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Review

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IgM Myeloma: A Comprehensive Overview and Practical Approach to Chemotherapeutic Management

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Abstract

IgM myeloma is a rare subtype of multiple myeloma (MM) comprising 0.5% of all of its cases. It is characterized by the unregulated proliferation of IgM-secreting plasma cells in the bone marrow. The underlying pathogenesis involves dysregulation of isotype switch recombination, leading to various translocations involving chromosomes such as 11q13 and 4p16. Patients usually present with symptoms of hyperviscosity syndrome, bone marrow infiltration, and organomegaly. Diagnostic workup includes clinical evaluation, laboratory tests (electrophoresis, bone marrow biopsy, cytogenetics, immunohistochemistry), and imaging. Treatment options for IgM myeloma include proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and autologous stem cell transplantation. However, no clear management guidelines are established for this rare subtype of MM. This article provides an up-to-date detailed overview of the pathogenesis, clinical features, and diagnostics of IgM myeloma.

Keywords: Multiple myeloma; IgM myeloma; Management; Chemotherapy; IgM

Introduction

Multiple myeloma (MM) is an entity characterized by the clonal and neoplastic proliferation of plasma cells in the bone marrow. It is considered by the World Health Organization as a lymphoproliferative B-cell disease [1]. MM accounts for 1% of cancers worldwide and 10% of all hematological cancers [2, 3]. In 2018, the global age-standardized incidence of MM was 2.1 per 100,000 [4]. MM evolves on the basis of a premalignant precursor termed "monoclonal gammopathy of undetermined significance" (MGUS). MGUS is diagnosed incidentally in 3-5% of people above the age of 50. It then proceeds to progress to MM at a rate of 1% per annum [5, 6]. MGUS can occasionally progress to a transitional phase named smoldering myeloma, which has a higher risk of further developing into the overt and symptomatic MM [7]. In the first 5 years of diagnosing smoldering myeloma, the risk of it developing into MM is 10% per year [8]. The diagnostic criteria of the International Myeloma Working Group (IMWG), for each of the three gammopathies, are summarized in Figure 1 [9].

The underlying pathogenesis of MM is the result of the unregulated proliferation of antibody producing plasma cells, leading to the accumulation of high molecular weight proteins in the bone marrow and blood. Patients can present with the characteristic hypercalcemia, renal failure, anemia, bone lesions (CRAB) symptoms (Table 1) [9], in addition to symptoms of hyperviscosity syndrome such as bleeding, visual disturbances, and neurological deficits due to the accumulation of the heavy IgM proteins. Patients can also present with signs and symptoms that indicate bone marrow infiltration such as cytopenias and bone lesions [10]. The type of antibody secreted can result in a complex and heterogenous group of plasma cell disorders that include non-secretory MM, immunoglobulin G (IgG) MM, immunoglobulin A (IgA) MM, and the exceedingly rare, immunoglobulin M (IgM) MM [11]. IgM MM, also known as IgM myeloma, is a subtype of MM that constitutes 0.5-1% of myeloma cases [12]. The diagnosis of IgM myeloma is defined by IMWG and is based on the presence of IgM monoclonal protein in the serum and/or urine, along with evidence of bone marrow involvement by malignant plasma cells (Table 1) [10].

IgM MM has significant clinical challenges, with most data derived from small series and case reports. Additionally, distinguishing IgM myeloma from Waldenstrom macroglobulinemia (WM) remains a recurrent difficulty [12]. This review aims to provide a comprehensive synthesis of the current literature on its pathogenesis, clinical presentation, diagnostic criteria, and therapeutic strategies. We also highlight key distinctions between IgM myeloma and other IgM gammopathies, particularly WM, to aid in accurate diagnosis. Our objective is to consolidate available data for clinicians managing this rare subtype of MM.

Methodology

We conducted a comprehensive literature review using Pub-

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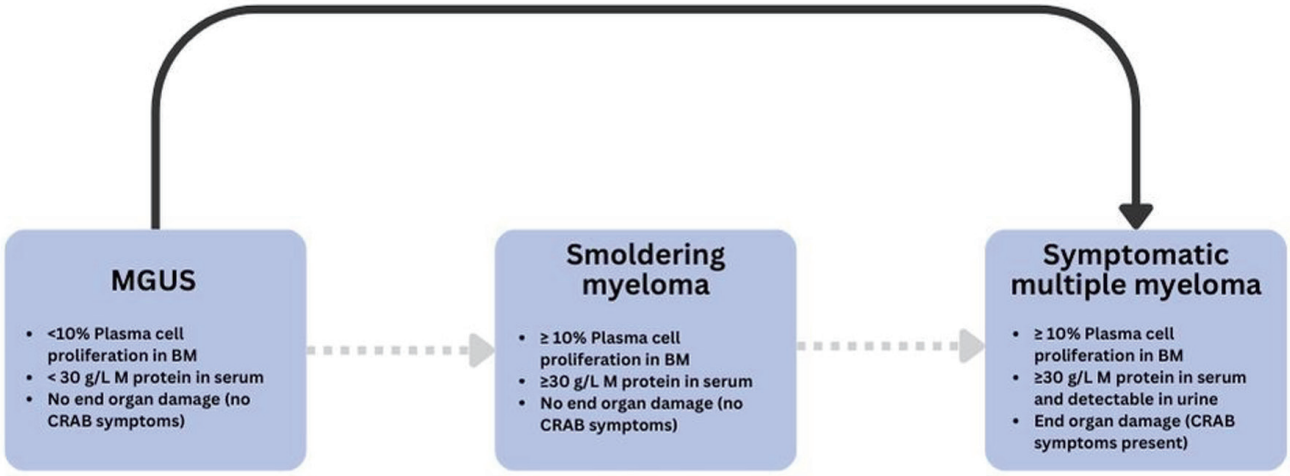

