



## Abnormal laboratory results

# Screening for multiple myeloma

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### Summary

**Patients with suspected multiple myeloma should be investigated with screening tests. They may have a paraprotein in the serum, Bence-Jones protein in the urine, or both. If these proteins are detected by a protein electrophoretogram, the patient requires further investigation to distinguish multiple myeloma from monoclonal gammopathy of uncertain significance. Identifying the paraprotein isotype assists in the diagnosis of multiple myeloma, but bone marrow biopsy is needed to show the percentage of plasma cells in the marrow.**

Key words: Bence-Jones protein, monoclonal gammopathies, paraproteins.

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### Introduction

Multiple myeloma has a wide range of clinical presentations. It should be considered as a possible underlying cause in patients presenting with anaemia associated with bone pain, vertebral crush fractures, unusually severe osteoporosis, susceptibility to recurrent bacterial infections, or renal failure.

In multiple myeloma there is a proliferation of abnormal plasma cells which produce a monoclonal protein. This protein is usually an immunoglobulin which consists of light and heavy polypeptide chains. The immunoglobulin can be deposited in the kidney tubules, reducing renal function, while the accumulation of plasma cells in the marrow leads to anaemia. The diagnosis of multiple myeloma therefore requires investigation of immunoglobulins in the blood and urine and plasma cells in bone marrow.

### Initial investigations

Patients suspected of having multiple myeloma first have screening tests and then more specialised tests to confirm the diagnosis. This sequence of investigations identifies the presence of a clonal plasma cell disorder, then differentiates whether it is behaving benignly (monoclonal gammopathy of uncertain significance) or malignantly (multiple myeloma) (Fig. 1). The basic tests include a full blood count, urea, creatinine, and electrolytes including calcium. All patients are screened with electrophoresis of serum and urine.

### Serum and urine protein electrophoresis

Protein electrophoresis of serum and urine is a sensitive means of detecting the abnormal monoclonal proteins found in myeloma. The test can identify intact immunoglobulin or free light chains in about 98% of cases.

During electrophoresis of serum proteins, intact monoclonal immunoglobulin molecules will migrate as a sharply defined band. This is called a paraprotein, and is detected in about 80% of patients with myeloma. It is almost always found in association with Bence-Jones protein in the urine protein electrophoretogram. Bence-Jones protein is a homogeneous kappa or lambda free light chain.

In most of the remaining 20% of cases of myeloma where a paraprotein is not detected in the serum electrophoretogram, monoclonal light chains are readily detected by protein electrophoresis of concentrated urine. This form of myeloma is usually referred to as Bence-Jones myeloma.

### Paraprotein heavy chain type isotype

Identification of the immunoglobulin isotype of a paraprotein by immunofixation of the paraprotein band enables it to be classified as an immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM) molecule. Other isotypes are extremely rare. The identity of the isotype is important in differentiating whether production of the paraprotein is by a clonal plasma cell disorder, or by a clonal lymphoproliferative condition.

