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Multiple Myeloma

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Multiple myeloma

Multiple myeloma is a rare but serious haematological malignancy which at any one time affects between 20 000 and 30 000 patients in the UK. Prior to diagnosis, most of these patients present to primary care with non-specific symptoms. A delay in diagnosis is associated with an increase in complications, such as anaemia, bone disease and renal failure. This may have an impact on patients' quality of life as well as their ability to tolerate toxic treatment options. The key steps in primary care are to identify those patients with symptoms suggestive of multiple myeloma, carry out timely investigations and be aware of the appropriate referral pathways. Once the diagnosis is confirmed, the GP has a vital role in supporting the patient throughout what is, for most, a chronic debilitating illness.

The GP curriculum and multiple myeloma

This article relates to **Curriculum statement 12: Care of people with cancer and palliative care**. GPs require:

- Knowledge of referral guidelines and protocols (both local and national) relevant to myeloma
- Knowledge of the signs and symptoms of the early presentation of cancer
- Ability to suspect cancer diagnosis early in the disease process
- Knowledge of the appropriate investigations of patients with cancer and of how they fit in with national guidelines
- Ability to manage pain
- Knowledge of palliative care emergencies and their appropriate management—hypercalcaemia and spinal cord compression
- Ability to manage cancer and non-cancer symptomatology in the same patient
- Ability to counsel and explain risk of disease, treatment options and symptom control

Epidemiology

Multiple myeloma accounts for 1% of cancers in the UK; there are approximately 4000 new cases each year and incidence has been increasing steadily (Fig. 1). However, at the same time, 1, 5 and 10 year survival rates have been improving. The median age of onset of myeloma is 70 years, with only 2% of new cases being in the under-40s. It is more common in men (2:1) and those of Afro-Caribbean origin (Cancer Research UK, 2010).

Most cases of myeloma occur spontaneously with a number of cases progressing from monoclonal gammopathy of

undetermined significance (MGUS). The evolution phase from MGUS was thought only to occur in a minority of patients, but recent evidence suggests that almost all cases of myeloma are preceded by an asymptomatic MGUS phase.

Pathophysiology

Myeloma is a malignant proliferation of plasma cells (derived from B cells) whose normal function is to produce immunoglobulins made up of heavy and light chains. This malignant process occurs in the bone marrow of the axial skeleton and long bones. Normal immunoglobulins are polyclonal; in myeloma, there is a monoclonal proliferation of an immunoglobulin of a single heavy chain and light chain—the paraprotein. IgG is the most common (55%) followed by IgA (21%) and rarely IgD, IgE or IgM.

It is important to note that in a proportion of patients with myeloma, serum electrophoresis may be negative. This occurs in the 20% of cases where only kappa or lambda light chains are produced (Bence-Jones or light chain myeloma) and also in the 5% of cases in which no monoclonal protein is secreted by the clonal plasma cell population (non-secretory myeloma). A negative electrophoresis makes the diagnosis more difficult and reliant solely on bone marrow examination and skeletal findings. Therefore, it is important to remember that if there is a strong clinical suspicion for myeloma, referral for further assessment is appropriate. Severe hypogammaglobulinaemia is common in these situations which may act as a clue to the diagnosis.

Clinical features

Around 90% of patients with myeloma are symptomatic at diagnosis. The few who have no symptoms or end-organ

