Multiple myeloma

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Multiple myeloma (MM) is a tumour of bone marrow plasma cells associated with bone pain, anaemia, infection and renal failure. A serum paraprotein is detectable in 80% of patients. Free light chains are often also detectable in urine as Bence-Jones protein (BJP), and 20% produce only light chains (BJP MM). Rarely, serum or urine paraprotein is undetectable (non-secretory MM).

Incidence and aetiology

The annual incidence of MM is approximately 40 per million (2,500 new cases per year in the UK). Incidence increases with age (median 65 years), it is rare under 40, and twice as common in Afro-Caribbeans. The only clearly defined epidemiological risk factor is radiation exposure[1].

Pathophysiology

Immunoglobulin heavy chain (IgH) analysis reveals that MM arises from a post-germinal centre B lymphocyte, then migrates to bone marrow where plasma cells proliferate[2]. Interactions with marrow stromal cells facilitate homing and growth of myeloma cells. Stromal cells produce interleukin (IL)-6 – an important growth factor for myeloma cells – which in turn produces osteoclast-activating cytokines including tumour necrosis factor α and interleukin (IL)-1β (Fig 1)[3]. These cytokines upregulate stromal cell secretion of receptor activator of nuclear factor 6B ligand (RANK-L), which stimulates osteoclast production. Secretion of osteo-protogerin, the major inhibitor of RANK-L, is reduced (Fig 2). Myeloma cells also produce vascular endothelial growth factor, resulting in increased microvessel formation and tumour growth. Normal B lymphocytes are suppressed, reducing polyclonal Ig production (immuneparesis).

Complex cytogenetic abnormalities are frequent, most commonly with translocations involving chromosome 14q (site of the IgH locus) and deletions of chromosome 13 (Fig 3)[4,5].

Clinical features

The commonest presenting symptom is bone pain (60%). Bone destruction may cause hypercalcaemia. A normal serum alkaline phosphatase (SAP) reflects suppressed osteoblast activity and radionuclide bone scans are usually negative. Plain radiology may reveal osteoporosis (5–10% of patients have only osteoporosis), lytic lesions, fractures and occasionally soft tissue extension.

Magnetic resonance imaging (MRI) is the most sensitive imaging method and is valuable in suspected cord compression where several levels may be involved. Both computed tomography and MRI are helpful in selected patients.

Renal impairment is common and usually due to tubular damage by BJP (cast nephropathy). Other causative factors include hypercalcaemia, dehydration, sepsis, glomerulonephritis, amyloidosis and non-steroidal anti-inflammatory drugs. Rehydration and reversal of remediable factors should precede chemotherapy. Plasmapheresis may be helpful. The vincristine, doxorubicin, dexamethasone (VAD) regimen is well tolerated and frequently produces improvement in renal impairment. When appropriate, dialysis should accompany chemotherapy.

Approximately 15% of patients are asymptomatic and are detected as a result of an elevated erythrocyte sedimentation rate or paraprotein on screening.

Other clinical features may include anaemia, recurrent infection, hyper-viscosity, lethargy and neuropathy.

