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Plasma Cell Dyscrasias: Laboratory Diagnostic Approach and Differential Diagnosis

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Abstract. A diverse spectrum of clonal disorders arising from terminally differentiated B cells that secrete monoclonal immunoglobulins or their components is collectively referred to plasma cell dyscrasias (PCDs). Clinical presentations vary widely, from early asymptomatic stages such as monoclonal gammopathy of undetermined significance, to organ-damaging conditions including multiple myeloma, AL amyloidosis, Waldenström macroglobulinemia, and other less common plasma cell related syndromes. Accurate laboratory diagnosis is essential because early recognition of monoclonal proteins can prevent irreversible organ damage involving bone, kidney, or hematopoietic systems. This review summarizes current laboratory diagnostic approaches for PCDs and discusses key differential diagnosis across major PCD entities. A narrative literature research was performed using open-access databases (PubMed, Scopus, ScienceDirect, and Google Scholar), focusing on publications from 2015-2025 addressing diagnostic modalities, disease-defining criteria, and distinguishing features relevant to clonal and reactive plasma cell processes. Findings highlight that optimal diagnosis relies on integrating serum and urine studies, immunofixation, serum free light chain assay with immunophenotyping, cytogenetic profiling, and bone marrow assessment. Flow cytometry enables clonal confirmation through aberrant plasma cell immunophenotypes, whereas FISH identifies recurrent genomic abnormalities with prognostic relevance. Molecular assays provide additional refinement in selected cases. Accurate interpretation requires correlation with clinical features to differentiate PCDs spectrum. A structured, multimodal diagnostic strategy is essential for precise classification, risk stratification, and guiding patient management across diverse healthcare settings.

Keywords: Differential Diagnosis; Laboratory Diagnosis; Monoclonal Gammopathy; Monoclonal Protein; Plasma Cell Dyscrasias

1. INTRODUCTION

The recognition of abnormal proteins in patients with unexplained bone disease traces back to the mid-19th century, when Henry Bence Jones described a peculiar protein in the urine of a patient with brittle bones, which later termed as Bence-Jones protein (Ramakrishnan & Jialal, 2023; Sewpersad & Pillay, 2021). Over subsequent decades, improved biochemical and electrophoretic techniques led to detections of monoclonal immunoglobulins, eventually enabling characterization of what is now known as multiple myeloma (MM) and related disorders (Ribatti, 2018).

The spectrum known as plasma cell dyscrasias (PCDs) refers to clonal expansions of end-stage B cells with the capacity to generate monoclonal immunoglobulins or their components (Hanbali, Alamer, & Alhayli, 2025; Wahed & Dasgupta, 2015). This disease may present as asymptomatic early lesions, exemplified by monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma, or as advanced malignancies capable of significant organ damage, such as MM, immunoglobulin light chain disease,

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systemic amyloidosis, and several uncommon clonal plasma cell disorders (de Kat Angelino & Jacobs, 2021).

Epidemiologically, MM remains one of the most common hematologic malignancies worldwide. According to recent analysis based on the GLOBOCAN 2022 database and the Global Burden of Disease 2021 study, the number of incident MM cases worldwide nearly tripled from 55,710 in 1990 to 148,755 in 2021, with a global estimate of 187,952 new cases in 2022 (Diao et al., 2025; Pan, Zhang, Wang, & Song, 2025). In Indonesia, although comprehensive national cancer-registry data remain limited, published reports and clinical registries suggest that MM constitutes a substantial portion of hematologic malignancies seen in referral centers. The median age at diagnosis in Indonesia exceeds 50 years, mirroring global age-related patterns (Tadjoedin, Reksodiputro, & Toruan, 2011). These findings underscore that PCDs, despite being less frequent than common solid tumors, represent an important and growing public health concern.

The clinical relevance of accurate laboratory diagnosis of PCDs cannot be overstated. Early detection of monoclonal protein, before overt organ damage such as bone lesions, renal failure, or anemia, enables timely intervention, improves prognosis, and facilitates monitoring of disease progression or therapeutic response (Sharma, Suri, & Kour, 2020; van de Donk, Pawlyn, & Yong, 2021). Given the wide biological heterogeneity, from benign to malignant, secretory to non-secretory, indolent to aggressive, precise and sensitive laboratory methods are essential to distinguish among them, guide therapy, and follow up appropriately (Sharma et al., 2020).

Therefore, the objective of this narrative review is to provide a comprehensive overview of current laboratory diagnostic strategies used in PCDs, including screening assays, confirmatory tests, bone marrow evaluation, and supportive studies, and to discuss key differential diagnoses across the spectrum of plasma cell disorders. Through this, we intend to highlight both common pitfalls and contextually relevant diagnostic considerations, especially in settings with limited resources.