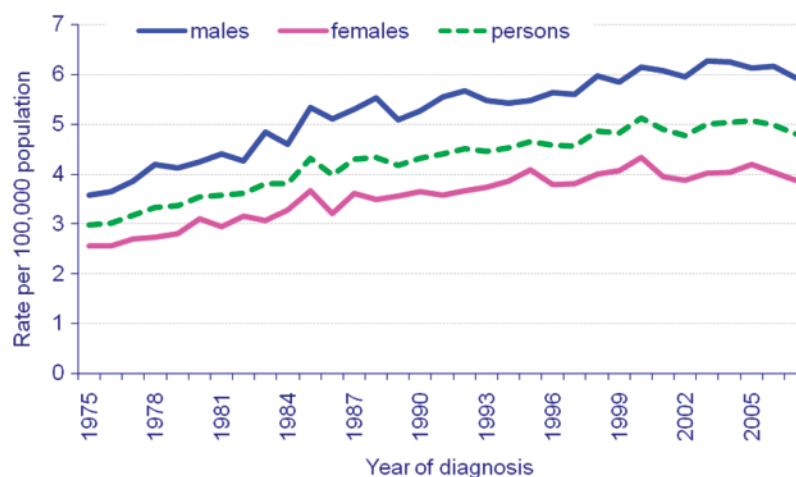


Figure 1. Age standardized (European) incidence rates, multiple myeloma, by sex, Great Britain 1975–2007.

Cancer Research UK. Multiple myeloma—UK incidence statistics <http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/incidence/> [date last accessed 21.01.2011].

damage are said to present with ‘asymptomatic myeloma’. The clinical presentation is often insidious and non-specific so a high index of suspicion is necessary.

Bone marrow

Many of the symptoms are due to the effect of the myeloma on the bone marrow such as reduced immune function or impaired bone marrow function which contributes to anaemia. The normal polyclonal immunoglobulin production is suppressed in 80% of patients. This is termed immune paresis. In clinical context, this impairs the normal humoral responses leading to increased risk of recurrent bacterial infection. Therefore, myeloma should be ruled out in all patients who present with recurrent bacterial infection. The anaemia is typically normochromic and normocytic and usually in the range of 9–10 g/dl.

Bone

Bone involvement is a presenting feature in up to 70% of patients. Patients may present with pain due to lytic lesions or pathological fractures (Fig. 2). Most patients have diffuse

bone demineralization leading to osteoporosis. Myeloma should always be considered as a cause of osteoporosis, particularly in men and premenopausal women.

Chronic back pain is a common symptom and it is always important to exclude myeloma in patients with red flag symptoms (Box 1). Acute back pain may represent a vertebral compression fracture. It is also important to consider the possibility of spinal cord compression. This presents with sensory loss, limb weakness or heaviness, walking difficulty and/or sphincter disturbance. Suspicion of cord compression necessitates referral for same day assessment with magnetic resonance imaging (MRI) as the test of choice.

Box 1. Red flag features that may indicate a serious underlying cause of back pain

- Age under 20 years or greater than 55 years
- Non-mechanical back pain—particularly pain that worsens when supine or night-time pain
- Thoracic pain
- History of carcinoma—consider spinal cord compression
- Human immunodeficiency virus (HIV) or other immune suppression
- Intravenous drug use
- Taking steroids
- Unwell or septic
- Weight loss
- Widespread neurology
- Structural deformity—gibbus



Figure 2. Plain radiograph showing a large lytic mass in the humerus.

Hypercalcaemia, renal impairment and hyperviscosity

Hypercalcaemia can be the first presenting feature of myeloma and is due to bone demineralization and renal disease (Box 2). Renal impairment occurs in up to 30% of patients and represents a serious complication of myeloma. Multiple factors contribute including dehydration, nephrotoxic drugs (commonly non-steroidal anti-inflammatories), infection,

hypercalcaemia, light chain nephropathy, amyloidosis and rarely plasma cell infiltration into the kidney. Deteriorating renal function represents a medical emergency and if renal function is to be preserved, patients must have urgent inpatient assessment. The hyperviscosity syndrome is rare in myeloma and is caused by increased plasma viscosity as a result of the paraprotein. Box 3 summarizes the clinical features of hyperviscosity syndrome.

Box 2. Features of hypercalcaemia

- Polydipsia
- Polyuria
- Depression
- Muscle weakness
- Malaise
- Renal stones
- Confusion
- Pancreatitis
- Constipation
- Nephrogenic diabetes insipidus

Box 3. Features of hyperviscosity

- Confusion
- Headache
- Vertigo
- Visual disturbance
- Mucosal bleeding
- Seizures

Investigations

Diagnosis of symptomatic myeloma requires the following to be present:

- Serum paraprotein or
- Urine Bence-Jones protein and
- Demonstration of more than 10% plasma cell infiltration in bone marrow and

- Evidence of myeloma-related organ or tissue impairment (ROTI) which includes hypercalcaemia, renal impairment, anaemia and bone disease.

