

CLINICAL PRACTICE

Monoclonal Gammopathy of Undetermined Significance

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 58-year-old man with no significant medical history is found to have an elevated total protein concentration (8.1 g per deciliter) on a routine blood chemical study. He is asymptomatic, and his physical examination is normal. Serum protein electrophoresis reveals a monoclonal spike of 2.1 g per deciliter at the gamma region; immunofixation shows a monoclonal IgG kappa protein. What further evaluation is warranted, and assuming the diagnosis of monoclonal gammopathy of undetermined significance is made, how should the patient be followed?

THE CLINICAL PROBLEM

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a monoclonal protein in persons with no features of multiple myeloma or other related malignant disorders such as Waldenström's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia.¹ Patients with MGUS have a serum monoclonal protein concentration lower than 3 g per deciliter, fewer than 10% plasma cells in the bone marrow (Fig. 1), and no clinical manifestations related to the monoclonal gammopathy.^{1,2} Table 1 summarizes the current diagnostic criteria for MGUS, according to the International Myeloma Working Group,² and the differences between MGUS and plasma-cell neoplasms. Although MGUS was initially considered a "benign" monoclonal gammopathy,^{3,4} the recognition that this disorder can evolve into a malignant monoclonal gammopathy^{1,5-8} has led to the use of the more appropriate term "monoclonal gammopathy of undetermined significance."^{1,5}

The prevalence of MGUS increases with age. In a recent population-based study involving residents of Olmsted County, Minnesota, the prevalence of this condition was 3.2% in persons older than 50 years of age and 5.3% in those older than 70 years.⁹ The median age at diagnosis is about 70 years, and less than 2% of patients with MGUS are younger than 40 years of age.¹⁰ The prevalence of MGUS is higher in men than in women (4.0% vs. 2.7% among persons 50 years of age or older).⁹ In the United States, rates of MGUS are higher in blacks than in whites.¹¹

In the Mayo Clinic series, IgG was the most common immunoglobulin affected (69% of cases), followed by IgM (17%) and IgA (11%).⁹ Biclinal gammopathies occurred infrequently. More than 25% of patients had a corresponding reduction in the concentration of uninvolved immunoglobulins.

The cause of MGUS is unknown. Monoclonal gammopathies are characterized by a rearrangement of immunoglobulin genes that results in the production of a monoclonal protein.¹²⁻¹⁴ In patients with MGUS, the plasma-cell clone and the associated monoclonal protein concentration usually remain stable for many years.

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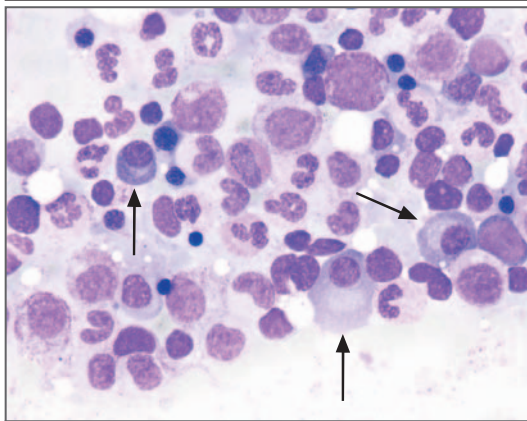


Figure 1. Bone Marrow Specimen from a Patient with MGUS (May-Grunwald-Giemsa Staining).
The arrows indicate plasma cells.

often of advanced age at the time of diagnosis of MGUS, do not die of other causes before malignant transformation occurs. Thus, the observed rate of progression at 25 years of follow-up in the Mayo Clinic cohort was 11.2% — far lower than the actuarial prediction²⁰; patients with MGUS are more likely to die of an unrelated disorder than from progression of their monoclonal gammopathy. The annual rate of progression of approximately 1% to multiple myeloma or other related malignant disorders is not affected by age or the duration of MGUS,⁹ although the cumulative risk of progression during one's lifetime is, of course, highest in younger patients. Malignant evolution has been observed even after 30 years of follow-up.^{7,10}

STRATEGIES AND EVIDENCE

EVALUATION

MGUS is usually detected after a routine blood test reveals an elevated total protein concentration (and follow-up serum protein electrophoresis shows a monoclonal spike). When discovered during evaluation for a medical problem, MGUS is generally an incidental finding unrelated to the reason for which the patient sought care. Patients with MGUS are asymptomatic from their monoclonal gammopathy and do not report bone pain, anemia-related symptoms, neurologic manifestations, or weight loss — symptoms that would suggest myeloma, Waldenström's macroglobulinemia, or primary amyloidosis. The physical examination is normal when a monoclonal gammopathy is due to MGUS. Pallor, bone tenderness, or soft-tissue masses suggests myeloma, whereas

