XY[9] |
| 4 | BM<br>LN | 80 | Atypical | 46,XX[20] |
| 5 | BM<br>PB 1%PC | 75 | Mature, CPC | 46,XY[20] |
| 6 | BM | 20 | Atypical | 46,XY[20] |
| 7 | BM | 40 | Mature, CPC | 46,XX[19]/47,XX,+17[1] |
| 8 | BM | 40 | Mature, LP | 45,XX,−13[3]/46,XX[17] |
| 9 | BM | 80 | Mature, LP | 45,XY,+1,add(1)(q21),dic(1;20)(p12;p13),−3,der(6)t(1;6)(q25;q21),<br>−8,t(11;14)(q13;q32), add(13)(q14),del(13)(q12q21),+mar[2]/46,XY[19]. |
| 10 | BM | 80 | Mature, LP | 46,XY,del(6)(q13q23),t(11;14)(q13;q32),add(12)(q23)[1]/46, XY[20] |
| 11 | BM | 60 | Mature, LP | 46,XX,inv(9)(p12q13)[30] |
| 12 | BM | 40 | Mature, CPC | 46,XY,del(4)(q21)[1]/46,XY[19] |
| 13 | BM | 95 | Atypical | 46,XY[20] |
| 14 | BM | 30 | Mature, LP | 46, XX[20] |
| 15 | BM<br>PB 12%-60% PC | 80 | Mature, LP | 46,XY,der(4)t(4;14)(q33.3;q32)t(11;14)(q13;q32),add(5)(q13),<br>del(6)(q15q21),t(11;14),add(13)(p11.2)[12]/46,XY[8] |
| 16 | BM<br>PB 15% PC | 80 | Mature, LP | 43~44,X,−X,add(1)(p12),−13,−13,−14,add(17)(p11.2),<br>del(17)(p12p13),der(19)t(13;19)(q14;p13.2), −22, +2mar[cp8]/46,XX[14] |
| 17 | BM | 30 | Atypical | 46,XY[20] |

Abbreviations: BM, bone marrow; CPC, well-differentiated, classic plasma cells; LN, lymph node; LP, lymphoplasmacytic; peripheral blood; PC, plasma cells; PB.

abnormalities of chromosome 6 (n = 5), monosomy 13 or loss of 1 RB1 locus (n = 4), and monosomy or loss of TP53 locus (n = 2). One patient (no. 15) had a translocation involving chromosomes 4, 11, and 14 as part of a complex karyotype, including t(11;14)/*IGH-CCND1*. There was no evidence of *IGH/FGFR3*.

FISH analysis (Fig. 3A) showed *IGH-CCND1* fusion in 13 (81.3%) of 16, *TP53* deletion or monosomy 17 in 5 (29.4%) of 17, and monosomy 13 or *RB1* deletion in 6 (37.5%) of 16. Two of 8 patients tested were positive for gain of *CKS1B*. No patients tested (n = 8) had *MYD88* mutations. One patient tested for *CXCR4* mutations was negative.

### 3.5. Therapy and outcomes

Treatment information was available in 16 patients, and all received systemic treatment (Table 1). Fifteen (94%) of 16 patients received PI with or without an immunomodulatory drug (IMID) during the course of their treatment. Frontline treatment modalities for IgM PCM included PI only (19%), IMID only (6%), PI + IMID (31%), chemotherapy + PI (19%), and rituximab-containing regimens 4 (25%). Multiple therapeutic regimens were explored in 10 (62%) of 16 patients because of persistent or relapsed disease. One patient received cyclophosphamide with rituximab and later switched to the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen. Treatment information was not available in one patient who was treated outside the country.

Follow-up data were available in all patients. Eleven (65%) of 17 patients underwent autologous stem cell transplant (ASCT), with 2 patients requiring a second ASCT. The median follow-up from initial diagnosis to last follow-up or patient death was 38 months (range, 3-106 months). At the last follow-up, 10 (59%) patients were alive; 5 achieved and remained in complete remission and 5 had persistent or refractory disease. The remaining 7 (41%) patients died. The most common cause of death was myeloma progression in 5 (71%) of 7 patients; 1 (14%) patient died of sepsis after initiation of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone chemotherapy for refractory disease. The patient who died of colon cancer had persistent IgM PCM. Both patients who progressed to plasma cell leukemia died within 6 months after the progression.