Figure 1. Progression and diagnostic criteria across the monoclonal gammopathy spectrum. Schematic overview of MGUS, smoldering myeloma, and symptomatic multiple myeloma with key thresholds (clonal plasma cells in bone marrow, serum M-protein) and CRAB/end-organ damage criteria [9]. BM: bone marrow; CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions; MGUS: monoclonal gammopathy of uncertain significance.

Med and Web of Science databases supplemented by referencing management software for article screening and citation management. Keywords including "IgM Multiple Myeloma", "IgM Myeloma", "Multiple myeloma", "gammopathies", and "monoclonal gammopathy" were employed resulting in 1,842 studies. Filters were applied to include only articles published in English, observational studies, systematic reviews, case reports, and case series within the past 10 years yielding 103 studies out of the originally obtained 1,842. Two independent reviewers (FE and RF) screened the 103 remaining articles based on screening of titles, abstracts, and full texts. Discrepancies between reviewers were resolved through discussion, and if consensus was not reached, a third reviewer (HE) served as adjudicator. A total of 49 studies were finally included (Table 2, Fig. 2).

Pathophysiology

The most frequent karyotypic alteration in IgM myeloma involves translocations at the immunoglobulin heavy chain (IgH) locus, located at 14q32. This locus is highly transcriptionally active in B and plasma cells, so transferring an oncogene to 14q32 will cause dysregulation. Errors during class-switch recombination or somatic hypermutation can generate these IgH translocations [13].

Table 1. Revised IMWG Diagnostic Criteria for MM (Adapted From IMWG Guidelines [9])

CRAB criteria				Any one or more of the following biomarkers of malignancy		
Elevated calcium: Serum calcium level > 0.25 mmol/L (or > 1 mg/dL) above the normal upper limit, or an absolute value exceeding 2.75 mmol/L (11 mg/dL)	Kidney dysfunction: Estimated creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (2 mg/dL)	Anemia: Hemoglobin more than 20 g/L below the lower reference limit or total hemoglobin < 100 g/L	Skeletal involvement: One or more osteolytic lesions identified on skeletal survey, CT, or PET-CT	Clonal plasma cells ≥ 60% in bone marrow	Serum free light chain ratio ≥ 100 (involved/uninvolved chains)	More than one focal lesion on MRI studies

The diagnosis requires either clonal plasma cells comprising 10% or more of the bone marrow, or a confirmed biopsy of a bony or extramedullary plasmacytoma, along with at least one of the following defining features of multiple myeloma. CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions; IMWG: International Myeloma Working Group; MM: multiple myeloma; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography.

Table 2. Summary of Literature Review Process

Stage	Number of articles
Records identified through database search (PubMed and Web of Science)	1,842
Titles and abstracts screened	103
Studies included in final review	49

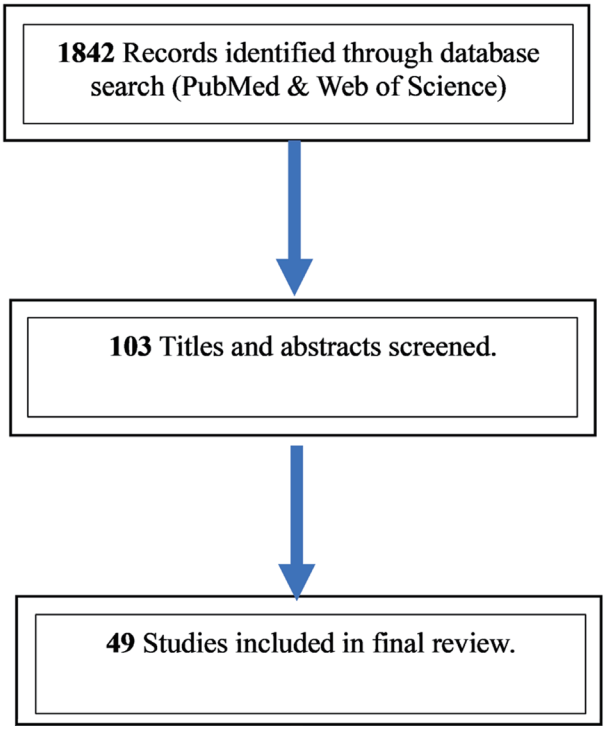

Figure 2. PRISMA-style study selection for the IgM myeloma review. Database searches of PubMed and Web of Science (English, human studies, last 10 years) identified 1,842 records; 103 full texts were assessed after limits/de-duplication; 49 studies were included in the qualitative synthesis.

