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A Comprehensive Review of Monoclonal Gammopathy of Undetermined Significance

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is characterized as a nonmalignant or premalignant state whereby monoclonal immunoglobulins are detected in plasma, urine, or both. Approximately 3% to 4% of the population over the age of 50 is diagnosed with MGUS. It is estimated that 1% will progress to multiple myeloma or lymphoma over 20 years and therefore require ongoing clinical monitoring. Monoclonal gammopathy of undetermined significance is categorized into three types that are determined by the paraprotein clone: immunoglobulin M (IgM) MGUS, non-IgM MGUS, and light chain MGUS. There are high-risk genetic, biochemical, and clinical factors that increase the risk of transformation to multiple myeloma or lymphoma. The incidence of MGUS is two- to threefold higher in the Black population compared with the White population, along with an earlier age of onset. Familial risk and modifiable lifestyle factors are also associated with the development of MGUS and multiple myeloma. Certain monoclonal gammopathies, known as monoclonal gammopathy of clinical significance (MGCS), are associated with various organs that are involved (kidney, brain, skin, lungs, liver, eyes, and heart). The most common MGCS are associated with renal and neurological abnormalities, and treatment may be considered. Early diagnosis and multidisciplinary approaches to mitigate organ damage and other complications are important for the recognition and management of MGCS. Monoclonal gammopathy of undetermined significance is monitored rather than treated unless there are clinical findings of progression or organ dysfunction. Ongoing research and clinical trials are essential to refine monitoring guidelines, develop targeted therapies, and explore preventive measures aimed at reducing progression to multiple myeloma and other malignancies.

CASE STUDY

Ms. Jones is a 54-year-old African American female. She is referred by neurology for a newly identified immunoglobulin A (IgA) lambda monoclonal gammopathy of undetermined significance (MGUS) identified on serum protein electrophoresis (SPEP)-immunofixation (IFE) on routine workup for worsening neuropathy. She has a past medical history of type 2 diabetes, hypertension, and chronic iron deficiency anemia. The results of further workup in the oncology clinic are shown in Table 1.

MGUS Diagnostic Labs

There is a 0.2 g/dL IgA lambda monoclonal protein present on SPEP-IFE. Her lambda light chains are elevated at about two times the upper limit of normal (ULN) with a kappa/lambda ratio that is elevated at 5. There is no monoclonal protein present on urine protein electrophoresis (UPEP). Her lactate dehydrogenase (LDH) is normal, and her beta-2-microglobulin is elevated at just above the ULN. Her complete blood count (CBC) findings are significant for anemia (in the setting of B12 deficiency, diabetes mellitus, and chronic kidney disease). Her basic metabolic panel is significant for mild renal impairment (in the setting of hypertension and diabetes mellitus) with a normal calcium. Imaging studies that were available in the emergency room, including recent CT scans, were unremarkable.

Table 1. Lab Results

Diagnostic labs	Value and normal ranges
SPEP-IFE	0.2 g/dL IgA lambda (absent)
IgG	900 mg/dL (768–1,632 mg/dL)
IgA	500 mg/dL (68–408 mg/dL)
IgM	78 mg/dL (35–263 mg/dL)
Kappa free light chains	8 mg/L (3.3–19.4 mg/L)
Lambda free light chains	40 mg/L (5.7–26.3 mg/L)
FLC ratio	5 (0.26–1.65)
UPEP-IFE	No monoclonal protein detected
Beta-2-microglobulin	3.7 mg/L (0.8–2.3 mg/L)
LDH	225 U/L (0–250 U/L)
Hgb	11 g/dL (12.6–15.9 g/dL)
Creatinine	1.3 mg/dL (0.57–1.1 mg/dL)
Calcium	9.2 mg/dL (8.9–10.7 mg/dL)
Ferritin	90 ng/mL (11–328 ng/mL)
Trans sat	25% (20%–50%)
B12	45 pg/mL (180–914 pg/mL)

Note. SPEP = serum protein electrophoresis; IFE = immunofixation; Ig = immunoglobulin; FLC = free light chain; UPEP = urine protein electrophoresis; LDH = lactate dehydrogenase; Hgb = hemoglobin; B12 = vitamin B12; trans sat = transferrin saturation.