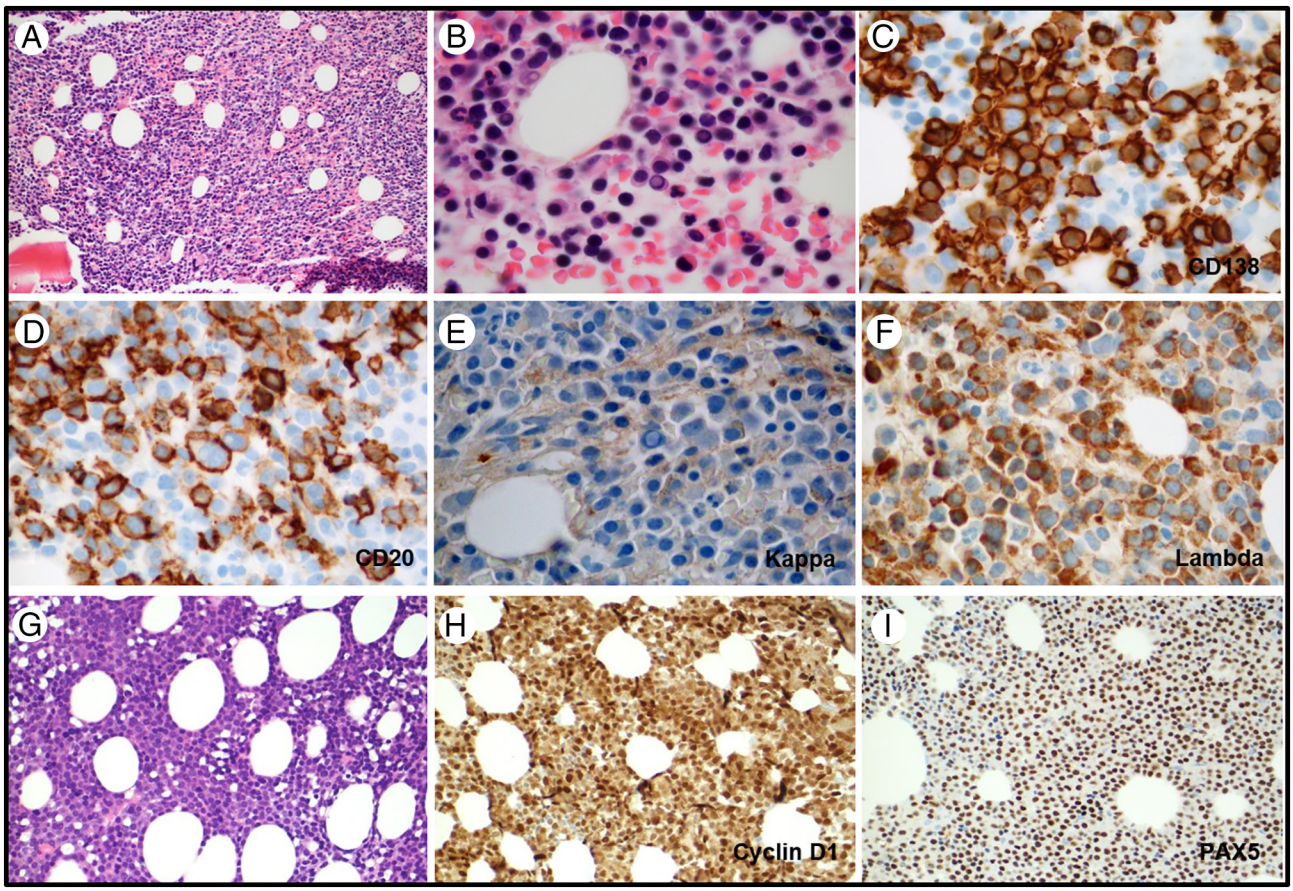


**Fig. 1** Bone marrow findings in IgM PCM. Bone marrow trephine biopsy (case 16) showing diffuse lymphoplasmacytic infiltrate (A and B, hematoxylin and eosin, original magnification ×200 and ×1000), highlighted by CD138 with a subset of plasma cells showing positivity for CD20. Plasma cells are λ light chain restricted and negative for κ light chains (C-F, immunohistochemistry, ×1000). Bone marrow involved by lymphoplasmacytic cells (case 15; G, hematoxylin and eosin, ×400), positive for cyclin D1 and PAX5 (H and I, immunohistochemistry, ×400).

