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Review

Uncommon Entities, Uncommon Challenges: A Review of Rare Plasma Cell Disorders

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Abstract: Rare plasma cell disorders—including IgD, IgE, and IgM multiple myeloma, non-secretory myeloma (NSMM), plasma cell leukemia (PCL), and heavy chain disease (HCD)—are biologically heterogeneous and often present with atypical features and aggressive behavior. This review synthesizes current evidence on their epidemiology, pathophysiology, diagnosis, and treatment. Advances in proteasome inhibitors, immunomodulatory agents, and autologous transplantation have improved outcomes in select subtypes. However, challenges persist in distinguishing IgM myeloma from Waldenström macroglobulinemia, monitoring non-secretory disease, and treating highly aggressive forms such as IgE myeloma and PCL. Standardized diagnostic criteria and prospective trials are essential to guide future management.

Keywords: rare plasma cell disorders; IgD multiple myeloma; IgE multiple myeloma; IgM multiple myeloma; non-secretory myeloma; plasma cell leukemia; heavy chain disease

1. Introduction

Plasma cell disorders represent a heterogeneous group of clonal disorders originating from terminally differentiated B cells, characterized by the production of a monoclonal immunoglobulin (Ig) or its subunits [1]. These disorders range from indolent conditions such as monoclonal gammopathy of undetermined significance (MGUS) to aggressive malignancies including multiple myeloma (MM) and plasma cell leukemia (PCL) [2]. MM, the most prevalent form, is a malignancy of bone marrow plasma cells and is typically associated with end-organ damage. Its classic clinical features are summarized by the acronym "CRAB," referring to hypercalcemia, renal failure, anemia, and bone lesions. The diagnosis of MM requires ≥10% clonal plasma cells in the bone marrow in combination with at least one CRAB feature or a myeloma-defining event [3]. Although MM accounts for approximately 1% of all cancers, it is the second most common hematologic malignancy after lymphoma. The global five-year prevalence of MM is estimated at around 230,000 patients [4].

In current clinical practice, the management of common MM subtypes—namely IgG, IgA, and light chain MM, which account for approximately 52%, 21%, and 16% of cases, respectively—is guided by well-established evidence-based protocols [5]. In contrast, evidence on rare MM subtypes, such as IgD, IgE, and IgM myeloma, as well as non-secretory myeloma, PCL, and heavy chain disease is limited. Information on these entities is primarily derived from isolated case reports and small case series, leading to ongoing challenges in diagnosis and a lack of consensus on optimal management strategies within the hematology community.

This article aims to provide a comprehensive review of the current literature concerning these rare plasma cell disorders, highlighting diagnostic nuances, clinical behavior, and emerging treatment paradigms.

2. IgD Multiple Myeloma (MM)

IgD MM (Table 1) is a rare and biologically distinct subtype of plasma cell disorder, accounting for only 1–2% of all MM cases worldwide. First described by Rowe and Fahey in 1965, it is

characterized by aggressive clinical behavior, lambda light chain restriction, and a tendency to present at an advanced stage with extensive organ involvement including renal dysfunction and amyloidosis [6,7]. Due to the inherently low serum concentration of IgD and the subtle or absent M-protein spike on standard serum protein electrophoresis, diagnosis is often delayed or missed unless specific immunofixation or free light chain assays are employed [8]. Patients with IgD MM typically present at a younger age than those with more common MM subtypes, often between 50 and 60 years, and more frequently in males [7,9].

Table 1. Clinical and Biological Overview of IgD Multiple Myeloma.

Category	Key Findings
Epidemiology	Accounts for 1–2% of MM; male predominance; younger age (50–60 years).
Clinical Presentation	Commonly presents with renal impairment, bone lesions, amyloidosis, hypercalcemia, and Bence Jones proteinuria.
Diagnosis Challenges	Delayed diagnosis due to low serum IgD and absent M-protein spike; immunofixation and free light chain assays crucial.
Light Chain Association	Lambda light chain restriction in >85% of cases.
Cytogenetic Abnormalities	Frequent del(13q), 1q21 gain, IGH rearrangements; t(11;14) common; t(14;16) and del(17p) variably reported.
Prognosis (Historical)	Median OS 13–21 months due to late diagnosis and renal dysfunction.
Prognosis (Modern)	Median OS improved to 48–50+ months with novel agents and ASCT.
Prognostic Factors	Renal dysfunction and high β2-microglobulin levels predict worse OS.
Therapeutic Advances	Novel agents (bortezomib, lenalidomide, thalidomide) and ASCT improved responses (up to 89% response rate).
Unmet Needs	Late diagnosis, variable cytogenetics, high-risk features continue to impact survival; need for risk stratification and trials.

Clinical features commonly include renal impairment, Bence Jones proteinuria, bone lesions, hypercalcemia, and systemic amyloidosis [10,11]. A multicenter Asian study involving 356 patients emphasized the high frequency of renal insufficiency, hypercalcemia, and advanced International Staging System (ISS) stage at presentation in IgD MM compared to non-IgD subtypes [6]. Lambda light chains predominate in over 85% of cases [9,12]. As mentioned earlier, due to low serum IgD levels (normal range: 0–10 mg/dL), standard electrophoresis often fails to detect a monoclonal peak, necessitating advanced diagnostic tools such as immunofixation, serum free light chain assays, or cytoplasmic IgD flow cytometry for accurate diagnosis [8,13]. In a recent Italian retrospective study of 15 patients with IgD MM, monoclonal protein was undetectable on serum protein electrophoresis in 60% of cases, highlighting the limitations of traditional diagnostic techniques [14].

IgD MM often exhibits complex cytogenetics, including deletion 13q, IGH rearrangements, 1q21 amplification, and less commonly, high-risk abnormalities such as t(4;14), t(14;16), and deletion 17p [6,9,14,15]. In the Asia Myeloma Network (AMN) study, 40.6% of IgD cases had cytogenetic abnormalities, with t(11;14) occurring in 29%—significantly more than in non-IgD subtypes [16]. Although deletion 17p is a high-risk feature in MM, its prognostic impact in IgD MM varies, with some cohorts showing no consistent association with inferior survival [15]. A Chinese cohort reported higher rates of 1q21 amplification and t(14;16) in IgD patients compared to others, both linked to poor outcomes [9]. Nonetheless, cytogenetic profiling in IgD MM remains limited and heterogeneous, highlighting the need for prospective studies to refine risk stratification.

Historically, IgD MM was considered to confer a poor prognosis, with median overall survival (OS) ranging between 13 and 21 months in early studies [7,12]. This was largely attributed to delayed diagnosis, high tumor burden, and a greater prevalence of renal failure and other adverse features at presentation. However, more recent data suggest that the prognosis of IgD MM has significantly improved due to the use of novel agents and autologous stem cell transplantation (ASCT). For instance, the UK National Trials Group reported a substantial increase in median OS from 22 months (1980–2002) to 48 months (2002–2016) among patients with IgD MM, coinciding with the adoption of thalidomide, lenalidomide, and bortezomib into frontline therapy regimens [9]. Similarly, the Greek

Myeloma Study Group found no significant survival difference between IgD and non-IgD MM patients treated in the era of novel agents, with both groups achieving median OS exceeding 50 months [10]. Nevertheless, renal insufficiency remains a strong negative prognostic factor. In a prospective cohort study from Zhengzhou University, 55% of newly diagnosed IgD MM patients presented with renal dysfunction, which was independently associated with a significantly shorter OS (29 months vs. >40 months in those without renal impairment) [15]. Beta-2 microglobulin was identified as a reliable predictor of renal damage in these patients, emphasizing the importance of early biochemical monitoring.