Based on the Mayo risk stratification model (Rajkumar et al., 2005; Turesson et al., 2014), she presents with intermediate-risk IgA lambda MGUS and has a 37% risk of progressing to multiple myeloma (smoldering/active) at 20 years. With competing causes of death factored in, her 20-year risk of progression decreases to 18%. At her recent clinic visit with a nurse practitioner (NP), Ms. Jones was offered the option to undergo a bone marrow biopsy to determine the percentage of plasma cells and identify possible high-risk genetic abnormalities.

During her clinic visit, the NP discussed new risk stratification data to aid in her decision in moving forward with a bone marrow procedure. The recent iSTOP study by Eythorsson et al. (2024) assessed the likelihood of having > 10% plasma cells in the bone marrow based on the following factors: MGUS isotype IgA or biclonal isotype, M protein concentration, free light chain ratio, and total IgG, IgA, and IgM concentrations. Based on this algorithm, she has an 18% risk of having 10% plasma cells in her marrow. The NP also discussed the Precursor Asymptomatic Neoplasms by Group Effort Analysis (PANGEA) model by Cowan et al. (2023). This model provides time-varying clinical biomarkers to aid in predicting the risk of active MM evolving in a single patient over time. The model is designed to be used for patients with or without bone marrow biopsy results. Using this model, she has only a 2.5% risk of progression to multiple myeloma in 2 years and a 7% risk in 5 years. After discussing the likelihood that the results of a bone marrow biopsy would not impact the current plan, Ms. Jones chose to monitor her condition and agreed to follow up with lab work every 6 months and proceed with a bone marrow biopsy when clinically indicated.

Monoclonal gammopathy of undetermined significance (MGUS) is characterized as an asymptomatic, nonmalignant or premalignant state whereby monoclonal (M) proteins or immunoglobulins are detected in plasma, urine, or both (Khwaja et al., 2022; Gozzetti et al., 2022; Liu & Parks, 2025). Monoclonal gammopathy of undetermined significance is often an incidental finding that is present in 3% to 4% of the population over the age of 50 (Kyle et al., 2018; Stern et al., 2023). It can be a precursor to smoldering multiple myeloma (SMM), active multiple myeloma (MM), or lymphoma. The relative risk of progression to malignancy is estimated at approximately 1% to 1.5% per year for immunoglobulin M (IgM) and non-IgM MGUS and 0.3% for light chain only abnormalities (Einarsson Long et al., 2025; Liu & Parks, 2025).

Certain monoclonal gammopathies, known as monoclonal gammopathy of clinical significance (MGCS), are associated with organ involvement. In these cases, treatment should be considered (Dispenzieri, 2023). Research is underway to help better understand MGUS and MGCS. This article describes the characteristics of MGUS, including pathophysiology, diagnosis, epidemiology, high-risk features, and management strategies.

As more patients are screened for MGUS, the number of patients diagnosed with MGUS will likely increase, requiring ongoing observation or medical interventions. Advanced practice providers (APPs) have the education, skills, and experience to provide comprehensive care and the clinical judgment needed to monitor MGUS patients.

MGUS OVERVIEW AND IMPLICATIONS

Monoclonal gammopathy of undetermined significance is categorized into three types: IgM, non-IgM, and light chain MGUS, determined by the paraprotein clone (Rajkumar et al., 2014). IgM MGUS is defined by an IgM monoclonal protein produced by lymphoplasmacytic or lymphocyte cells. It has the potential to develop into Waldenstrom macroglobulinemia (WM) and rarely into chronic lymphocytic leukemia (CLL) and IgM MM. Non-IgM MGUS is produced by clonal plasma cells and is the potential precursor to SMM or MM. In the case of light chain MGUS, clonal plasma cells produce abnormal levels of kappa or lambda light chains. In addition to progressing to MM or SMM, light chain MGUS carries a concurrent increased risk for renal dysfunction or amyloid-associated organ damage (Lomas et al., 2020; Chen et al., 2023).