Appropriate tests in primary care are summarized in Table 1. The preliminary tests (blood and urine) must be sent urgently in keeping with [National Institute for Health and Clinical Excellence \(2005\)](#) guidance; further investigations in primary care should not delay the referral process.

Once referred to hospital, tests are undertaken to confirm or refute the diagnosis, stage the disease, assess for end-organ complications and identify adverse prognostic factors. Imaging includes a skeletal survey to assess fully for bone involvement and MRI if further clarification of a particular anatomical area is needed. One of the essential investigations is a bone marrow aspiration and trephine to confirm the degree of plasma cell marrow infiltration (Fig. 3).

These investigations along with clinical assessment help to distinguish symptomatic myeloma from asymptomatic myeloma and MGUS. Serum-free light chain assessment is important for both diagnosis (in those with negative serum protein electrophoresis) and monitoring of treatment. There is well-established evidence to suggest that high beta 2-microglobulin and low albumin levels have adverse prognostic significance and must be measured as part of the staging workup.

Monoclonal gammopathy of undetermined significance

MGUS is a condition in which there is evidence of a serum paraprotein or urinary light chain excretion but no abnormal plasma cell infiltration in the bone marrow nor evidence of end-organ damage. As with myeloma, it is more common with increasing age, and about 4–5% of those older than 70 years will have MGUS.

Table 1. Basic investigations needed from primary care if suspected myeloma

Sample	Test	Interpretation
Blood	Haematology (full blood count)	Normocytic normochromic anaemia (in 50%) Raised plasma viscosity
	Biochemistry (urea and electrolytes, estimated glomerular filtration rate and calcium)	Renal impairment (in 30%) Hypercalcaemia (in 20%)
	Erythrocyte sedimentation rate (ESR)	Raised but may be normal in Bence-Jones myeloma
	Serum electrophoresis and immunoglobulins	Monoclonal band and paraprotein. Immunoparesis
Urine	Electrophoresis	Bence-Jones protein
Radiology	Radiograph of symptomatic area	Lytic bone disease or pathological fracture (note bone scan is normal in myeloma unless fracture)

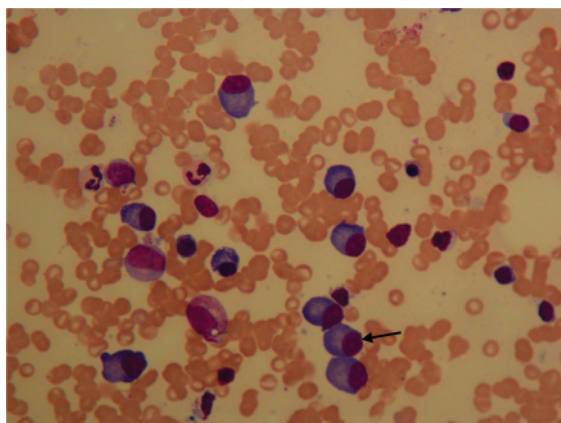


Figure 3. Bone marrow aspirate showing varying shapes and sizes of plasma cells (dark blue cells with eccentric nucleus indicated with arrow).

MGUS is an important clinical entity to recognize as 10% of patients develop myeloma within 5 years and 50% by 15 years. From tests done in primary care, it is not possible to differentiate between myeloma and MGUS; therefore, all patients should be referred for specialist haematology review at this stage. Table 2 summarizes the differences between myeloma (both asymptomatic and symptomatic) and MGUS.

Most patients with MGUS are monitored as haematology outpatients; they undergo regular careful clinical assessment for end-organ damage coupled with blood tests (full blood count, renal function and calcium and paraprotein/immunoglobulin levels). If discharged for follow-up in primary care (usually those with lower risk MGUS only), it is important to establish the frequency of monitoring required and what the criteria for re-referral are.

