Monoclonal gammopathy of undetermined significance (MGUS): where is the hidden danger? Definition and work-up

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Summary Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant hematological condition arising from B-cells, characterized by the presence of monoclonal immunoglobulin production, also known as paraprotein. It is found in up to 3% of individuals over the age of 50 years. The overall progression rate is low at around 1% per year, with most patients progressing to multiple myeloma (MM). Other diseases that may arise from MGUS include non-Hodgkin lymphomas, Waldenström macroglobulinemia, amyloid light-chain (AL) amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes), cryoglobulinemia, monoclonal gammopathy of renal significance (MGRS), and additional paraprotein-driven diseases. Every case of monoclonal gammopathy warrants careful investigation to rule out the presence of a malignant form. In recent years, paraprotein-associated conditions such as MGRS have been increasingly recognized. Accurate diagnosis and work-up of these cases require a multidisciplinary approach, and it is paramount to accurately distinguish them from true MGUS in order to prevent end-organ damage. Follow-up of MGUS should be lifelong; however, a risk-adapted approach involving the primary care setting is recommended.

Keywords MGUS · Paraproteinemia · MGRS · MGCS · Multiple myeloma

Definition and epidemiology

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant B-cell neoplasia usually arising from plasma cells and less frequently from lymphoplasmacytic cells. It is defined as a serum monoclonal protein of less than 30 g/L, less than 10% of clonal plasma or lymphoplasmacytic cells in the bone marrow, and the absence of end-organ damage, myeloma defining events, or any constitutional symptoms [1]. Its prevalence increases with age. While it is a rare occurrence in patients younger than 50 years, it is found in 1.7% of individuals aged between 50 and 59 years, with slightly more men being affected. This proportion increases to up to 7.5% in persons older than 85 years. The most common immunoglobulin isotypes are immunoglobulin G (IgG) and Kappa light chain [2].

Progression and risk stratification

MGUS has an overall low risk of progression to multiple myeloma (MM) or other associated diseases. Depending on the immunoglobulin subtype, the rate of progression can vary from 0.3% per year in light-chain MGUS to 1.5% in IgM MGUS. While the rate of progression remains stable in non-IgM MGUS, it decreases in IgM MGUS from 2% in the first decade to 1% after 10 years. The vast majority of IgM MGUS progress to Waldenström macroglobulinemia (WM), while IgM MM is exceedingly rare [3]. In more than 90% of WM patients the MYD88 L265P mutation can be detected [4], while it is not found in MM. In a very rare subset of patients with lymphoplasmacytic lymphoma, IgG, or IgA paraprotein may be found;

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Table 1 Mayo Clinic risk model [7]

Risk factors	Percentage of patients	Risk of progression at 20 years (%)
Low risk (serum M-protein <15 g/L, IgG subtype and FLC ratio 0.26–1.65)	39	5
Low-intermediate risk (any one factor abnormal)	37	21
High-intermediate risk (any two factors abnormal)	20	37
High risk (all three factors abnormal)	5	58
<i>IgG immunoglobulin G, FLC free light chain</i>		

however, the MYD88 mutation frequency appears to be lower in these cases [5].

Several risk factors for progression have been identified. An M-spike of ≥ 15 g/L is the most important determinant for progression. Further important risk factors include an IgA isotype, an abnormal light chain ratio, a rise in the M-protein level over time, a bone marrow plasma cell percentage of more than 5%, a reduction of both uninvolved isotypes, and circulating plasma cells in the blood [6].

Based on the known risk factors, Rajkumar et al. developed a model that incorporates the following biomarkers: non-IgG MGUS, M-protein of ≥ 15 g/L, and abnormal free light chain (FLC) ratio of <0.125 or >8 . Depending on the presence of none, one, two, or all three risk factors, the rate of progression at 20 years was 5%, 21%, 37%, and 58%, respectively (see Table 1; [7]).

Work-up

Due to its high prevalence in the elderly population, screening for MGUS is not recommended [6], even though it has been suggested that MM is virtually always preceded by MGUS and early detection and subsequent close monitoring may prevent the occurrence of end-organ damage [8]. However, serum electrophoresis and immunofixation are frequently performed in patients presenting with various symptoms ranging from anemia or bone pain to unspecific symptoms like fatigue. Once detected, any paraprotein always warrants thorough work-up. First and foremost, any symptoms or laboratory features suspicious for MM, chronic lymphatic leukemia (CLL), or WM must be investigated. Here it is important to not only evaluate all patients for the presence of the traditional CRAB (elevated calcium level, renal failure, anemia, bone lesions) criteria, but also for the 2014 Slim crite-