However, over a prolonged period of follow-up, a substantial proportion of patients progress to a malignant plasma-cell disorder (multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia). The reasons for this transformation remain unclear.^{15,16}

Among 241 patients with MGUS who were followed longitudinally from the time of diagnosis at the Mayo Clinic, the actuarial probabilities of transformation into one of the above-mentioned malignant plasma-cell disorders were 17%, 34%, and 39% at 10, 20, and 25 years of follow-up, respectively.⁷ Other series have shown similar actuarial risks of progression, with rates at 10 years ranging from 12 to 17% and at 20 years, from 25 to 34%.^{10,17-19} However, these actuarial probabilities are clinically relevant only if patients, who are

Table 1. Diagnostic Criteria for MGUS, Multiple Myeloma, and Other Conditions.*

Variable	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma	Waldenström's Macroglobulinemia	Primary Amyloidosis
Bone marrow plasma cells (%)	<10	≥10	≥10	>10†	<10
	and	and/or	and/or	and	and
Circulating monoclonal protein (g/dl)	<3	≥3	≥3	>3	<3
Clinical manifestations	Absent	Absent	Present‡	Present§	Present¶

* Data are from the International Myeloma Working Group.²

†The diagnostic criteria include more than 10% lymphoplasmacytoid cells.

‡Clinical features may include increased serum calcium concentrations, renal failure, anemia, skeletal involvement (lytic lesions), recurrent bacterial infections, and extramedullary plasmacytomas.

§Clinical features include anemia, mucocutaneous bleeding, hepatosplenomegaly, and IgM type of immunoglobulin.

¶Clinical features include fatigue, weight loss, purpura, the nephrotic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, and massive hepatomegaly.

hepatosplenomegaly, purpura, and edema are characteristic findings of Waldenström's macroglobulinemia or amyloidosis.

Monoclonal gammopathy occasionally occurs secondary to another disease process, such as acquired immunodeficiency syndrome or immunodeficiency after organ transplantation. In such patients, further evaluation is generally unwarranted, since the monoclonal gammopathy disappears with the recovery of the immune system.²¹ By contrast, the disappearance of a monoclonal protein in patients with MGUS is exceedingly rare.¹⁰ Secondary monoclonal gammopathies have also been reported in patients who have chronic liver disease (due to hepatitis C virus, in particular), rheumatologic diseases such as rheumatoid arthritis, and other conditions, such as chronic myelomonocytic leukemia, chronic neutrophilic leukemia, lichen myxedematosus, or pyoderma gangrenosum.²¹

LABORATORY TESTING

Table 2 summarizes recommended testing in patients with suspected MGUS. Serum protein electrophoresis is the preferred method for the detection of a monoclonal protein. The immunofixation will distinguish the immunoglobulin class and type of light chain. The use of densitometry to measure the monoclonal protein that is visible on serum electrophoresis is more reliable and less costly than the use of nephelometry to measure the immunoglobulin levels.²¹ A 24-hour urine protein excretion measurement as well as urine protein electrophoresis and immunofixation are indicated to detect and quantify the monoclonal protein in the urine. Of note, patients with light-chain myeloma usually have a very low serum monoclonal protein concentration, but light-chain excretion usually exceeds 1 g per 24 hours.²¹ Measurement of β_2 -microglobulin, suggested previously as part of the baseline evaluation and follow-up, has not proved predictive of malignant transformation and is no longer recommended.²¹ Examination of aspirated bone marrow and a skeletal survey in patients with suspected MGUS are generally performed to rule out myeloma (although, because of the extremely low likelihood of myeloma, they are not considered necessary when the serum monoclonal spike is less than 1.5 g per deciliter and other laboratory tests, such as those for hemoglobin, calcium, and creatinine concentrations, are normal).

A monoclonal protein concentration of less

Table 2. Recommended Testing in Patients with Suspected MGUS.

History and physical examination
Hemoglobin concentration
Serum calcium and creatinine concentrations
Protein studies
Total serum protein concentration and serum electrophoresis (serum monoclonal protein concentration)
24-hour urine protein excretion and urine electrophoresis (urine monoclonal protein concentration)
Serum and urine immunofixation (type of monoclonal protein)
Determination of serum free light-chain ratio (kappa and lambda free light chains)*
Examination of bone marrow aspirate†
Skeletal survey†

* This determination is not yet standard procedure but is useful in assessing prognosis.