The median OS for the entire cohort was 67 months (95% confidence interval, 9.7-124), and the 5-year OS was 48% (Fig. 4). Although the survival tended to be lower in men and patients of older age, or with higher International System for Staging stage and *TP53* alterations, the difference did not attain statistical significance likely because of a limited sample size.

## 4. Discussion

IgM PCM is an extremely rare disease with only a limited number of cases reported in the literature, as summarized in Table 4. Nevertheless, much of what we know about IgM PCM is based on studies focusing on morphology alone or patients treated heterogeneously [6,12,13,16]. Published cohorts are difficult to compare because of varying inclusion criteria used over the years. The current study represents the largest single-institution experience with IgM PCM patients.

The diagnosis of IgM myeloma can be challenging. Indeed, 5 patients in our study were considered initially having lymphoplasmacytic lymphoma (LPL)/Waldenstrom macroglobulinemia (WM) on clinical grounds. The presence of lytic bone lesions and the t(11;14)(q13;q32) were added to the selection criteria by Schuster et al [12] in 2010 to aid the exclusion of LPL/WM. However, this stringent approach will miss a portion of patients with less advanced disease [11,28] and will limit the opportunity to fully explore the spectrum of IgM PCM. The recent recognition of the role of *MYD88* and *CXCR4* mutations in LPL/WM is very helpful in the differential diagnosis, allowing for reliable exclusion of LPL/WM [19,28,29]. Similarly, in our study, all tested cases were negative for *MYD88* L265P mutation. In this study, lytic bone lesions were present in about 70% of patients, similar to the prevalence reported previously [6,16]. Four patients lacking bone lesions presented with at least one CRAB criterion and/or t(11;14). Those types of cases were defined in the study by Castillo et al [13] as "possible cases" and were shown to have similar laboratory characteristics and survival as the "definitive cases" (lytic lesions and/or t(11;14)), which supports the concept that lytic bone lesions and cytogenetics are not required criteria for IgM PCM [11].

Although lymphoplasmacytic morphology and t(11;14) are considered low-grade cytology and a standard risk factor, this group of patients had a propensity for leukemic dissemination and a risk of progression to high-risk plasmablastic PCM. Only 3 cases of IgM plasma cell leukemia have been reported