2. METHODS

This review employed a narrative literature review design to synthesize current evidence on the laboratory diagnostic approach and differential diagnosis of PCDs. A comprehensive search of major electronic databases, such as PubMed, Scopus, ScienceDirect, and Google Scholar, was conducted to identify relevant literature addressing diagnostic modalities and comparative diagnostic criteria across major PCD entities. Literature searches

used combinations of the following keywords and phrases: “plasma cell dyscrasias” OR “monoclonal gammopathy” OR “plasma cell disorders”, “serum protein electrophoresis” OR “immunofixation electrophoresis”, “serum free light chain assay”, “bone marrow plasma cells”, “flow cytometry immunophenotyping”, “cytogenetics” OR “FISH analysis”, “monoclonal protein detection”, and “PCD differential diagnosis”. To ensure broader coverage, the search strings were expanded using conceptual phrases such as “laboratory diagnosis of plasma cell dyscrasias”, “diagnostic approach to monoclonal gammopathies”, “evaluation of M-protein disorders” “amyloidosis laboratory diagnosis”, “Waldenström macroglobulinemia diagnosis”, and “integrated laboratory evaluation in PCDs”. Articles published between 2015 and 2025 were evaluated, with prioritization of full-text English-language publications describing laboratory techniques, diagnostic performance, or disease-defining criteria relevant to PCDs. Eligible literature included clinical guideline, consensus documents, review articles, original research, and relevant cases series that discussed screening tests, confirmatory assays, bone marrow evaluation, and differential diagnostic considerations. Extracted information was narratively synthesized to highlight diagnostic principles, interpretation of laboratory data, and discriminating features used in distinguishing plasma cell disorders. No quantitative or statistical analyses were conducted. Ethical clearance was unnecessary because the study did not include research involving human or animal subjects.

3. RESULTS AND DISCUSSION

Pathophysiology of Plasma Cell Dyscrasias

In normal immune physiology, plasma cells arise when naive B lymphocytes encounter antigen, become activated, and undergo somatic hypermutation within germinal centers (ElTanbouly et al., 2023; Giordano et al., 2024; Song & Matthias, 2018). Antigen exposure, together with T-cell, facilitates affinity maturation and class-switch recombination, while transcription factors such as Blimp-1, XBP-1, and IRF4 orchestrate the transition of germinal-center B cells into antibody-secreting plasma cells (ElTanbouly et al., 2023; Song & Matthias, 2018). This maturation pathway generates a spectrum of plasma cell populations, from short-lived plasmablasts that mediate immediate responses to long-lived plasma cells that maintain antibody production (Giordano et al., 2024; Nutt, Hodgkin, Tarlinton, & Corcoran, 2015). Once fully mature, plasma cells enter a terminal, non-proliferative state and may persist in the marrow when provided with interleukin-6 (IL-6), A proliferation-inducing ligand (APRIL), B-cell activating factor, and other signals from stromal and hematopoietic elements, including eosinophils. Each plasma cell produces a single class of immunoglobulin and release vast

quantities of antibody molecules per second, underscoring their essential role in humoral immune response (Soh, Tario Jr, & Wallace, 2017).

Like other leukocyte lineages, plasma cells can undergo malignant transformation. Most PCDs arises after germinal-center affinity maturation, as the resulting neoplastic cells generally exhibit hypermutated immunoglobulin genes and share the phenotype of long-lived marrow plasma cells (Clarke, Fuller, & Erber, 2024; Soh et al., 2017). Once a clonal plasma cell population acquires genetic alterations that confer a survival or proliferative advantage, it may remain indolent or evolve into more aggressive disease, depending on secondary genetic events (Soh et al., 2017). The most common initiating events involve chromosomal translocations of the immunoglobulin heavy chain (IGH) locus at 14q32, which place oncogenes such as CCND1 (11q13), FGFR3 (4p16), or MAF (16q23) under the influence of the potent IGH enhancers. Subsequent abnormalities, such as MYC or RAS pathway activation and loss of TP53 function, contribute to further clonal expansion, genomic instability, and resistance to therapy (Clarke et al., 2024; Cristóbal-Vargas, Cuadrado, & Gutiérrez, 2025; Musto et al., 2021). These abnormalities underlie the biological continuum observed among PCDs, reflecting progressive accumulation of genetic and microenvironmental alterations within a shared pathogenic framework (Dutta et al., 2019; Plano et al., 2023; van de Donk et al., 2021).