The therapeutic landscape of IgD MM has evolved significantly with the introduction of proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and stem cell transplantation. The AMN cohort demonstrated that patients receiving novel agents had superior OS compared to those treated with conventional chemotherapy [6]. The response rate following induction therapy in more recent UK trials reached as high as 89%, compared to only 43% in earlier studies [9]. Despite these improvements, real-world outcomes can vary. A Chinese single-center study reported inferior survival among IgD patients despite access to novel agents, with median OS remaining below 25 months, suggesting that late-stage presentation and high-risk biology may still override treatment benefits in some cases [16]. This underscores the continued need for early diagnosis, personalized risk stratification, and integration of next-generation therapeutics such as CAR T-cell therapy and bispecific antibodies into clinical trials for IgD MM.

In conclusion, IgD MM is a rare but clinically aggressive subtype of MM with unique biological and clinical features. While historically associated with dismal outcomes, recent data indicate that the incorporation of novel therapeutic agents and ASCT has markedly improved survival. However, the disease remains challenging due to diagnostic delays, high rates of renal impairment, and complex cytogenetic profiles. Advances in diagnostic precision, risk-adapted therapy, and prospective clinical trials are essential to further optimize outcomes, guide therapeutic decision-making, and develop consensus-based management strategies tailored to this rare and understudied plasma cell disorder.

3. IgE Multiple Myeloma

IgE MM (Table 2) is the rarest immunoglobulin subtype of MM, accounting for fewer than 0.1% of cases. Since its first description by Johansson and Bennich in 1967, few case reports and small series have been published, making comprehensive understanding and evidence-based management challenging. Compared to more common isotypes like IgG and IgA, IgE myeloma exhibits a more aggressive clinical behavior, with frequent extramedullary involvement, PCL, and rapid progression, often resulting in inferior outcomes and shorter survival times [17–19].

Table 2. Clinical and Biological Overview of IgE Multiple Myeloma.

Category	Key Findings
Epidemiology	Rarest MM subtype (<0.1%); described in 1967; predominantly male; younger onset.
Clinical Behavior	Aggressive course; frequent extramedullary disease, plasma cell leukemia, and poor survival.
Clinical Presentation	Features similar to MM (anemia, bone pain, hypercalcemia); more frequent hyperviscosity and PCL.
Diagnosis Challenges	Low serum IgE causes false-negatives in electrophoresis; immunofixation and sFLC assays critical.
Rare Presentations	Reported dual IgE/IgA monoclonal proteins with shared clonal origin.
Evolution Progression	andMay evolve from MGUS; some cases progress to secondary PCL, median survival 1–2 months.
Complications	Hyperviscosity syndrome and elevated CA125 reported in absence of solid tumors.
Molecular Features	IgE plasma cells are transcriptionally unique; high ER stress, TACI, and BCMA expression.

Genomic Insights	High mutation burden and tumor-reactive T cells suggest potential for personalized immunotherapy.
Treatment and Prognosis	No IgE-specific protocols; treated as conventional MM; survival remains shorter than IgG/IgA MM.
Research and Directions	Future Case reports and immunogenetic studies offer insights; future strategies may improve outcomes.

The clinical presentation of IgE MM mirrors other MM subtypes in terms of anemia, bone pain, hypercalcemia, renal impairment, and osteolytic lesions. However, some studies suggest a higher incidence of aggressive features such as PCL and hyperviscosity syndrome [20–22]. In one of the earliest series, IgE MM was frequently associated with male sex and younger age at onset, and patients often presented with a severe disease burden [17]. A rare presentation involving both IgE and IgA monoclonal proteins in the same patient has also been reported, with molecular analysis confirming a common clonal origin of the dual-secreting plasma cells [23].

Laboratory diagnosis remains complex, as the low concentration of IgE in serum often leads to false-negative results in standard protein electrophoresis. Immunofixation using IgE-specific antisera and serum free light chain assays are essential for accurate detection. In certain cases, using undiluted serum samples or repeat testing may be required to confirm the diagnosis [24,25]. A case described by Altinier et al. highlighted the inconsistency between immunofixation and immunometric techniques, suggesting that IgE degradation or modification during renal filtration could interfere with epitope recognition [26].

IgE MM may infrequently arise from MGUS or progress to secondary PCL. Galakhoff et al. reported a case with IgE MGUS that eventually transformed into IgE-producing PCL over several years, underscoring the need for long-term vigilance in such patients [20]. PCL is the most aggressive manifestation among plasma cell disorders and carries a median survival of only one to two months in its secondary form [20].

Another uncommon but clinically important complication of IgE MM is hyperviscosity syndrome, which may arise due to markedly elevated IgE levels in the serum. Yates et al. documented a case where IgE paraproteinemia led to classical signs of hyperviscosity syndrome and required urgent medical intervention [21]. Moreover, elevated CA125—a tumor marker commonly associated with epithelial ovarian cancer—has been reported in IgE myeloma without underlying solid malignancy, indicating potential cross-reactivity or paraneoplastic phenomena [19].

Recent studies have provided insights on the biology of IgE plasma cells. Using murine models and single-cell RNA sequencing, Vecchione et al. showed that IgE plasma cells are transcriptionally distinct from other isotypes. Short-lived IgE plasma cells arise early during antigen exposure in lymphoid tissues, while long-lived cells accumulate in the bone marrow after prolonged stimulation. These cells express high levels of protein synthesis, endoplasmic reticulum stress, and survival markers like TACI and BCMA, supporting their persistence and high immunoglobulin secretion [25]. A case report by Kehl et al. revealed a hypermutated phenotype in IgE MM, suggesting potential for neoantigen-directed immunotherapy [26]. These discoveries position IgE MM as both a clinical rarity and a model for immunogenetic research and targeted treatments.

There is no standardized treatment protocol specifically designed for IgE MM due to its rarity. However, most patients are managed using regimens used for conventional MM, including proteasome inhibitors, immunomodulatory drugs, and autologous stem cell transplantation (ASCT). Some cases have shown durable remissions with modern triplet or quadruplet induction followed by ASCT, while others progressed rapidly despite aggressive therapy [19,27]. Overall, reported median survival is shorter than that observed in IgG or IgA myeloma, though this gap may be narrowing with the availability of novel agents [17,25].

IgE multiple myeloma is an exceptionally rare and biologically distinct variant of plasma cell myeloma. It poses significant diagnostic challenges due to its subtle laboratory profile and low serum immunoglobulin concentration. Clinically, it often presents aggressively, with features like PCL or hyperviscosity syndrome. However, ongoing advances in molecular diagnostics, immunogenomics,

and therapeutic strategies hold promise for improving the management and prognosis of affected patients. Increased awareness and case documentation are needed to enhance our understanding of this enigmatic disease.

4. IgM Multiple Myeloma

IgM MM (Table 3) is an exceptionally rare plasma cell disorder, constituting less than 0.5% of all MM cases. Its clinical presentation often overlaps with Waldenström macroglobulinemia (WM), a more common B-cell lymphoproliferative disorder that also secretes IgM. Due to overlapping features, accurate differentiation is critical for therapeutic decisions and prognostication [27,28].