† This is not recommended if the serum monoclonal protein concentration is below 1.5 g per deciliter.

than 3 g per deciliter, the absence of a substantial amount of light chain in the urine, and a bone marrow aspirate with less than 10% plasma cells (in the absence of osteolytic lesions, anemia, hypercalcemia, and renal insufficiency) are all consistent with the diagnosis of MGUS. In contrast, a monoclonal protein value of 3 g per deciliter or greater, at least 10% plasma cells on examination of the bone marrow, or both indicates multiple myeloma. Patients who meet these criteria but have none of the symptoms or complications listed in Table 1 are considered to have "smoldering" myeloma.

In patients with a monoclonal protein concentration of less than 3 g per deciliter and less than 10% plasma cells on examination of the bone marrow, the presence of other laboratory abnormalities such as anemia, renal insufficiency, or hypercalcemia is probably due to an associated disease rather than the monoclonal gammopathy. In a patient with constitutional symptoms, osteolytic lesions, a moderate monoclonal spike, and less than 10% plasma cells in the bone marrow, the most likely diagnosis is metastatic carcinoma with a coincidental MGUS. If the monoclonal protein and the percentage of plasma cells in the bone marrow are consistent with MGUS but there is a nephrotic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, carpal tunnel syndrome, massive hepatomegaly, or any combination of these, the most likely diagnosis is primary systemic amyloidosis resulting

from deposition of light chains in organs and tissues (Table 1).

PREDICTORS OF PROGRESSION TO MULTIPLE MYELOMA OR OTHER RELATED MALIGNANT DISORDERS

Several laboratory tests performed at the time of diagnosis of MGUS are considered useful in predicting the risk of progression to multiple myeloma or to other related malignant conditions. A strong predictor of progression is the serum monoclonal protein concentration.^{10,18-20,22} In a large series (1384 patients) with long follow-up (median, 15.4 years), the actuarial risks of progression at 20 years were 14%, 25%, 41%, and 49% for a monoclonal protein concentration of 0.5, 1.5, 2.0, and 2.5 g per deciliter, respectively.¹⁰ Several reports show that the presence of an IgA or IgM monoclonal protein, rather than IgG,^{10,18-20,23,24} and a high percentage of plasma cells in the bone marrow^{18,19,22} are additional predictors of progression. In one study,¹⁸ after a median follow-up of 65 months, the incidence of malignant conditions was about two times as great in persons with an IgA or IgM monoclonal spike as in persons with an IgG spike. The incidence was also about two times as great in persons with 6 to 9% plasma cells in the bone marrow as in persons with 5% or less. In two series,^{18,22} a reduction in polyclonal immunoglobulins was associated with a higher probability of malignant transformation, but this finding was not reproduced in other series.^{7,8,10,19}

More recently, the free light-chain ratio — that is, the ratio of free kappa to free lambda chains (light chains that are not bound to intact immunoglobulins) — has been recognized to predict progression to malignant conditions in patients with MGUS, independent of the concentration and type of the serum monoclonal protein.²⁰ The normal free light-chain ratio is 0.26 to 1.65. An abnormal free light-chain ratio, defined as below 0.26 (indicating excess of lambda chains) or above 1.65 (indicating excess of kappa chains), is considered a marker of clonal expansion.²⁵ Among the Mayo Clinic cohort, the risk of progression to myeloma or to a related malignant condition at 20 years was 35% among patients with an abnormal ratio and 13% among those with a normal ratio.²⁰ With the use of this information and the results of testing to determine the serum monoclonal protein concentration and the type of immunoglobulin, the investigators divided pa-

tients into high-risk and low-risk groups. Patients with an abnormal serum free light-chain ratio, a monoclonal protein other than IgG, and a serum protein concentration higher than 1.5 g per deciliter had an actuarial risk of progression of 58% at 20 years (high-risk MGUS), as compared with a 5% risk when none of these risk factors were present (low-risk MGUS).²⁰ A highly sensitive serum free light-chain assay is now available for clinical use.²⁵ However, the prognostic effect of the free light-chain ratio has not yet been validated in other populations of patients with MGUS.