In IgM myeloma, IgH translocations mirror those seen across MM, most commonly t(11;14)(q13;q32) with CCND1 activation, and less frequently t(4;14)(p16;q32) (involving FGFR3/NSD2) and t(14;16)(q32;q23) (MAF); rarer t(6;14) events may involve IRF4/MUM1 or CCND3. Across published cohorts, the prevalence of t(11;14) in IgM myeloma is about 40% in multicenter series and 60-80% in small, focused cohorts, reflecting methodological and population differences [13-19]. Immunophenotypically, IgM-myeloma plasma cells typically lose CD19, CD27, and CD45, with frequent aberrant expression of CD56, CD20, CD117, and cyclin D1, the latter two being enriched in t(11;14) disease. In the same series [18], involving 134 patients, CD20 expression was positive in 58% of the cases evaluated. Cyclin D1 expression was observed in approximately two-thirds of the cases. These features overlap with other MM isotypes; therefore, immunophenotyping should be interpreted alongside cytogenetics and clinical context (Fig. 3) [20].

In contrast, WM shows a lymphoplasmacytic phenotype with retention of B-cell antigens (e.g., CD19, CD20) and a distinct genetic profile; critically, IgM myeloma is typically MYD88 L265P-negative, which supports its separation from WM (see section "Diagnostics") [21, 22].

Clinical Features

The median age of presentation and diagnosis of IgM myeloma is reported to be 65 years, with a male-to-female ratio of 2:1. The typical myeloma symptoms such as hypercalcemia, renal failure, and anemia are equally common in IgM myeloma as it is in other types of myelomas [18, 23, 24]. Lytic bone findings are also seen with IgM myeloma and are part of the diagnostic criteria [25]. This was demonstrated in a retrospective study done on 134 patients, where the median age at diagnosis was 65.5 years. Males had a higher predominance than females (68%) and the typical myeloma features such as anemia, elevated serum calcium levels, renal dysfunction, and skeletal lytic lesions were found in 37%, 43%, 19%, and 70% of patients, respectively [18].

In the same study [18], hyperviscosity has been more commonly reported in IgM myeloma in comparison to the other myeloma types, which is likely due to the unique biophysical properties of IgM antibodies. IgM is a pentameric immunoglobulin with a molecular weight of about 970 kDa, significantly larger than IgG or IgA. This structural characteristic increases serum viscosity even at relatively modest monoclonal protein levels. In contrast to IgG MM, where viscosity usually rises only when paraprotein levels exceed 4 - 5 g/dL, patients with IgM paraprotein may develop symptomatic hyperviscosity (e.g., visual disturbances, mucosal bleeding, neurologic changes) at lower concentrations. This phenomenon is also prominent in WM but is mechanistically relevant to IgM MM as well, due to the same immunoglobulin class [26].

Additionally, acquired von Willebrand disease (aVWD) has been documented in IgM myeloma, likely caused by the adsorption and clearance of von Willebrand factor by the monoclonal IgM paraprotein, contributing to bleeding diatheses [27].

Organomegaly is a feature more commonly reported in other types of gammopathies, specifically WM. However, some IgM myeloma patients can also present with organomegaly as reported in Avet-Loiseau et al, where a prevalence of organomegaly in 25% (two out of eight) was reported [21]. Lymphadenopathy and hepatosplenomegaly may be present in some patients, as reported by De Gramont et al and Zarrabi et al, although these symptoms are typically more common in lymphoma than in myeloma [28, 29]. Histopathologically, IgM myeloma is characterized by a pure plasmocytic morphology, which differentiates it from WM, which has a lymphoplasmacytic morphology [17, 30].

Diagnostics

It is essential to distinguish IgM myeloma from other monoclonal gammopathies, as the management approach differs significantly from other types (Table 3) [18, 19, 30, 31].

