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Asymptomatic Monoclonal Gammopathies

Claire Bories,[1] Sundar Jagannath[2]

Abstract

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) represent the earlier phases of plasma cell dyscrasias. Their definition is based on absence of end-organ damage with presence of a malignant clone that grows in the bone marrow. They share, as a common feature, the risk of progression to a symptomatic disease. MGUS progression risk is approximately 1% per year, and SMM has a risk of progression of 10% for the first 5 years which tapers off over time. The main purpose of identification of these earlier phases of the plasma cell dyscrasia was to identify patients who do not warrant treatment with chemotherapy, in whom the risk of treatment outweighs the benefit. Over the years, the definitions have not been modified to incorporate developments in imaging (magnetic resonance or positron emission and computed tomography), or genomics to identify patients at highest risk of progression within 2 years, where wait and watch might not be an appropriate option. In the absence of such definition, patients who have only a 50% chance of progression within 2 years are being offered therapy, which might also not be an optimal approach. In this review, we provide an overview of the definition, current prognostic factors, and risk stratifications in asymptomatic gammopathies, and discuss clinical trial outcomes in high-risk SMM.

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Introduction

Asymptomatic gammopathies represent early stages of plasma cell (PC) dyscrasias, also named monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) or asymptomatic myeloma. The term MGUS was introduced at the end of the late 1970s by Kyle to denote a presence of a monoclonal protein in persons without evidence of multiple myeloma (MM), macrogloblinemia, amyloidosis, or other related PC or lymphoproliferative disorder.[1] The term smoldering myeloma was introduced by Kyle and Greipp[2] in 1980 to describe a group of patients with $\geq$ 10% PC in the bone marrow (BM) and a serum M-protein $\geq$ 3 g/dL who had an indolent course of disease and did not require treatment for 5 years after diagnosis. The same year, Alexanian[3] coined the term indolent myeloma to describe patients with $\geq$ 15% of BM PC, $<$ 3 lytic lesions, minimal monoclonal protein level depending on the type of immunoglobulin of 25 g/L for immunoglobulin (Ig)G and 10 g/L for IgA and a time to progression $>$ 2 years. The current definition of smoldering or asymptomatic myeloma was determined by the International Myeloma Working Group (IMWG) consensus in 2003[4] that included $\geq$ 10% BM PC and/or serum M-protein $\geq$ 3 g/dL without end organ damage. The major objective was to use simple tests to identify patients who did not merit treatment where the risk of treatment outweighed the benefit. This definition was universally adopted for the simplicity and reproducibility. As we now know, MGUS consistently precedes MM.[5] MGUS and SMM carry the potential of becoming symptomatic and progressing into the MM disease. Therefore risk stratification was developed to identify patients with greater risk for progression to symptomatic disease.

During the past decade, dramatic progress has been made in disease assessment. Tumor cytogenetics, fluorescence in situ hybridization (FISH) analysis, flow cytometry, and genomic studies have shed better understanding of the biology of the disease and newer imaging techniques with higher resolution that can survey the skeleton such as magnetic resonance imaging (MRI) and positron emission tomography (PET)-computed tomography (CT) have allowed earlier detection of skeletal involvement. The advent of novel agents with lower toxicity and greater depth of response has also made treatment more attractive than conventional chemotherapy of the past. Recently, investigators from Spain have shown in a randomized trial that early treatment intervention of asymptomatic myeloma patients at high risk for progression not only delays disease progression but also improves survival. This has set the stage for a critical review of asymptomatic myeloma patients who are candidates for early intervention.

[1]Service des Maladies du Sang, CHRU Lille, France
[2]Department of Hematology/Oncology, Mt Sinai Medical Center, New York, NY

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Address for correspondence: Sundar Jagannath, MD, Mt Sinai Medical Center, Hematology/Oncology, 1 Gustave L. Levy Place, Box 1185, New York, New York 10029
E-mail contact: Sundar.Jagannath@mountsinai.org

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Diagnosis

Epidemiology

Monoclonal Gammopathy of Undetermined Significance. Kyle et al[6] reported a prevalence of 3.2% of MGUS in a population older than 50 years, with a male predominance (4% vs. 2.7%). This number increased with advanced age and was almost 4 times as high among persons 80 years of age or older. IgG monoclonal protein was mostly reported (68.9%), IgM accounted for 17.2%, IgA isotype was seen in 10.8%, and biclonal protein in 3.2%. The light chain was κ in 62% of the patients and λ in 37.9%. When considering the light chain MGUS, the prevalence changed to 4.2% in a population older than 50 years (light chain MGUS: 0.8%).[7]

Smoldering Multiple Myeloma. Since the criteria defining the SMM were established by the IMWG,[4] studies report a median age of diagnosis between 60 and 70 years.[8-10] SMM represents almost 8% of all diagnoses of MM and are predominantly IgG SMM (74%) or IgA (22.5%).[8] At the time of presentation of SMM Spanish group noted, 28% had a previous diagnosis of MGUS.[9]

Current Criteria. Definitions of MGUS and SMM are given in Table 1.[11] Three subgroups of MGUS have been described by Rajkumar et al, from the Mayo Clinic in 2010[11]: non-IgM MGUS, IgM MGUS, and light chain MGUS.

