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Special article

Management of smoldering myeloma: Recommendations of the Spanish Myeloma Group☆

Tratamiento del mieloma múltiple asintomático: recomendaciones del Grupo Español de Mieloma

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Introduction

Asymptomatic or smoldering multiple myeloma (SMM) was first defined in 1980 by Kyle and Greipp after observing the clinical course of 6 patients who met the criteria for multiple myeloma (MM) but experienced a painless course.[1]

Based on data from the Swedish MM Registry, Kristinsson et al. reported that 14% of patients with newly diagnosed MM are SMM, equivalent to 0.44 new cases per 100,000 inhabitants/year.[2]

The concept of SMM was updated by the *International Myeloma Working Group* (IMWG), agreeing on the following diagnostic criteria: serum monoclonal component (MC) ≥3 g/dl, and/or between 10% and 60% of plasma cells (PC) in bone marrow (BM) without organic damage, that is, without CRAB (*Calcium, Renal insufficiency, Anaemia or Bone lesions*) symptoms. A subgroup of asymptomatic patients with a very high risk of progression (ultra-high risk) to MM (>80% at 2 years) who had one or more of the following biomarkers: (i) presence of 2 or more focal lesions on whole body or spine and pelvis magnetic resonance imaging (MRI); (ii) ratio of free light chains in serum over 100; or (iii) PC infiltration in BM ≥60% were excluded from this new definition of SMM.[3] These patients are now considered as MM and therefore need to start treatment.

Differential diagnosis

Table 1 shows the criteria that define monoclonal gammopathy of undetermined significance, SMM and MM. Monoclonal gammopathy of undetermined significance is characterized by a MC <3 g/dl and <10% of PC in BM, in the absence of organic damage data. On the contrary, the MM, as we have already pointed out, is defined by the presence of ≥10% clonal PCs in BM or in a bone or extramedullary plasmacytoma. However, for the diagnosis of MM, the presence of any CRAB symptomatology is essential, either that or the presence of one or more of the three biomarkers referred to above, which, in the absence of CRAB, are associated with an imminent risk of progression to MM.

Symptomatology, especially CRAB, should be carefully evaluated so as not to confuse it with concomitant diseases whose manifestations may mimic MM symptomatology; for example, nutritional anaemia, menopausal osteoporosis, impaired renal function due to hypertension or diabetes, hypercalcemia due to hyperparathyroidism, or an isolated single bone cyst.

The diagnosis of SMM requires some additional examinations whose results should also be interpreted in the context of the clinical symptoms:

(1) For the evaluation of bone lesions, the IMWG recommends the performance, according to availability, of a bone series or a CT

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Table 1
Differential diagnosis between monoclonal gammopathy of undetermined significance, smoldering multiple myeloma and multiple myeloma.

Characteristic	MGUS	SMM	MM
Serum M protein	<3 g/dl, and	≥3 g/dl and/or	
Clonal infiltration by PC in BM	<10%	10–60%	≥10% or plasmacytoma evidenced on biopsy
Symptomatology	Absence of CRAB[a]	Absence of MDE[b] or amyloidosis	Presence of MDE[**]

PC: plasma cells; CRAB: *Calcium, Renal insufficiency, Anaemia or Bone lesions*; MDE: myeloma defining episodes; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; SMM: smoldering multiple myeloma; BM: bone marrow.

[a] CRAB symptomatology includes (1) hypercalcemia: serum calcium >0.25 mmol/l (>1 mg/dl) above the upper limit of normal or >2.75 mmol/l (>11 mg/dl); (2) renal failure: serum creatinine >177 μmol/l (2 mg/dl) or creatinine clearance <40 ml/min; (3) anaemia: haemoglobin >2 g/dl below the low limit of normal, or haemoglobin <10 g/dl; (4) bone lesions: one or more lytic lesions evidenced by conventional radiology, CT, or PET-CT.

[b] Events that define myeloma and include the CRAB symptoms described above or one or more of the following biomarkers that predict progression to MM: ≥60% clonal plasma cells in the bone marrow; ratio of free light chains in serum affected/unaffected ≥100; >1 focal lesion in MRI studies.

scan of individual low dose or combined with a positron emission tomography (PET/CT) using ^{18}F fluorodeoxyglucose as a tracer, although the latter 2 techniques are more sensitive. Low-dose CT is the most cost-effective technique to detect lesions in up to 30% of the cases in which the bone series was negative (the lytic lesion must measure at least 5 mm to be considered as such). It is also necessary to perform a whole body or spine and pelvis MRI, since MM should be considered if there is more than one focal bone lesion. In this sense Hillengas et al. reported that the presence of more than one MRI focal lesion in patients with SMM is associated with a high risk of progression to MM (median time to progression [TTP]) of 13 months),[4] data confirmed by Kastritis et al.[5] in a small study in which 9 cases with more than one focal lesion were evaluated, with a 2-year risk of transformation of 69%.