The distinction between IgM myeloma and other IgM-related gammopathies, particularly WM is essential due to their divergent biology, clinical behavior, and treatment. IgM myeloma typically shows a pure plasmacytic morphology, lytic bone lesions, hypercalcemia, renal dysfunction, and the absence of organomegaly, features that are rare in WM. Immunophenotypically, IgM myeloma frequently lacks normal B-cell markers such as CD19 and CD20 and instead exhibits

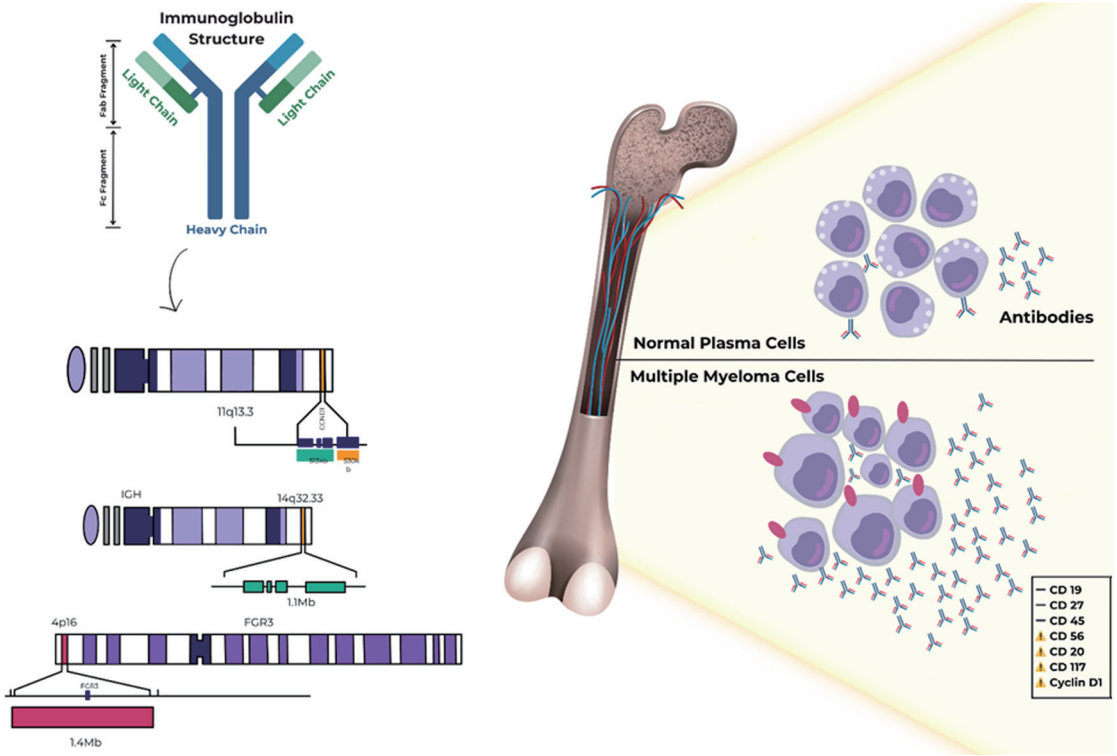

Figure 3. Immunophenotype and IGH translocations in IgM myeloma. Common IGH rearrangements at 14q32 (e.g., t(11;14) → CCND1, t(4;14) → FGFR3/NSD2, t(14;16) → MAF; rarer t(6;14) → IRF4/MUM1/CCND3) and representative immunophenotype of IgM myeloma plasma cells: loss of CD19/CD27/CD45 with aberrant CD56/CD20/CD117/cyclin D1. IGH: immunoglobulin heavy chain; WM: Waldenstrom macroglobulinemia.

aberrant expression of CD56 and cyclin D1, especially in the presence of the t(11;14) translocation. In contrast, WM characteristically retains B-cell markers and has a lymphoplasmacytic morphology. A pivotal molecular distinction is the absence of the MYD88 L265P mutation in IgM myeloma, which is present in over 90% of WM cases. This mutation serves as a critical biomarker that helps differentiate between the two entities in diagnostically challenging cases. Additionally, WM often presents with organomegaly and hyperviscosity, whereas IgM myeloma is more commonly associated with skeletal involvement and CRAB symptoms [19, 31].

In addition to plasma-cell IgM myeloma and WM, IgM gammopathies include IgM MGUS and IgM MGCS. IgM MGUS is defined by an asymptomatic circulating IgM M-protein < 30 g/L with < 10% lymphoplasmacytic marrow infiltration. Its natural history is indolent, with a progression risk of about 1.1 events per 100 person-years (most commonly to lymphoma/chronic lymphocytic leukemia (CLL)/AL amyloidosis); notably, in the largest series (n = 210), no patients progressed to plasma-cell IgM myeloma. IgM MGCS denotes

Table 3. Differential Diagnoses of IgM Myeloma

Differential diagnosis	Monoclonal IgM in serum	Bone marrow findings	Clinical features	MYD88 L265P mutation
IgM myeloma	Positive	≥ 10% pure plasmocytic morphology	Lytic bone lesions, hypercalcemia, renal failure, anemia	Absent
WM	Positive	≥ 10% lymphoplasmacytic morphology	Hyperviscosity is more common	Present in > 90% of cases
AL amyloidosis	positive	< 20% plasma cells	Pulmonary symptoms, polyneuropathy, lymphadenopathy	Typically absent
IgM MGUS	< 3 g/dL	< 10%	Asymptomatic	Variable
Other IgM-related disorders	Positive	Typically absent	Cold-induced symptoms (e.g., Raynaud's, acrocyanosis), neuropathy	Variable

Adapted from Castillo et al [18], Schuster et al [19], Owen et al [30], and Treon et al [31]. IgM MGUS: IgM monoclonal gammopathy of undetermined significance; WM: Waldenstrom's macroglobulinemia.