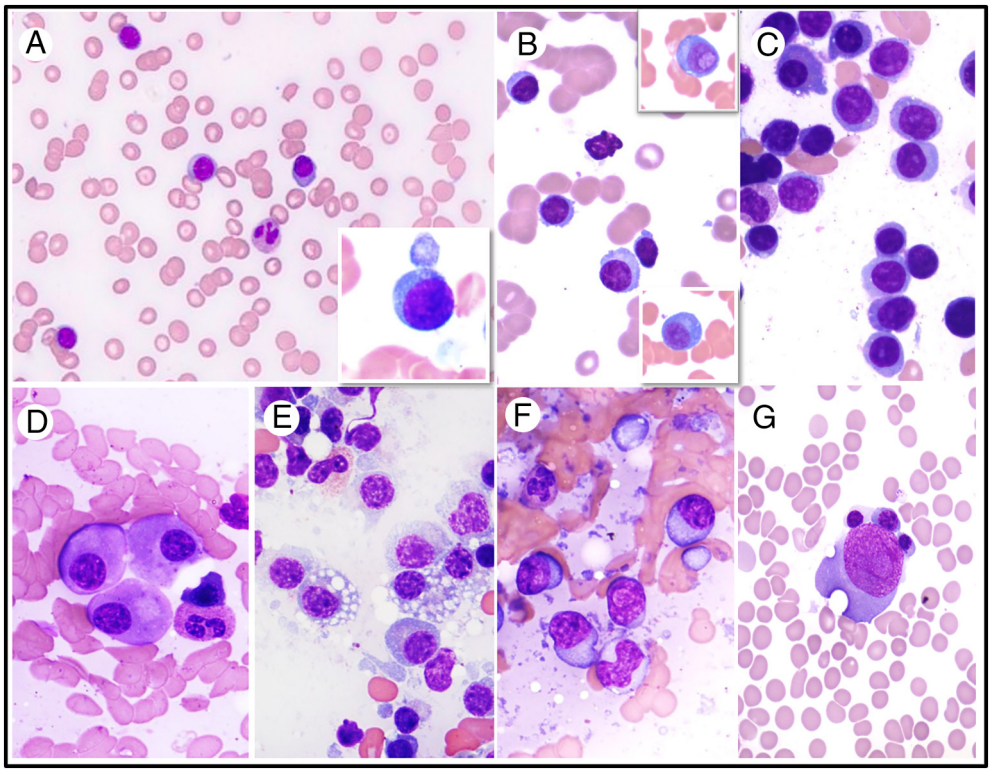


**Fig. 2** Morphologic variants of IgM PCM. Peripheral blood smear (case 15) showing circulating small plasma cells with lymphoplasmacytic morphology comprising 75% of total leukocytes (A, Wright-Giemsa, original magnification ×400; inset, 1000). B and C, Bone marrow aspirate smear showing plasma cells with various morphology. Mature plasma cells with lymphoplasmacytic morphology, some of which with perinuclear huff (B, lower inset) and small intranuclear inclusions (B, upper inset), can be appreciated. D, Mature plasma cells with abundant cytoplasm. E, Plasma cells with cytoplasmic globules (Russell bodies). F, Atypical plasma cells with increased nuclear-to-cytoplasmic ratio and prominent nucleoli. G, Large plasmablast with immature chromatin and prominent nucleolus (B-G, Wright-Giemsa, ×1000).