Kariyawasan *et al.* (2007) looked specifically at the causes and consequences of a delay in diagnosis of myeloma. This retrospective case analysis looked at who patients initially presented to and what symptoms they reported. They found that 40% of patients had their symptoms for more than 6 months before diagnosis and 67% had presented with these symptoms to their GP. Bone pain was the most common presenting symptom and was present in two-thirds of patients, emphasizing that any bone pain, particularly in older patients, should be taken seriously. Delay in

diagnosis of more than 6 months increased the likelihood of complications (anaemia, bone disease and renal failure) being present at diagnosis. This seemed to affect disease-free survival but not overall survival. The study recognized the need for reduction of the delay between first symptom and diagnosis accepting the clinical challenges that this can pose in primary care.

Myeloma therapy: a basic overview

Myeloma is an incurable disease and the aims of treatment are to control disease, prolong survival and maximize quality of life. All patients with a diagnosis of myeloma are discussed in a multidisciplinary team meeting where a plan of treatment is outlined. Chemotherapy is indicated only in patients with symptomatic myeloma. Those with asymptomatic disease need close follow-up and monitoring in a haematology outpatient setting. Symptomatic patients are classified into two groups:

- the younger fitter patients (less than 65 years of age) suitable for intensive therapy
- the older less fit patients in whom high-dose chemotherapy would be intolerable

Younger fitter patients are given oral cyclical outpatient-based chemotherapy initially to debulk the disease. The most common regime in the UK is cyclophosphamide, thalidomide and dexamethasone (CTD). Subsequently, they are treated with high-dose chemotherapy and autologous stem cell transplantation (ASCT).

Older patients receive less toxic chemotherapy with a view to achieving maximum disease control. Examples include attenuated CTD (CTDa) or melphalan and prednisolone with or without thalidomide.

Very few patients gain complete remission, but most go through a phase of disease control whereby paraprotein readings remain stable for 3 months or more. The length of this plateau phase is very variable and patients need close monitoring for evidence of relapse.

Primary refractory disease and first and second relapses are managed with novel therapies such as bortezomib and

Table 2. Differentiation of MGUS from myeloma

MGUS	Asymptomatic myeloma	Symptomatic myeloma
Paraprotein less than 30 g/l	Paraprotein more than 30 g/l	Paraprotein in serum and/or urine
Bone marrow plasma cells less than 10%	and/or bone marrow plasma cells more than 10%	Bone marrow plasma cells more than 10%
No evidence of end-organ damage	No evidence of end-organ damage	Evidence of end-organ damage (bone lesions, anaemia, renal failure and hypercalcaemia)

Source: British Committee for Standards in Haematology. Guidelines for the investigation of newly detected M-proteins and the management of Monoclonal Gammopathy of Undetermined Significance (MGUS) (2009).

lenalidamide, with or without dexamethasone. These novel agents have significantly improved survival in patients with myeloma. Figure 4 summarizes the key treatment strategies. Of note, many regimes utilize corticosteroids and this may complicate the stability of glucose control in diabetics. Liaison with the diabetes team may be necessary.

Supportive care

With newer therapies developed over the years, disease control can be achieved in a significant proportion of patients. For these patients, myeloma can be viewed as a chronic illness. Few patients with myeloma are inpatients; this places a strong emphasis on community care falling at the hands of the GP. Supportive care requires knowledge of the natural history of the condition, complications of the disease and its treatment, coupled with effective communication with other specialist teams (such as the pain team or palliative care team). The [British Committee for Standards in Haematology \(2010\)](#) publishes a useful resource about supportive care in myeloma.

Anaemia

Anaemia (haemoglobin concentration less than 12.0 g/dl) is common in myeloma, both at diagnosis and during treatment. This is often due to myeloma itself; however, it is important to ensure other causes such as bleeding or haematinic deficiency are ruled out. Patients with myeloma-related anaemia are managed with red cell transfusion or erythropoietic-stimulating agents (ESAs). In symptomatic patients with moderate to severe anaemia, transfusion provides the most rapid correction of the haemoglobin to a satisfactory level. Many haematology departments have a day unit where patients can attend for transfusion.