Monoclonal gammopathy of undetermined significance is defined by having less than 10% monoclonal plasma cells in the bone marrow and a serum or urine monoclonal protein of less than 3 g/dL and 500 mg/24 hours, respectively, or the presence of an abnormal serum free light chain (FLC) ratio. Along with monoclonal gammopathy (MG), MGUS is also defined as the absence of end-organ damage, referred to as CRAB criteria: no hyperCalcemia, Renal insufficiency, Anemia, or Bone lesions (Leung et al., 2021; Abeykoon et al., 2022; Rajkumar et al., 2014). Monoclonal gammopathy of undetermined significance is a condition requiring monitoring and not necessarily treatment, although it may be associated with other medical conditions such as thrombosis, autoimmune diseases, infections, nonpathologic bone fractures, and neuropathy (Sigurbergsdóttir et al., 2023).

Scientific advancements and improved awareness of MGUS characteristics have led to better stratification of long-term monitoring for patients with MGUS. Research is ongoing to explore early treatment options for patients with high-risk features (Kang et al., 2021).

PATHOPHYSIOLOGY AND HIGH-RISK FEATURES

A monoclonal protein is produced by a malignant clonal plasma cell or B lymphocyte. M proteins can present as heavy-chain immunoglobulins (IgG, IgA, IgM, and rarely IgD or IgE). These immunoglobulins can be bound to kappa or lambda light chains. Light chain MGUS can also present unbound to heavy-chain immunoglobulins (Kang et al., 2021; Liu & Parks, 2025).

The pathophysiology of MGUS includes cytogenetic alterations and changes in the bone marrow microenvironment. At diagnosis, common genetic changes include amplifications, deletion 13q, and translocations involving the immunoglobulin heavy chain (IgH) on chromosome 14q32. The translocation of IgH with the cyclin D1 gene

(CCND1) on chromosome 11q13 results in an altered expression of cyclin D1 (an important regulator of the cell cycle) and is present in 25% of patients (Jain et al., 2019; Lee et al., 2024).

Patients with high-risk MGUS features are at an increased risk for progressing to MM or lymphoma compared with low-risk MGUS and should be monitored as clinically indicated. Identification of serological protein profiles (initially) and genetic markers (secondarily) are determinants of high-risk MGUS features (Chen et al., 2023; Da Vià et al., 2022). Approximately 50% of patients with MGUS demonstrate aneuploidy, particularly hyperploidy (Testa et al., 2024). In addition, 50% of patients with MGUS have chromosome 14q32 translocations with 11q13, 4p16, 6p21, 16q23, or 20q11, all of which carry an increased risk of progression (Lakshman et al., 2018; Abeykoon et al., 2022). Mutations or deletions of 17p13 (TP53) and 8q24 (MYC) translocations occur less frequently but are associated with a high risk of progression (Merz et al., 2018; Abeykoon et al., 2022; Testa et al., 2024). All these genetic abnormalities are present at a higher frequency in SMM or MM than in precursor MGUS.

Various MGUS risk stratification models exist and are used to identify patients at an increased risk of developing MM or lymphoplasmacytic lymphoma (LPL). The most common risk model is the Mayo Model (Figure 1). The model lists immunoglobulin isotype, M protein, and FLC ratio as metrics that determine MGUS risk. The model categorizes risk into low (0 of the 3 criteria), intermediate (1–2 of the 3 criteria) and high risk (all 3 of the criteria). The risk of progression is 5%, 21% to 37%, and 58% for low, intermediate, and high risk, respectively. Other models are also used to determine high-risk MGUS and are discussed in Table 2.

EPIDEMIOLOGY

The prevalence of MGUS increases with age, affecting about 3.5% of individuals over the age of 50 to 5% of those over the age of 70. Non-IgM MGUS, including IgG and IgA subtypes, accounts for approximately 80% of cases, with IgG being the most common. Men are diagnosed with MGUS at about twice the rate of women, with an incidence of 120 per 100,000 men compared with 60 per 100,000 women (Li et al., 2024; Kyle et al., 2018).

The incidence of MGUS is two- to threefold higher in the African American population compared with the Caucasian population, along with an earlier age of onset (Abeykoon et al., 2022; Gonsalves & Rajkumar, 2022). There is a familial risk associated with the development of MGUS and MM. In 2009, Landgren et al. compared Swedish relatives of a control population (n = 58,387) to relatives of MGUS patients (n = 14,621). The relatives of MGUS patients had an increased risk of developing MGUS, MM, LPL/WM, or CLL compared with the control group. Relatives of patients with IgG/IgA MGUS had a 4-fold, 2.9-fold, and 20-fold elevated risk of developing MGUS, MM, or LPL/WM, respectively. Relatives of patients with IgM MGUS had a fivefold increased risk of developing CLL.