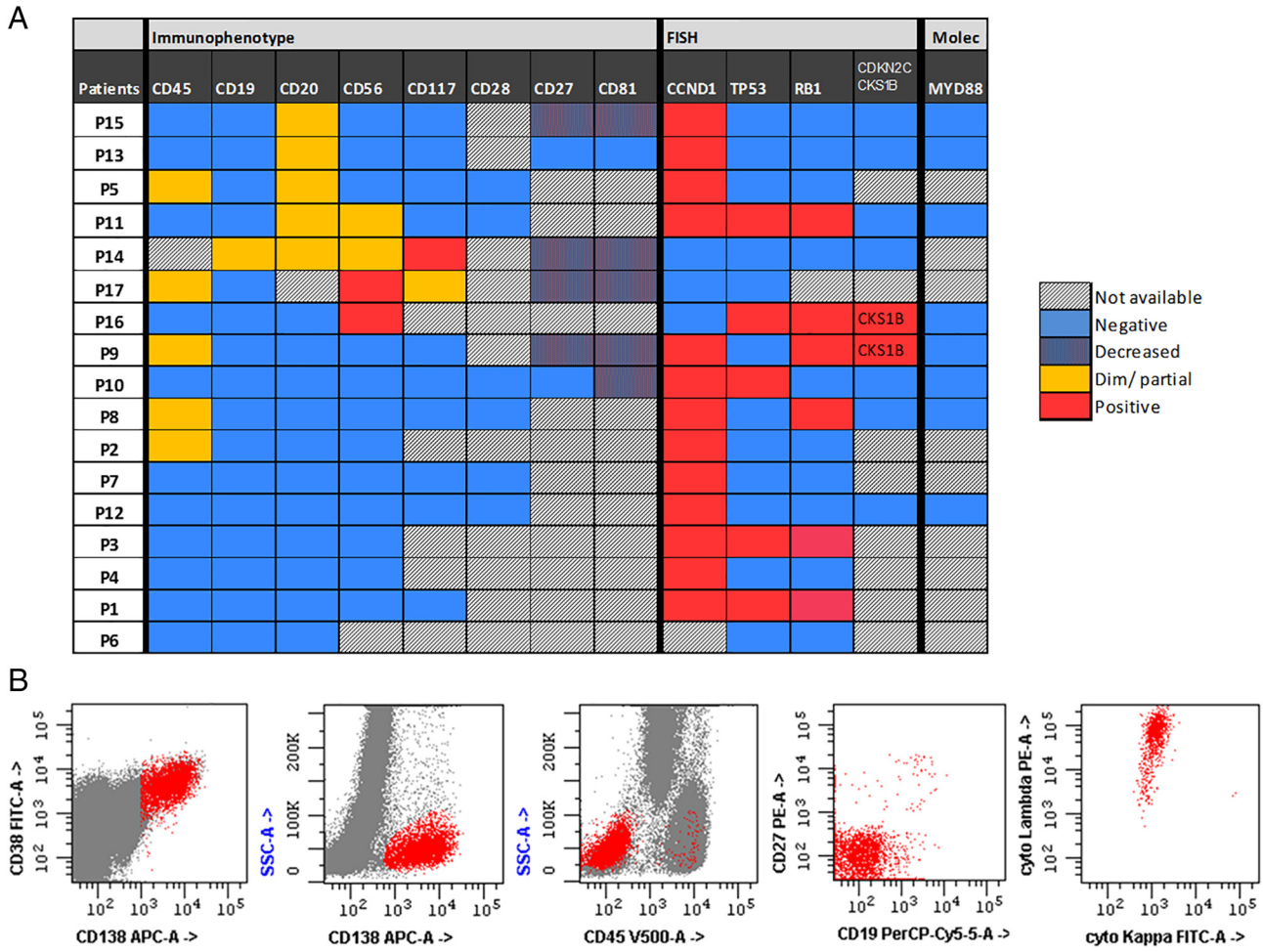


**Fig. 3** A, Immunophenotypic profile, and cytogenetic and molecular findings of IgM myeloma cases. The colored boxes for FISH indicate alterations for *CCND1*/*IGH* rearrangement, *TP53* deletion, *RB1* deletion, *CKS1B* gain/amplification, and deletion of *CDKN2C*. B, Flow cytometry immunophenotyping of a representative IgM myeloma case. The neoplastic plasma cells are cytoplasmic λ light chain$^{+}$/CD138$^{+}$/CD38$^{+}$/CD45$^{-}$/CD19$^{-}$/CD27$^{-}$.

in the literature, all of which were primary disease [15,20,26]. In this study, we report significant numbers of circulating plasma cells in 4 patients, 2 at initial diagnosis and 2 at leukemic transformation. The prevalence of IgM plasma cell leukemia in our study is comparable with 12.5% prevalence reported by Avet-Loiseau et al [15], but much higher than the 2% to 4% reported for all PCM cases [30]. Those findings suggest underlying aggressive disease biology [31]. Notably, all patients with circulating plasma cells in this study showed lymphoplasmacytic morphology and a high association with t(11;14) as described in plasma cell leukemia [30]. Thorough review of peripheral blood smear for all patients with IgM PCM is strongly recommended, especially in those with lymphoplasmacytic morphology, leukocytosis, and an elevated LDH [30].

The neoplastic plasma cells in IgM PCM displayed an immunophenotype that differs from the immunophenotype of IgM-secreting B-cell lymphomas. In IgM PCM, the plasma cells universally express CD38 and CD138. Unlike plasma cells in B-cell lymphoma in which CD19 and CD45 are