Table 3. Clinical and Biological Overview of IgM Multiple Myeloma.

Category	Key Findings
Epidemiology	Extremely rare (<0.5% of MM); overlaps clinically with Waldenström macroglobulinemia (WM).
Clinical Features	Presents with CRAB features; IgM monoclonal protein present; may include WM-like symptoms.
Diagnostic Criteria	≥10% plasma cells, IgM M-protein, CRAB criteria, bone lesions, and absence of MYD88 mutation.
Cytogenetics	Commonly harbors t(11;14)(q13;q32); cyclin D1 dysregulation seen in ~39–50% of cases.
Immunophenotype	CD138+, cyclin D1+; lacks CD20, CD19, CD56, CD117 — distinguishes from WM clones.
Differentiation from WM	MYD88 L265P mutation absent; histology reveals plasma cells (vs. lymphoplasmacytic in WM).
Survival and Prognosis	Median OS ~61 months; comparable to IgG/IgA MM, inferior to indolent WM outcomes.
Therapeutic Strategies	Responds to MM regimens (PI, IMiDs, ASCT); anti-CD20 (e.g., rituximab) not effective.
Case Reports and Variants	Reports of rare presentations (e.g., spinal cord compression); diagnostic reclassification not uncommon.
Clinical Implications	Accurate distinction from WM is critical for therapy; integrated diagnostic approach essential.

IgM MM is characterized by a clonal proliferation of plasma cells producing IgM paraprotein, with ≥10% plasma cell infiltration in the bone marrow and typical MM-related organ damage (CRAB features: hypercalcemia, renal dysfunction, anemia, bone lesions). The presence of lytic bone lesions or translocation t(11;14) further supports the diagnosis [29,30]. Cytogenetically, IgM MM frequently harbors t(11;14), leading to cyclin D1 dysregulation. This alteration, detected in up to 39–50% of cases, is absent in WM and supports the diagnosis of IgM MM over WM [30,31]. Immunophenotypically, IgM MM plasma cells may show expression of CD38 and cyclin D1, but lack CD20, CD56, and CD117, distinguishing them from WM clones [32].

Patients typically present with MM features—bone pain, anemia, renal impairment, and hypercalcemia. A monoclonal IgM protein is typically detected. However, WM-like manifestations (lymphadenopathy, hepatosplenomegaly, hyperviscosity) can coexist, complicating the diagnosis [27,33]. Histologically, WM shows lymphoplasmacytic infiltration, whereas IgM MM reveals sheets of plasma cells [29]. Immunophenotyping and mutational profiling aid in differentiation: IgM MM lacks the MYD88 L265P mutation (>90% in WM), aiding differentiation, along with t(11;14), lytic lesions, and immunophenotypic markers (CD20⁻CD56⁻CD117⁻) [29,31–34]. A case report described spinal cord compression from plasmacytomas in IgM MM [35].

Castillo et al. conducted the largest retrospective analysis of 134 patients with IgM MM and found a median overall survival (OS) of 61 months, with higher ISS stage correlating with poorer outcomes [30]. This survival is comparable to non-IgM MM, but inferior to WM, which generally has an indolent course [29,30].

Therapeutically, patients respond to conventional MM regimens including proteasome inhibitors, immunomodulatory agents, and ASCT when feasible. Anti-CD20 therapy (e.g., rituximab) is ineffective due to the CD20⁻ immunophenotype of IgM MM, reinforcing the distinction from WM [29,30]. In a multicenter analysis from the CIBMTR, Reece et al. showed that patients with IgM MM had 3-year progression-free and overall survival rates of 47% and 68%, respectively—outcomes comparable to IgG and IgA myeloma, underscoring that ASCT is a viable option for IgM MM patients [36]. Notably, this supports that despite its rarity, IgM MM responds well to modern myeloma-directed therapies.

IgM multiple myeloma is a rare but clinically significant subtype of MM. Accurate diagnosis requires integration of clinical, radiologic, immunophenotypic, and genetic data. The presence of t(11;14), absence of MYD88 L265P mutation, and lytic bone lesions are pivotal in differentiating IgM MM from WM. Continued awareness and application of these diagnostic tools are essential to guide appropriate treatment and improve patient outcomes.

5. Non-Secretory Multiple Myeloma (NSMM)

Non-secretory multiple myeloma (NSMM) (Table 4) is a rare and diagnostically challenging subtype of multiple myeloma (MM), historically defined as lacking detectable monoclonal protein (M-protein) in both serum and urine using conventional electrophoresis. It accounts for approximately 1–5% of all MM cases and encompasses a heterogeneous group with distinct biological and clinical features [37,38]. With advancements in diagnostic technologies, particularly serum free light chain (FLC) assays and sensitive immunofixation techniques, the definition of NSMM has evolved, revealing a spectrum that includes truly non-secretory, oligosecretory, and hyposecretory forms [39,40].

Table 4. Clinical and Biological Overview of Non-Secretory Multiple Myeloma.

Category	Key Findings
Epidemiology	Accounts for 1–5% of MM; initially defined by absence of M-protein in serum/urine.
Definition and Evolution	Definition has evolved with FLC assays; now includes truly non-secretory, oligosecretory, and hyposecretory forms.
Subtypes	Two main types: oligosecretory (detectable by FLC/immunofixation) and true non-secretory (no detectable Ig).
Diagnostic Challenges	Diagnosis requires bone marrow, imaging, and advanced assays; 'missing M-band' cases reclassified with repeat testing.
Clinical Features	Presents with CRAB features; diagnosis often delayed due to lack of measurable M-protein.
Prognosis	May have lower tumor burden at diagnosis; survival comparable or better than secretory MM in some studies.
Therapeutic Approaches	Treatment mirrors MM: PI, IMiDs, antibodies, ASCT; modern regimens benefit NSMM patients.
Response Monitoring	Response assessment challenging; relies on bone marrow and imaging rather than serum biomarkers.
Cytogenetics	Cytogenetic risks (del(17p), t(4;14), gain(1q)) occur at similar rates as in secretory MM.
Future Directions	Research needed on molecular markers and surrogate endpoints to guide therapy and monitoring.

NSMM can be subclassified into two main categories: (1) oligosecretory myeloma, where M-protein levels are detectable only by highly sensitive methods such as FLC assays or immunofixation, and (2) true NSMM, which lacks detectable immunoglobulin production even by the most sensitive assays [38,41,42]. The latter is exceedingly rare and may result from defective immunoglobulin synthesis or secretion at the cellular level [40]. The diagnostic approach requires a combination of bone marrow biopsy, imaging, and advanced immunological assays [41,42]. Some cases initially classified as non-secretory are reclassified as oligosecretory with sensitive testing —commonly referred to as "the missing M-band" [43].

The clinical presentation of NSMM mirrors that of secretory MM, with patients often exhibiting anemia, bone lesions, renal dysfunction, or hypercalcemia. However, due to the absence of measurable M-protein, diagnosis is often delayed, and disease monitoring becomes more reliant on imaging (MRI, PET-CT) and bone marrow evaluation [39,41,44]. Studies indicate that NSMM may present with a lower tumor burden at diagnosis, and some cohorts suggest comparable or even superior survival to secretory MM when treated with modern agents [42,43]. Conversely, outcomes may be worse for truly non-secretory cases where disease tracking is particularly difficult, though evidence is limited [45].