Lifestyle may also play a role in MGUS progression (Lee et al., 2024; Kleinstern et al., 2022). A recent report from the Progression of Developing Myeloma in a High-Risk Screened Population (PROMISE) study reported an increased incidence of MM in MGUS patients associated with modifiable risk factors such as obesity, smoking, and short sleep duration (Lee et al., 2024). Kang et al. (2021) reported that patients with MGUS and a concomitant comorbidity of hypertension, hyperlipidemia, diabetes, or osteoarthritis demonstrated a higher rate (33%) of progression to MM over 10 years compared with healthy patients.

MGUS DIAGNOSIS

The diagnosis of MGUS is determined by obtaining serum protein electrophoresis (SPEP), immunofixation (IFE), and FLC in 97% of patients. Blood tests should also include a complete blood count and chemistry panel to screen for end-organ dysfunction. A 24-hour urine protein electrophoresis should be considered if there is an increase in the FLC ratio (Gonsalves & Rajkumar, 2022; Liu & Parks, 2025). A bone marrow biopsy should be considered if there are intermediate or high-risk features. Imaging for bone lesions should also be considered if patients report worrisome clinical symptoms or present with intermediate- or high-risk MGUS (Go & Rajkumar, 2018; Gonsalves & Rajkumar, 2022). Table 3 lists clinical tests and scans that may be obtained based on clinical findings.

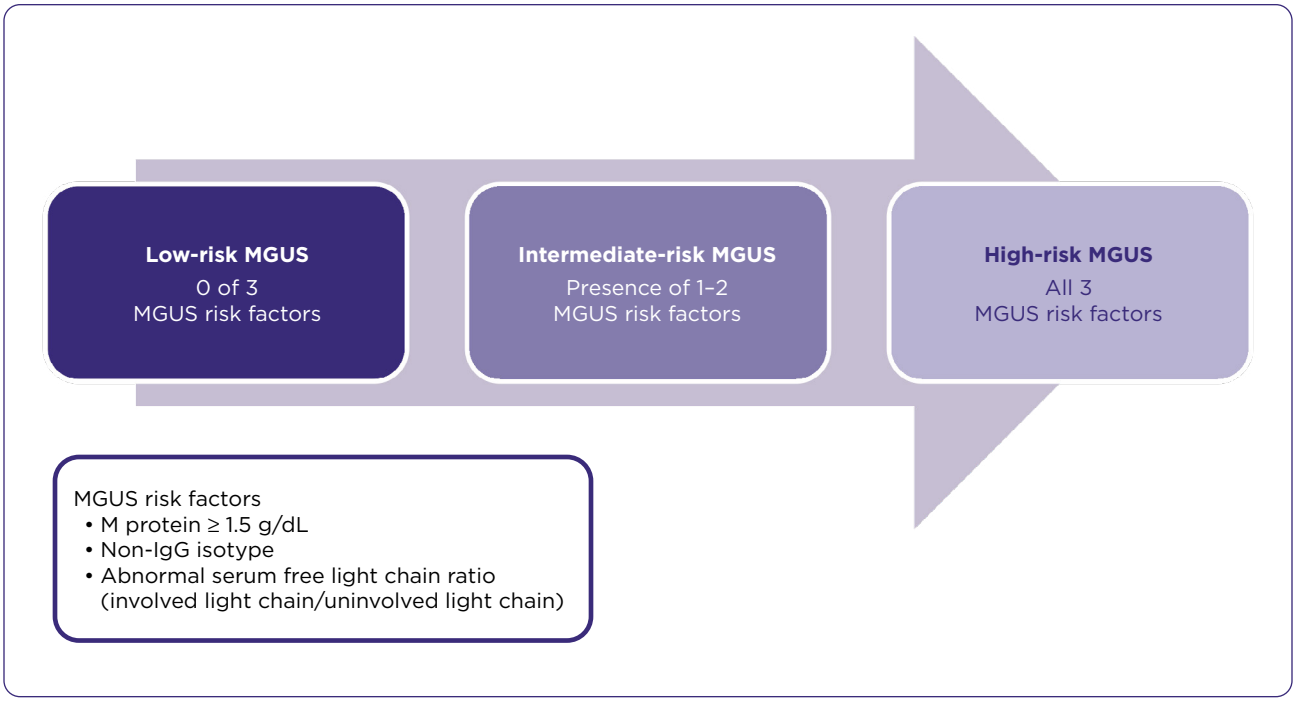

Figure 1. MGUS risk stratification. Information from Rajkumar et al. (2014); Kyle et al. (2018); Abeykoon et al. (2022); Lee et al. (2024).