Fig 1. Interaction between myeloma cells and bone marrow stroma cells (IL = interleukin; TNF = tumour necrosis factor).
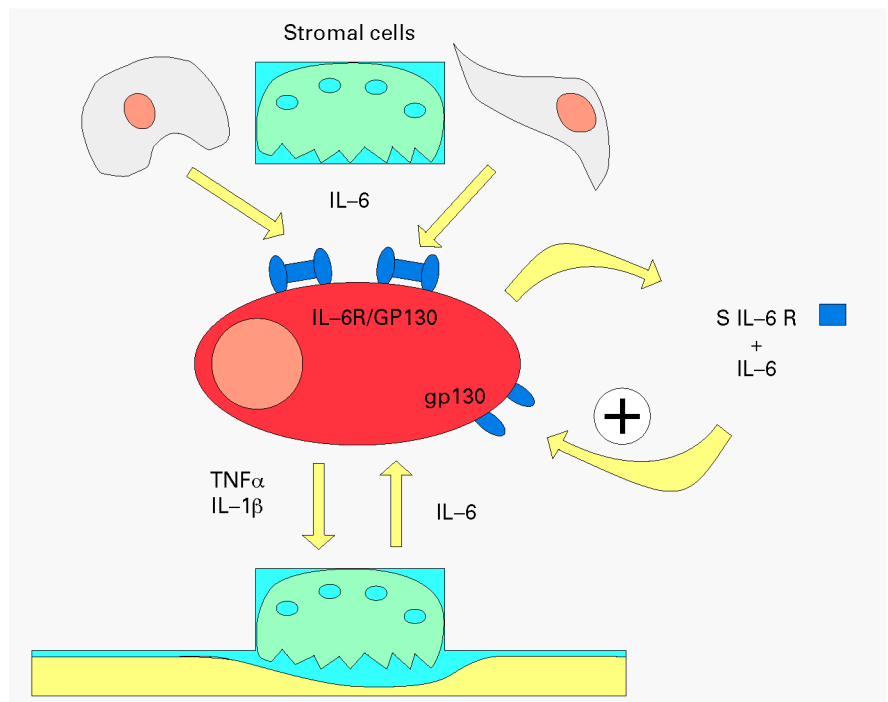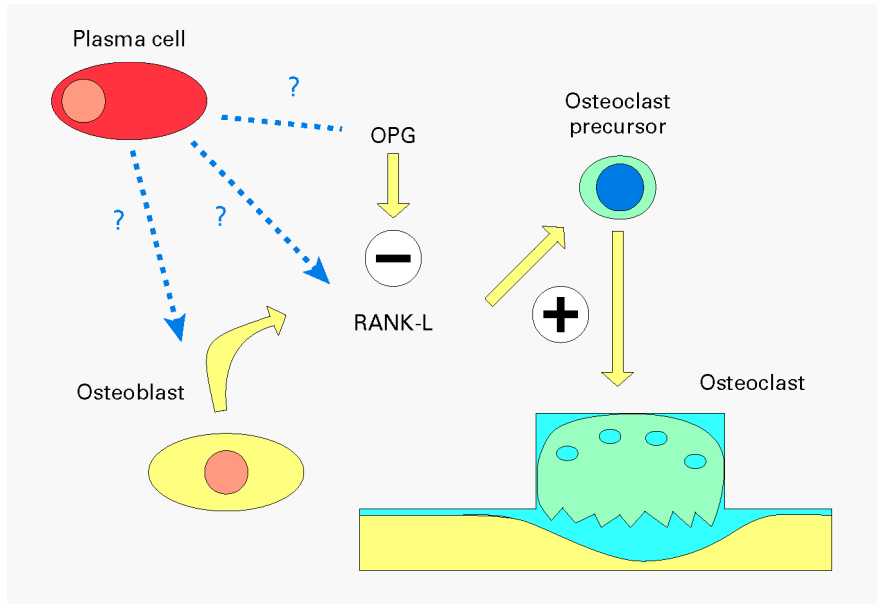
Fig 2. Osteoclast activation by myeloma cells
(OPG = osteoprotogerin; RANK-L = receptor activator of nuclear factor 6B ligand).

