

New Strategies for MGUS and Smoldering Multiple Myeloma

Robert A. Kyle, MD
Professor of Medicine and Laboratory Medicine
Mayo Clinic Medical School

What are the characteristics of monoclonal gammopathy of undetermined significance?

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of a monoclonal protein in the serum of <3 g/dL, and a bone marrow with less than 10% plasma cells. In addition, the patient must have no anemia, renal insufficiency, skeletal lesions, or hypercalcemia related to a plasma cell proliferative process. Patients with MGUS are generally not treated. The patient is simply observed and followed for evidence of progression.

Are there specific symptoms that trigger suspicion of MGUS in an individual?

A patient with MGUS is asymptomatic and the monoclonal protein is found only if the physician orders a serum protein electrophoresis. Subsequently, immunofixation is done to determine the type of monoclonal protein. If a patient presents with any type of disease and the physician suspects that there may be a reduction in serum albumin, which occurs in many chronic diseases, a serum protein electrophoresis will be performed. This test provides not only the serum albumin level, but also allows identification of a monoclonal gammopathy.

What percentage of MGUS patients experience disease progression?

Approximately 1% of patients with MGUS progress each year. Over a 25-year time span, 25% of patients will progress to a malignant plasma cell proliferative process, such as multiple myeloma (MM), Waldenström's macroglobulinemia (WM), primary amyloidosis or related diseases. Of the patients who do progress, approximately 70% progress to MM. If a patient has an immunoglobulin (Ig) M MGUS, the patient is at risk mainly for lymphoma or WM.

How are patients likely to progress identified?

Identifying prognostic factors in MGUS patients that indicate likely progression is an area of major importance. It is useful to identify patients who are at higher risk of progression and evaluate these patients in a prospective fashion using various therapeutic modalities in order to determine if treatment will either prevent or slow progression of the disease.

In a large study of 1,384 patients with MGUS, we found that the size of the monoclonal protein at diagnosis was the most important prognostic feature. Another prognostic feature was the type of monoclonal protein: patients with IgA or IgM are more likely to progress than those with IgG.

The presence of a monoclonal light chain in the urine and/or a reduction of uninvolved immunoglobulins are not of prognostic significance. A reduction in uninvolved immunoglobulins occurs in almost 40% of patients with MGUS.

In an attempt to identify risk factors for progression, we are currently measuring free light chains in the serum. Our findings thus far indicate an association between an abnormal $\kappa:\lambda$ ratio and greater risk for progression. We have studied a modest number of patients and are in the process of studying more than 1,000 patients.

What is the relationship of the kappa:lambda ratio to progression of MGUS?

A clone of plasma cells produces the monoclonal protein that is found in the blood. This monoclonal protein consists of heavy chains and light chains. In the normal individual, the correct amount of heavy chain and the correct amount of light chain (κ or λ) is produced. If a clone of plasma cells is abnormal, it will often produce more light chain than can be bound to the heavy chain, or there may be a defect in the binding of the heavy chain to the light chain. In short, the presence of excessive amounts of light chain is indicative of an unstable or an abnormal clone of plasma cells. The more abnormal the clone, the more likely it is malignant and goes on to develop symptomatic MM.

Are patients who progress to MM from MGUS treated in the same way as patients who present with MM?

Yes. If a patient with an MGUS subsequently develops symptomatic MM, that patient would be treated in the same manner as a patient who presents with bone pain, anemia, or other features of MM de novo. In fact, it is likely that the vast majority of patients with MM have an MGUS preceding their diagnosis.

What characterizes smoldering MM?

Smoldering MM is characterized by the presence of a monoclonal protein in the serum that is ≥ 3 g/dL or the presence of 10% or more plasma cells in the bone marrow. We don't know if just 1 of these 2 abnormalities characterizes smoldering MM, or if both are necessary. We are in the process of reviewing a large number of patients with smoldering MM in an attempt to answer this question. Patients with smoldering MM are asymptomatic and do not have anemia, hypercalcemia, renal insufficiency, or lytic bone lesions.