In patients with renal impairment and anaemia, there is a role for the use of ESAs; this often will be initiated by a nephrologist. An important complication of ESA treatment is an increased thrombotic risk.

Renal failure

Some degree of renal impairment is seen in up to 30% of patients with myeloma with between 3 and 12% requiring haemodialysis. Importantly, renal impairment is reversible in up to 50% of patients; therefore, aggressive treatment is required. Simple measures such as rehydration, treating hypercalcaemia with bisphosphonates, early treatment of infections, discontinuing nephrotoxic drugs and treatment with steroids usually results in an improvement in renal function.

Thrombotic risk

Myeloma, like other cancers, is a significant risk factor for venous thromboembolism. This is compounded by the further increased risk associated with some of the treatments offered (thalidomide, lenalidomide or ESA). Patients should be risk assessed and if indicated can be offered prophylactic anticoagulation in the form of low molecular weight heparin or warfarin.

Bone disease

Bony involvement is a significant cause of morbidity in patients with myeloma. A skeletal survey should be a part of the diagnostic workup of these patients. Pain is common and its impact on quality of life and mobility can be significant. Assessment of pain involves a thorough

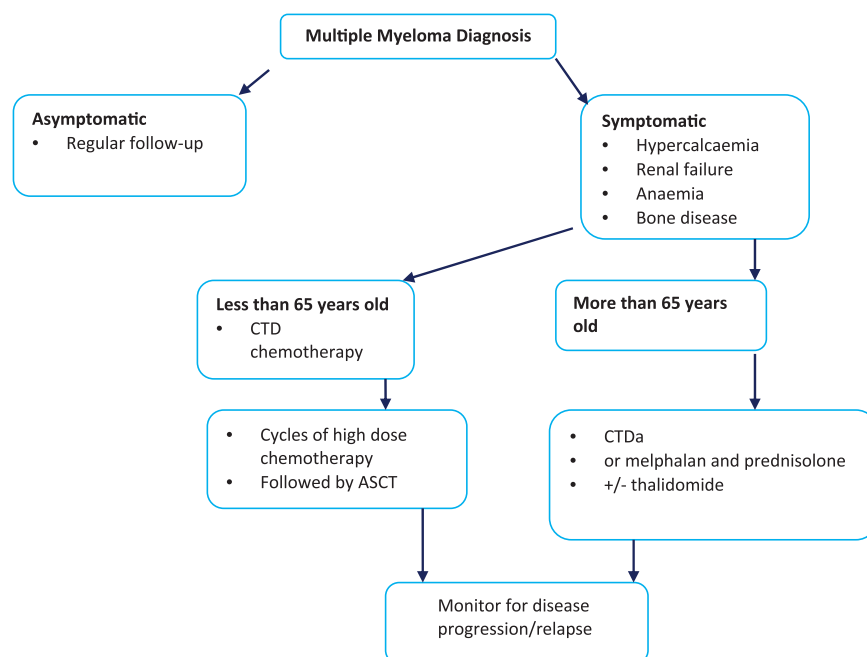


Figure 4. Flow chart demonstrating treatment options.

history of the pain, its effect on activities of daily living along with investigations such as plain radiography or MRI. Use pain scores to assess the impact of any intervention. Pain management should follow the World Health Organization (WHO) three step cancer analgesic ladder. Of note, non-steroidal anti-inflammatories should be avoided in patients with myeloma due to possible renal complications.

Opioids have an important role in the management of moderate to severe chronic pain. The use of fentanyl or buprenorphine patches may be preferred by some patients due to their convenience. Patients on opioids should have regular reviews of their regime and be screened for the common side effects, such as nausea and constipation. Liaison with the local pain service can be extremely helpful for patients with non-responsive chronic pain or acute severe pain.