Fig 3. Myeloma plasma cell nuclei which have been probed for two areas of 13q14. Most of the cells shown are deleted for one signal of each probe, but one cell (top right) has two normal signals for both. The probes used were Rb in green (Milan YAC centre) and D13S319 in red (Vysis). Kindly donated by Dr Fiona Ross, Wessex Cytogenetics Centre.
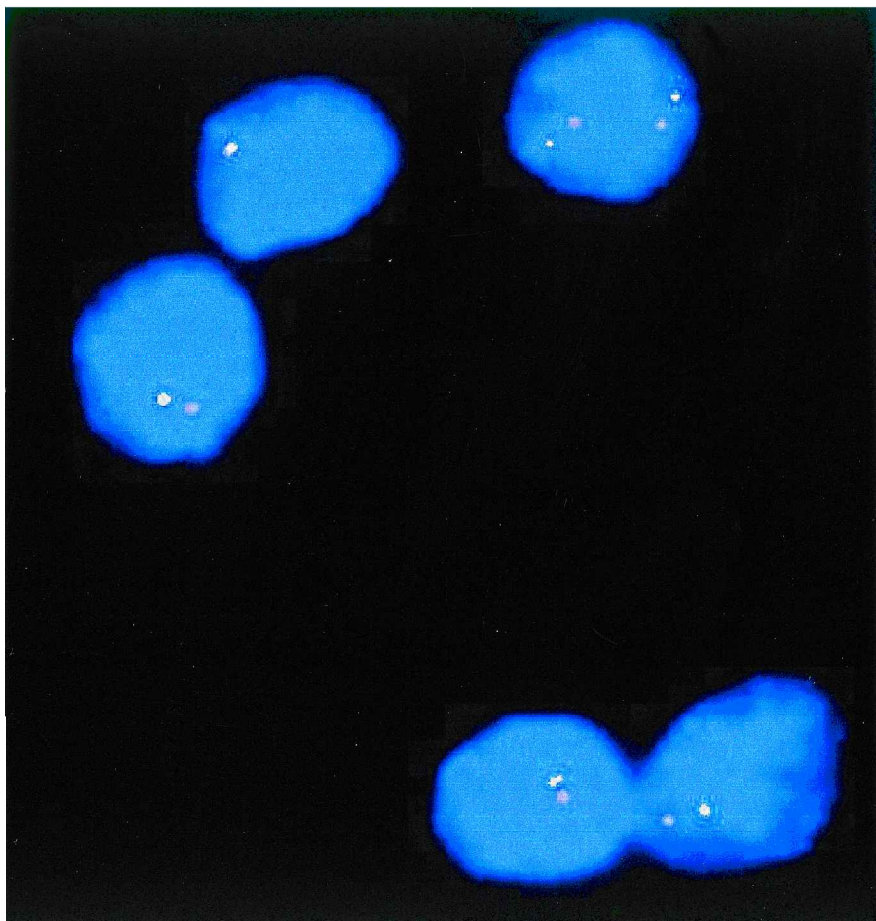
Ten per cent of patients with MM develop primary amyloid which causes nephrotic syndrome, renal and cardiac failure. Peripheral and autonomic neuropathies occur, and liver, gut and skin may be involved. The extent of amyloid deposition can be assessed using radiolabelled serum amyloid P-component. If production of amyloidogenic protein is arrested by chemotherapy, amyloid can regress[6].

Differential diagnosis

MM should be suspected particularly in patients over 50 with any of the features previously discussed. Minimal diagnostic criteria have been agreed (Table 1)[7]. Table 2 details useful investigations. It is important to exclude monoclonal gammopathy of undetermined significance (MGUS) and other conditions which may be associated with a paraprotein (Table 1). These include solitary plasmacytoma, primary amyloidosis and lymphoproliferative conditions (chronic lymphocytic leukaemia, non-Hodgkin's lymphoma and Waldenström's macroglobulinaemia).

Monoclonal gammopathy of undetermined significance

MGUS describes the presence of a paraprotein without evidence of MM, Waldenström's macroglobulinaemia, amyloidosis or lymphoma (Table 1)[8]. There is a risk of transformation to MM (actuarial rate 16% at 10 years). The incidence of MGUS increases with age (3% over the age of 70). Patients do not have anaemia, renal failure or bone lesions. Differentiation between MGUS and early MM may be difficult, and no single test is reliable. If uncertainty persists after investigation, serial paraprotein measurements and review of clinical and laboratory parameters are necessary.

The term smouldering myeloma (SMM) identifies asymptomatic patients fulfilling diagnostic criteria for MM rather than MGUS, but without bone disease and with a stable paraprotein without treatment. Patients with MGUS or SMM should be closely monitored

Table 1. Diagnostic criteria for myeloma and MGUS.

Myeloma

At least two out of the following three findings:

- \>10% plasma cells in bone marrow or plasmacytoma on histology
- Serum paraprotein (usually IgG>30g/l; IgA>20g/l) or Bence Jones proteinuria
- Osteolytic lesions on skeletal survey

MGUS

All of the following:

- no symptoms suggestive of myeloma
- serum paraprotein <30 g/l
- <10% plasma cells in bone marrow
- little or no urine paraprotein (BJP)
- no bone lesions
- no anaemia, hypercalcaemia or renal impairment
- stable paraprotein and other parameters on observation

Table 2. Investigation of patients with suspected myeloma.

Useful screening tests
- Full blood count and film: anaemia often present: film may show rouleaux
- ESR or plasma viscosity: raised in the presence of a serum paraprotein
- Urea and creatinine: may indicate renal impairment
- Calcium, phosphate, alkaline phosphatase and albumin: may reveal hypercalcaemia or low albumin
- Serum immunoglobulins: to detect immuneparesis
- Serum protein electrophoresis: to detect paraprotein
- Routine urinalysis: to detect proteinuria
- Urine electrophoresis for BJP: to detect paraprotein
- X-ray of sites of bone pain: may reveal pathological fracture or lytic lesion(s)