Once malignant plasma cell clones expand, organ injury arises through disruption of the bone marrow and skeletal microenvironment and through direct tissue damage mediated by secreted monoclonal immunoglobulins, particularly light chain proteins (Giannandrea et al., 2022; Giordano et al., 2024; Kanzaki et al., 2019). In bone, clonal plasma cells dysregulate the RANK-RANKL-OPG axis, enhancing osteoclast activity and inhibiting osteoblasts, which leads to osteolytic lesions and pathologic fractures (Mukkamalla & Malipeddi, 2021; Pop et al., 2021). In the kidney, free light chains precipitate in distal tubules, induce cast nephropathy and cause tubular toxicity (Kanzaki et al., 2019; Royal et al., 2020). In amyloid light chain (AL) amyloidosis, misfolded light chain fibrils deposit in heart, kidney and nerves, triggering organ failure (Morè et al., 2024; G. Palladini, Milani, & Merlini, 2020). Additional mechanisms, such as hyperviscosity (most prominently from IgM but also possible with markedly elevated IgA) and bone-marrow infiltration leading to hematopoietic suppression, further contribute to the organ damage observed in many PCDs (Bouchnita, Eymard, Moyo, Koury, & Volpert, 2016; Rajkumar, 2020; Weaver, Rubinstein, & Cornell, 2020).

Building upon these diverse mechanisms of organ injury, the clinical spectrum of PCDs ranges from asymptomatic precursor conditions to aggressive, organ-threatening diseases

(Hanbali et al., 2025). Premalignant stages such as MGUS may evolve into SMM and ultimately active MM through accumulating genetic aberrations and microenvironmental influences (Giordano et al., 2024; Soh et al., 2017). Beyond this core progression, other distinct entities include Waldenström macroglobulinemia, featuring lymphoplasmacytic infiltration and IgM-mediated hyperviscosity (Bibas, Sarosiek, & Castillo, 2024; Gertz, 2023); AL amyloidosis, marked by amyloid deposition from misfolded light chains leading to multi-organ dysfunction (Al Hamed et al., 2021; A. Palladini et al., 2024; G. Palladini et al., 2020); and rarer paraneoplastic syndromes like POEMS, characterized by polyneuropathy, organomegaly, and vascular endothelial growth factor elevation (D'Sa et al., 2022; Dispenzieri, 2023; Ishii et al., 2024). Key features of these major PCD entities are summarized in the table 1.

Table 1. Overview of major plasma cell dyscrasias.

Entity	% Plasma Cells	M-Protein Type	Clinical Features
MGUS	<10%	Any, <3 g/dL	Asymptomatic, no end-organ damage
Smoldering Myeloma	10-60%	≥3 g/dL	Asymptomatic, no end-organ damage
Multiple Myeloma	≥10%	Any	CRAB (hyperCalcemia, Renal failure, Anemia, Bone lesions)
Waldenström macroglobulinemia	Variable	IgM	Hyperviscosity, lymphadenopathy, neuropathy
AL Amyloidosis	<10%	Light chains	Organ failure (heart, kidney, nerves)
POEMS Syndrome	Variable	IgG/IgA (λ)	Polyneuropathy, organomegaly, endocrinopathy, skin changes

Sources: (Abeykoon, Tawfiq, Kumar, & Ansell, 2022; Al Hamed et al., 2021; Bibas et al., 2024; D'Sa et al., 2022; Dispenzieri, 2023; Gertz, 2023; Giordano et al., 2024; Ishii et al., 2024; Musto et al., 2021; A. Palladini et al., 2024; G. Palladini et al., 2020; Rajkumar & Kumar, 2020; van de Donk et al., 2021; Visram, Cook, & Warsame, 2021).

Laboratory Diagnostic Approach

Screening Tests

Clinical laboratories employ several methods to identify, measure, and characterize immunoglobulins as part of routine screening, diagnostic evaluation, and follow-up of PCDs (Genzen et al., 2018; Rubinstein & Stockerl-Goldstein, 2021). Quantifying the M-protein is important to establishing the diagnosis and guiding subsequent management. Among the available assays, serum protein electrophoresis (SPEP) remains the primary tool for detecting an M-protein. This technique separates serum constituents into albumin, α1, α2, β, and γ fractions on the basis of their electrical charge and molecular size. Intact immunoglobulins

migrate mainly within the γ fraction, so a monoclonal population typically manifests as a sharp, narrow peak known as an M-spike. Quantification is performed by densitometric analysis, integrating the proportion of the M-spike relative to the total serum protein. Although SPEP provides an overview of the albumin-globulin pattern and is effective for detecting most monoclonal gammopathies, it does not determine heavy or light chain isotype and may miss small or exclusively free light chain clones (de Kat Angelino & Jacobs, 2021; Rubinstein & Stockerl-Goldstein, 2021). Technical variability between methods, platforms, and operator expertise may also affect interpretation (Cho, Lee, Yoo, Kim, & Uh, 2022).