Monoclonal Gammopathy of Clinical Significance

Monoclonal gammopathy can rarely cause organ damage, known as MGCS. Monoclonal gammopathy of clinical significance is characterized by organ damage caused by a clonal protein, including the kidneys, liver, eyes, skin, or heart, as well as complications related to the nervous system, bones, infections, and thrombosis (Atkin et al., 2018; El-Khoury et al., 2022; Chen et al., 2023; Lomas et al., 2020; Kapoor & Rajkumar, 2022; Lyle et al., 2022; Liu & Parks, 2025; Go & Rajkumar, 2018).

The most recognized forms of MGCS are monoclonal gammopathy of renal significance (MGRS), monoclonal gammopathy of neurological significance (MGNS), and monoclonal gammopathy of cutaneous significance, which are listed in Figure 2 (Chen et al., 2023). The incidence of individuals with MGCS is unknown, and there is a need to recognize MGCS as a subcategory to improve diagnosis, monitoring, and early interventions. The development of national and international diagnostic criteria as well as nationally accepted management guidelines should be integrated into clinical practice (Chen et al., 2023; Atkin et al., 2018; Lee et al., 2024; Stern et al., 2023).

Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy of renal significance was first defined in 2012 by the International Kidney and Monoclonal Gammopathy Research Group. It is characterized by the presence of one or more kidney lesions caused by the presence of a monoclonal immunoglobulin, without evidence of malignancy such as WM, CLL, or MM (Leung et al., 2021; Karam et al., 2023). Monoclonal gammopathy of renal significance is associated with significant morbidity and mortality due to renal impairment (Jain et al., 2019). Although its prevalence is not well-defined, it is estimated to account for approximately 10% of all MGUS cases (Jain et al., 2019).

More than a dozen conditions are classified under MGRS (Figure 2; Ciocchini et al., 2017; Leung et al., 2019). A renal biopsy is required for diagnosis. Studies have found that few patients undergo a biopsy, and when performed, up to 60% of cases reveal causes of renal dysfunction

Table 2. MGUS Risk Stratification Models

Model	Description	Criteria
Mayo	Based on MGUS risk stratification, the presence of 0 risk factors constitutes low-risk MGUS and 3 factors is suggestive of high-risk MGUS	• M protein ≥ 1.5 g/dL • Non-IgG isotype • Abnormal serum FLC ratio
Spanish (2010)	Multiparametric flow cytometry as a valuable tool and the identification of aberrant plasma cell populations predicts the risk of MGUS progression to MM	• aPC/BMPC: > 95% • DNA aneuploidy (such as trisomies) • Immunoparesis
IMWG (2014)	Differentiates non-IgM, IgM, and light chain MGUS	• Serum M protein < 30 g/L • Bone marrow PC/LPC < 10% • Abnormal FLC ratio (< 0.26 and > 1.65)
PANGEA	Multivariate Cox regression with time-varying biomarkers collected at defined clinic visits by selecting clinically significant predictors of progression	• Age • FLC ratio • M-spike (g/dL) • Creatinine (mg/dL)
iSTOP MM	Multivariable predictive model for low-risk vs. high-risk MGUS patients and the need for bone marrow biopsy	• Serum M protein • FLC ratio • Total concentration of immunoglobulin isotype

Note. MGUS = monoclonal gammopathy of undetermined significance; IgG = immunoglobulin G; FLC = free light chain; MM = multiple myeloma; aPC = aberrant plasma cells; BMPC = bone marrow plasma cells; DNA = deoxyribonucleic acid; IgM = immunoglobulin M; PC = plasma cells; LPC = lymphoplasmacytic cells; M-spike = monoclonal protein spike; IMWG = International Myeloma Working Group; PANGEA = Precursor Asymptomatic Neoplasms by Group Effort Analysis. Information from Abeykoon et al. (2022); Zuern et al. (2024); Sidiqi et al. (2020); Stern et al. (2023); Pérez-Persona et al. (2010); Turesson et al. (2014); Rajkumar et al. (2005); Eythorsson et al. (2024); Cowan et al. (2023); Gonsalves & Rajkumar (2022); Liu & Parks (2025).