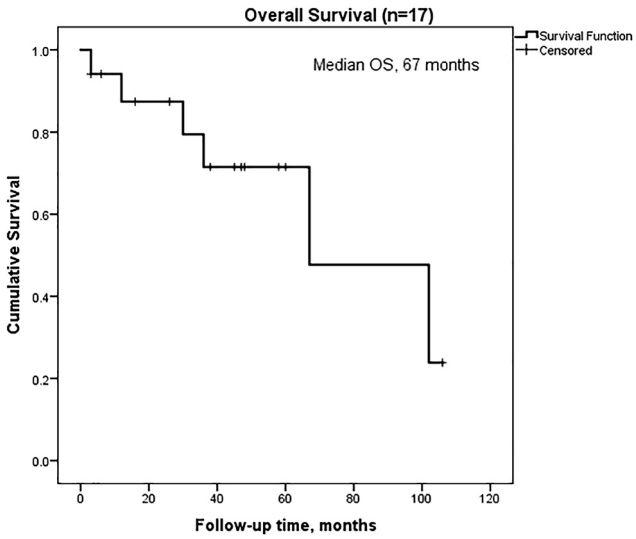


**Fig. 4** The OS probability for the series (n = 17).

**Table 4** Studies and case reports of IgM myeloma published in the English literature (1999-2018)

| Study | No. of cases | Age (y), M/F | IgM (g/dL) | Hgb (g/dL) | Ca (mg/dL) | BM PC (%) | Bone lesions |
|---|---|---|---|---|---|---|---|
| Kondo and Yokoyama [5] | 1 | 85F | 2.1 | 9.0 | 8.2 | 5 | Present |
| Dierlamm et al [14] | 4 | 56.5 (52-70), 3:1 | 2.69 (0.7-6.1) | | 1/4 high levels | 18 (5-80) | 2/4 (50%) |
| Avet-Loiseau et al [15] | 8 | 68 (53-85) | | NA | NA | 27 (11-59) | 4/9 (44%) |
| Annibali et al [4] | 4 | 67.5 (44-72), 2:2 | | 9.8 (9.4-11.2) | 9.2 | 30 (16-60) | 2/4 (50%) |
| Oka et al [20] | 1 | 67F | 4.6 | 6.7 | Normal | 60 | No |
| Tahan et al [21] | 1 | 83F | 3.6 | Normal | Normal | 20 | Present |
| Feyler et al [16] and Ackroyd et al [22] | 10 | 71 (54-83), 5:5 | 1.9 (0.5-8.7) | NA | NA | 49 (14-70) | NA |
| Morris et al [7] | 72 | 56.2 | NA | 9.35 | 11.0 | NA | NA |
| Reece et al [8] | 11 | 58 (29-64), 4:7 | NA | <10 (27%) | NA | NA | 9/9 (100%) |
| Owen et al [11] | 2 | 64F, 72F | | | | | 1/2 |
| Cabrera et al [23] | 3 | 69-78, 2:1F | 0.62; 2.2 | 8.2-11.7 | 7.9-13.6 | 14-40 | 1/3 |
| Schuster et al [12] [b] | 21 | 66 (51-71) | 4.7 (0.2-11.4) | 10.2 (6.1-13.3) | 10.4 (8.5-14.4) | 50 (20-100) | 100% (see criteria) |
| King et al [6] [b] | 15 | 65 (48-76) | 2.6 (0.3-5.1) | 10.4 (7.5-12.7) | 9.9 (8.5-14.6) | 55 (10-95) | 10/15 (67%) |
| Ryu et al [24] | 2 | 61 and 70 | 2.2-3.9 | NA | 10.2-10.3 | 30 | NA |
| Greuter et al [25] | 1 | 41M | 4.9 | 15 | 9.04 > > 11.0 | 12 | No |
| Castillo et al [13] | 134 | 65.5 (37-86), 1.9:1 | 2.9 (0.3-12.1) | Hgb < 10 (37%) | Elevated Ca (19%) | NA | 87/128 (70%) |
| Chhabra et al [26] | 1 | 68F | 6.5 | 12 | 13.2 | 90 | No |
| Bonilla-Valentin et al [27] | 1 | 64M | 2.1 | 12.3 | High | 24 | Present |
| Present study | 17 | 63 (42-79), 11:6 | 6.4 (0.7-12.1) | 9.25 (5.3-11.7) | 10.6 (9.7-16) | 80 (20-95) | 12/17 (71%) |

| LAD | t(11;14) | Other CG and molecular abnormalities | Immunophenotype | Cytomorph |
|---|---|---|---|---|
| Yes | NA | NA | NA | LP |
| No | 1/1 Neg | NA | NA | Mature |
| NA | 7/8 (87%) | | Limited:<br>$CD19^+$ (50%)<br>$CD22^-$ (100%) | Small cell, mature |
| 1/3 | NA | NA | NA | NA |
| No | | Complex karyotype including −13 and −17 | $CD20^+$, $CD56^-$ | Mature |
| No | NA | NA | $CD20^-$, $CD19^-$, $CD56^-$, $CD45^-$ | NA |
| NA | 5/8 (63%) | Del 13q (50%)<br>1/8 t(4;14)<br>IGH rear 100% | $CD20^-$, $CD56^-$, $CD117^-$ | NA |
| NA | NA | NA | NA | NA |
| NA | NA<br>1/2 | NA<br>1/2 t(14;16)<br>2/2—13 monosomy | NA<br>$CD19^-$, $CD56^-$, $CD27^+$, $CD45^+$, $CD20^-$, cyD1$^+$ $PAX5^-$<br>and<br>$CD19^-$, $CD56^-$, $CD27^-$, $CD45^+$, $CD20^-$ | NA<br>NA |
| NA | 0/2 | NA | $CD19^-$, $CD20^-CD56^-$(67%)<br>$CD117^-$, $CD27^-$, $CD45^-$ | NA |
| None (see criteria) | 6/16 (38%) | 1/21 t(4;14)<br>and 1/21 t(14;16) | Limited:<br>$CD20^+$ (25%) | NA |
| NA | 5/6 (83%) | NA | IHC: $CD19^+$ (67%); $CD20^+$ (40%); $CD45^+$ (47%), $CD117^+$ (20%) | LP (6/15, 40%) |
| NA | 2/2 (100%) | +3, +11, t(1;22)(q12;q13)<br>*DIS3* mutation<br>*IRF4* overexpression | NA | NA |
| No | Present | Loss of one copy of *MAF* (16q23), deletion of *FGFR* (4p16) | | |
| NA | 26/67 (39%) | Del(13q)—25/67 (33%)<br>Del (17p)—6/76 (8%) | Limited data<br>$CD20^+$ in 15/26 (58%)<br>Cyclin D1 10/15 (67%) | NA |
| No | Present | Complex karyotype, 1q amp, del 13q and *TP53*<br>*MYD88* neg | NA | NA |
| No | Present | *MYD88* neg | $CD20^-$, $CD56^-$, $CD117^-$ | Dutcher bodies; lymphocytes present ~25% |
| 12.5% | 81.3% | Complex karyotype 41%;<br>*TP53* 29%<br>*RB1* 38% | $CD20^+$ (31%) $CD56^+$ (25%), $CD117^+$ (17%) | Variable, LP in 47% |

