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EDITORIAL

MGUS: Proposal for outpatient management

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Abstract

The term monoclonal gammopathy of undetermined significance (MGUS) indicates the presence of a monoclonal protein (M-protein) without features of multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis or malignant lymphoproliferative disorders (LPD). While several guidelines on the treatment of LPD exist, many doubts and perplexities still exist on who should treat a MGUS, when and how. Even where MGUS does not require any therapy, the risk of progression to a LPD is 1% per year. This risk does not diminish over time and persists even in patients (pts) whose condition has remained stable for decades, and a prolonged follow up is, therefore, recommended. We met primary care doctors to share and agree on criteria for the management of outpatients with MGUS. Our aim is to draw up guidelines or, at least, suggestions that may help to determine which MGUS pts could be cared for by the primary care doctor and which should be followed by the hematologist. We suggest that once a MGUS is diagnosed, the primary care physician will attend patients with M-protein < 15 g/L if IgG and pts with M-protein < 10 g/L if IgA or IgM, without end-organ damage and without signs and symptoms of LPD. However, a hematological evaluation is recommended for patients with M-protein IgG > 15 g/L, or M-protein IgA > 10 g/L, or IgM > 10 g/L, or any M-protein with end-organ damage (not attributable to any others causes) or with signs and symptoms of LPD, or rapidly increasing M-protein (> 5 g/L per year).

Key words: Monoclonal gammopathy; Multiple myeloma; Macroglobulinaemia; End-organ damage; Serum protein electrophoresis

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MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

The term monoclonal gammopathy of undetermined significance (MGUS) indicates the presence of a monoclonal protein (M-protein) without features of multiple myeloma (MM), Waldenström's macroglobulinemia, primary amyloidosis or other malignant lymphoproliferative disorder (LPD). The MGUS represents a large portion of the total M-protein. The overall prevalence of MGUS in people older than 50 years is 3.2% in a predominantly white population. The prevalence increases with age and in black people.

Even where MGUS does not require any therapy, the

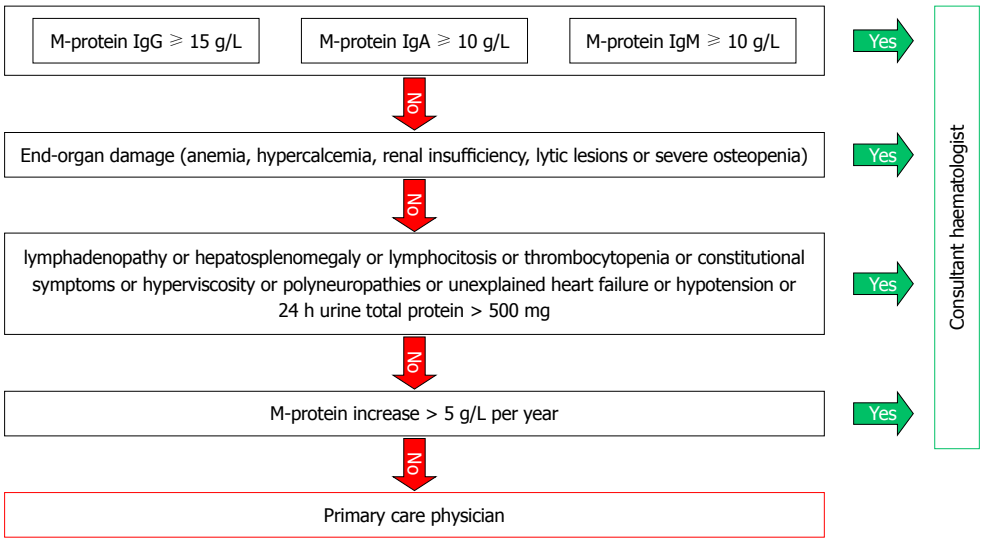

Figure 1 An easy reference guide for primary care physicians and other clinicians.

risk of progression to a LPD is 1% per year. This risk does not diminish over time and persists even in patients (pts) whose condition has remained stable for decades, and a prolonged follow up is, therefore, recommended[1].

