# A 72-Year-Old Woman With an Abnormality on Incidental Blood Testing

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A 72-year-old woman presented for her annual routine Medicare examination. She reported that she does not routinely visit a primary care physician but undergoes sporadic blood pressure checks for mild essential hypertension, which is managed by an angiotensin-converting enzyme (ACE) inhibitor. There were no other significant findings in the patient's history, systems review, and physical examination.

A routine complete blood cell count, basic chemistry panel, and biochemical screen were obtained. Results of these tests—specifically her hemoglobin level, creatinine level, and chemistries—were within normal limits, except for an elevated total protein level of 8.5 g/dL (normal range, 6.0-8.0 g/dL). The reference laboratory performed a "reflex" serum protein electrophoresis (SPEP) test suspicious for the presence of an IgG kappa monoclonal (M) protein level of 0.7 g/dL.

After a telephone consultation with a hematologist, the attending general internist ordered an immunofixation blood test, which confirmed an M protein level of IgG kappa of 0.8 g/dL with normal levels and ratios of free gamma and lambda light chains.

## Which of the following is the best strategic option for further managing this patient's condition?

A. She should be managed by clinical observation and repeat blood studies at 6 to 12 months.
B. She should be monitored at 3-month intervals with initiation of therapy if there is any increase in the M protein levels.
C. She should be started on a standard multiple myeloma regimen to prolong her overall survival.
D. She should be referred for autologous bone marrow transplantation while her tumor burden is minimal and a cure is possible.

## Correct answer: A

Many years ago, early in my training, we all had seen some nasty historical pictures and specimens of patients with severe and deforming skeletal lesions; we were aware of an illness characterized by diffuse replacement and destruction of bones by malignant marrow masses, hence the name "multiple myeloma," which was relatively uncommon and uniformly fatal within 18 to 36 months. In the 1970s, as more sophisticated biochemical blood testing and analyses became available, Kyle and colleagues described a group of patients who were clinically well and asymptomatic but showed abnormal M proteins similar to those seen in patients with multiple myeloma.[1] Yet the patients Kyle and colleagues described were in good health even years into follow-up, hence the term "monoclonal gammopathy of undetermined significance" (MGUS).[1,2] Decades later, with the advent of more advanced and frequent blood analysis capabilities, we now know that MGUS is quite common and that multiple myeloma are related entities in the spectrum of malignant plasma cell dyscrasias. The patient in our case presented with the entry-level form of this spectrum, MGUS.

## Discussion

MGUS is defined as a "premalignant, clonal plasma cell disorder characterized by the presence of an M protein."[3] In my opinion, anything that is monoclonal fulfills a biological definition of malignancy; however, the timing for the malignancy to clinically manifest may be prolonged such that the patient dies of something else beforehand. Nonetheless, current definitions of the entity itself include (1) presence of the aforementioned protein in the blood, which can be IgG (70% of cases), IgA (12%), IgM (15%), or light

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chains, gamma or lambda, or alone; (2) any type of M protein less than 3 g/dL; (3) less than 10% monoclonal plasma cells in the bone marrow; and (4) the absence of myeloma-defining clinical events, the so-called CRAB criteria (hypercalcemia, renal insufficiency, anemia, and lytic bone lesions).[3] The prevalence of MGUS is estimated as high as 3% in the general population older than 50 years but is much lower in younger people. It also tends to be more common in the Black population and progresses at a rate of about 1% per year into a more serious malignant disease, including multiple myeloma, Waldenstrom macroglobulinemia (when the M protein is IgM), or amyloidosis.[3,4]

Our patient had the classic presentation such that she was the typical age and otherwise well and asymptomatic, with the essential incidental finding on biochemical profile of the presence of a low M protein level. With today's sophisticated testing, the laboratory recognized the presence of a small protein "spike" and defaulted into proving it was monoclonal (an immunofixation assay proved the "spike" was homogeneous in its composition—all IgG heavy chain and all kappa light chain, making it monoclonal). Then, they measured the M protein specifically as 0.8 g/dL and ascertained there was no imbalance in light chains, as the kappa/lambda ratio was within normal limits (between 0.26-1.65). If a resident or fellow presented these findings, they would receive a high grade, and clinical follow-up and downstream testing would be required. With the working diagnosis in hand, we need to determine what further evaluation is required, what is the appropriate follow-up, what is the best estimate of prognosis, and what is the current landscape of therapeutics.

## Management and treatment

We know a dangerous yet treatable disease is at the other end of the spectrum, so how can we approach this situation? First, if we start with a random sample of 100 patients who fulfill the core definition of MGUS, approximately 1% of cases per year will "graduate" (a better word might be devolve) into a more formal diagnosis of multiple myeloma or lymphoproliferative malignancy.[4,5] But if we bore into the characteristics of those 100 patients at their original MGUS starting point, we can more accurately predict behavior using the following set of initial and follow-up findings: (1) the type of M protein being manifested; (2) the levels of these proteins at initial diagnosis; (3) the basic demographics of the individual, such as age, sex, and race; and (4) the presence of any organ damage caused by the proteins themselves (especially the kidneys or nerves) or the malignant plasma cells in the marrow that produce them (anemia, hypercalcemia, bone lesions). You may recognize the target organs by the so-called CRAB acronym: Calcium, Renal, Anemia, Bone. With these characteristics in mind, we can produce and utilize data-driven schemes for effective and predictive follow-up to help accurately determine when and in whom therapeutics should be initiated. Here are several issues to consider.