Because SPEP alone cannot establish clonality, serum immunofixation electrophoresis (IFE) is required when an abnormal or suspicious pattern is present (de Kat Angelino & Jacobs, 2021; Rubinstein & Stockerl-Goldstein, 2021). Combining SPEP with IFE improves specificity and allows isotype identification. IFE uses targeted antisera to determine the heavy chain type (IgG, IgA, IgM) and light chain type (κ or λ) of an immunoglobulin and is commonly performed reflexively (Rubinstein & Stockerl-Goldstein, 2021). IFE also has high sensitivity and specificity to detect a small M-protein early in patient with MM (Uddin, Rahman, Sultana, & Saha, 2018). Accordingly, SPEP and IFE function as complementary assays: SPEP serves as the initial screening method for protein abnormalities, whereas IFE remains as the gold standard for confirming and characterizing monoclonal immunoglobulin in the diagnostic workup of PCDs (Fadili et al., 2025).

Although IFE improves specificity, low-level M-proteins, particularly in AL amyloidosis, may still be difficult to detect. In up to 30% of AL amyloidosis cases, no visible M-spike appears on SPEP because the small plasma cell clone produces only free light chains that migrate outside the γ region or are rapidly excreted in urine. The serum free light chain (sFLC) assay has become an indispensable component of screening, particularly for light chain myeloma and AL amyloidosis. By directly quantifying circulating κ and λ free light chains and deriving the κ/λ ratio, the sFLC assay overcomes many limitations of SPEP and IFE in detecting low-level or light chain only disease. sFLC is more sensitive than SPEP/IFE for identifying oligo-secretory disorders and is useful for monitoring disease burden or response, especially in the follow-up of patients with low levels of monoclonal proteins. However, the interpretation of sFLC must account for factors affecting clearance and production, including renal dysfunction, inflammation, and polyclonal immune activation. Laboratories must interpret abnormal κ/λ ratio within clinical context and be aware that reference intervals vary across analytical platforms (Cho et al., 2022; Rubinstein & Stockerl-Goldstein, 2021; Veskovski et al., 2024).

Urine protein electrophoresis (UPEP) and urine IFE provide complementary information, particularly for detecting Bence-Jones proteins (Cho et al., 2022; Rubinstein & Stockerl-Goldstein, 2021). Despite having lower analytical sensitivity compared with serum-based methods, UPEP/uIFE are still required when serum findings provide limited clarity. This includes cases with isolated sFLC abnormalities or when new renal impairment raises concern for monoclonal gammopathy associated renal disease (Rubinstein & Stockerl-Goldstein, 2021). 24-hour collections remain the standard when quantification is required, but random urine samples may be used in settings where complete collections are impractical (Reddy, Rapiti, & Gounden, 2021). Combining SPEP, serum IFE, and sFLC provides the highest screening sensitivity, with reported detection rates approaching 99% in AL amyloidosis when all three are used together. For patients with suspected light chain disease or unexplained renal impairment, adding 24-hour UPEP/uIFE ensures detection of urinary monoclonal proteins and may guide diagnosis and management (Genzen et al., 2018; Rubinstein & Stockerl-Goldstein, 2021).

Confirmatory Tests

Flow cytometry immunophenotyping is also useful in the diagnosis of PCDs by providing clonal confirmation through detection of aberrant plasma cell surface marker profiles. Normal plasma cells exhibit bright CD38 and CD138 expression and retain CD19, with variable CD45 (Das et al., 2022; Wahed & Dasgupta, 2015). In contrast, neoplastic plasma cells demonstrate aberrancies such as loss of CD19 and CD45 and acquisition of CD56, with occasional expression of CD117 depending on the clone (Fend, Dogan, & Cook, 2023; Wahed & Dasgupta, 2015). Identification of an immunophenotypically restricted population supports monoclonality and assists in differentiating reactive plasmacytosis from clonal disorders. Flow cytometry is also valuable in assessing marrow involvement, minimal residual disease, and distinguishing between entities such as MGUS, SMM, and MM (Das et al., 2022).

Cytogenetic and fluorescence in situ hybridization (FISH) analyses further characterize the plasma cell clone and provide critical prognosis information (Morè et al., 2025; Rajkumar, 2022). FISH on enriched CD138+ plasma cells allows detection of recurrent abnormalities associated with PCDs (Morè et al., 2025). In MM, FISH identifies major primary abnormalities such as t(11;14), t(4;14), and t(14;16), as well as secondary lesions including del(17p), gain(1q), and del(1p), which carry important prognostic implications (Dhabe, Das, & Parihar, 2023; Morè et al., 2025; Rajkumar, 2020). In AL amyloidosis, t(11;14) is highly prevalent and assists in distinguishing AL from conventional myeloma (Ozga et al., 2021). Waldenström macroglobulinemia commonly shows deletions in 6q, providing supportive evidence in the

differential diagnosis of IgM-associated disorders (Dogliotti et al., 2023). While cytogenetic findings significantly aid classification and risk stratification, they are increasingly complemented by molecular assays that provide more refined characterization of clonal abnormalities (Rajkumar, 2022).