At the present there are no formal guidelines regarding follow-up for patients with MGUS. Clinical trials have provided very little evidence to inform the guidelines published; most of the recommendations are based on the outcomes of large observational studies and evidence from expert committee reports and/or clinical experiences of respected authorities and are therefore grade C, level Ⅳ[2].

We met the primary care physicians to share criteria for classification and to agree on criteria for the management MGUS.

Our aim is to draw up guidelines or, at least, suggestions that may help to determine which MGUS pts could be cared for by the primary care doctor and which should be referred to the specialist.

MGUS is characterized by a serum M-protein < 30 g/L, plasma cells in the bone marrow < 10% and absence of end-organ damage: anemia (normochromic, normocytic with a haemoglobin value of > 2 g/dL below the lower limit of normal or a hemoglobin value < 10 g/dL), renal failure (creatinine > 2 mg/dL. or estimated creatinine clearance < 40 mL/min), hypercalcemia (serum calcium > 11.5 mg/dL), bone lesions (lytic lesions or osteoporosis with compression fractures)[3].

Agarose gel serum protein electrophoresis and immunofixation allow detection, quantification and to typing of the M-protein.

Once M-protein is detected the primary care physician needs full blood count, serum creatinine, serum calcium, 24 h urine total protein (easily quantifiable, can reveal a nephrosic syndrome, due to myeloma or amyloidosis, unlike Bence Jones proteinuria that does not predict progression).

Clinical attention should be addressed to the presence of constitutional symptoms (night sweats, fever, and weight loss), bone pain, lymphadenopathy and splenomegaly.

At this point β-2 microglobulin, serum quantitative imunoglobulins, urine protein electrophoresis, Bence Jones proteinuria are not necessary.

In the absence of end-organ damage, and with M-protein < 30 g/L, MGUS can be discriminated from asymptomatic myeloma only with bone marrow biopsy. In any case, since the latter does not require any therapy, this discrimination is not essential.

Once a MGUS is diagnosed the primary care physician will attend patients with M-protein < 15 g/L if IgG and pts with M-protein < 10 g/L if IgA or IgM, without end-organ damage and without signs and symptoms of LPD (lymphocitosis, thrombocytopenia, lymphadenopaty, hepatosplenomegaly, constitutional symptoms, hyperviscosity, unexplained heart failure, polyneuropathy).

Six-month follow-up testing is suggested. This should include full blood count, serum creatinine, serum calcium, serum protein elecrophoresis and 24 h urine total protein.

However, hematological evaluation is recommended for patients with M-protein IgG > 15 g/L, or M-protein IgA > 10 g/L, or IgM > 10 g/L, or any M-protein with end-organ damage (not attributable to any others causes) or with signs and symptoms of LPD, or showing rapid increase in M-protein (> 5 g/L per year).

DISCUSSION

Prediction of which MGUS will remain stable and which will progress to LPD is very difficult at the time of diagnosis of MGUS. Risk factors for transformation of MGUS to malignant conditions have been addressed in several studies. A major shortcoming of most of these studies has been their relative small size and the inclusion of patients who today would be classified as asymptomatic MM. The data are conflicting but the initial con-

centration of M-protein[4,5] and the type of M-protein, IgA or IgM, are consistent risk factors for progression[5-7].

In other hand, the risk of progression in patients with abnormal free light chain ratio was found to be significantly higher than in patients with a normal ratio, and was independent of the size and the type of serum M-protein so the authors proposed a risk stratification model based on concentration of the serum M-protein, the type of immunoglobulin and the presence of an abnormal free light chain ratio[4]. However these findings need to be confirmed by other studies before this model can be recommended for all the patients.

The risk of progression to LPD does not diminish over time and persists even in patients whose condition has remained stable for decades, so a prolonged follow up is recommended. There is no published evidence on which to base recommendations for the frequency of follow-up so guidance is, of necessity, pragmatic.

Even if a patient is seen by the physician at 3-montly or even shorter intervals, symptoms may rapidly develop in the meantime. The patient is the best person to be aware of the onset of relevant symptoms. It is essential therefore that patients are fully aware of important symptoms and they should encouraged to report these if they occur outside appointment visits.

These recommendations have been summarised in an algorithm (Figure 1) intended as an easy reference guide for primary care physicians and other clinicians to use when deciding whether referral to a consultant haematologist is necessary.

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