(*continued on next page*)

**Table 4** (*continued*)

| Study | Tx | FU (mo) | Outcome | Criteria for diagnosis/patient selection |
|---|---|---|---|---|
| Kondo and Yokoyama [5] | Prednisone and melphalan | NA | NA | IgM paraprotein + CRAB |
| Dierlamm et al [14] | 1/4Chemo + ASCT<br>2/4 chemo with melphalan<br>1 observation only | 25 (16-60) | 1/4 DOD<br>2/4 SD [a]<br>1/4 CR | IgM paraprotein + CRAB |
| Avet-Loiseau et al [15] | NA | NA | NA | NR/NA<br>1/8 plasma cell leukemia |
| Annibali et al [4] | Melphalan-prednisone, RT, gemcitabine | 15 (4-31) | 3/3 PD | NA |
| Oka et al [20] | VAD and EDAP with rituximab | 20 | Alive | Plasma cell leukemia |
| Tahan et al [21] | CTD regimen + RT | 12 | PD | Multiple osseous and extraosseous plasmocytomas |
| Feyler et al [16] and Ackroyd et al [22] | NA | NA | NA | IgM paraprotein, BM PC >10%, absence of B-lymphoid component |
| Morris et al [7] | ASCT | NA | Med OS 44.7 mo | NA/post-ASCT |
| Reece et al [8] | Melphalan-based + ASCT | 58 (5-101) | 3-y OS 68% 5/11 dead | NA/post-ASCT |
| Owen et al [11] | NA | NA | NA | IgM paraprotein, BM PC >10%, absence of B-lymphoid component |
| Cabrera et al [23] | NA | NA | NA | IgM paraprotein + CRAB |
| Schuster et al [12] [b] | Various 87% received TLB at some point in the course of treatment<br>ASCT (38%) | NA | Median OS 30 mo | IgM paraprotein +<br>BM PC >10%, inclusion: lytic bone lesions and/or t(11;14)<br>Exclusion criteria: hyperviscosity, LAD, and splenomegaly |
| King et al [6] [b] | NA | NA | NA | IgM paraprotein + BM PC >10%, CRAB criteria and lack of B-lymphocyte disease |
| Ryu et al [24] | NA | NA | Alive | NA |
| Greuter et al [25] | CyBorD | 105 | Alive | IgM MGUS> IgM MM |
| Castillo et al [13] | Various regimens<br>ASCT 29% | 47 | Med OS 61 mo<br>5-y OS 52% (95% CI 40%-60%) | Multicentric (20 centers) clinical study<br>IgM paraprotein (regardless of size), BM PC >10%<br>Presence of lytic lesions and/or t(11;14) (definitive cases, n = 101)<br>No bone lesions or t(11;14) but at least 1 CRAB (probable, n = 33) |
| Chhabra et al [26] | VRD + ASCT | 19.5 | DOD | Primary plasma cell leukemia |
| Bonilla-Valentin et al [27] | VRD | 22 d | DOD | IgM paraprotein + CRAB |
| Present study | Novel agents in 94%<br>ASCT 65% | 38 | 6 DOD<br>1 DOC | IgM paraprotein, BM PC >10% and MDE, absence of B-lymphoid component |

usually expressed on CD138$^+$ plasma cells [32], cases in this study showed negative or dim CD45 (100%), negative CD19 (94%), decreased or negative expression of CD27 and CD81. In addition, aberrant CD56 or CD117 expression was observed in 25% and 17%, respectively, compared with 75% and 30%, respectively, in other subtypes of myeloma. Expression of these 2 markers, although at a lower frequency than other subtypes, helps to distinguish PCM from LPL/WM, which typically does not express these markers [23,33]. B-cell makers, such as CD19 and CD20, are usually dim/partial and rarely simultaneously expressed, further distinguishing IgM PCM from LPL/WM.