Therapeutic strategies for NSMM largely mirror those of conventional MM, including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and autologous stem cell transplantation [37,39,43]. Notably, patients benefit from novel agent-based induction therapies similar to their secretory counterparts. However, monitoring treatment response poses a significant challenge. In the absence of measurable paraprotein, response assessments must rely on serial bone marrow examinations and imaging, which can limit sensitivity and delay detection of relapse [39,42].

Recent studies suggest that the cytogenetic risk profile of NSMM is comparable to that of secretory MM, with high-risk abnormalities such as del(17p), t(4;14), and gain(1q) occurring at similar frequencies [46]. These markers retain prognostic value and should guide risk-adapted therapy. Importantly, cytogenetic evaluation is essential in NSMM due to the lack of measurable serum biomarkers.

NSMM represents a biologically diverse spectrum of plasma cell disorders. The evolution of diagnostic methods, particularly FLC assays and functional imaging, has significantly improved detection and reclassification of cases previously labeled as "non-secretory". Despite the inherent challenges in disease monitoring, patient outcomes have improved in the era of novel therapeutics. Future research should focus on refining molecular stratification and identifying reliable surrogate markers to optimize disease tracking and therapeutic decision-making in NSMM.

6. Plasma Cell Leukemia (PCL)

Plasma cell leukemia (PCL) (Table 5) is a rare, aggressive plasma cell disorder, characterized by the presence of circulating plasma cells in peripheral blood exceeding 2×10^9/L or accounting for more than 20% of leukocytes. It may present as either primary (de novo) or evolve from previously diagnosed MM, termed secondary PCL (sPCL) [47–49].

PCL constitutes 1–4% of all plasma cell disorders and is more frequently observed in younger patients compared to MM [50,51]. Clinically, PCL presents with aggressive features including hepatosplenomegaly, lymphadenopathy, high tumor burden, anemia, thrombocytopenia, and renal impairment. Central nervous system and extramedullary involvement are more common than in MM [47,52].

Table 5. Clinical and Biological Overview of Plasma Cell Leukemia (PCL).

Category	Key Findings
Definition	Defined by >5% circulating plasma cells in peripheral blood (IMWG 2021 criteria).
Epidemiology	Accounts for 1–4% of plasma cell malignancies; often affects younger patients.
Clinical Features	Aggressive presentation with hepatosplenomegaly, CNS/extramedullary disease, anemia, and renal dysfunction.
Genomic and Cytogenetic Features	High-risk cytogenetics (e.g., del(17p), t(11;14), t(14;16), complex karyotypes); distinct transcriptional profile.
Revised Diagnostic Criteria	IMWG revised diagnostic cutoff from 20% to >5% circulating plasma cells based on recent evidence.
Treatment Strategies	Initial therapy typically includes bortezomib + dexamethasone + alkylator/IMiD; improved response with novel agents.
Transplantation Approaches	ASCT used in eligible patients; allo-HCT and tandem transplant (auto-allo) associated with better PFS in some studies.

Maintenance Therapy	Maintenance therapy (lenalidomide, pomalidomide, PIs) explored post-transplant; data remain inconclusive.
Emerging Therapies	Anti-CD38 mAbs, venetoclax (t(11;14)), CAR T-cells under investigation for refractory disease.
Prognosis	Prognosis poor (median OS 7–12 months); adverse factors include high LDH, β2-M, extramedullary disease.
Future Directions	Further research on early diagnosis, novel agents, and consensus criteria urgently needed.

Genomic studies have demonstrated that PCL harbors high-risk cytogenetic features such as del(17p), t(11;14), t(14;16), and complex karyotypes, which contribute to its aggressive behavior [53–55]. A genome-wide analysis highlighted significant transcriptional changes and chromosomal imbalances distinguishing PCL from MM [53]. The International Myeloma Working Group (IMWG) and subsequent studies emphasized that primary PCL (pPCL) has a distinct molecular signature and carries a worse prognosis [51,55].

The definition of PCL has undergone a significant revision in recent years to better reflect disease biology and prognosis. Historically, PCL was diagnosed when peripheral blood contained ≥20% circulating plasma cells and an absolute plasma cell count >2 × 10⁹/L [51]. However, emerging data demonstrated that patients with lower levels of circulating plasma cells—specifically those with >5%—exhibited similarly aggressive clinical behavior and poor outcomes. As a result, in 2021, the International Myeloma Working Group (IMWG) lowered the PCL diagnostic threshold to >5% circulating plasma cells, reflecting similar aggressive behavior to the prior ≥20% cutoff [56]. pPCL tends to be more genetically unstable and aggressive compared to sPCL, with poorer outcomes if not promptly diagnosed and treated [48,49].

Treatment of PCL has evolved significantly with the advent of proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies. Initial therapy typically includes bortezomib-based regimens combined with dexamethasone and an alkylating agent or immunomodulator [48,57]. The incorporation of bortezomib has led to improved response rates and prolonged survival, particularly in pPCL [57].

Autologous stem cell transplantation (ASCT) is commonly recommended for eligible patients with PCL after induction therapy; however, the durability of response remains limited, with many patients relapsing early [48,59]. To enhance disease control, consolidation strategies such as tandem ASCT or allogeneic hematopoietic cell transplantation (allo-HCT) are increasingly considered. A retrospective study analyzing 16 PCL patients undergoing either ASCT or allo-HCT reported that maintenance therapy was administered to 56% of patients post-ASCT [60]. The study found that patients receiving allo-HCT had a median progression-free survival (PFS) of 18 months compared to 6 months in the ASCT group, suggesting a potential benefit of allo-HCT in prolonging disease control [60]. Similarly, Lawless et al. demonstrated that patients undergoing ASCT followed by allo-HCT (auto-allo transplantation) had significantly improved PFS after 100 days compared to those receiving a single ASCT [61]. These findings support the role of tandem transplantation strategies, particularly for patients who fail to achieve complete remission prior to the first transplant.

Maintenance therapy post-transplant has also been explored as a means to sustain remission. In the aforementioned retrospective study, maintenance regimens such as lenalidomide, pomalidomide, and combinations with proteasome inhibitors were utilized [61]. However, no statistically significant association between maintenance therapy and improved PFS or overall survival (OS) was observed, likely due to the small sample size [61].

Novel agents, including anti-CD38 monoclonal antibodies (e.g., daratumumab), venetoclax for t(11;14) subsets, and CAR T-cell therapies, are being investigated for refractory PCL and offer hope for improved survival [62–64].

Despite therapeutic advances, the prognosis of PCL remains poor, with median overall survival of approximately 7–12 months in most series, though novel agents may improve outcomes [47,50,51]. Factors associated with poor outcomes include high LDH, elevated β2-microglobulin,

extramedullary disease, and adverse cytogenetics [50,55,58]. A recent analysis showed that the presence of extraosseous plasmacytomas significantly worsened survival outcomes in pPCL patients [58].

PCL remains a formidable challenge in hematologic oncology, requiring prompt recognition and intensive therapy. While outcomes remain suboptimal, the landscape is shifting with novel targeted agents and immunotherapies. Collaborative research and standardized diagnostic criteria are essential to advance the understanding and management of this aggressive plasma cell disorder.

