

Secondary Monoclonal Gammopathy of Undetermined Significance: A Sign Of Cure Or A Harbinger Of Relapse.

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Multiple myeloma (MM) is a clonal expansion of plasma cells, characterized by the production of a monoclonal protein, as well as end-organ damage^[1].

The types of heavy and lightchain of this M-protein are specific to the myeloma clone. Therefore, it is used as a marker for diagnosis and monitoring of disease and response in MM^[2].

Until relatively recently, the prognosis for myeloma patients has been poor. Median survival before 1997 was 2.5 years. Kumar et al. reported a study of 2981 myeloma patients diagnosed and treated in the last decade, showing a 50% improvement in overall survival (OS) compared with the previous decade (44.8 vs 29.9 months; $P < 0.001$). This change in outcome reflects the introduction of novel therapeutic agents, including immunomodulatory drugs and proteasome inhibitors, in addition to refinement of autologous hematopoietic progenitor cell transplant (AHPCT) protocols. AHPCT is now an integral part of standard care for MM patients^[3].

Virtually all cases of MM are preceded by an indolent, premalignant disease known as monoclonal gammopathy of undetermined significance (MGUS) that can evolve to asymptomatic (or smoldering) MM and later to symptomatic MM^[1].

Robert Kyle coined the term monoclonal gammopathy of undetermined significance (MGUS) in 1978 after the observation that asymptomatic patients with a monoclonal protein (M-protein) had higher risk of developing multiple myeloma (MM), Waldenström macroglobulinemia (WM), light-chain amyloidosis (AL), or related conditions^[4].

Monoclonal gammopathy of undetermined significance (MGUS) is present in 3%-4% of the general population over the age of 50 years. The prevalence of MGUS increases with age and toxin exposure. MGUS progresses to multiple myeloma (MM) or related malignancy at a rate of 1% per year. At 25 years of follow-up, the probability of

progression is 11% with adjustment for competing causes of mortality. Osteoporosis, neuropathy, and thrombophlebitis have been associated with MGUS^[5].

MGUS may progress toward symptomatic conditions, requiring the initiation of treatment, through 2 general mechanisms: (1) progression of the proliferative characteristics toward smoldering MM (SMM), MM, and other lymphoplasmacellular disorders, which account for approximately 90% of the progression; or (2) the development of end-organ damage caused by the M-protein such as AL amyloidosis, light chain deposition disease (LCDD), and other rarer conditions, which account for approximately 10% of the progression^[4].