Table 4. ISS for Multiple Myeloma and Estimated Median Survival

ISS stage	Criteria	R-ISS additional criteria	Estimated median survival (years)
I	Sβ2M < 3.5 mg/L; serum albumin ≥ 3.5 g/dL	ISS I + standard-risk cytogenetics + normal LDH	> 8 years
II	Sβ2M < 3.5 mg/L; serum albumin < 3.5 g/dL; or β2M 3.5 to 5.5 mg/L, irrespective of serum albumin	Does not meet I or III.	about 6 years
III	Sβ2M ≥ 5.5mg/L	ISS III + (high-risk cytogenetics OR elevated LDH)	about 3 years

Standard-risk cytogenetics = absence of del(17p), t(4;14), or t(14;16). High-risk cytogenetics = presence of del(17p), t(4;14), and/or t(14;16). Adapted From International Staging System for Multiple Myeloma [39, 44]. β2M: β2 microglobulin; Sβ2M: serum β2 microglobulin; ISS: International Staging System; LDH: lactate dehydrogenase.

IgM-mediated organ damage (e.g., neuropathy, cryoglobulinemia, cold agglutinin disease (CAD)) without meeting criteria for WM or myeloma; management targets the IgM-driven pathology [32].

To establish a definitive diagnosis, bone marrow morphology and immunophenotypic analysis are essential to establish a definitive diagnosis. The diagnostic workup typically begins by taking a focused history and physical examination, looking for possible features of organomegaly, a history of bone pain, and features of amyloidosis such as heart failure, chronic diarrhea, and orthostatic hypotension. Consequently, specific tests are conducted to help in ruling out differential diagnoses for IgM myeloma such as WM, IgM MGUS, IgM amyloidosis, and IgM-related disorders such as IgM neuropathies, cryoglobulinemia (type I and type II), CAD, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, Schnitzler syndrome, pyoderma gangrenous, scleromyxedema, and monoclonal gammopathy of renal significance [19, 30, 33-37].

Electrophoresis is used as an initial screening test in patients with suspected myelomas. After establishing a possible diagnosis of a monoclonal gammopathy, unilateral bone marrow aspirate and biopsy, including immunohistochemistry and/or flow cytometry, and cytogenetics are done next. Fluorescence *in situ* hybridization (FISH) is often utilized to reveal chromosomal abnormalities such as the translocations described before. Immunohistochemistry is also used to detect myeloma surface cell markers, which helps in differentiating IgM myeloma from other gammopathies [38]. When evaluating patients with suspected IgM-related disorders, special attention must be paid to cryoglobulin detection, which requires samples to be taken in pre-warmed tubes and maintained at 37 °C until serum separation to prevent precipitation and false-negative results. Even minimal amounts of measurable cryoglobulin may result in symptoms, and repeat testing is indicated if clinical suspicion remains high [32].

Since most MM patients have bone involvement, imaging techniques such as skeletal bone survey are considered to be the standard diagnostic approach in diagnosing lytic bone disease in MM [39]. However, skeletal bone surveys have their own limitations; in order for it to detect osteolytic lesions, 30% of the bone cortex should have been destroyed by the time of diagnosis [40]. ^{18}F-FDG-PET/CT, multidetector computed tomography (MDCT), and low-dose computed tomography (LDCT) have shown to be superior in diagnosing MM bone disease than skeletal bone surveys [41-43].

The diagnosis of IgM myeloma currently requires the detection of IgM monoclonal gammopathy, at least 10% plasma cells in a bone marrow biopsy, and the presence of lytic bone lesions and/or the t(11;14) translocation identified through FISH [18, 39]. Additionally, the expression of cyclin D1, the presence of the t(11;14) translocation, and the absence of the MYD88 L265P gene mutation can aid in distinguishing IgM myeloma from WM [18].

Prognosis

The International Staging System (ISS) is a staging system established by the IMWG in 2005 to classify MM based on several prognostic factors (Table 4) [39, 44].

The ISS is based on two variables, serum albumin and β2-microglobulin, which have proved to be reliable predictive factors for survival. This system was developed in North America, Europe, and Asia, in patients younger and older than age 65 years, and with standard therapy or auto transplant where it continued to display effectiveness [44]. This system was compared to the Durie-Salmon Staging System, which was developed in 1975, and it was found to remain effective [45]. A revised version of the ISS was then introduced in 2015, and it incorporated additional risk stratifiers such as cytogenetic abnormalities and lactate dehydrogenase (LDH) [44]. The prognosis of IgM myeloma specifically depends on the ISS stage and the clinical condition of the patient [46]. Castillo et al reported a more ominous prognosis in IgM myeloma compared to other types of myelomas. The same study suggested that factors like advanced age, female sex, and a high ISS may be associated with worse outcomes, even though there are limited data on whether IgM myeloma has disease-specific prognostic factors compared to other monoclonal gammopathies. Notably, patients classified as ISS stage III had a median survival of approximately 30 months, whereas those in stages I and II often lived more than 5 years [18].