7. Heavy Chain Disease (HCD)

Heavy Chain Disease (HCD) (Table 6) is a rare and heterogeneous group of B-cell lymphoproliferative disorders characterized by the production of truncated, monoclonal immunoglobulin heavy chains without associated light chains. The condition is subclassified based on the isotype of the heavy chain involved: gamma (γ-HCD), alpha (α-HCD or Seligmann's disease), and mu (μ-HCD) [65,66]. Among them, γ-HCD is the most commonly reported variant in Western countries [65,70].

Table 6. Clinical and Biological Overview of Gamma Heavy Chain Disease (γ-HCD)**.**

Category	Key Findings
Definition	Rare B-cell disorder with production of truncated heavy chains lacking light chains.
Subtypes	Includes γ-HCD (most common), α-HCD (Seligmann's disease), and μ-HCD.
Pathogenesis	Defective assembly of immunoglobulin chains leads to secretion of free heavy chains.
Epidemiology	Median age ~65 years, slight female predominance; γ-HCD most common in Western populations.
Clinical Presentation	Variable symptoms: lymphadenopathy, splenomegaly, fever, weight loss, autoimmune disease.
Histopathology	Histology shows lymphoplasmacytic, marginal zone, or DLBCL-like features.
Immunophenotype	Cytoplasmic heavy chain expression; CD19+, CD20+, CD79a+; lacks light chains.
Autoimmune Associations	Frequently associated with SLE and RA; some cases initially mimic autoimmune disease.
Renal Involvement	Rare cases show renal cast nephropathy similar to light chain disease.
Diagnostic Approach	Requires serum/urine electrophoresis, immunofixation, mass spectrometry, and biopsy.
Treatment Strategies	No standard therapy; managed per associated lymphoma or autoimmune condition.
Prognosis	Highly variable; indolent forms may be stable; aggressive forms have poor prognosis.
Clinical Implications	Often misdiagnosed; awareness and advanced diagnostics critical for accurate classification.

HCD is characterized by the production of truncated immunoglobulin heavy chains without light chains due to defects in the variable region and constant domain assembly or somatic mutations during B-cell development [66,67]. These truncated chains escape normal quality control mechanisms within the endoplasmic reticulum and are secreted into serum without light chains [68].

γ-HCD exhibits marked clinical heterogeneity, presenting as either a monoclonal gammopathy of undetermined significance (MGUS), a chronic lymphoproliferative disorder, or overt high-grade lymphoma [65,69]. The median age of diagnosis is around 65 years, with a slight female predominance [70].

Patients may present with lymphadenopathy, splenomegaly, constitutional symptoms (fever, weight loss, fatigue), autoimmune phenomena, including associations with systemic lupus erythematosus (SLE) and rheumatoid arthritis [71]. HCD patients may also have renal complications, such as cast nephropathy [72]

Wahner-Roedler et al. reviewed 23 cases of γ-HCD, highlighting its variable course—ranging from indolent disease to aggressive lymphomas, particularly diffuse large B-cell lymphoma (DLBCL) [70]. Histologic analysis frequently reveals lymphoplasmacytic, marginal zone, or DLBCL-like morphology [69,73]. In some cases, no discernible tissue involvement is seen despite the presence of

the monoclonal protein. Bieliauskas et al. found that among 13 γ-HCD cases, over half were associated with defined lymphomas, and a few with autoimmune disease without overt neoplasia [69].

Immunohistochemistry typically shows cytoplasmic expression of heavy chains without associated light chains, often with positive staining for CD19, CD20, and CD79a [69].

Autoimmune disorders, particularly SLE, are strongly associated with γ-HCD, possibly due to chronic antigenic stimulation and B-cell dysregulation [65,67]. Slaughter et al. presented a unique case of γ-HCD initially mimicking autoimmune pathology that later progressed to DLBCL [65]. Although rare, renal involvement has been described. A recent case reported cast nephropathy due to γ-HCD, mimicking light chain cast nephropathy, emphasizing the diagnostic challenges in atypical presentations [66].

Diagnosis involves: serum and urine protein electrophoresis with immunofixation, quantification of immunoglobulin isotypes, bone marrow biopsy and flow cytometry. Tissue biopsy where lymphoma is suspected should be considered. Mass spectrometry offers a highly sensitive method for identifying heavy chain fragments in atypical cases [66].

There is no standard treatment for γ-HCD. Management depends on the associated lymphoproliferative disorder. Indolent cases may be monitored without immediate therapy [69,70]. DLBCL-type γ-HCD is treated using R-CHOP or other anthracycline-based regimens [74]. In the presence of autoimmune disease, immunosuppressive agents or corticosteroids may be used initially [65]. The prognosis varies considerably. Patients with isolated γ-HCD and no underlying lymphoma may remain stable for years, while those with aggressive lymphomas have poorer outcomes [66,69,70].

γ-HCD represents a rare, under-recognized B-cell neoplasm with variable clinical and pathological features. It may mimic autoimmune diseases, manifest as indolent monoclonal gammopathy, or present as aggressive lymphoma. Accurate diagnosis requires a high index of suspicion, particularly in patients with unexplained monoclonal gammopathy lacking light chains. As molecular diagnostics advance, future classification and targeted treatments may improve outcomes for this enigmatic disease spectrum.

8. Conclusion

Rare plasma cell disorders represent a diverse and complex spectrum of hematologic malignancies that continue to challenge clinicians in terms of timely diagnosis, prognostication, and management. Entities such as IgD, IgE, and IgM MM, NSMM, PCL, and HCD each exhibit unique biological behaviors, clinical presentations, and molecular profiles that distinguish them from more common plasma cell disorders. Advances in diagnostic modalities, including sensitive immunoassays, cytogenetic and molecular profiling, and functional imaging, have significantly enhanced the ability to accurately identify and classify these rare variants. Moreover, the introduction of novel therapeutics—proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and cellular therapies—has begun to improve outcomes even in historically poor-prognosis subtypes. Emerging therapies, such as CAR T-cell and bispecific antibody treatments, hold promise for improving survival. Nevertheless, significant gaps remain in understanding the pathogenesis and optimal treatment strategies for these uncommon disorders due to the paucity of large, prospective studies. Collaborative efforts for standardized diagnostics, prospective registries, and clinical trials are urgently needed. Future research should prioritize standardized diagnostics, molecular stratification, and clinical trials to optimize outcomes for these rare disorders

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Ethics Statement: This study is a review of previously published literature and did not involve human participants, animal subjects, or the use of identifiable personal data. Therefore, ethical approval was not required.

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References

1. Soh KT, Tario JD Jr, Wallace PK. Diagnosis of Plasma Cell Dyscrasias and Monitoring of Minimal Residual Disease by Multiparametric Flow Cytometry. Clin Lab Med. 2017 Dec;37(4):821-853.

2. Barlogie B, Alexanian R, Jagannath S. Plasma cell dyscrasias. Jama. 1992 Nov 25;268(20):2946-51.

3. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The lancet oncology. 2014 Nov 1;15(12):e538-48.

4. Zhuge Linmin , Lin Xiaowu , Fan Ziwei , Jia Mengxian , Lin Chaowei , Zhu Minyu , Teng Honglin , Chen Guoliang. Global, regional and national epidemiological trends of multiple myeloma from 1990 to 2021: a systematic analysis of the Global Burden of Disease study 2021. Frontiers in Public Health. Volume 13 - 2025

5. Elsabah H, El Omri H, Habas E, Taha RY, ElKourashy SA, Ibrahim F, Nashwan AJ, Kassem N, Ojha L, Singh R, Ghasoub R. Real world evidence of epidemiological trends, clinical presentation, and prognostic outcomes of multiple myeloma (2007-2021). Frontiers in Medicine. 2024 Feb 20;11:1338552.