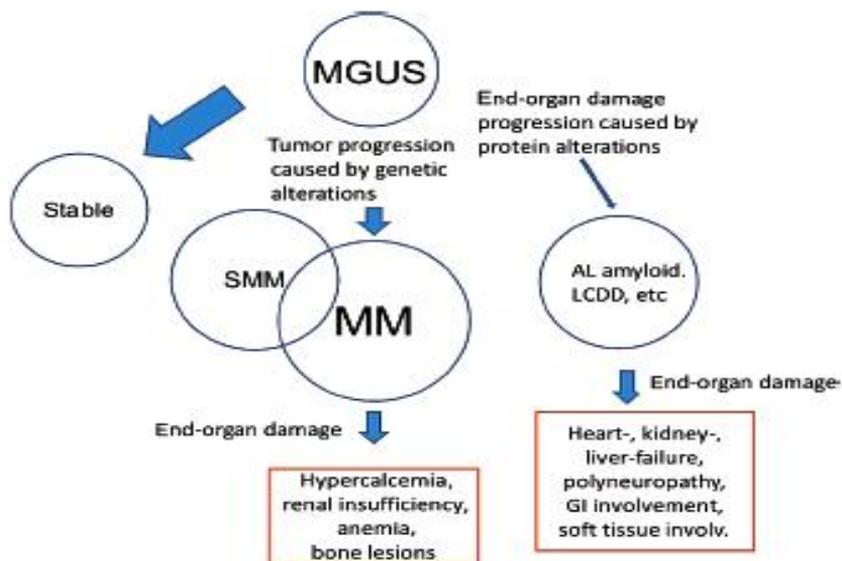


Figure 1. Conditions associated with an M-protein. Although MGUS is a premalignant condition, approximately 40% of all MGUS patients are considered low-risk MGUS and have a lifetime risk of progression of only 2%. Acquisition of somatic genetic abnormalities in the tumor cells and changes in the BM microenvironment may lead to progression to SMM and MM. SMM includes patients with premalignancy and patients with early asymptomatic malignancy. The clone may produce a protein with altered conformation, which may aggregate improperly, causing progressive organ dysfunction. These conditions include AL amyloidosis, LCDD, and type I cryoglobulinemia. Other conditions, such as type II cryoglobulinemia, chronic cold agglutinin disease, and autoimmune neuropathies, are caused by the autoantibody activity of the M-protein, which in most cases is an IgM. Finally, other rare diseases are associated with

monoclonal gammopathies, but their pathogenesis is still unclear. This is the case for POEMS syndrome, scleromyxedema, and Schnitzler syndrome [4].

In the course of MM, patients may develop monoclonal bands of different isotypes than the original myeloma M-protein. Several terms have been used to describe this phenomenon, including abnormal protein band, oligoclonal protein bands, transient mono- or oligoclonal gammopathy, apparent isotype switch, oligoclonal humoral response, atypical serum immunofixation pattern, and secondary MGUS (sMGUS)[6].

sMGUS occurs more frequently after treatment with autologous stem cell transplantation (auto-SCT) (10-73%), than in patients who have not undergone auto-SCT (1.6-3.1%). Several studies also showed a higher frequency of sMGUS in patients treated with novel agents, when compared to conventional chemotherapy. Importantly, sMGUS is not a sign of relapse or progression of MM. In fact, some studies found that patients who develop sMGUS have a superior prognosis in terms of progression-free survival (PFS) and overall survival (OS) than those without sMGUS[7].

Secondary MGUS was defined as appearance of a protein band on immunofixation or electrophoresis that is different from the original myeloma M-protein in heavy-chain or light-chain isotype, or in its migration pattern. The emergence of sMGUS reflects a strong humoral immune response and is a sign of immune reconstitution after allo-SCT, autologous SCT, or novel agent-containing regimens. There is no evidence that these abnormal protein bands are related to the myeloma clone. Guikema et al used allele specific oligonucleotide- polymerase chain reaction (ASO-PCR) and deoxyribonucleic acid (DNA) sequencing to demonstrate that new serum M-components after auto-SCT are not produced by myeloma cells but rather by the regenerating B-cell compartment. Furthermore, sMGUS not only occurs in MM patients but also after treatment for other hematologic malignancies and even solid organ transplantations^{19[2]}.

In a study by Schmitz et al.[2], total of 138 myeloma patients were enrolled, who underwent 139 allo-SCTs. A hundred and thirty-four patients (96.4%) were diagnosed with MM while 5 patients (3.6%) had primary plasma cell leukemia (pPCL). Sixty-seven (48.2%) of the patients developed at least one sMGUS after allo-SCT. Remission status after transplantation was associated with occurrence of sMGUS. Patients who achieved complete remission (CR) or very good partial response (VGPR) more frequently developed a new protein band compared to patients who achieved partial response (PR) or less (54.8 vs. 26.5%; $P=0.005$). Secondary MGUS also occurred more often in newly diagnosed MM patients compared to relapsed patients (60.0% vs. 40.5%; $P=0.037$).

Patients with a sibling donor had a higher incidence of sMGUS, compared to matched unrelated donor (57.0% vs. 36.7%; $P=0.026$). Patients treated with novel agent-based induction therapy had a lower incidence of sMGUS compared to patients treated with conventional chemotherapy alone (39.6% vs. 67.4%; $P=0.003$). There was no difference in the frequency of sMGUS in patients treated with bortezomib, thalidomide, or lenalidomide. Furthermore, sMGUS was less often observed after T-cell depletion with anti-thymocyte globulin (ATG) or alemtuzumab (39.3% vs. 61.8%; $P=0.025$). There was a trend towards a higher frequency of sMGUS in patients who developed chronic graft versus host disease (GvHD) (41.8% vs. 56.7%; $P=0.090$). Figure 2 represents PFS and OS in patients according to development of sMGUS. Figure 3 demonstrates data in relation to patients with denovo disease or relapsed ones.