Molecular testing serves as an adjunct in selected clinical settings. Next-generation sequencing (NGS) panels can identify somatic mutations associated with clonal plasma cell disorders, including alterations in KRAS, NRAS, BRAF, DIS3, FAM46C, and TP53, among others. While not universally required for diagnosis, molecular profiling improves understanding of clonal evolution, helps differentiate indolent from progressive disease, and may uncover mutations relevant for targeted therapy (Dragomir et al., 2024; Perroud et al., 2023).

Bone Marrow Examination

Bone marrow examination remains essential for the diagnosis and classification of PCDs. It enables both qualitative and quantitative assessment, including immunophenotypic characterization of plasma cells (Elsabah et al., 2020). The proportion of plasma cells is typically determined by counting them relative to other nucleated hematopoietic cells within 200-500 cells differential. However, aspirate smears frequently yield lower plasma cells estimates than biopsies, resulting a lack of consensus on the reliability of aspirate morphology alone for accurately determining marrow plasma cell percentages (Gantana, Musekwa, & Chapanduka, 2024).

In bone marrow aspirate smears, plasma cells generally preserve at least some of their morphological features, most notably their abundant, intensely basophilic cytoplasm. Aspirate smears can assess plasma cell morphology such as binucleation, eccentrically placed nucleus, or prominent Golgi, and provide a differential count but aspirates can underestimate burden because infiltration is often focal. Bone marrow biopsy offers a more reliable estimate of marrow involvement and better demonstrates architectural patterns (focal, interstitial, diffuse) and marrow replacement. When present, morphologic atypia (binucleation, prominent nucleoli, variation in N:C ratio) supports a neoplastic plasma cell process (Batool et al., 2022; Ribourtout & Zandecki, 2015).

Immunohistochemistry (IHC) facilitates clearer recognition of plasma cells within bone marrow tissue by employing antibodies directed against markers such as CD138 or MUM1. For this reason, IHC is most informative when interpreted alongside bone marrow aspirate smears. CD138 staining enhances plasma cell detection compared with hematoxylin-eosin stain sections (Gantana et al., 2024; Lee et al., 2017). Demonstration of κ or λ light chain

restriction by IHC or in-situ hybridization on biopsy material strengthens evidence of clonality, particularly in non-secretory or light chain only cases. Use of CD138 and MUM1 staining also reduces sampling/interpretation variability (Fend et al., 2023).

The proportion of plasma cells in the bone marrow was emphasized for distinguishing MGUS from MM (Lee et al., 2017). Current diagnostic standards define MM by the presence of ≥10% clonal plasma cells in the marrow together with myeloma-defining events. However, because aspirate and biopsy counts can differ, it is recommended to consider the higher value when discrepancy exists (Amini, Yellapragada, Shah, Rohren, & Vikram, 2016; Gantana et al., 2024). Trephine biopsy with CD138 IHC is therefore recommended for accurate quantification and to avoid misclassification of MGUS, SMM, or MM (Lee et al., 2017).

Other Supportive Tests

Supportive laboratory and imaging parameters provide complementary prognostic information and help detect organ involvement across the spectrum of PCDs (Amini et al., 2016). Serum β_2-microglobulin is an established marker of tumor burden and renal clearance and is incorporated into contemporary staging systems because higher levels are associated with inferior progression-free and overall survival (Rajkumar, 2020; T. Zhang et al., 2024). β_2-microglobulin remains informative across PCD phenotypes where tumor burden or renal function are relevant (T. Zhang et al., 2024). Lactate dehydrogenase (LDH) is an accessible marker of cell turnover and aggressive biology. Elevated LDH is associated with higher proliferation, extramedullary disease, and worse prognosis and is commonly used to create a unified prognostic index that helps in clinical care (Rajkumar, 2020). Routine assessment of serum calcium and creatinine (or estimated glomerular filtration rate) is mandatory at baseline and during follow-up because hypercalcemia and renal impairment are disease-defining organ lesions in PCDs and directly influence staging and treatment urgency (G. Palladini et al., 2020; Rajkumar, 2022). In AL amyloidosis, early detection of renal involvement is particularly important because prompt reduction of circulating pathogenic light chains improves renal outcomes (G. Palladini et al., 2020).