The first issue is the basic characteristics of the M protein. IgG paraproteins have the best prognosis such that non-IgG cases—IgM, IgA, or light chains alone—comprise a risk factor for progression. Note that IgM cases (which usually progress to Waldenstrom macroglobulinemia or lymphoma rather than multiple myeloma) tend to cause neuropathy symptoms, whereas light chains tend to cause renal disease/amyloidosis rather than classical myeloma.[4] The level of paraproteins at diagnosis is also helpful as a predictor of progression risk. This may be due to diagnosis of the patient at a later time in the slope of disease, or the faster intrinsic progression rate of the malignancy, or both. In any event, key values in the literature include an M protein level greater than 1.5 g/dL and free light chain ratio (eg, how many are kappa and how many are lambda, which physiologically should be roughly balanced 1:1) at less than 0.26 or greater than 1.65.[4]

The second issue is demographics. The risk of more aggressive disease progression is higher in Black persons and younger individuals (ie, <50-60 years of age). Interestingly, clusters of MGUS cases are seen in a higher percentage of the population and at a younger age have been found in survivors of atomic bomb exposure in Japan, veterans exposed to Agent Orange in Vietnam, and firefighters exposed to airborne carcinogens after the September 11, 2001, attacks on the World Trade Center.[3]

Another issue is determining whether there is damage to the CRAB target organs. Once a patient with MGUS presents with any signs of CRAB involvement, it can be argued that the diagnosis is multiple myeloma. Hematologists and oncologists may divide myeloma into further subgroups and classifications, but we will not discuss those here. As a general rule, there will be a correlation between protein level and CRAB disease, but occasionally, patients with a value well within MGUS levels will manifest target organ damage, which triggers the need for therapy.

The remaining issue to consider is the most appropriate initial evaluation and frequency of follow-up evaluations, if needed, for a patient presenting with MGUS.[6] Once there is progression to myeloma, there are excellent and effective therapeutics available, even to the point of operational "cure."[4] However, many (if not the majority) of patients aged 70 years or older who receive an MGUS diagnosis will never progress to myeloma and should not be exposed to the risk of toxicity and morbidity from certain therapies without indication or need.

Usually, as was the case in our patient, the diagnostic process begins when, during routine and unrelated blood work, an abnormal protein is identified (sometimes even being flagged without our asking and at no additional fee). It is important to note that at this point we do not and should not routinely screen patients older than 70 years for MGUS. There is far too much psychological and economic stress and discomfort in relation

to any benefit from this.[3,4] However, if a potential abnormal protein is encountered, studies to confirm a blood diagnosis can easily be performed in a general internist's office and include SPEP, serum immunofixation (very important as they confirm monoclonality), free light chains, and urine electrophoresis.

These tests will detect essentially all cases, all varieties, and establish baseline values for a patient with MGUS. The findings of these tests should trigger referral to a hematologist to stratify risk as discussed above and complete the evaluation as indicated (eg, more detailed blood studies, such as B2-microglobulin and lactate dehydrogenase, and determine whether a bone marrow biopsy for plasma cell count or skeletal imaging, or both, is required).

The above create a baseline data-driven risk assessment that will determine the nature and timing of follow-up. My favorite is the Mayo Clinic Risk Stratification Model,[4] which initially uses protein levels to determine the degree of risk and whether bone marrow or skeletal survey evaluation are needed; using these data, the first follow-up should be at 6 months and then annually, using clinical signs and symptoms, MGUS protein studies, complete blood cell count, calcium level, and creatinine level to monitor presence and rate of progression.[4]

## The Answer

Answer A is the correct choice because our patient's baseline data clearly indicated low risk by specifics of the MGUS protein (IgG, kappa); levels of proteins (<1.5 g/dL and normal light chain ratio), demographics, and absence of CRAB clinical signs and symptoms or other laboratory abnormalities. Answer B is incorrect such that a serial 3-month schedule is too aggressive by current guidelines. Answers C and D are also incorrect because initiating any therapeutics at this time is inappropriate.

## Patient Follow-Up

The findings and their significance were discussed in detail with the patient. In agreement with the Mayo Clinic model,[4] bone marrow biopsy and skeletal survey were deferred because of her low risk. After 12 months of clinical follow-up, the patient reported no new symptoms, and her laboratory values remained without evidence of hypercalcemia, renal insufficiency, or anemia. She has undergone 2 subsequent M protein studies, results of which were essentially unchanged from her baseline values. In her next clinical follow-up at 1 year, she will undergo a set of protein studies unless new symptoms or issues present in the interim.

## What's The Take Home?

Plasma cell dyscrasias cover a broad spectrum of disorders; multiple myeloma is the most significant malignant entity on the spectrum, but MGUS is the most common entry situation. We now know a lot of the true "significance" attached to MGUS. It is a clinically premalignant condition in which the important trigger of monoclonality has been pulled and to what degree it will eventuate into a myeloma situation if enough time elapses (which is often not the case as the disease affects older adults). Reasonably accurate schemes can help us understand and predict the potential of disease progression. Similarly, effective follow-up algorithms allow us to follow these patients and accurately initiate the use of the many effective therapeutics.

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