6. Intra J, Pezzatti S, Brivio R, Carpenedo M, Romano R, Spinoni N, Casati M. Characteristics of 15 Subjects Affected by IgD Multiple Myeloma and the Key Role of the Laboratory in Diagnosis: A Retrospective Study Report and Literature Review. International Journal of Translational Medicine. 2024 Jul 25;4(3):498-504.

7. Selene II, Jose JA, Khalil MJ, et al. Presentation Patterns, Diagnostic Markers, Management Strategies, and Outcomes of IgD Multiple Myeloma: A Systematic Review. Cureus. 2019;11(2):e4011.

8. Pandey S, Kyle RA. Unusual myelomas: a review of IgD and IgE variants. Oncology (Williston Park). 2013 Aug;27(8):798-803. PMID: 24133829.

9. Agbuduwe C, Iqbal G, Cairns D, Menzies T, Dunn J, Gregory W, Kaiser M, Owen R, Pawlyn C, Child JA, Davies F, Morgan GJ, Jackson GH, Drayson MT, Basu S. Clinical characteristics and outcomes of IgD myeloma: experience across UK national trials. Blood Adv. 2022 Sep 13;6(17):5113-5123.

10. Zagouri F, Kastritis E, Symeonidis AS, Giannakoulas N, Katodritou E, Delimpasi S, Repousis P, Terpos E, Dimopoulos MA; Greek Myeloma Study Group. Immunoglobulin D myeloma: clinical features and outcome in the era of novel agents. Eur J Haematol. 2014 Apr;92(4):308-12.

11. Zhao Q, Li F, Song P, Zhou X, An Z, Mei J, Shao J, Li H, Wang X, Guo X, Zhai Y. Poor outcomes of immunoglobulin D multiple myeloma patients in the era of novel agents: a single-center experience. Cancer Commun (Lond). 2019 Sep 27;39(1):51.

12. Li Y, Cai Z. Clinical characteristics and survival of patients with IgD multiple myeloma. Blood Sci. 2021 Apr 27;3(2):57-58.

13. Wang W, Zhang CX, Li ZL, Gong M, Ma YG. Detection of intracellular IgD using flow cytometry could be a novel and supplementary method to diagnose IgD multiple myeloma. BMC Cancer. 2018 Jun 11;18(1):650.

14. Intra J, Pezzatti S, Brivio R, et al. Characteristics of 15 subjects affected by IgD multiple myeloma and the key role of the laboratory. Int J Transl Med. 2024;4(3):498–504.

15. Yan G, Li H, Zhang Y, Xia C, Wang M, Jia Y, Shang J, Zhao Z. Renal insufficiency predicts worse prognosis in newly diagnosed IgD multiple myeloma patients. Front Oncol. 2022 Nov 23;12:1012889.

16. Liu J, Hu X, Jia Y, Lu J, Lee JH, Kim K, Chen W, Liu A, Liu Y, Chen Q, Zhang C, Suh C, Kim MK, Zhou F, Chng WJ, Kumar SK, Durie B, Hou J, Fu W, Du J. Clinical features and survival outcomes in IgD myeloma: a study by Asia Myeloma Network (AMN). Leukemia. 2021 Jun;35(6):1797-1802.

17. Pandey S, Kyle RA. Unusual myelomas: a review of IgD and IgE variants. Oncology (Williston Park). 2013 Aug;27(8):798-803.

18. Nafría Jiménez B, Oliveros Conejero R. IgE multiple myeloma: detection and follow-up. Adv Lab Med. 2021 Dec 30;3(1):79-90.

19. Wang ML, Huang Q, Yang TX. IgE myeloma with elevated level of serum CA125. J Zhejiang Univ Sci B. 2009 Jul;10(7):559-62.

20. Galakhoff N, Leven C, Eveillard JR, Tempescul A, Kerspern H, Aubron C, Buors C, Lippert É, Carré JL, Padelli M. A case of IgE myeloma transformed into IgE-producing plasma cell leukaemia. Biochem Med (Zagreb). 2020 Feb 15;30(1):010801.

21. Proctor SJ, Chawla SL, Bird AG, Stephenson J. Hyperviscosity syndrome in IgE myeloma. Br Med J (Clin Res Ed). 1984 Oct 27;289(6452):1112.

22. Weiner E, DiCamelli R, Showel J, Osmand AP, Sassetti RJ, Gewurz H. IgE myeloma presenting with classical myeloma features. J Allergy Clin Immunol. 1976 Sep;58(3):373-80.

23. Bakkus MH, Schots R, Gomez La Fuente PB, Van Riet I, Thielemans K, De Waele M, Van Camp B. Clonally related IgA- and IgE-secreting plasma cells in a myeloma patient. Eur J Haematol. 2000 Nov;65(5):348-55.

24. Altinier S, Barberio G, Varagnolo M, Zaninotto M, Furlan A, Caberlotto L, Plebani M. An IgE multiple myeloma: contradictory findings in clinical laboratory testing. Clin Chim Acta. 2013 Oct 21;425:114-6.

25. Vecchione A, Devlin JC, Tasker C, Ramnarayan VR, Haase P, Conde E, Srivastava D, Atwal GS, Bruhns P, Murphy AJ, Sleeman MA, Limnander A, Lim WK, Asrat S, Orengo JM. IgE plasma cells are transcriptionally and functionally distinct from other isotypes. Sci Immunol. 2024 Sep 6;9(99):eadm8964.

26. Kehl N, Kilian M, Michel J, Wagner TR, Uhrig S, Brobeil A, Sester LS, Blobner S, Steiger S, Hundemer M, Weinhold N, Rippe K, Fröhling S, Eichmüller SB, Bunse L, Müller-Tidow C, Goldschmidt H, Platten M, Raab MS, Friedrich MJ. IgE type multiple myeloma exhibits hypermutated phenotype and tumor reactive T cells. J Immunother Cancer. 2022 Oct;10(10):e005815.

27. Haghighi, B., Yanagihara, R. and Cornbleet, P.J. (1998), IgM myeloma: Case report with immunophenotypic profile. Am. J. Hematol., 59: 302-308

28. Bonilla-Valentín FJ, Cerra J, Cáceres-Perkins W, Alsina M. Case report of IgM multiple myeloma: Diagnosing a rare hematologic entity. Cancer Control. 2018;25(1):1073274817744448.

29. Schuster SR, Rajkumar SV, Dispenzieri A, Morice W, Aspitia AM, Ansell S, Kyle R, Mikhael J. IgM multiple myeloma: disease definition, prognosis, and differentiation from Waldenstrom's macroglobulinemia. Am J Hematol. 2010 Nov;85(11):853-5.

30. Castillo JJ, Jurczyszyn A, Brozova L, Crusoe E, Czepiel J, Davila J, Dispenzieri A, Eveillard M, Fiala MA, Ghobrial IM, Gozzetti A, Gustine JN, Hajek R, Hungria V, Jarkovsky J, Jayabalan D, Laubach JP, Lewicka B, Maisnar V, Manasanch EE, Moreau P, Morgan EA, Nahi H, Niesvizky R, Paba-Prada C, Pika T, Pour L, Reagan JL, Richardson PG, Shah J, Spicka I, Vij R, Waszczuk-Gajda A, Gertz MA. IgM myeloma: A multicenter retrospective study of 134 patients. Am J Hematol. 2017 Aug;92(8):746-751.