MANAGEMENT

Once the diagnosis of MGUS has been established, the usual practice is to reevaluate patients annually, although data are lacking to guide the optimal frequency of reassessment. Follow-up testing typically includes measurement of total serum protein by means of serum electrophoresis, 24-hour urine protein excretion with the use of urine electrophoresis, hemoglobin concentration, serum creatinine concentration, and serum calcium concentration. The rationale is to detect multiple myeloma before complications such as renal failure or pathologic fractures occur.^{9,26} The monoclonal protein concentration usually remains stable until myeloma develops. However, clinical experience suggests that in some patients, the concentration gradually increases preceding the diagnosis of multiple myeloma¹⁰; these patients probably have slowly evolving myelomas rather than “true” cases of MGUS. Small changes in the monoclonal protein concentration are likely to reflect random variation. If there is a confirmed increase in the monoclonal protein size above 3 g per deciliter with no symptoms and no end-organ damage, the disease fulfills the diagnosis of smoldering myeloma, and more frequent follow-up (e.g., every 4 months) is recommended.

Patients with an IgG monoclonal protein concentration below 1.5 g per deciliter may not warrant follow-up for their MGUS, because of the very low lifetime risk of progression²⁰; a finding of a normal light-chain ratio would provide further support for a decision not to pursue serial monitoring. Since about 40% of all patients with MGUS have low-risk MGUS (IgG type of immunoglobulin, monoclonal protein less than 1.5 g per deciliter, and normal light-chain ratio),²⁰ the distinction between low-risk and high-risk MGUS

has important implications for patient care. No treatment is currently recommended for MGUS.

AREAS OF UNCERTAINTY

The pathogenesis of MGUS remains poorly understood. Evidence suggests that the MGUS clone is already “malignant” at the time of its initial appearance.^{27,28} Indeed, the clonal plasma cells of patients with MGUS show a phenotypic profile similar to that of myelomatous plasma cells (CD38+, CD56+, and CD19–), although the proportion of phenotypically normal plasma cells is higher in patients with MGUS than in those with myeloma.²⁹ Thus, there are two populations of plasma cells in persons with MGUS — one is normal and polyclonal (CD38+, CD56–, CD19+), and the other is clonal and has an abnormal immunophenotype (CD38+, CD56+, CD19–). In one report, the proportion of bone marrow plasma cells that was polyclonal (as assessed by flow cytometry of bone marrow aspirate with the use of four monoclonal antibodies — CD38 or CD138, CD56, CD19, and CD45) was the best single factor for distinguishing between MGUS and multiple myeloma.²⁹ Less than 2% of patients with myeloma had more than 3% normal plasma cells, whereas 98% of patients with MGUS had more than 3%.²⁹ Such testing is currently not part of routine practice; the usefulness of this measurement requires confirmation in longitudinal studies, which are currently in progress³⁰ (San Miguel J: personal communication).

Factors limiting plasma-cell expansion in patients with stable MGUS remain uncertain; it seems that a second oncogenic event is necessary for the development of multiple myeloma. Some studies are assessing the effects of medications that are intended to reduce the risk of progression in patients with high-risk MGUS (i.e., a high serum monoclonal protein concentration, an immunoglobulin type other than IgG, and an abnormal free light-chain ratio). These medications, which include dehydroepiandrosterone and the COX-2

inhibitor celecoxib³¹ (Rajkumar V: personal communication), have no current role in practice for this indication; the efficacy of such interventions is currently unknown.

GUIDELINES

There are no formal guidelines regarding evaluation and follow-up for patients with MGUS.

SUMMARY AND RECOMMENDATIONS

In a patient who presents with a monoclonal gammopathy, such as the one described in the vignette, additional testing is warranted, including examination of aspirated bone marrow and a skeletal survey, to rule out multiple myeloma and confirm the diagnosis of MGUS. In patients with MGUS, the actuarial risk of myeloma at 25 years of follow-up is 30% and the actual risk (when competing causes of death are taken into account) is 11%. A high monoclonal protein concentration, a high percentage of plasma cells in the bone marrow, an IgA monoclonal protein, and an abnormal free light-chain ratio are predictors of an increased risk of progression to multiple myeloma or other malignant plasma-cell disorder. Although data are lacking to effectively guide the frequency of follow-up and the specific testing warranted, a reasonable strategy is to follow a patient such as the one described and reevaluate him yearly, including measurement of total protein concentrations and electrophoresis of serum and urine. Patients should be informed that in the majority of cases, the monoclonal protein concentration will remain stable, and that currently no treatment is indicated for MGUS.

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