Therapeutic Management

Due to the rarity of IgM myeloma, most therapeutic recommendations are extrapolated from studies of broader MM

populations. Specific clinical trials exclusively evaluating IgM MM are lacking; thus, treatment strategies are adapted from the standard-of-care approaches used in other MM subtypes.

Front-line induction

Treatment strategies for IgM myeloma follow standard MM protocols with induction therapy consisting of triple or quadruple therapy (steroids, proteasome inhibitors, immunomodulators, monoclonal antibodies), followed by hematopoietic stem cell transplant depending on cytogenetic findings and transplant eligibility, then maintenance therapy [18, 22]. This management differs from WM management, which is based on the symptoms and depends on emergent plasmapheresis for hyperviscosity when IgM levels exceed 4,000 mg/dL, along with rituximab-based therapies or Bruton's tyrosine kinase (BTK) inhibitors as first-line treatment [22].

Immunomodulatory drugs (IMiDs)

IMiDs, like thalidomide (thal) and lenalidomide (len), have demonstrated efficacy in treating IgM myeloma. Both thalidomide and its structural derivative, lenalidomide, are used to treat various illnesses. They exert their antimyeloma activity through multiple, now partially elucidated mechanisms. A key pathway involves binding to the cereblon (CRBN) E3 ubiquitin ligase complex, leading to targeted degradation of transcription factors Ikaros (IKZF1) and Aiolos (IKZF3), which are critical for myeloma cell survival. Additionally, IMiDs enhance T-cell and natural killer (NK) cell activation, inhibit regulatory T cells, suppress pro-inflammatory cytokine production, and exert anti-angiogenic effects within the tumor microenvironment [47, 48].

Lenalidomide plus dexamethasone has shown deep and durable responses in non-IgM MM, achieving ≥ 50% serum M-protein reduction in approximately 90% of patients in early and larger trials [49, 50]. Although direct data in IgM myeloma are limited, retrospective studies suggest similar benefit in this subgroup [18].

Moreover, lenalidomide and thalidomide's ability to boost interleukin (IL)-2 production and suppress IgM secretion supports their rationale for use in IgM myeloma. The trend is moving towards substituting thalidomide/dexamethasone with lenalidomide/dexamethasone, with some guidelines even proposing lenalidomide monotherapy [51, 52].

Anti-CD38 monoclonal antibodies

Daratumumab, a monoclonal antibody targeting CD38, has become a significant treatment option for resistant or relapsed MM. Recent data from large-scale phase III trials have reshaped the first-line therapy for transplant-eligible and ineligible MM patients. The PERSEUS trial demonstrated that adding subcutaneous daratumumab to VRd (D-VRd) significantly improved progression-free survival (PFS), depth of response (complete response or better), and minimal residual disease (MRD) negativity rates compared to VRd alone. The estimated 48-month PFS rates were 84.3% for D-VRd versus 67.7% for VRd [53]. Additionally, the CEPHEUS trial demonstrated that the D-VRd regimen also led to a significantly deeper and more durable increase in MRD negativity, higher rates of complete response or better, and a 43% lower risk of progression or death compared to VRd alone [54]. Consequently, quadruplet therapy is now increasingly adopted as the global standard of care for newly diagnosed MM. While these data are not specific to IgM myeloma, the principles are likely applicable and support the inclusion of CD38-targeted therapies in front-line regimens when available.

Relapsed/refractory disease and targeted therapy (t(11;14))

In the context of innovative treatments, venetoclax has become the first approved selective B-cell lymphoma 2 (Bcl-2) inhibitor in its class, particularly beneficial for MM patients carrying the t(11;14) (q13; q32) translocation. Venetoclax monotherapy has shown effectiveness in treating relapsed/refractory multiple myeloma (RRMM). However, combining venetoclax with dexamethasone, in the presence or absence of bortezomib, has demonstrated even greater efficacy [55, 56]. The BELLINI trial, a phase III study assessing venetoclax in combination with bortezomib and dexamethasone, demonstrated improved PFS, particularly in patients harboring the t(11;14) translocation. However, an unexpected increase in treatment-related mortality, primarily due to infections in the overall study population, prompted the FDA to place a partial clinical hold on venetoclax trials in MM. Subsequent analyses clarified that this increased mortality was not observed in the t(11;14) subgroup, who derived the most benefit and had acceptable safety outcomes. Accordingly, venetoclax use in MM, including IgM MM, should be restricted to carefully selected t(11;14) patients, with attention to infection risk [56, 57]. Case experiences with venetoclax/carfilzomib/dexamethasone (VenKD) show rapid responses but relapses in some individuals within months [58].