unrelated to MGRS, highlighting the complexity of the diagnosis and the need for a multidisciplinary approach (Leung et al., 2019; Klomjit et al., 2020; Dimopoulos et al., 2023; Jain et al., 2019). A retrospective study identified predictors of MGRS, including higher levels of proteinuria, increased hematuria, lower mean C3 levels, and less frequently, concurrent diabetes.

Monoclonal Gammopathy of Neurological Significance

The association between MGUS and MGNS was established in a population study by Bida et al. (2009). Among the various MGUS isotypes, the IgM paraprotein is most commonly linked to peripheral neuropathy (PN), highlighting its unique neurological implications compared with other MGUS subtypes. Peripheral neuropathy-associated IgM gammopathy typically presents with symmetrical sensory deficits rather than motor deficits and often begins in the lower extremities prior to impacting the fingers and hands (Castillo et al., 2021; Visentin et al., 2022). The presentation of PN is insidious, occurring over months to years. These clinical findings are known as distal acquired demyelinating symmetric neuropathy with M protein (DADS–M). It is found in approximately 50% of patients with IgM MGNS and is linked to significant disabilities, with symptoms progressing slowly over a 10-to-15-year period from diagnosis (Figure 2).

The diagnosis of MGNS is a diagnosis of exclusion, and other causes such as diabetes, peripheral vascular disease, medications, vitamin deficiencies, thyroid disease, and alcohol dependency should be considered. The International Workshop on WM Consensus Panel created guidelines to diagnose and manage peripheral neuropathies associated with IgM monoclonal gammopathy (D'Sa et al., 2017). Approximately 50% of patients with DADS-M are noted to have high titers of anti-myelin-associated glycoprotein (MAG); therefore, this should be evaluated in all patients presenting with possible IgM-associated PN. Individuals with MGNS should consult with neurology to determine the extent of symptoms. Nerve conduction studies should also be considered to aid with diagnosis.

TREATMENT OPTIONS

For patients with MGUS, clinical evaluations and the frequency of visits are based on risk stratification.