31. Feyler S, O'Connor SJ, Rawstron AC, Subash C, Ross FM, Pratt G, Drayson MT, Ashcroft J, Cook G, Owen RG. IgM myeloma: a rare entity characterized by a CD20-CD56-CD117- immunophenotype and the t(11;14). Br J Haematol. 2008 Mar;140(5):547-51.

32. Willenbacher, W., Willenbacher, E., Brunner, A. and Manzl, C. (2013), Improved accuracy of discrimination between IgM Multiple Myeloma and Waldenström Macroglobulinaemia by testing for MYD88 L265P mutations. Br J Haematol, 161: 902-904

33. Elba S, Castellino A, Soriasio R, Castellino C, Bonferroni M, Mattei D, Strola G, Drandi D, Mordini N, Foglietta M, Rapezzi D, Celeghini I, Grasso M, Giordano F, Fraternali Orcioni G, Massaia M. Immunoglobulin M (IgM) multiple myeloma versus Waldenström macroglobulinemia: diagnostic challenges and therapeutic options: two case reports. J Med Case Rep. 2020 Jun 22;14(1):75.

34. Willenbacher E, Erdel M, Strasser U, Gastl G, Schmidt S, Gunsilius E, Willenbacher W. IgM myeloma: more on a rare entity. Br J Haematol. 2008 Oct;143(1):146-8.

35. Tahan I, Seale J, Edwards D. IgM multiple myeloma presenting with spinal cord compression caused by a plasmacytoma: A case report. Cases J. 2008 Oct 2;1(1):207. doi: 10.1186/1757-1626-1-207. PMID: 18831763; PMCID: PMC2566563.

36. Reece DE, Vesole DH, Shrestha S, Zhang MJ, Pérez WS, Dispenzieri A, Milone GA, Abidi M, Atkins H, Bashey A, Bredeson CN, Boza WB, Freytes CO, Gale RP, Gajewski JL, Gibson J, Hale GA, Kumar S, Kyle RA, Lazarus HM, McCarthy PL, Pavlovsky S, Roy V, Weisdorf DJ, Wiernik PH, Hari PN. Outcome of patients with IgD and IgM multiple myeloma undergoing autologous hematopoietic stem cell transplantation: a retrospective CIBMTR study. Clin Lymphoma Myeloma Leuk. 2010 Dec;10(6):458-63.

37. Lonial S, Kaufman JL. Non-secretory myeloma: a clinician's guide. Oncology (Williston Park). 2013 Sep;27(9):924-8, 930. PMID: 24282993.

38. Corso A, Mangiacavalli S. Non-Secretory Myeloma: Ready for a new Definition? Mediterr J Hematol Infect Dis. 2017 Aug 18;9(1):e2017053.

39. Chawla SS, Kumar SK, Dispenzieri A, Greenberg AJ, Larson DR, Kyle RA, Lacy MQ, Gertz MA, Rajkumar SV. Clinical course and prognosis of non-secretory multiple myeloma. Eur J Haematol. 2015 Jul;95(1):57-64.

40. Dimopoulos MA, Kastritis E, Terpos E. Non-secretory myeloma: one, two, or more entities? Oncology (Williston Park). 2013 Sep;27(9):930-2.

41. Charliński G, Jurczyszyn A. Non-secretory multiple myeloma: Diagnosis and management. Adv Clin Exp Med. 2022 Jan;31(1):95-100.

42. Migkou M, Avivi I, Gavriatopoulou M, Cohen YC, Fotiou D, Kanellias N, Ziogas D, Eleutherakis-Papaiakovou E, Terpos E, Roussou M, Kastritis E, Dimopoulos MA. Clinical characteristics and outcomes of oligosecretory and non-secretory multiple myeloma. Ann Hematol. 2020 Jun;99(6):1251-1255.

43. Mahto M, Kumar A, Rai N, Kumar V, Kumar S, Kumar T, Sinha R, Singh P. The Missing M Band: Is it Really Non Secretory Multiple Myeloma? EJIFCC. 2025 Feb 28;36(1):74-82.

44. Ouzzif Z, Eddair Y, Laassara W, El Maaroufi H, Mahtat EM. Non-Secretory Multiple Myeloma: A New Observation and Review of the Literature. Cureus. 2024 Feb 19;16(2):e54479.

45. Núñez-Cortés AK, Olivares-Gazca JC, Cantero-Fortiz Y, Vallejo-Villalobos MF, et al. True non-secretory multiple myeloma: An infrequent variant. Hematol Méx. 2019 January-March;20(1):54-58.

46. Nandakumar B, Kumar SK, Dispenzieri A, Buadi FK, Dingli D, Lacy MQ, Hayman SR, Kapoor P, Leung N, Fonder A, Hobbs M, Hwa YL, Muchtar E, Warsame R, Kourelis TV, Russell S, Lust JA, Lin Y, Go RS, Siddiqui M, Zeldenrust S, Kyle RA, Gertz MA, Rajkumar SV, Gonsalves WI. Cytogenetic Features and Clinical Outcomes of Patients With Non-secretory Multiple Myeloma in the Era of Novel Agent Induction Therapy. Clin Lymphoma Myeloma Leuk. 2020 Jan;20(1):53-56.

47. Albarracin F, Fonseca R. Plasma cell leukemia. Blood Rev. 2011 May;25(3):107-12.

48. van de Donk NW, Lokhorst HM, Anderson KC, Richardson PG. How I treat plasma cell leukemia. Blood. 2012 Sep 20;120(12):2376-89.

49. Gundesen MT, Lund T, Moeller HEH, Abildgaard N. Plasma Cell Leukemia: Definition, Presentation, and Treatment. Curr Oncol Rep. 2019 Jan 28;21(1):8.

50. Gertz MA, Buadi FK. Plasma cell leukemia. Haematologica. 2010 May;95(5):705-7.

51. Fernández de Larrea C, Kyle RA, Durie BG, Ludwig H, Usmani S, Vesole DH, Hajek R, San Miguel JF, Sezer O, Sonneveld P, Kumar SK, Mahindra A, Comenzo R, Palumbo A, Mazumber A, Anderson KC, Richardson PG, Badros AZ, Caers J, Cavo M, LeLeu X, Dimopoulos MA, Chim CS, Schots R, Noeul A, Fantl D, Mellqvist UH, Landgren O, Chanan-Khan A, Moreau P, Fonseca R, Merlini G, Lahuerta JJ, Bladé J, Orlowski RZ, Shah JJ; International Myeloma Working Group. Plasma cell leukemia: consensus statement on diagnostic requirements, response criteria and treatment recommendations by the International Myeloma Working Group. Leukemia. 2013 Apr;27(4):780-91.

52. Naseem S, Kaur S, Gupta R, Kashyap R, Nityanand S. Plasma cell leukemia: case series from a tertiary center with review of literature. Indian J Hematol Blood Transfus. 2012 Mar;28(1):10-4.