(2) With regard to PC infiltration of BM, in a series of 651 patients with SMM of the Mayo Clinic, the median TTP in cases of one infiltration ≥60% was 7.7 months, with a 2-year progression risk of 95%.[6] This finding was corroborated in 2 other series, one of 96 patients, confirming the TTP of 15 months[7] and another of 121 patients identifying 6 (5%) cases with this biomarker and development of MM in all cases within 2 years.[8]

(3) *Serum free light chains* (sFLC) quantification is required in the initial assessment. The Mayo Clinic group analyzed the value of the ratio between the affected and unaffected free light chains in serum in 586 patients with SMM and when the ratio was higher than 100, present in 15% of patients, the risk of progression to MM at 2 years was 71%.[9] The results of the Greek Myeloma Group confirmed these results in a series of 96 patients, detecting a progression rate of 80% in the first 24 months.[7] This biomarker is probably the most conflicting and, in fact, a recent analysis published by the Danish Myeloma Group on 321 patients with SMM has not confirmed the significant influence of abnormal sFLCr values on TTP.[10]

In summary, if after considering the above aspects, a patient meets SMM criteria (Table 2), this should be confirmed 2–3 months after the first evaluation and then the therapeutic approach should be determined by the risk to progress to MM.

Risk assessment in the patient with smoldering multiple myeloma

The annual risk of developing MM in a patient with SMM depends on the time elapsed since diagnosis: 10% per year for the first 5 years; 3% per year for the next 5 years and only 1% after the first 10 years.[11] Although most patients with SMM will develop MM, the risk is not homogeneous and is conditioned by the presence of biomarkers that have been used to create models aimed at evaluating the risk of each patient with SMM, in order to support an individualized management of this disease (Table 3).

Table 2
Tests performed at the time of smoldering multiple myeloma diagnosis.

Clinical history and physical examination
Blood count
Biochemical studies, including serum and calcium creatinine; beta2-microglobulin, LDH and albumin
Protein studies
Total serum proteins and electrophoresis (monoclonal component)
Protein electrophoresis in 24 h urine sample (urine monoclonal component or Bence Jones proteinuria)
Immunofixation in serum and urine
Ratio of free light chains in serum (sFLC ratio)
Aspirate ± bone marrow biopsy: clonal plasma cell infiltration, flow cytometry and In situ *fluorescence hybridization in selected plasma cells*
Bone series, CT, or PET-CT
MRI of the spine and pelvis, although, ideally, it should be whole-body MRI

LDH: lactate dehydrogenase; PET-CT: positron emission tomography using ^{18}F-fluorodeoxyglucose as tracer; MRI: magnetic resonance imaging; sFLC: *Serum Free light chain;* CT: computed tomography.

Table 3
Smoldering multiple myeloma: factors that predict progression to multiple myeloma. Characteristics to identify high-risk smoldering multiple myeloma (approximately 50% in 2 years).

Tumour mass
≥10% clonal plasma cells in BM plus
≥3 g/dl of monoclonal component and serum free light chains ratio <0.125 or >8
Positive Bence Jones proteinuria in 24 h urine
Circulating plasma cells in peripheral blood >5 × 10^6/l
Circulating plasma cells in peripheral blood by cytometry ≥150
Immunophenotypic characterization and immunoparesis
≥95% of aberrant plasma cells by cytometry in the BM plasma cells plus Immunoparesis (>25% decrease in one or both immunoglobulins not affected with respect to the low level of normality)
Cytogenetic abnormalities
Presence of t (4; 14)
Presence of del17p
1q24 gain
Hyperdiploidy
Score >−0.26 by gene expression profile
Monoclonal component and haemoglobin progression pattern
Type in progression: if monoclonal component ≥3 g/dl, increase of at least 10% during the first 6 months. If monoclonal component <3 g/dl, annual increase over 3 years
Increase of monoclonal component up to ≥3 g/dl during the 3 months following the previous determination
Decreased haemoglobin in ≥0.50 g/dl in the first year since diagnosis
Imaging techniques
MRI: progressive disease by MRI when new focal lesions are detected or the diameter of the existing lesion increases (if previously detected) or progressive diffuse infiltration
Positive PET/CT without osteolytic lesions

BM: bone marrow; PET-CT: positron emission tomography using ^{18}F-fluorodeoxyglucose as tracer; MRI: magnetic resonance imaging.