ria (myeloma defining events, i.e., bone marrow blast cell count of $>60\%$, ratio of the involved and uninvolved FLC of ≥ 100 , and $>one$ focal lesion in MRI) [1]. Also, it is important to make the correct distinction between MGUS and smoldering myeloma (SMM) as the latter shows a significantly higher rate of progression of about 10% per year and therefore requires closer monitoring [9]. Laboratory testing should include a complete blood count with differential, blood chemistry, serum and urine electrophoresis with immunofixation, and measurement of FLCs. According to both the European Myeloma Network (EMN) and the International Myeloma Working group (IMWG) guidelines, bone marrow examination can be deferred in patients with low risk disease (i.e. IgG, M-protein of ≤ 15 g/L, and normal FLC ratio) without symptoms or laboratory anomalies. In all other patients, i.e. IgA or IgM subtypes, an M-protein of >15 g/L, or an abnormal FLC ratio, bone marrow biopsy is recommended [6, 9]. If no bone pain is present, bone imaging studies can also be omitted in low risk settings (IgG >15 g/L or IgA >10 g/L) as the probability of bone lesions has been shown to be very low in patients with an M spike of less than 15 g/L [6, 10]. Regarding the choice of imaging technique, whole-body low dose computed tomography (CT) is becoming the new standard of care rather than conventional skeletal surveys due to its ability to detect osteolytic lesions at much earlier stages than conventional X-rays, which may result in upstaging and earlier initiation of treatment [11]. Due to its very low rate of progression in patients with light-chain MGUS, the EMN does not recommend bone marrow biopsy or imaging studies except in cases with highly abnormal FLC ratio (i.e., >10 or <0.10) [6].

In patients with impaired renal function, evaluation of any underlying conditions that may be the cause for these changes is paramount. This is particularly important, since MGUS usually affects older patients with numerous comorbidities. If no cause can be determined, referral to a nephrology specialist for further investigation and possible kidney biopsy may be advisable. In MGUS with an abnormal FLC ratio, work-up and monitoring should also include N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels, as well as urinary protein either from 24-h urine collection or protein/creatinine ratio in the spot urine for early detection of organ damage that may herald the onset of amyloid light-chain (AL) amyloidosis [6].

Table 2 Risk-based recommendations for follow-up in monoclonal gammopathy of undetermined significance (MGUS) patients [6]

Follow-up	Low-risk MGUS	Non-low-risk MGUS	Light-chain MGUS	MGUS and life expectancy <5 years
–	At 6 months, and if stable, every 1–2 years or No further follow-up but additional investigations only in the case of symptoms suggestive of progression	At 6 months and annually thereafter	At 6 months and annually thereafter	No further follow-up, but additional investigations only in the case of symptoms suggestive of progression

Follow-up

Due to the steady progression rate, most MGUS patients need lifelong follow-up. The recommendations on follow-up from the various guidelines differ somewhat in certain aspects [12]. The most recent guidelines from the EMN recommend a risk-adapted approach (Table 2) based on the Mayo Clinic risk stratification model [6, 7]. Patients in the low-risk cohort with a 20-year risk for progression of 5% should be followed-up at 6 months and then every 1–2 years if there is no change in the paraprotein levels. In select cases follow-up can be suspended if the disease remains stable for a long time and only picked up in the case of symptoms suggestive for progression. Intermediate and high-risk, as well as light-chain MGUS cases, should be followed-up after 6 months and annually thereafter. In patients with a life expectancy of 5 years or less due to age or other comorbidities, no follow-up is recommended in asymptomatic patients. Appropriate follow-up can be provided in a primary care setting and should include history, physical examination, quantification of the M-protein, complete blood count, creatinine, calcium levels, NT-pro-BNP/proBNP, and urinary albumin [6].

When to suspect more: determining the undetermined

There are a number of conditions that are associated with a monoclonal gammopathy and organ damage without fulfilling the criteria for MM. For these increasingly recognized disorders, the term monoclonal gammopathy of clinical significance (MGCS) was recently coined [13]. The common feature of all MGCS is that, while there is only a small plasma cell clone in the bone marrow, the paraprotein causes organ damage through various mechanisms such as deposition in organ tissues, interaction with the complement system, or through direct autoantibody activity of the monoclonal immunoglobulin itself. Kidney dysfunction with proteinuria should trigger evaluation for monoclonal gammopathy of renal significance (MGRS) or kidney AL amyloidosis, while cardiac failure that is rapidly progressing without any prior history of cardiac dysfunction or hypertrophic left ventricular cardiomyopathy can be suggestive for cardiac AL amyloidosis [14]. Early recognition of these disorders can help prevent progression and loss of organ function, which is associated with a very poor outcome. Also, any unexplained symptoms such as bleeding, skin lesions, polyneuropathy, or B-symptoms should trigger intensified evaluation. Conversely, the condition caused by the paraprotein is sometimes known well before the discovery of the paraproteinemia. This is frequently the case in situations where the presenting syndrome did not respond to conventional treatment. Often, treatment of the causative paraproteinemia rapidly improves

the condition. The exact prevalence rate of MGCS is unknown, since it remains underdiagnosed as the connection between symptoms and the underlying paraproteinemia are often overlooked.

Conclusion

MGUS is a common premalignant condition found in over 3% of people over the age of 50 years that can precede the development of MM, WM, NHL, AL amyloidosis, or MGRS. While progression rates are low, careful and thorough work-up time of diagnosis is necessary to adequately distinguish MGUS from paraprotein-associated diseases. Follow-up should be lifelong and risk-based, focusing on the early detection of end-organ damage.

Take-home messages

- MGUS is a premalignant condition common in patients over the age of 50 years with a low risk for progression to MM and associated conditions.
- A thorough risk-adapted approach for initial diagnosis, follow-up, and investigations is recommended.
- Under certain circumstances, a paraprotein may warrant treatment even when criteria for MM are not fulfilled.

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Conflict of interest G. Jeryczynski and M.-T. Krauth declare that they have no competing interests.

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