

PRACTICE

EASILY MISSED?

Multiple myeloma

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

A 62 year old man presents to his general practitioner with new onset lower back pain and fatigue for the past few weeks. The patient denies any recent trauma and has otherwise been in good health except for a chest infection treated with oral amoxicillin three months ago. On examination there is midline tenderness over the L5 vertebra with no evidence of neurological signs. The general practitioner requests a full blood count, liver function tests, and a biochemistry panel, which showed mild normocytic normochromic anaemia with rouleaux in the blood film, mild renal impairment, and a raised total protein concentration. Serum electrophoresis confirms the presence of a monoclonal paraprotein. The general practitioner refers the patient to the haematology unit, where myeloma is diagnosed after further investigation and management.

What is multiple myeloma?

Multiple myeloma is a neoplasm of plasma cells characterised by the production of monoclonal immunoglobulin by the malignant cells. This disease predominantly affects older adults, and because of the protean manifestations of the disease patients can initially present to their primary care physicians with vague and confusing symptoms.

Why is multiple myeloma missed?

In a small retrospective UK case review more than half of symptomatic patients who had initially presented to their general practitioners had a delay of more than six months (>12 months in 33% of cases) before specialist referral.⁶ A large retrospective review of data from a US cancer registry also confirmed that considerable delays occur in diagnosis, with the median time from onset of symptoms or signs to the diagnosis of myeloma

being 99 days.⁷ As most patients with myeloma are in their late 60s, they may accept symptoms such as diminished energy, various aches and pains, and slight weight loss as “normal” for their age, especially if symptom onset was gradual.

The protean presentations of myeloma may not initially suggest a haematological diagnosis, especially as non-specific early symptoms such as fatigue, bone pain, and weight loss may overlap with those of more common conditions such as depression, osteoarthritis, and diabetes. In the absence of trauma or neurological symptoms (“red flags”), routine radiography of the back is usually not indicated in the investigation of non-specific back pains. Although no single, specific finding is diagnostic of myeloma, one of the key features of the disease that is often clinically “silent” is the presence of monoclonal paraproteinaemia in blood or urine. The findings of rouleaux (stacks of red cells) in the peripheral blood film or a raised erythrocyte sedimentation rate may be the only indications of underlying paraproteinaemia. Therefore, the findings of bone pain associated with renal disease or anaemia with rouleaux may suggest that a haematologist’s opinion is necessary.

Why does this matter?

Patients with untreated myeloma can develop debilitating complications such as pathological fractures from lytic lesions, irreversible renal failure requiring long term haemodialysis, or more rarely spinal cord compression from extramedullary plasmacytomas. Delays in diagnosis are associated with a higher rate of complications and reduced disease-free survival.⁶ Timely diagnosis of myeloma may prevent the potentially serious complications of the disease.

How is myeloma diagnosed?

Clinical features

The symptoms and signs of myeloma result from malignant plasma cells infiltrating the bones or other organs (such as myelosuppression from marrow infiltration,

How common is multiple myeloma?

- In the United Kingdom and the United States myeloma accounts for about 10% of all haematological malignancies^{1 2}
- The reported annual incidence of myeloma in the UK and the US is about 3-4 per 100 000³
- The incidence of myeloma varies across different ethnic groups; in the US the incidence is twice as high in African Americans as in white people⁴ but in ethnic Chinese people in Taiwan it is as low as 0.75 per 100 000⁵

hepatosplenomegaly), as well as from an increased amount of paraprotein (which causes, for example, hyperviscosity symptoms or paraesthesia from peripheral neuropathy) or light chains in the serum (which result, for example, in renal failure from light chain nephropathy). Patients with early stage disease may remain completely asymptomatic until complications arise. The box lists the most common presenting symptoms or signs, according to a large, single centre retrospective analysis.⁸

Investigations

When myeloma is suspected in a patient, the baseline screening investigations should include:

- A full blood count to detect cytopenias resulting from marrow infiltration
- Inspection of the peripheral blood film to look for rouleaux, which may suggest underlying paraproteinaemia
- Serum biochemistry to detect the presence of renal impairment, hypercalcaemia (from widespread bony destruction, as cytokine expression by myeloma cells results in osteoclastic bone resorption), and raised uric acid (from increased tumour cell turnover)
- Liver function tests to look at the total protein concentration.

At times, the only clue to underlying paraproteinaemia may be an unexpectedly raised total protein concentration, which is brought to the clinician's attention by the clinical chemistry laboratory. A markedly raised erythrocyte sedimentation rate may also suggest the diagnosis of myeloma, with one study showing an average rate of 85 mm/h in newly diagnosed patients.⁹ We have to be aware that in patients aged over 50 with a raised erythrocyte sedimentation rate and systemic symptoms, polymyalgia rheumatica is a reasonable differential diagnosis, but treatment with steroids should not be started before considering further investigations to exclude myeloma. The C reactive protein concentration can also be mildly raised in patients with myeloma, but typically it is about 1 mg/dL (9.52 nmol/L) and is not as useful as the erythrocyte sedimentation rate as a screening test. To confirm the presence of monoclonal paraproteins, general practitioners may order serum protein electrophoresis and immunofixation, and serum-free light chains (if available).