T-cell-redirecting therapies

Historically labeled as "novel agents," bortezomib, lenalidomide, and thalidomide revolutionized multiple myeloma therapy in the early 2000s. However, this terminology has become outdated given the emergence of more recent immunotherapies that have substantially reshaped the treatment landscape. These include bispecific T-cell engagers such as teclistamab, talquetamab, and elranatamab, as well as chimeric antigen receptor (CAR) T-cell therapies like idecabtagene vicleucel and ciltacabtagene autoleucel, which are now incorporated into international treatment guidelines for RRMM. These agents have demonstrated high response rates in heavily pretreated patients and are increasingly considered earlier in the treat-

ment algorithm [59-61]. Bispecific antibodies such as teclistamab (targeting BCMA and CD3) have shown response rates of about 63% in patients with RRMM [59], while CAR T-cell therapies like idecabtagene vicleucel and ciltacabtagene autoleucel have demonstrated overall response rates of 70-97%, including durable remissions in some cases [62, 63]. However, their application to rare subtypes like IgM myeloma remains largely theoretical due to a lack of subtype-specific data.

Autologous stem cell transplantation (ASCT)

In transplant-eligible patients, the contemporary standard mirrors other MM isotypes: induction therapy followed by ASCT and post-transplant maintenance. Induction typically comprises triplet or quadruplet regimens such as bortezomib, lenalidomide, and dexamethasone (VRd), or combinations incorporating monoclonal antibodies like daratumumab. Indeed, daratumumab-based quadruplets have become front-line standard-of-care regimens in many parts of the world, including both standard- and high-risk patients, as supported by the CASSIOPEIA (D-VTd), GRIFFIN (D-VRd), and MAIA (D-Rd in transplant-ineligible) trials [64-66]. In our setting, the availability and reimbursement of daratumumab may currently limit its use primarily to high-risk patients or those with relapsed/refractory disease. Nonetheless, we acknowledge its global role in first-line treatment and encourage its integration as access improves.

Regarding ASCT, it remains the cornerstone of therapy for eligible patients and is associated with improved PFS. While transplant-related risks exist, they are generally low in contemporary practice (< 1-2%) and outweighed by the survival benefits conferred in properly selected patients. Long-term outcomes are optimized when patients achieve deep responses prior to transplant, and post-ASCT maintenance further enhances durability [67]. Factors influencing ASCT success include patient-specific and biological variables, such as baseline albumin, β2-microglobulin levels, and chemotherapy sensitivity [68, 69]. The type of M-protein present at transplantation is a reliable indicator of the effectiveness of initial chemotherapy, impacting the likelihood of achieving a complete remission after ASCT [70]. Some studies propose that double transplantation may be more beneficial in treating patients with MM or preventing relapses compared to single transplantation [71]. Following ASCT, patients experience a good quality of life, with some requiring only maintenance therapy rather than sequential chemotherapy [72]. The DETERMINATION trial, a randomized trial, focuses on the importance of individualizing the management strategies for MM patients. It shows that VRd therapy followed by early ASCT provides a PFS advantage; however, overall survival rates do not significantly differ whether ASCT is performed early or delayed. This concludes that the management should be tailored according to several factors including patient preferences and disease characteristics [73]. Notably, the last 15 to 20 years have seen significant advancements in treating IgM myeloma. The current protocol for transplant-eligible patients includes induction, stem cell mobilization, and ASCT, followed by maintenance or consolidation [72].

Historical outcomes context

Earlier series reported limited complete responses with conventional chemotherapy and a median survival of about 3 years in IgM MM [68]. In a cohort transplanted between 1997 and 2006 following ≥ 2 chemotherapy cycles (n = 122; including one IgM case among predominantly IgG/IgA subtypes), resistance to older regimens supported high-dose therapy with ASCT as the standard for fit patients < 65 years with adequate organ function [68, 74].

Supportive Management

Supportive strategies for IgM myeloma mirror standard MM practice; major guidelines do not distinguish by heavy-chain isotype. Care should include risk-adapted infection prophylaxis, structured skeletal management, evidence-based analgesia, and targeted treatment of anemia [75].

Infections remain a major driver of early morbidity and mortality in MM, with the highest risk in the first months after starting therapy. However, there are no IgM-specific data, so recommendations are extrapolated from general MM guidance [75]. For newly diagnosed patients beginning induction, a time-limited 12-week course of oral levofloxacin can be considered to reduce febrile episodes and early deaths, with no routine extension beyond 12 weeks (TEAMM trial) [76]. Antiviral prophylaxis (acyclovir/valacyclovir) is recommended for patients receiving proteasome inhibitors or anti-CD38 antibodies and routinely around ASCT [77, 78]. Pneumocystis prophylaxis (e.g., trimethoprim-sulfamethoxazole (TMP-SMX)) is reserved for higher-risk settings such as prolonged high-dose corticosteroids, intensive therapy, or the early post-ASCT period [79]. Seasonal influenza and pneumococcal vaccinations should be administered per schedules. IVIG is not routine but may be used in selected patients with recurrent/severe infections and marked hypogammaglobulinemia [75]. Collectively, these measures should be applied to IgM myeloma with the same risk-adapted approach used in other MM isotypes.