Diagnostic Tests
- Bone marrow aspirate: to identify plasma cell infiltration
- Skeletal survey: to identify lytic bone lesions not already detected
- Paraprotein typing and quantification: to characterise paraprotein

Tests to establish tumour burden and prognosis
- Serum beta 2 microglobulin: measure of tumour load
- Serum C reactive protein: surrogate measure of IL-6
- Serum LDH: measure of tumour aggression
- Serum albumin: when low reflects poor prognosis
- Cytogenetics: prognostic value

Tests which may be useful in some patients
- Creatinine clearance & 24 hour proteinuria
- MRI: not routine but useful in patients with cord compression or solitary plasmacytoma and abnormal in 30% of patients with normal skeletal survey
- CT: where clinically indicated
- Biopsy for amyloid and SAP scan: where suspected

without treatment. Review and paraprotein requantification should occur after 3–6 months, and then annually in MGUS patients and 3–6 monthly for SMM, unless symptoms supervene.

Prognostic factors

Median survival is 3–4 years, but ranges from a few months to over 10 years. Several adverse prognostic factors have been identified, including high paraprotein levels, low Hb, hypercalcaemia, advanced lytic bone lesions, and abnormal renal function. These factors are combined in the widely used Durie-Salmon staging system[9] (Table 3). Serum $\beta 2$ microglobulin (β 2 m), which is a measure of tumour mass, is the most powerful prognostic factor and alone predicts survival regardless of renal function or Durie-Salmon stage. Other adverse prognostic factors are a raised CRP (a surrogate marker for raised serum IL-6) and low serum albumen. A new staging system based on β 2 m and CRP usefully divides patients into three

risk groups when no other cause of raised CRP is present:

- both markers below 6 mg/L: low risk, median survival 54 months
- either elevated: intermediate risk, median survival 27 months
- both elevated: high risk, median survival six months.

Deletion of 13q is an important adverse prognostic factor[11]. Renal impairment is a risk factor only because of its association with high tumour burden[12].

Initial treatment

It is important to address general aspects of care (Table 4).

Standard chemotherapy: melphalan and prednisolone

An objective response (≥50% paraprotein reduction) is produced in 50% of patients with melphalan 6–8 mg/m^2/day combined with prednisolone 40–60

mg/day given for four days at 4–6 week intervals[13]. Treatment should continue until maximum response, which may take 9–12 months, and a plateau phase may be achieved. Complete response is rare. Maintenance chemotherapy in plateau phase is ineffective and adds toxicity[14]. Patients should be monitored to detect a rising paraprotein as progression occurs after a median time of 18 months. Those who achieve a durable plateau will often have further responses with the same chemotherapy. However, eventual resistance to melphalan is inevitable. Melphalan and prednisolone remain an appropriate treatment for older patients with MM as it is well tolerated.

Combination chemotherapy

Many combination regimens have been examined. The most widely used in the UK is doxorubicin, carmustine, cyclophosphamide and melphalan (ABCM). Only two large multicentre studies have reported survival benefit

Table 3. The Durie-Salmon staging system.

Patients are staged as I, II or III and A or B. Stage represents tumour burden not sites involved.

Tumour cell mass	Stage I low all of the following:	Stage II medium not fitting Stage I or III	Stage III high one or more of the following:
Monoclonal IgG (g/l)	<50		>70
Monoclonal IgA (g/l)	<30		>50
BJP excretion (g/24 hr)	<4		>12
Hb (g/dl)	>10		<8.5
Calcium (mmol/l)	<2.6		>2.6
Lytic lesions	none or one		advanced

Stage A: Serum creatinine >175 μmol/l
Stage B: Serum creatinine >175 μmol/l

over melphalan and prednisolone[15,16], though complete response is more common (but still <10%). A meta-analysis of 27 randomised trials also showed no survival benefit[17].

The VAD regimen involves continuous intravenous infusion of vincristine and doxorubicin over four days with dexamethasone. This produces improved overall (60–80%) and complete (10–25%) response rates[18]. Although not durable, maximum response is rapidly achieved. This regimen is non-toxic to stem cells, so VAD is used in patients proceeding to stem cell harvest and autologous transplantation. The substitution by methylprednisolone of dexamethasone (VAMP) has similar effects.

Bisphosphonates

Osteoclast bone resorption is inhibited by bisphosphonates. Patients on long-term bisphosphonates experience less bone pain and fewer fractures[19]. There is evidence that bisphosphonates may prolong survival[20,21]. Long-term bisphosphonate treatment is recommended for patients with MM[7].