As part of the diagnostic investigations after haematology referral, most haematologists would arrange for a bone marrow biopsy to assess the presence of atypical, clonal plasma cells and a 24 hour urine collection for electrophoresis and immunofixation (to detect urinary light chain excretion). Once the diagnosis is confirmed, other tests would include serum immunoglobulin concentrations (to exclude secondary hypogammaglobulinaemia, which may cause recurrent infections) and a radiological skeletal survey (to look for lytic bone lesions).

In 97% of patients with myeloma, the combination of serum and urine electrophoresis and immunofixation can detect a monoclonal paraprotein (M protein). Serum or urine electrophoresis is used to quantitate the amount of detectable paraprotein, whereas immunofixation is used to confirm the

monoclonal nature of the protein as well as characterise the specific immunoglobulin subclass. It is important to note that other plasma cell disorders (such as plasmacytomas) and lymphoproliferative disorders (such as chronic lymphocytic leukaemia and non-Hodgkin's lymphoma) can also be associated with an M protein.

To diagnose symptomatic myeloma, three diagnostic criteria must be fulfilled¹⁰:

1. The presence of an M protein in serum or urine (no specific cut-off as 40% of symptomatic patients with myeloma will have a level <30 g/L)
2. The presence of >10% clonal plasma cells in the bone marrow aspirate
3. Evidence of end organ damage (the so called CRAB features of hyperCalcaemia from bone destruction, Renal impairment, Anaemia, and lytic Bone lesions on imaging).

Patients who meet criteria 1 and 2 without evidence of the CRAB features are said to have smouldering myeloma. An asymptomatic patient (without CRAB features) whose bone marrow biopsy shows <10% plasma cells or whose serum or urinary M protein concentrations are <30 g/L has monoclonal gammopathy of undetermined significance. This condition is much more common than myeloma, with an estimated prevalence of 3% in the general population aged over 50 years.¹¹ This premalignant condition confers a risk of progression into myeloma (or into related lymphoproliferative disorders) of 1% a year.

How is myeloma managed?

Refer patients with suspected myeloma to a specialist haematology unit for further investigation and management. Conventionally, after confirmation of the diagnosis with tests including a diagnostic bone marrow biopsy and skeletal survey, patients with evidence of end organ damage need treatment. Patients with smouldering myeloma are generally monitored closely as historically there has been no evidence that early treatment of these patients confers a superior long term outcome. However, with the development of new therapeutic agents with more favourable toxicity profiles, there are now phase III trials challenging this dogma and looking at the outcomes of early treatment of patients with monoclonal gammopathy of undetermined significance or smouldering myeloma.

Patients with myeloma are broadly divided into two main groups: those who are or are not eligible for an autologous stem cell transplant. This division is important as cytotoxic agents form the backbone of modern treatment for myeloma, and in patients eligible for transplantation the excessive use of alkylating agents may jeopardise a successful stem cell collection. Patients often receive repeated cycles of induction chemotherapy—usually in combination with thalidomide, lenalidomide, or bortezomib—before stem cell mobilisation and autologous transplantation.

Patients who are not eligible for transplantation are typically treated with combination chemotherapy until resolution of end organ damage and absence of detectable paraprotein. All patients

Most common presenting symptoms or signs^a

- Normochromic, normocytic anaemia—about 70% of patients
- Bone pain—about 60%
- Renal impairment—about 50%
- Fatigue—about 30%
- Weight loss—about 25%
- Hypercalcaemia—about 15%
- Hyperviscosity symptoms*—<7%
- Paraesthesia—5%
- Spinal cord compression—5%
- Hepatomegaly—4%
- Splenomegaly—1%
- Lymphadenopathy—1%
- Fever <1%

*Such as headache, visual disturbance, cognitive impairment

with myeloma require bisphosphonates, which reduce pathological fractures and skeletal related events in myeloma.¹² A recent randomised controlled trial suggests that zoledronic acid may be the bisphosphonate of choice.¹³ Adjuvant treatments in the form of localised radiotherapy may also be used for patients with symptomatic lytic lesions. Patients with recurrent infections resulting from secondary hypogammaglobulinaemia may benefit from regular intravenous immunoglobulin replacement.

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Key points

- The common manifestations of multiple myeloma, such as bone pain, fatigue, and weight loss, may be non-specific and are often initially ignored or missed by patients and medical practitioners
- Early diagnosis of myeloma may prevent debilitating complications such as pathological fractures, irreversible renal impairment, or spinal cord compression
- The finding of rouleaux in the blood film and/or a raised total protein concentration may suggest an underlying paraproteinaemia, especially in a patient with anaemia and bone pain, and would therefore warrant consultation with a haematology specialist