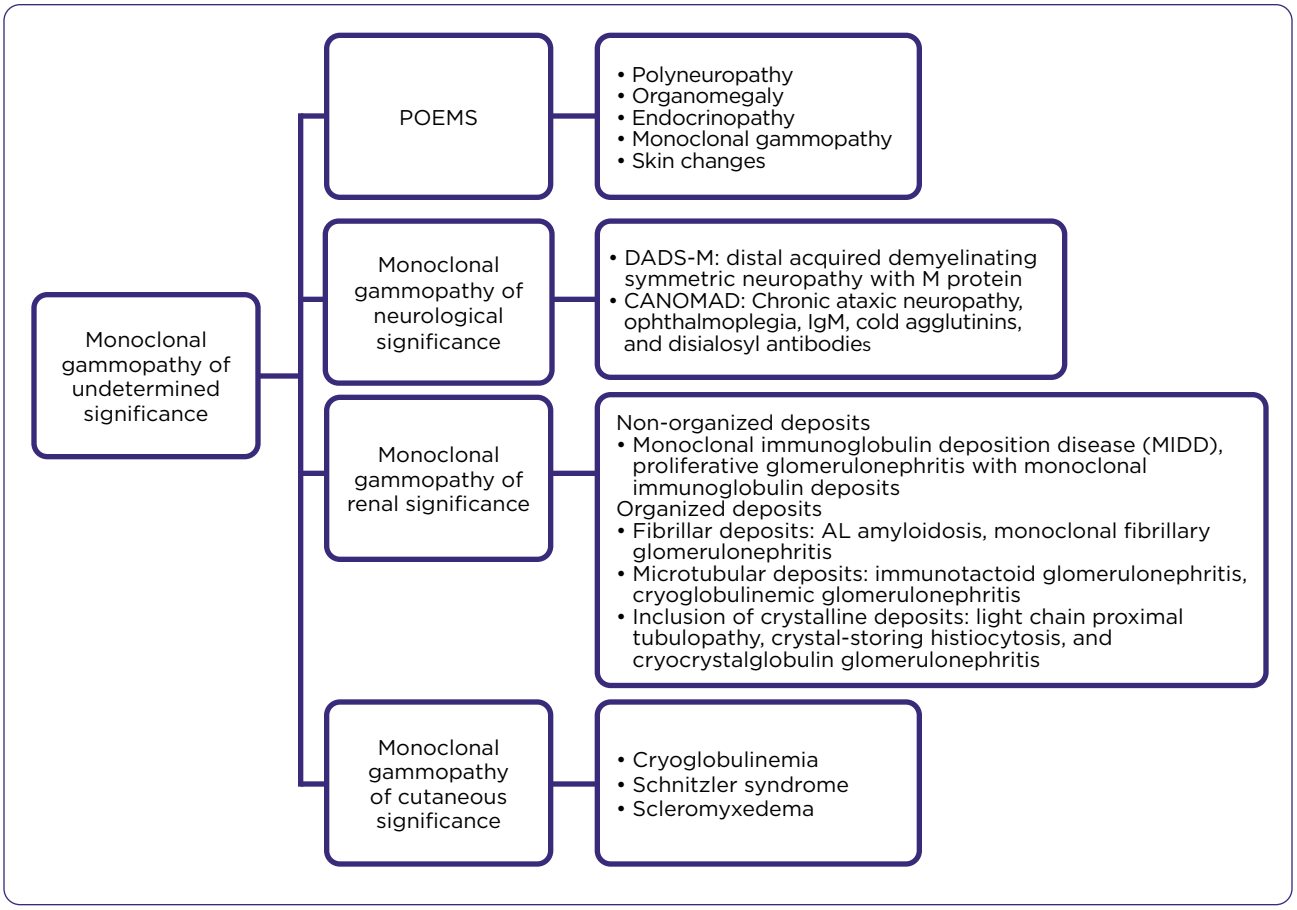

Figure 2. Dimensions of MGUS. POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes; AL = amyloid light-chain amyloidosis. Information from Dispenzieri (2023); Castillo et al. (2021); Bridoux et al. (2015); Ríos-Tamayo et al. (2022); Oganesyan et al. (2022); Iberri & Liedtke (2024); Leung et al. (2021); Liu & Parks (2025).

There are international guidelines that outline monitoring strategies. For low-risk MGUS, clinical evaluation should be performed 6 months after diagnosis, followed by annual evaluation or less frequently for stable patients (Stern et al., 2023; Go & Rajkumar, 2018). For intermediate- or high-risk MGUS, follow-up is recommended every 6 months, transitioning to annual evaluations if the patient remains stable. Table 3 describes the appropriate testing for monitoring MGUS patients (Mouhieddine et al., 2019; Lomas et al., 2020; Stern et al., 2023; Bird et al., 2009; Berenson et al., 2010; Abeykoon et al., 2022). The care of MGUS patients often involves a team of health-care providers that consists of oncologists, subspecialists (such as neurologists and nephrologists), APPs, and registered nurses. The role of the APP is evident in MM and MGUS clinics and is necessary to meet the needs of MGUS patients by monitoring, educating, and navigating a multidisciplinary approach to manage their care.

The treatment of MGRS and MGNS is varied and based on the clinical presentation. Determinants such as age, clinical presentation, comorbidities, genetic findings, patient preferences, and potential treatment toxicities should be considered (Moreno et al., 2021). For MGUS, protocol-driven treatments are recommended to best define the appropriate approach to future treatment strategies (Lomas et al., 2020; Castillo et al., 2021; Choudhuri & Rainone, 2023; Oganesyan et al., 2022; Lee et al., 2024).