Radiologic evaluation contributes to suggesting the diagnosis, identifying skeletal involvement, and monitoring treatment response or disease progression. Whole-body low-dose computed tomography (WBLD-CT), 18F fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT (PET/CT), and magnetic resonance imaging (MRI) each serve well-defined roles in initial staging, detection of focal marrow or lytic lesions, and evaluation of extramedullary involvement or therapeutic response. In low-resource settings, conventional skeletal surveys remain common because advanced imaging modalities are not widely

accessible, particularly for identifying vertebral and pelvic lytic lesions. PET/CT and MRI are valuable for assessing tumor burden and disease activity, with both providing high sensitivity for detecting metabolically or structurally active bone lesions (Amini et al., 2016; Gantana et al., 2024). PET/CT differentiates metabolically active from inactive sites by measuring glucose uptake, whereas MRI assesses tissue characteristics based on water and fat content. As a result, MRI excels in identifying diffuse marrow infiltration, while PET/CT is superior for delineating focal lesions, especially those located outside the typical MRI field of view (Gantana et al., 2024).

Integration of Laboratory Data

The diagnosis of PCDs requires integrated interpretation of multiple laboratory modalities rather than reliance on a single diagnostic test. Screening begins with serum-based studies (SPEP, IFE, and sFLC), which together detect most monoclonal proteins and establish isotype characteristics. When abnormalities are identified, urine studies help clarify the presence and excretion pattern of monoclonal light chains, particularly in suspected light chain mediated renal injury (Genzen et al., 2018; Rajkumar, 2020; Rubinstein & Stockerl-Goldstein, 2021). Bone marrow examination provides definitive confirmations of clonality and quantification of plasma cell burden, allowing distinction among MGUS, SMM, MM, and other clonal entities (Gantana et al., 2024; Ribourtout & Zandecki, 2015). Flow cytometry and FISH further refine the diagnostic picture by identifying immunophenotypic aberrancies and cytogenetic risk features that influence classification and prognosis (Fend et al., 2023; Morè et al., 2025). Supportive markers such as β_2-microglobulin, LDH, calcium, and renal indices contextualize the degree of organ involvement and are incorporated into contemporary staging frameworks (G. Palladini et al., 2020; Rajkumar, 2020, 2022; T. Zhang et al., 2024). Imaging modalities, especially MRI and PET/CT, complement these findings by detecting focal or diffuse marrow infiltration and extramedullary disease (Amini et al., 2016; Gantana et al., 2024). Synthesizing these datasets ensures accurate identification of the underlying plasma cell disorder, appropriate risk stratification, and informed clinical decision-making. This integrated framework is particularly useful for resolving diagnostic ambiguities, such as distinguishing reactive from clonal processes or indolent from progressive states.

Differential Diagnosis

Reactive Plasmacytosis

Reactive plasmacytosis refers to a polyclonal expansion of plasma cells within the bone marrow and can occur in a range of settings, including viral infection, autoimmune disorders, chronic inflammation, certain anemias, medication effects, and some malignancies. Although

plasma cells typically account for only 10-20% of marrow nucleated cells, the proportion can occasionally rise above 50%. Distinguishing this benign reactive process from PCDs requires a combined assessment using morphology, immunohistochemistry, serum protein studies, and flow cytometry analysis (Batool et al., 2022; J. Zhang et al., 2018).

Morphologically, the marrow is typically normocellular with mature plasma cells, scattered reactive or binucleate forms, increased histiocytes with hemophagocytosis, lymphocytosis, eosinophilia, and dyserythropoiesis. In contrast, PCDs show both mature and immature plasma cells and often reduced hematopoietic elements (Batool et al., 2022). Immunophenotyping reveals a preserved κ/λ ratio and absence of the aberrant markers characteristic of clonal plasma cells (Das et al., 2022). Reactive plasmacytosis may simulate neoplasia when plasmacytosis is marked, making correlation with serum/urine protein studies showing polyclonal hypergammaglobulinemia, flow cytometry demonstrating polytypic light chain expression, and the clinical setting essential for accurate distinction (Jawad et al., 2017).

MGUS vs Smoldering Myeloma vs Multiple Myeloma

MGUS is an asymptomatic, premalignant disorder marked by a clonal expansion of plasma cell or lymphoplasmacytic cells. It is the most frequent form of PCD, occurring in over 3% of adults older than 50 years, and is clinically relevant because it constitutes the initial stage in the progression toward MM (Abeykoon et al., 2022; Amini et al., 2016; Wahed & Dasgupta, 2015). MGUS can be further classified into risk categories using the M-protein isotype, its concentration, and the sFLC ratio, all of which assist in estimating the expected annual risk of progression. SMM represents an intermediate condition between MGUS and MM, both biologically and clinically. Compared with MGUS, SMM typically demonstrates higher serum M-protein levels and a larger proportion of clonal plasma cells within the bone marrow. Differentiation from overt MM is essential because many SMM cases remain stable for years without therapy (Amini et al., 2016; Musto et al., 2021; Visram et al., 2021). MM itself is a systemic malignancy of post-germinal center plasma cells and is almost always preceded by both MGUS and SMM (Amini et al., 2016; Caers et al., 2018; Wahed & Dasgupta, 2015). Distinguishing SMM from MM requires integration of clinical, laboratory, and radiologic findings, except in cases where marrow plasma cell infiltration exceeds 60%, which alone constitutes a myeloma-defining event (Fend et al., 2023; van de Donk et al., 2021; Wahed & Dasgupta, 2015). The diagnostic spectrum encompassing MGUS, SMM, and MM is defined by combined laboratory, bone marrow, imaging, and clinical assessment, with the principal differentiating features summarized in the table 2.