Bisphosphonates have been shown to reduce skeleton-related events (SREs) such as pathological fractures, surgery for fractures and spinal cord compression. They also improve quality of life and pain control even in those patients with no bony disease at presentation. One important complication to make patients aware of is bisphosphonate osteonecrosis of the jaw (BONJ), which typically presents with pain and evidence of local infection with subsequent necrosis of bone. Dental hygiene should be assessed before commencing treatment with oral bisphosphonates and is essential for those having intravenous therapy. Any teeth which require extraction should be removed prior to treatment.

Radiotherapy is an option for patients with symptomatic bone lesions and post surgery to aid healing. Myeloma is relatively radio-responsive with excellent symptomatic relief. Often, only a small dose is needed with an option to offer further radiotherapy to the same area in the future.

Kyphoplasty and vertebroplasty have been shown to be of symptomatic benefit in vertebral collapse. These are both techniques which involve percutaneous injection of bone cement into the vertebral bodies and are best performed soon after the vertebra has collapsed. There remains a role for surgery in complex fractures and stabilization of long bones where impending fracture is a concern.

Infections

Infections are a significant cause of morbidity and mortality in patients with myeloma, both at presentation and during the course of their treatment. Early recognition and management of septic episodes, particularly for those patients that are on chemotherapy, saves lives. It is important to note that patients with myeloma, owing to an impaired cell mediated and humeral immune response, may not mount a temperature despite an acute infective illness. There is a role for prophylactic immunoglobulin therapy in

some patients with hypogammaglobulinaemia and recurrent severe bacterial infections. All patients with myeloma should be offered vaccinations against influenza and *Streptococcus pneumoniae*.

Psychosocial support

A diagnosis of cancer triggers a range of emotions such as shock, sadness and anxiety. It is important therefore to offer ongoing support with regular review, anticipating a proportion of patients may go on to suffer from depression. This should be treated actively with use of self help advice, local counselling services and antidepressant therapy. The effect on other members of the family should not be underestimated and they too, should be offered support, in particular those who become carers.

Knowledge of benefits available can ease the burden of financial worries. The CancerHelp UK (www.cancerhelp.org.uk) and Macmillan Cancer Support (www.macmillan.org.uk) websites are good starting points both for information about the disease and also about support available. Patients with mobility difficulties and problems with activities of daily living may benefit from referral to occupational therapy and/or physiotherapy services.

Palliative care

Supportive care in myeloma is complex and utilization of the local specialist palliative care team is essential. They can offer advice on difficult symptom control and provide further psychological, social and spiritual support for the patient. They may often facilitate discussions around a preferred place of care, what treatments a patient may or may not wish to have and the difficult discussion of cardiopulmonary resuscitation. Inevitably, some patients will have progressive disease and recognition of the end of life phase is important. This allows us to focus on keeping patients symptom free and comfortable in the last few days of life.

Considerations in primary care

Multiple myeloma has a varied and insidious presentation. A high index of suspicion should be applied when dealing with patients who present with symptoms such as chronic bone pain. Simple tests should be undertaken in primary care if myeloma is suspected. We must also be aware of the emergency presentations, such as hypercalcaemia, renal failure and spinal cord compression.

Due to advances in treatment, people with myeloma are living longer. As GPs, we must strive to offer high quality supportive care throughout the different stages of treatment. This requires excellent communication between primary care and a range of specialist services.

Key points

- Myeloma is a serious haematological malignancy with an increasing incidence in the UK
- Presentation is often non-specific; we must think of myeloma when dealing with bone pain (including premature osteoporosis), anaemia or unexplained renal failure. There are few patients with myeloma who are asymptomatic
- A delay in diagnosis increases the likelihood of end-organ damage
- Simple tests to be done in primary care include full blood count, renal function, calcium, erythrocyte sedimentation rate, serum electrophoresis, urine electrophoresis and plain radiographs of affected areas
- Patients are mostly managed on oral chemotherapy and therefore may well present to primary care with complications (such as infections); therefore, prompt liaison with haematology is advised
- Supportive care in myeloma is essential to try and optimize quality of life; this requires excellent communication with specialist teams

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