The revised International System for Staging for myeloma proposed recently by the IMWG considers chromosome abnormalities detected by FISH a key element in defining the biological features of PCM [9]. The t(11;14), a standard risk finding, was common in 81% of our patients, a frequency similar to previous studies [6,15,16]. However, a complex karyotype, an adverse risk factor [34], was noted in about 40% in our cohort, notably with t(11;14) as part of the complex karyotype. Other rare adverse risk factors such as t(4;14)/*FGFR3/MMSET-IGH* or t(14;16)/*MAF-IGH*, reported rarely in IgM PCM [11,12,22], were not observed in this cohort. Deletion of chromosome 17p13/*TP53* was also detected in about 30% of cases, with 2 cases as part of a complex karyotype [30].

Historically, IgM PCM patients fared poorly with a median survival of less than 3 years [4,12,16]. Outcomes have improved with IMIDs and PIs, as well as the widespread adoption of high-dose melphalan and ASCT [13,25,31]. In this cohort, almost two-thirds of patients underwent ASCT. A recent study comparing the outcomes of patients with unusual subtypes of PCM (IgD, IgE, and IgM) showed that the OS (45 months) is poor compared with common IgG and IgA PCM (62 months), even after ASCT [7]. Although the proportion of patients with IgM PCM achieving complete remission before transplantation was the lowest of all myeloma subtypes, the transplant seemed to be beneficial for complete and partial remission [7]. Novel agents were the most frequently used in our cohort as frontline therapy (77% of patients) or during the course of treatment (94% of patients). The median OS of the patients in this study was 68 months with a 5-year OS of 48%. Our results are in keeping with the recent study of Castillo et al [13] that included 134 patients of 20 centers and reported a median OS of 61 months and a 5-year OS of 52%. Despite improved survival compared with the pre–novel therapy era, a significant number of patients in this cohort required multiple regimens because of refractory/resistant disease, and the survival of this group is inferior to patients with other subtypes of PCM, especially those with t(11;14).

In summary, IgM PCM is an uncommon variant of PCM frequently associated with lymphoplasmacytic morphology and t(11;14). The aberrant expression pattern of plasma cells in IgM PCM (CD45$^-$/dim, CD19$^-$) differs from the pattern of plasma cells derived from B-cell lymphomas with plasmacytic differentiation. This feature, in conjunction with cyclinD1 expression or t(11;14), helps to establish the diagnosis in the appropriate clinical setting. Although cytologically low grade, this tumor has a high propensity for leukemic dissemination or progression to high-risk disease that coincides with t(11;14) detected in a background of a complex karyotype. Despite improved outcome since the introduction of novel therapy, a significant subset of patients suffers from refractory/resistant disease, highlighting a need for alternative strategies for this disease. These patients may benefit from Venetoclax, a BCL2 inhibitor that has been shown effective in myeloma with t(11;14).

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Notes to Table 4:

Abbreviations: BM, bone marrow; Ca, calcium; CI, confidence interval; CR, complete remission; CRAB criteria, hypercalcemia, renal dysfunction, anemia and bone lesions; CTD, cyclophosphamide, thalidomide and dexamethasone; CyBorD, cyclophosphamide + bortesomib + dexamethasone; DOC, dead of other cause; DOD, dead of disease; EDAP, etoposide, cisplatin, cytarabine, and dexamethasone; F, female; FU, follow-up; IHC, immunohistochemistry; LAD, lymphadenopathy; M, male; MDE, myeloma defining event; mo, months; NA, not assessed/not available; Neg, negative; LP, lymphoplasmacytic morphology; PC, plasma cells; PD, persistent disease; RT, radiotherapy; TLB, thalidomide, lenalidomide, bortezomib; VAD, vincristine-doxorubicin-dexamethasone; VRD, bortezomib, lenalidomide, dexamethasone.

[a] Some of those cases will be classified today as IgM MGUS.

[b] Significant overlap of patients included in the studies of Schuster et al [12] and King et al [6].

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