Table 2. Diagnostic comparison of MGUS, SMM, and MM.

Entity	M-protein	Plasma cells (%)	CRAB symptoms	Progression risk
MGUS	<3 g/dL	<10%	None	1% per year
SMM	≥3 g/dL	10-60%	None	10% per year
MM	Any	≥10%	Present	Active disease

Sources: (Amini et al., 2016; Fend et al., 2023).

Diagnostic differentiation relies on quantitative protein studies (SPEP, IFE, sFLC), accurate marrow plasma cell quantification (preferably biopsy supported by CD138 IHC), and modern imaging modalities such as MRI or PET/CT to identify occult bone disease (Rajkumar, 2020, 2022). Diagnostic cut-offs, follow-up strategies, and risk stratification continue to follow guidance from the International Myeloma Working Group (IMWG) and European Myeloma Network (EMN) (Musto et al., 2021; Rajkumar, 2020). High-risk cytogenetics such as t(4;14), t(14;16), t(14;20), deletion 17p, gain 1q, or TP53 mutation support progression toward MM but are not required for the diagnosis of MGUS or SMM. MGUS and SMM commonly harbor the same primary cytogenetic abnormalities as MM, such as IGH translocations and hyperdiploidy, but secondary high-risk lesions predominantly occur in MM and are strongly associated with disease progression (Abeykoon et al., 2022; Musto et al., 2021; Rajkumar & Kumar, 2020).

Waldenström Macroglobulinemia

Waldenström macroglobulinemia is a lymphoplasmacytic neoplasm characterized by IgM monoclonal secretion, bone-marrow infiltration by lymphoplasmacytic cells, and clinical manifestations often driven by IgM-related hyperviscosity or peripheral neuropathy. Patients frequently present with constitutional B symptoms, bleeding tendencies, peripheral neuropathy, hyperviscosity syndrome, hepatosplenomegaly, and lymphadenopathy (Amini et al., 2016; Gertz, 2025; Guha et al., 2022). A useful diagnostic clue is the presence of IgM-dominant M-protein accompanied by a marrow infiltrate with lymphoplasmacytic morphology rather than a pure plasma cell pattern (Gertz, 2025). The MYD88 L265P mutation is detected in the majority of cases and, although not entirely specific, provides valuable diagnostic support. Molecular testing for MYD88 and CXCR4 variants further helps refine classification and guide management in IgM-related monoclonal gammopathies (Bibas et al., 2024; Gertz, 2023, 2025). Immunophenotyping typically shows expression of surface IgM along with markers such as CD5, CD19, CD20, CD22, CD23, CD25, CD27, CD103, and CD138 (Bibas et al., 2024). Integration of immunophenotypic findings, bone marrow morphology, and MYD88 mutation analysis allows reliable distinction of Waldenström macroglobulinemia from other IgM and non-IgM PCDs (Gertz, 2025).

Amyloidosis (AL type)

AL amyloidosis is a multisystem disease resulting from extracellular accumulation of misfolded monoclonal light chains produced by a typically small plasma cell clone, often comprising <10% of marrow plasma cells (Amini et al., 2016; G. Palladini et al., 2020). These misfolded proteins from β-pleated sheet fibrils that characteristically demonstrate Congo red and thioflavin positivity, making histologic confirmation essential (Amini et al., 2016; Morè et al., 2024). Accurate amyloid typing, most reliably performed by mass spectrometry on Congo red positive tissue, is required to differentiate AL amyloidosis from other amyloid subtypes (Morè et al., 2024). Because the underlying clone may secrete only free light chains and be quantitatively subtle, comprehensive serum and urine monoclonal protein studies (SPEP/IFE, sFLC, and 24-hour UPEP/IFE) are necessary (Genzen et al., 2018; Rubinstein & Stockerl-Goldstein, 2021). Bone marrow examination supplemented by FISH, particularly assessing for t(11;14), which is frequently observed in AL, can further assist in identifying the pathogenic clone (Ozga et al., 2021; G. Palladini et al., 2020). Clinically, AL amyloidosis may coexist with PCDs such as MGUS, MM, or Waldenström macroglobulinemia, and organ involvement, particularly heart and kidneys, typically dictates the presentation (Amini et al., 2016; Fend et al., 2023). Early recognition, targeted tissue biopsy, and integration of laboratory and clinical findings are critical to prevent delayed diagnosis and to distinguish AL amyloidosis from other PCDs.