Smoldering multiple myeloma is a point of transition between MGUS and MM and must meet both criteria: a serum M-Protein (IgA or IgG) $\geq$ 30 g/L and/or BM clonal PC infiltration $\geq$ 10%, and absence of hyper Calcemia, Renal impairment, Anemia, Bone disease (CRAB) criteria. The point of transition between light chain MGUS and light chain MM is called idiopathic Bence Jones proteinuria and meet the following criteria: urinary monoclonal protein in urine protein electrophoresis $\geq$ 500 mg per 24 hours and/or clonal BM PC $\geq$ 10%, no immunoglobulin heavy-chain expression on immunofixation, and absence of end-organ damage.

Cytogenetics. Few studies have described the chromosome abnormalities encountered in the precursor diseases of MM. The paucity of PC in the BM of patients, together with the low proliferative capacity of these cells are a barrier for establishing a conventional karyotype. FISH analysis might be an alternative to study the genetic background of PC dyscrasias.

Chiecchio et al[12] have reported cytogenetic finding in 189 MGUS patients, 127 SMM patients, and 400 patients with newly diagnosed MM using FISH analysis. Deletion 13, deletion of p53, IgH heavy chain locus translocation, and ploidy were studied in all groups of PC dyscrasias. Most of the patient had copy number changes or at least 1 chromosomal alteration for the region tested (89% in MGUS, 98% in SMM, and 99% in MM). A lower frequency of del13 was seen in the premalignant conditions than in MM. The incidence of 16q23 and TP53 deletion was also significantly progressively increased from MGUS to MM. Rearrangement involving the IgH heavy chain locus were detected with similar frequencies for t(6;14), t(11;14), and t(14;16). t(4;14) was rare in MGUS but presented the same incidence in SMM and MM. IgH rearrangement involving 4p16, 6p21, 11q13, 16q23, and 20q11 were highly associated with a nonhyperdiploid karyotype in the 3 different groups.

These results highlight that none of the chromosomal aberrations are exclusive to a single diagnostic group but rather consist of many overlapping oncogenic events from MGUS to MM.

Gene Expression Profiling

Advances in molecular biology and genetics have demonstrated distinct genetic subtypes of the MM disease. Gene expression profiling (GEP) of purified CD138-positive ($CD138^+$) PC has been used to identify distinct molecular subgroups of MM and a high-risk group in myeloma validated by the IMWG in 2009.[13] Because MGUS consistently precedes MM,[5] genomic analysis of asymptomatic monoclonal gammopathies might be relevant in characterizing the molecular pathway associated with progression. However, GEP analysis might be a challenge in MGUS because it depends on the ability to isolate aberrant $CD138^+$ clonal PC, which is low in MGUS by definition.

Dhodapkar et al[14] have shown, in a cohort of 126 patients from the SWOG intergroup who had available GEP data, that all major molecular subtypes of MM were detected in MGUS (n = 39) and SMM (n = 87) patients. Indeed, patients with SMM had a greater proportion of hyperdiploid subtype and a lower proportion of cyclin D2 subtype than patients with MGUS. In comparison with the MGUS cohort, the SMM cohort had a greater proportion of GEP signature of high-risk, according to the GEP-70 model.[15]

Prognosis

Monoclonal Gammopathy of Undetermined Significance. Kyle et al[16] reported a large series of 1384 patients with IgG, IgA, IgM, or biclonal MGUS. The cumulative probability of progression to MM, lymphoma, amyloidosis, Waldenström macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma was approximately 1% per year and this risk of progression remained the same after 25 years or more.

Prognostic Factors. Risk factors for progression in the MGUS condition have been well described in the literature and include a broad spectrum of parameters. Isotype (IgA or IgM) and level of the monoclonal component,[10,16-18] or the light chain-associated,[10] BM PC infiltration,[10,18] evolution of serum M-protein level,[19] immunoparesis (diminution of the uninvolved immunoglobulins),[10,18] presence of a Bence Jones proteinuria,[10,18] DNA ploidy,[10] proportion of abnormal BM PC within the BM PC compartment (aPC/BMPC) identified using flow cytometry[10,19] have been the most described risk factors in MGUS. Although MRI or PET-CT is not recommended for evaluation in case of MGUS, investigators noted that detection of 2 or more focal lesions without lytic lesion predicted for earlier progression to MM.[20]

Of note, Dispenzieri et al[7] have shown that risk of progression for light chain MGUS is not significantly different from the low-risk MGUS: 0.3% a year (vs. 0.6% for the other MGUS). However, light chain MGUS patients have increased incidence of renal impairment and they have to be worked up for light chain deposition disease or amyloidosis.