Maintenance interferon-α

A meta-analysis of 12 trials[22] demonstrated improved response duration (median 6 months) but no survival benefit in patients receiving maintenance interferon (IFN)-α during plateau phase. IFN-α has frequent side effects and an unfavourable cost-utility profile.

High-dose therapy and stem cell transplantation

Autologous transplantation

High-dose therapy (HDT) has been used to improve disease control and prolong survival. It usually comprises high-dose melphalan (140–200 mg/m^2) with or without total body irradiation, supported with peripheral blood progenitor cell or bone marrow transplantation after initial response to VAD. This is a safe procedure for patients under 65 years but is not curative. Median remission duration is two years. In a single prospective randomised trial which compared standard therapy with HDT[23], MM patients receiving HDT had significantly better five-year survival (52% vs 12%, $p = 0.03$). A case-control study has also shown a survival advantage for HDT[24]. HDT should form part of the primary treatment strategy in patients aged 60 years or less[7].

Allogeneic transplantation

Allogeneic transplantation from a matched sibling is applicable to patients up to the age of 50 years. Transplant-related mortality from graft versus host disease and infection is high, and relapse is also a problem. Nevertheless, donor marrow exerts a graft versus myeloma effect[25] and there is projected long-term survival of 35%[26]. Allogeneic bone marrow transplantation in first remission offers 33% risk of transplant-related mortality, 33% chance of survival with recurrence, and 33% chance of durable remission and possible cure. Lower intensity non-myeloablative conditioning regimens are being examined to exploit the graft versus myeloma effect with less toxicity.

Disease progression

Good supportive therapy is essential. Radiotherapy to sites of bone pain is usually effective palliative therapy. Oral dexamethasone may achieve further responses[27] and low-dose oral cyclophosphamide may slow progression. Thalidomide achieves responses in 30% of chemorefractory patients[28].

Table 4. General aspects of care.

Pain control	Analgesia (caution with NSAIDs) Local radiotherapy
Limitation of renal damage	Good fluid intake Caution with nephrotoxic drugs including NSAIDs Rapid treatment of hypercalcaemia
Hypercalcaemia	Rehydration Intravenous bisphosphonate
Bone disease	Local radiotherapy Long-term bisphosphonates Fixation of potential fractures
Cord compression	MRI scanning to localise lesions Local radiotherapy
Anaemia	Blood transfusion Erythropoietin
Infection	Vigorous antibiotic therapy Annual influenza vaccination
Hyperviscosity syndrome	Plasmapheresis Prompt chemotherapy

The future

Recent results suggest that thalidomide and dexamethasone in combination produce responses in 70% of patients. The mode of action of thalidomide is complex, but appears to be immunomodulatory rather than anti-angiogenic. Less toxic derivatives are under examination. Proteasome inhibitors affect intracellular signalling, induce apoptosis and show early promise. Immunisation strategies are also on trial.

Key Points

Differentiation of multiple myeloma from monoclonal gammopathy of undetermined significance can be difficult and may require a period of observation

Prognostic factors can identify patients with multiple myeloma in whom treatment may not be necessary and others who may need aggressive treatment

Renal impairment can be reversed by early chemotherapy, and dialysis is appropriate supportive therapy in some patients

Bisphosphonate therapy appears to provide a beneficial reduction in bone complications

Allogeneic bone marrow transplantation should be discussed with younger patients (<55 years) with myeloma with a compatible sibling donor as this may be curative

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CME General Internal Medicine for the Physician SAQs

Answers to the CME SAQs published in *Clinical Medicine* July/August 2001

Q1	Q2	Q3	Q4	Q5	Q11	Q12	Q13	Q14	Q15
a) T	a) F	a) F	a) F	a) T	a) F	a) F	a) F	a) F	a) F
b) F	b) T	b) T	b) T	b) F	b) T	b) T	b) T	b) F	b) T
c) F	c) F	c) F	c) T	c) T	c) F	c) T	c) T	c) T	c) T
d) T	d) F	d) F	d) F	d) F	d) T	d) T	d) T	d) F	d) F
e) T	e) F	e) T	e) T	e) F	e) F	e) F	e) F	e) T	e) T

Q6	Q7	Q8	Q9	Q10	Q16	Q17	Q18	Q19	Q20
a) T	a) T	a) F	a) F	a) F	a) T	a) T	a) F	a) T	a) F
b) F	b) F	b) F	b) F	b) F	b) T	b) F	b) F	b) F	b) F
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