POEMS Syndrome

POEMS syndrome, named for its defining features of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes, is a rare paraneoplastic disorder driven by a small monoclonal plasma cell clone, most often λ-restricted. Diagnostic clues include a progressive demyelinating sensorimotor neuropathy, predominantly sclerotic rather than osteolytic bone lesions, and markedly increased circulating vascular endothelial growth factor (VEGF) (D'Sa et al., 2022; Fend et al., 2023; Guha et al., 2022). Because the plasma cell clone is usually minimal, conventional myeloma diagnostics may lack sensitivity. Therefore, protein electrophoresis with immunofixation remains crucial, as sFLC assays may appear within normal limits due to concurrent polyclonal stimulation. When identified, the M-protein is usually less than 10 g/L and myeloma-defining features are generally absent. Accurate recognition is crucial, as misclassification as MGUS/SMM may delay necessary therapy, whereas treating POEMS as MM or plasmacytoma can lead to unnecessary toxicity. A comprehensive diagnostic approach, including evaluation for λ-restricted monoclonal protein, VEGF measurement, neurophysiologic studies, and targeted imaging for sclerotic

lesions, helps distinguish POEMS from other PCDs (D'Sa et al., 2022; Dispenzieri, 2023; Ishii et al., 2024).

Challenges and Future Perspectives

Diagnosis of PCDs remains challenging because of biological heterogeneity and variability in laboratory resources. A key diagnostic pitfall is the presence of atypical or subtle monoclonal components, such as in biclonal gammopathies, non-secretory or oligosecretory myeloma, and light chain only disorders, which may produce little or no detectable M-protein on routine electrophoresis. This makes diagnosis heavily dependent on immunofixation, sFLC assays, and careful bone marrow evaluation, while rare immunoglobulin isotypes and low-burden clones contribute to misdiagnosis or delayed classification, especially when clinical features are nonspecific (He et al., 2021; Isaias et al., 2024). Laboratory variability remains another barrier, with differences in electrophoresis platforms, sFLC assay types, flow cytometry panels, and FISH coverage leading to inconsistent interpretation across institutions. This affects risk stratification and longitudinal follow-up, particularly when patients are referred between hospitals. The lack of harmonized protocols is especially problematic in low- and middle-income settings.

Mass spectrometry-based methods are emerging as a highly sensitive approach for M-protein detection. They can differentiate therapeutic monoclonal antibodies from endogenous M-proteins and may improve minimal residual disease monitoring (Murray et al., 2021; Thoren, 2021). However, implementation is limited by equipment cost, need for specialized personnel, and absence of standardized workflows, making near-term adoption challenging for many Indonesia laboratories (Thoren, 2021; Wenk, Zuo, Kislinger, & Sepiashvili, 2024). Resource limitations are a major concern in Indonesia, where access to sFLC testing, cytogenetics/FISH, multiparameter flow cytometry, and advanced imaging varies widely across regions. In practice, several supporting diagnostic modalities are unavailable or not covered by the national health insurance. Moreover, bone marrow examination may not be consistently performed due to limited equipment availability and occasional patient refusal (Kurniawati, Reksodiputro, & Atmakusuma, 2020). Strengthening referral networks and improving access to essential diagnostic assays would help reduce disparities. Addressing these challenges through policy-driven investments in training, infrastructure, and research will be key to advancing PCD management, ultimately supporting earlier detection, accurate classification, and improved patient outcomes in diverse global settings.

4. CONCLUSION

PCDs comprise a wide range of clonal plasma cell related conditions in which early and accurate laboratory diagnosis is essential for preventing irreversible organ injury and guiding appropriate management. Diagnosis relies on a multidimensional assessment that brings together serum and urine protein studies, immunofixation techniques, serum free light chain testing, bone marrow examination, flow cytometry immunophenotyping, cytogenetic evaluation, and supportive biochemical and imaging assessment. Through this combined strategy, monoclonal protein production can be confirmed, disease can be delineated, and differentiation among related disorders such as MGUS, SMM, MM, Waldenström macroglobulinemia, AL amyloidosis, and POEMS syndrome can be achieved. The combined evaluation of cellular morphology, immunophenotypic profiles, and molecular abnormalities enhances diagnostic precision and supports risk stratification across the PCD spectrum. Strengthening clinician and laboratorian awareness of the heterogeneity of PCDs, as well as recognition of diagnostic pitfalls and context-specific challenges, is crucial for timely detection, accurate classification, and improved patient outcomes.

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