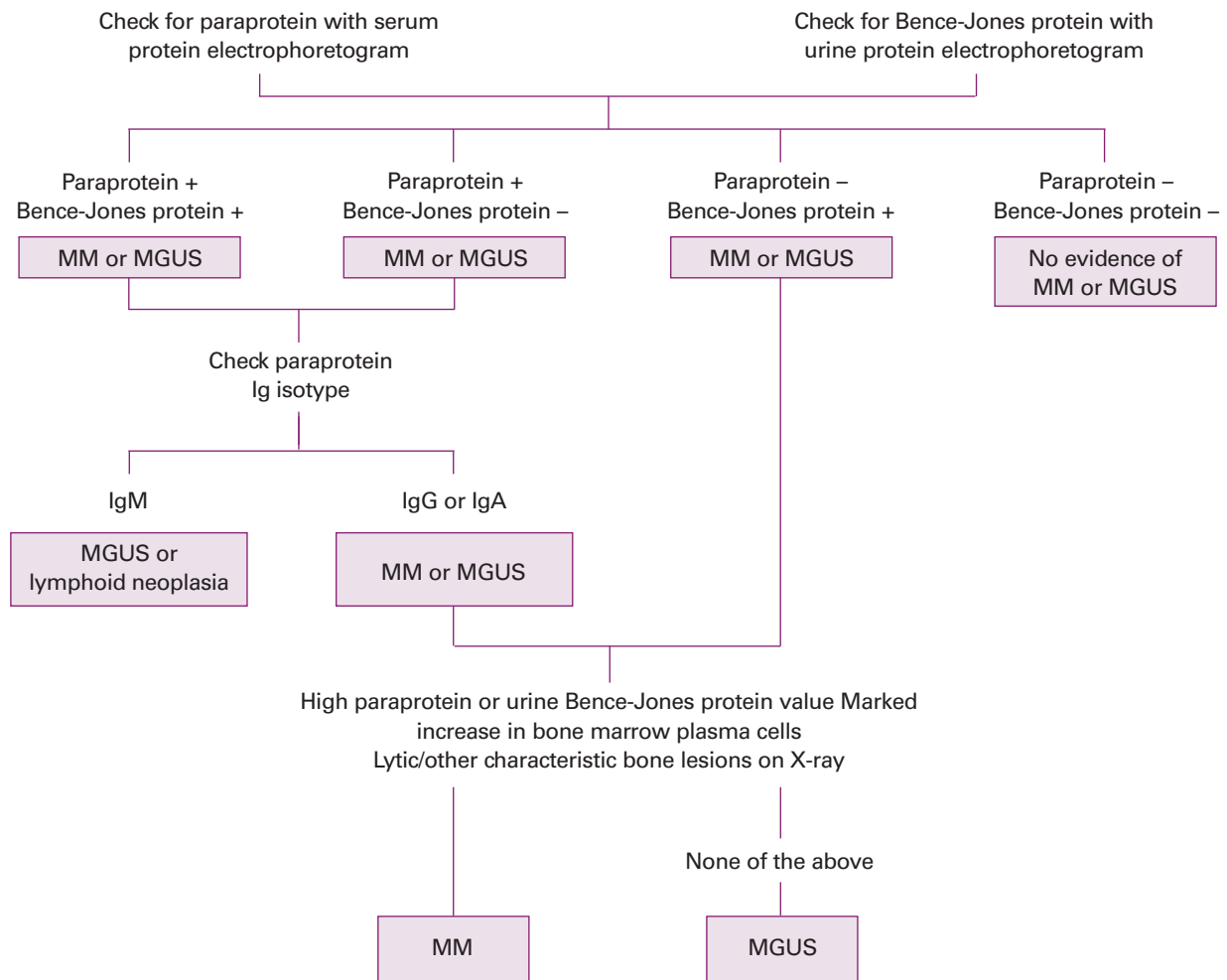
IgG and IgA paraproteins suggest a clonal plasma cell disorder. In myelomas which produce paraproteins, IgG paraproteins occur in approximately 75%, and IgA paraproteins in the remaining 25% of cases. An IgM paraprotein is extremely uncommon in myeloma. It is more indicative of a clonal lymphoproliferative disorder, such as low-grade non-Hodgkin's lymphoma. Waldenstrom's macroglobulinaemia is an example of one form of low-grade non-Hodgkin's lymphoma that is characteristically associated with a serum IgM paraprotein.

### Serum immunoglobulin quantitation

Measuring total concentrations of IgG, IgA and IgM in serum can reveal elevation of a specific immunoglobulin isotype that is suggestive of the presence of a paraprotein. However, the test does not distinguish between the normal polyclonal and abnormal monoclonal forms of a particular immunoglobulin.

Fig. 1

**Screening and diagnosis of multiple myeloma**



MM multiple myeloma  
 MGUS monoclonal gammopathy of uncertain significance  
 Ig immunoglobulin

This test is therefore not a substitute for the serum electrophoresis for identifying the presence of a paraprotein in screening for myeloma.

**Erythrocyte sedimentation rate**

The erythrocyte sedimentation rate (ESR) was used in screening for myeloma before the ready availability of serum and urine protein electrophoresis. Very high values are often observed in association with a serum paraprotein, but there are many other causes of a very high ESR and it therefore lacks specificity. Another limitation is that typically the ESR is not significantly elevated in Bence-Jones myeloma.