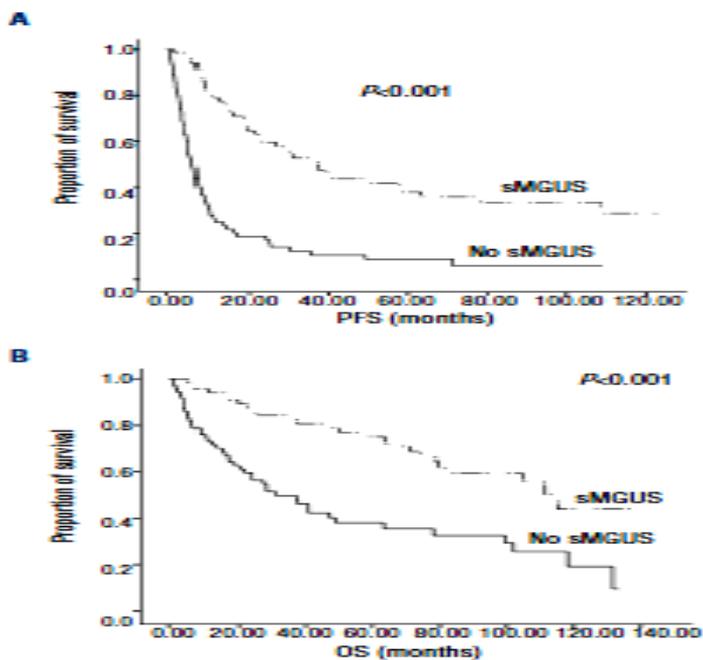


Figure 2 Progression-free survival (PFS) (A) and overall survival (OS) (B) according to the presence of secondary monoclonal gammopathy of undetermined significance (sMGUS). Kaplan-Meier analysis was used to test the statistical significance of differences between the survival curves [2] .

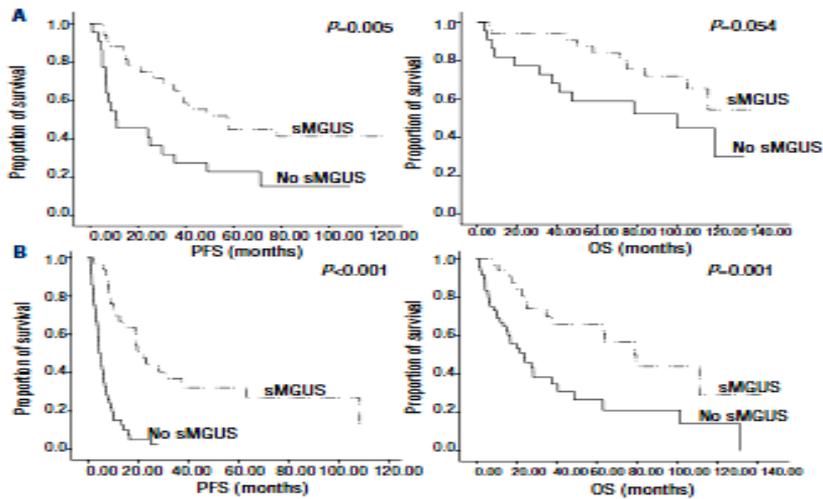


Figure 3. Progression-free survival (PFS) and overall survival (OS) for patients who received allogeneic stem cell transplantation (allo-SCT) as part of first-line treatment (A) or after relapse (B) according to the development of secondary monoclonal gammopathy of undetermined significance (sMGUS). Kaplan-Meier analysis was used to test the statistical significance of differences between the survival curves [2].

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