Do patients who present with smoldering MM receive treatment?

Generally speaking, we advise no therapy unless the patient has evidence of progression, although there are some exceptions. We conducted a study in which patients with smoldering MM received a modest dose of oral thalidomide (Thalomid, Celgene). Approximately 35% of these patients had a reduction in the size of the monoclonal protein. The drug was reasonably well tolerated. Whether treating patients with smoldering MM with thalidomide will prevent the development of MM or significantly delay it is not yet known. This must be studied in a prospective, randomized trial.

There are also 2 intravenous bisphosphonates that are approved for MM: pamidronate (Aredia, Novartis) and zoledronic acid (Zometa, Novartis). In a small, study of limited duration, patients with smoldering MM were randomized to receive either a bisphosphonate for a year or no therapy. There was no apparent benefit from bisphosphonate therapy. This treatment approach might also be considered for a subset of MGUS patients at high risk for progression.

What other treatment options are being explored for MGUS and/or smoldering MM?

Recently, we have also been exploring the use of dehydroepiandrosterone (DHEA), a steroid-like substance, and also clarithromycin (Biaxin, Abbott), an antibiotic, in early clinical trials for MGUS. Also, inhibitors of interleukin-1 β might be effective. This cytokine is frequently found in patients with MM but not in MGUS patients. There are no data yet on the efficacy of this approach, and it will only be possible to determine its therapeutic value in the context of a prospective, randomized study.

Are enough clinical studies focusing on treatment in these disease settings currently being done?

No. The challenges of conducting therapeutic studies for these patients are that therapy can be quite expensive, and the patient could experience undesirable side effects that are not recognized until later. As Henry Bence Jones said 150 years ago, "there is no such thing as a safe drug." Even common drugs such as aspirin result in a number of deaths from anaphylaxis each year in hypersensitive patients. All of the agents we could study for MGUS or smoldering MM have potential side effects. For a 40-year-old person with MGUS, it might be 30 years or longer before progression. It doesn't necessarily make sense to take drugs over those 30 years to prevent something that might never occur.

How is this study conducted if so few individuals with MGUS progress?

This study must be done retrospectively. Since only 1% of patients progress each year, a prospective study would take many years to complete. At our institution, we have a serum bank with 150,000 samples from patients with MM, WM, MGUS, lymphoma with monoclonal protein, and other related hematologic malignancies. These samples have been collected since 1960. This collection enables studies to be done quickly.

How has the technology for identifying prognostic factors advanced over the years?

Serum protein electrophoresis was first used in MM in 1939. In the 1940s, the instrument used to perform a serum protein electrophoresis would fill an entire room, and a trained technician would need a full day to complete 1 serum protein electrophoresis. In our laboratory today, we are able to complete over 400 per day. In the 1940s, distinguishing between proteins was very difficult. A refractive index was used to determine the different types of protein. In the early 1950s, paper was introduced as a supporting medium, and in the late 1960s, cellulose acetate was introduced. Today, high-resolution agarose gel is used.

The identification of the size of monoclonal protein has also improved markedly. In the 1970s and 1980s, immunoelectrophoresis was used, and in the last 15 years or so, immunofixation, which is faster and more accurate, has become the main technology.

Over the last 30 years, many companies producing anti-sera agents attempted to develop an antibody that would recognize only free κ and free λ light chain. However, when these antibodies were tested, they would be either nonspecific, measuring the free as well as the bound light chain, or too weak to recognize all of the free light chain present. About 4 or 5 years ago, an antibody that is able to recognize free light chain, developed at the University of Birmingham in England, was found to be both very accurate and reproducible. This technology uses a nephelometer, an automated instrument that is used for measuring IgG, IgA, and IgM. This new technology is a marked improvement and has enabled us to identify the κ : λ ratio as an important prognostic factor.

Suggested Reading

Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ 3rd. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. *Mayo Clin Proc.* 2004;79(7):859-866.

Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood.* 2003;102(10):3759-3764.

Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2002;346(8):564-569

Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood.* 2001;97(9):2900-2902.