**Differentiation of monoclonal gammopathy of uncertain significance from multiple myeloma**

Sometimes a patient has a monoclonal protein, but no other features of multiple myeloma. This is called monoclonal

gammopathy of uncertain significance. It is relatively common and its prevalence in the community increases with age to about 3% in people aged 50–60 years, and about 5% in persons over 70 years old.<sup>1</sup> This clonal plasma cell or lymphoproliferative condition usually runs a non-progressive, clinically benign course and investigations fail to show a substantial tumour burden. Occasionally monoclonal gammopathy of uncertain significance transforms into clinically aggressive disease, although the rate of transformation is on average only about 1% per year. Transformation in a patient with an IgM paraprotein is usually to lymphoproliferative malignancy, while in patients with an IgA or IgG paraprotein the transformation is usually to myeloma.<sup>1</sup>

The detection of a paraprotein is often an incidental finding and insufficient to confirm a diagnosis of myeloma. Further information is required to establish whether the paraprotein disorder is monoclonal gammopathy of uncertain significance or myeloma.

## Serum paraprotein concentration

The serum paraprotein concentration can be used for differentiating between the conditions. Concentrations below the threshold value are more likely to be monoclonal gammopathy of uncertain significance and those above are more likely to be myeloma. These values are:

- IgG paraprotein disorders 30 g/L
- IgA paraprotein disorders 20 g/L.

Patients with Bence-Jones myeloma have very low serum concentrations of the protein. However, they usually excrete more than 1 g of Bence-Jones protein in a 24-hour collection of urine.

Experience suggests that these values are only an approximate guide, especially in the case of borderline values.

## Skeletal radiology

A major distinction between myeloma and monoclonal gammopathy of uncertain significance is increased lysis of bone resulting from the activation of osteoclasts by myeloma cells. In myeloma a skeletal X-ray survey commonly reveals abnormalities such as multiple, discrete lytic lesions, vertebral crush fractures, or even areas of diffusely reduced bone density. These findings are some of the most important means for detecting the malignant characteristics of myeloma.

## Bone scan

Conventional bone scanning with technetium-99 labelled methylene diphosphonate measures localisation of the tracer in many tissues, including newly formed bone due to increased osteoblastic activity. The tracer is not selectively accumulated by myeloma tissue. While there may be quiescent osteoblast activity in myeloma, increased osteoblastic activity also occurs at sites of repair after fracture and sites affected by infection or inflammation. Bone scanning therefore lacks specificity for myeloma and is not a suitable alternative to radiological examination.

## Bone marrow examination

A bone marrow aspirate and trephine biopsy is a key procedure in establishing a definitive diagnosis of myeloma. The procedure is usually performed when there is any suggestion from other screening tests of the possibility of underlying myeloma. It provides a direct measure of the degree of plasma cell infiltration in the bone marrow. In myeloma there is an abnormally high percentage of plasma cells (greater than 10%), compared to an approximately normal percentage in monoclonal gammopathy of uncertain significance.

Bone marrow biopsy may be unnecessary as part of initial screening if the patient has the typical features of monoclonal gammopathy of uncertain significance. An example would be

the incidental detection of a very low paraprotein concentration in someone with an entirely normal blood count, normal renal function, absence of skeletal X-ray abnormalities, and no Bence-Jones protein in the urine.

Approximately 10–15% of patients, in whom the degree of plasma cell bone marrow infiltration and concentration of serum paraprotein fulfil the criteria for myeloma, have little or none of the skeletal, haematological or renal complications typical of clinically aggressive myeloma. They have a relatively protracted, indolent clinical course in the absence of therapy. This form of myeloma is designated as smouldering or indolent myeloma on the basis of its activity compared to that of the clinically aggressive form of the disorder.<sup>2</sup>

## Newer tests

Assay of free light chains in the serum has become available relatively recently. While it does not supersede protein electrophoresis, it can detect a small but significant elevation of one or other free light chain in the very rare condition designated as non-secretory myeloma. This is characterised by the classical clinical and morphological features of myeloma, but lacks a paraprotein or urinary Bence-Jones protein on protein electrophoresis.

## Conclusion

Multiple myeloma causes widely varied clinical manifestations. Early diagnosis will lead to the correct management. Screening tests to detect paraproteins are followed by biopsy to confirm the increased presence of plasma cells in the bone marrow.

## References

1. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006;354:1362-9.
2. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356:2582-90.

*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 115)*

1. Most patients with a low serum concentration of paraprotein will develop multiple myeloma.
2. An X-ray skeletal survey is the recommended investigation for assessing the effect of multiple myeloma on bone.

**Patient support organisation: Myeloma Foundation of Australia**  
see p. 107