53. Mosca L, Musto P, Todoerti K, Barbieri M, Agnelli L, Fabris S, Tuana G, Lionetti M, Bonaparte E, Sirchia SM, Grieco V, Bianchino G, D'Auria F, Statuto T, Mazzoccoli C, De Luca L, Petrucci MT, Morabito F, Offidani M, Di Raimondo F, Falcone A, Caravita T, Omedè P, Boccadoro M, Palumbo A, Neri A. Genome-wide analysis of primary plasma cell leukemia identifies recurrent imbalances associated with changes in transcriptional profiles. Am J Hematol. 2013 Jan;88(1):16-23.

54. Avet-Loiseau H, Roussel M, Campion L, Leleu X, Marit G, Jardel H, Dib M, Decaux O, Lamy T, Tiab M, Cony-Makhoul P, Banos A, Lepeu G, Lifermann F, Macro M, Kolb B, Hulin C, Caillot D, Traulle C, Mathiot C, Royer B. Cytogenetic and therapeutic characterization of primary plasma cell leukemia: the IFM experience. Leukemia. 2012 Jan;26(1):158-9.

55. Papadhimitriou SI, Terpos E, Liapis K, Pavlidis D, Marinakis T, Kastritis E, Dimopoulos MA, Tsitsilonis OE, Kostopoulos IV. The Cytogenetic Profile of Primary and Secondary Plasma Cell Leukemia: Etiopathogenetic Perspectives, Prognostic Impact and Clinical Relevance to Newly Diagnosed Multiple Myeloma with Differential Circulating Clonal Plasma Cells. Biomedicines. 2022 Jan 19;10(2):209.

56. Fernández de Larrea C, Kyle R, Rosiñol L, Paiva B, Engelhardt M, Usmani S, Caers J, Gonsalves W, Schjesvold F, Merlini G, Lentzch S, Ocio E, Garderet L, Moreau P, Sonneveld P, Badros A, Gahrton G, Goldschmidt H, Tuchman S, Einsele H, Durie B, Wirk B, Musto P, Hayden P, Kaiser M, Miguel JS, Bladé J, Rajkumar SV, Mateos MV. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. Blood Cancer J. 2021 Dec 2;11(12):192.

57. Katodritou E, Terpos E, Kelaidi C, Kotsopoulou M, Delimpasi S, Kyrtsonis MC, Symeonidis A, Giannakoulas N, Stefanoudaki A, Christoulas D, Chatziaggelidou C, Gastari V, Spyridis N, Verrou E, Konstantinidou P, Zervas K, Dimopoulos MA. Treatment with bortezomib-based regimens improves overall response and predicts for survival in patients with primary or secondary plasma cell leukemia: Analysis of the Greek myeloma study group. Am J Hematol. 2014 Feb;89(2):145-50.

58. Vela-Ojeda J, Ramirez-Alvarado A, Sanchez-Rodriguez AS, Garcia-Chavez J, Montiel-Cervantes LA. Extraosseous Plasmacytoma Confers Poor Outcomes in Primary Plasma Cell Leukemia. Arch Med Res. 2025 Mar 24;56(5):103207.

59. Drake MB, Iacobelli S, van Biezen A, Morris C, Apperley JF, Niederwieser D, Björkstrand B, Gahrton G; European Group for Blood and Marrow Transplantation and the European Leukemia Net. Primary plasma cell leukemia and autologous stem cell transplantation. Haematologica. 2010 May;95(5):804-9.

60. Lemieux C, Johnston LJ, Lowsky R, Muffly LS, Craig JK, Shiraz P, Rezvani A, Frank MJ, Weng WK, Meyer E, Shizuru J, Arai S, Negrin R, Miklos DB, Sidana S. Outcomes with Autologous or Allogeneic Stem Cell Transplantation in Patients with Plasma Cell Leukemia in the Era of Novel Agents. Biol Blood Marrow Transplant. 2020 Dec;26(12):e328-e332.

61. Lawless S, Iacobelli S, Knelange NS, Chevallier P, Blaise D, Milpied N, Foà R, Cornelissen JJ, Lioure B, Benjamin R, Poiré X, Minnema MC, Collin M, Lenhoff S, Snowden JA, Santarone S, Wilson KMO, Trigo F, Dreger P, Böhmer LH, Putter H, Garderet L, Kröger N, Yaukoub-Agha I, Schönland S, Morris C. Comparison of autologous and allogeneic hematopoietic cell transplantation strategies in patients with primary plasma cell leukemia, with dynamic prediction modeling. Haematologica. 2023 Apr 1;108(4):1105-1114.

62. Yang CL, Jiang NG, Zhang L, Shen K, Wu Y. Relapsed/refractory multiple myeloma-transformed plasma-cell leukemia successfully treated with daratumumab followed by autologous stem cell transplantation. Ther Adv Hematol. 2021 Jan 28;12:2040620721989578.

63. Elsabah H, Ghasoub R, El Omri H, Benkhadra M, Cherif H, Taha RY. Venetoclax in the treatment of secondary plasma cell leukemia with translocation t(11;14): a case report and literature review. Front Oncol. 2024 Jul 10;14:1390747.

64. Deng J, Lin Y, Zhao D, Tong C, Chang AH, Chen W, Gao W. Case report: Plasma cell leukemia secondary to multiple myeloma successfully treated with anti-BCMA CAR-T cell therapy. Front Oncol. 2022 Sep 21;12:901266.

65. Fermand JP, Brouet JC. Heavy-chain diseases. Hematol Oncol Clin North Am. 1999 Dec;13(6):1281-94.

66. Bianchi G, Anderson KC, Harris NL, Sohani AR. The heavy chain diseases: clinical and pathologic features. Oncology (Williston Park). 2014 Jan;28(1):45-53.

67. Bloch KJ, Lee L, Mills JA, Haber E. Gamma heavy chain disease--an expanding clinical and laboratory spectrum. Am J Med. 1973 Jul;55(1):61-70.

68. Stoyle CL, Stephens PE, Humphreys DP, Heywood S, Cain K, Bulleid NJ. IgG light chain-independent secretion of heavy chain dimers: consequence for therapeutic antibody production and design. Biochem J. 2017 Sep 7;474(18):3179-3188.

69. Bieliauskas S, Tubbs RR, Bacon CM, Eshoa C, Foucar K, Gibson SE, Kroft SH, Sohani AR, Swerdlow SH, Cook JR. Gamma heavy-chain disease: defining the spectrum of associated lymphoproliferative disorders through analysis of 13 cases. Am J Surg Pathol. 2012 Apr;36(4):534-43.

70. Wahner-Roedler DL, Witzig TE, Loehrer LL, Kyle RA. Gamma-heavy chain disease: review of 23 cases. Medicine (Baltimore). 2003 Jul;82(4):236-50.

71. Chang L, Zhou DB, Cao XX. Gamma heavy chain disease: a retrospective analysis of 6 cases. Orphanet Journal of Rare Diseases. 2023 Apr 11;18(1):77.

72. Vakiti A, Padala SA, Hashmi MF, Mewawalla P. Renal Disease in Monoclonal Gammopathies. 2024 Mar 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan

73. Wester SM, Banks PM, Li CY. The histopathology of gamma heavy-chain disease. Am J Clin Pathol. 1982 Oct;78(4):427-36.

74. Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, Pocock C, Ardeshna KM, Radford JA, McMillan A, Davies J, Turner D, Kruger A, Johnson P, Gambell J, Linch D. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;381(9880):1817. Epub 2013 Apr 22.