Non–IgM and FLC–associated MGRS should be managed with treatment strategies similar to active MM unless there is a confirmed

Table 3. Tests and Scans to Consider for MGUS Diagnosis and Monitoring

Laboratory tests	Radiological tests	Pathologic tests	Neurological tests
• Complete blood count • Comprehensive metabolic panel • SPEP with immunofixation • Serum free light chain • Cryoglobulins: Type 1 cryoglobulins with vasculitis or inflammation symptoms in patients with IgG or IgM abnormalities • Anti–MAG antibodies: IgM MGUS isotype, often associated with peripheral neuropathy • Anti–ganglioside antibodies: IgM pure sensory peripheral neuropathy • Hemoglobin A1c, fasting glucose: if POEMS is suspected or h/o diabetes • Serum cobalamin level (vitamin B12): peripheral neuropathy • Serum TSH level: if peripheral neuropathy symptoms or POEMS is suspected • Serum troponin: if heart failure is suspected or cardiac amyloidosis • Serum NT–proBNP: if heart failure is suspected or cardiac amyloidosis • VEGF: if POEMS is suspected	• WBLDCT: one of the following should be considered with MGUS diagnosis and when clinically indicated: WBLDCT, PET/CT scan, or WBMRI (may be deferred with low-risk MGUS) • PET/CT scan: see above • Whole-body MRI: see above • Skeletal survey: may be ordered with MGUS diagnosis and obtained when clinically indicated • Brain and spine MRI with gadolinium: if there are brain/cognitive or spinal issues • CT scan chest, abdomen/pelvis: when clinically indicated	• Bone marrow biopsy: intermediate or high-risk MGUS or as clinically indicated • FISH: for the detection of high-risk cytogenetics • *MYD88* mutation: IgM isotype • CSF cytology: if leptomeningeal involvement or meningitis is suspected • Flow cytometry: Ordered with bone marrow aspirations • Fat pad biopsy: if AL amyloidosis is suspected • Nerve biopsy: IgM MGUS with significant neurologic findings • Renal biopsy: AKI stage 3 and proteinuria	• Nerve conduction studies: significant neurologic findings. More common in IgM myeloma • Electromyography: see above

Note. WBLDCT = whole-body low-dose computed tomography; WBMRI = whole-body magnetic resonance imaging; MGUS = monoclonal gammopathy of undetermined significance; FISH = fluorescence in situ hybridization; IgM = immunoglobulin M; SPEP = serum protein electrophoresis; CSF = cerebrospinal fluid; AL = amyloid light chain; AKI = acute kidney injury; MAG = myelin-associated glycoprotein; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; TSH = thyroid-stimulating hormone; NT-proBNP = N-terminal pro–B-type natriuretic peptide; VEGF = vascular endothelial growth factor. Information from Ciocchini et al. (2017); Leung et al. (2019); Castillo et al. (2021); D'Sa et al. (2017); Dimopoulos et al. (2023); Dispenzieri (2023); Bridoux et al. (2015); Choudhuri & Rainone (2023); Stern et al. (2023); Go & Rajkumar (2018); Bergstrom et al. (2020); Liu & Parks (2025).

lymphoproliferative diagnosis (Dimopoulos et al., 2016; Leung et al., 2019; Karam, et al., 2023; Choudhuri & Rainone, 2023). The treatment of MGNS is not well-defined and remains challenging, with limited studies supporting a standard of care. Management may involve observation or therapy, depending on clinical findings. If treatment is indicated, the International Myeloma Working Group recommends avoiding the use of neurotoxic therapy (Treon et al., 2018; Dimopoulos et al., 2018; Castillo et al., 2021).

CONCLUSION

Monoclonal gammopathy of undetermined significance is a precursor of hematologic malignancy, with significant variability in the risk of progression based on genetic, biochemical, and clinical factors. Over the years, advancements in understanding the pathophysiology and high-risk features of MGUS have enhanced risk stratification and monitoring strategies, allowing for more personalized care. The recognition and management of MGCS have further emphasized the importance of early diagnosis and multidisciplinary approaches in mitigating organ damage and other complications. Ongoing research and clinical trials are essential to refine monitoring guidelines, develop targeted therapies, and explore preventive measures aimed at reducing progression to multiple myeloma and other malignancies.

Disclosure

Dr. Brigle has served on the speakers bureau for Bristol Myers Squibb, Johnson & Johnson, Karyopharm, Sanofi, and Pfizer. Dr. Steinbach has served on the speakers bureau and advisory board for Johnson & Johnson, Pfizer, and Regeneron, and on the advisory board for Bristol Myers Squibb. Ms. Bellerive has served on the advisory board for Bristol Myers Squibb and has received an honorarium from GLC Insights.

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