In MM, the unregulated growth of malignant plasma cells in the bone marrow leads to osteolysis and bone loss, which significantly increases morbidity. Several studies have shown the importance of bisphosphonates for palliative care due to their effectiveness in lowering the risk of hypercalcemia and skeletal complications associated with myeloma. The IMWG Bone Working Group recommends zoledronic acid (or pamidronate) for all patients with active MM, regardless of baseline lytic lesions, with renal-adjusted dosing and mandatory dental evaluation and calcium/vitamin D supplementation. After about 12 months, dosing can be de-escalated (e.g., every 3 months) in deep responders, with continuation or re-initiation at biochemical/clinical relapse [80, 81].

Analgesia should follow cancer-pain guidelines: use regular non-opioids and strong opioids for moderate-severe nociceptive pain, titrated with breakthrough dosing and functional reassessment. For neuropathic components, adjuvant agents such as gabapentinoids or duloxetine can be added; randomized data support duloxetine for chemotherapy-induced

painful neuropathy. Non-pharmacologic and interventional measures (e.g., radiotherapy, vertebral augmentation) can be used when indicated [82-84].

Anemia is a common complication in MM, including IgM MM, resulting from marrow infiltration, inflammation-driven hepcidin-mediated iron restriction, relative erythropoietin deficiency from renal dysfunction, and treatment-related myelosuppression [85]. Erythropoiesis-stimulating agents (ESAs, epoetin alfa or darbepoetin alfa) may be considered for chemotherapy-associated, symptomatic anemia in non-curative settings to raise hemoglobin (Hb) and reduce transfusions; however, they require risk-benefit discussion given increased venous thromboembolism risk and signals of higher mortality in meta-analyses [86, 87]. Current guidelines recommend ESAs selectively (typically when Hb < 10 g/dL), aiming for the lowest Hb sufficient to avoid transfusion, and after correcting iron deficiency [86]. Adding intravenous iron improves ESA response and further lowers transfusion needs [88]. For hospitalized, hemodynamically stable hematology-oncology patients, a restrictive red blood cell (RBC) transfusion threshold around 7 g/dL is recommended, individualized to symptoms/comorbidity [89]. There are no IgM-specific trials; practice is extrapolated from general MM/oncology data [90, 91].

Given the limited body of literature discussing IgM myeloma, most of the management guidance in this review is extrapolated by data from broader MM populations. Wherever possible, we have cited IgM-specific findings, but for certain therapeutic strategies and prognostic frameworks, extrapolation from general MM studies remains necessary. We highlight the urgent need for dedicated prospective studies focused on this rare subtype.

Conclusion

IgM myeloma is reported to have a more ominous prognosis compared to the remaining MM subtypes in some cases. This places heavy emphasis on timely diagnosis and effective management. Current diagnostics rely on a combination of clinical assessment, laboratory investigations, bone marrow biopsies, cytogenetics, and immunohistochemistry studies. Following diagnosis, appropriate management is imperative to prevent the progression of the disorder. The current treatment options for IgM myeloma are primarily adapted from those used for other types of MM, but there is a need for more specific and tailored therapies. We invite future studies that investigate the efficacy of the current treatments of IgM myeloma and the development of standardized guidelines for the management of this rare subtype of MM.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Hadeel Elwaheidi: conceptualization, literature search, data curation, manuscript drafting, and critical revisions. Alaa Hamad: literature search, writing - original draft, figure preparation, and reference management. Farah Salameh: data extraction, writing - review and editing, and formatting. Fadwa Elkordy: draft refinement, table construction, and proofreading. Rojina FathAlrahman: writing - background and clinical features sections, and figure design. Amr Hanbali: supervision, expert review of hematologic content, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability

The data supporting the conclusions of this review article are available from the cited references.

Abbreviations

ASCT: autologous stem cell transplantation; Bcl-2: B-cell lymphoma 2; CD: cluster of differentiation; CRAB: hypercalcemia, renal failure, anemia, bone lesions; D-VRd: daratumumab, bortezomib, lenalidomide, and dexamethasone regimen; FISH: fluorescence *in situ* hybridization; IgM: immunoglobulin M; ISS: International Staging System; LDCT: low-dose computed tomography; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; Sβ2M: serum beta-2 microglobulin; t(11;14): translocation between chromosomes 11 and 14; VRd: bortezomib, lenalidomide, and dexamethasone regimen; WM: Waldenstrom's macroglobulinemia

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