Myeloma

Synonyms: multiple myeloma, plasma cell neoplasm, myelomatosis

Pathogenesis

In myeloma there is malignant proliferation of plasma cells. This produces diffuse bone marrow infiltration causing bone destruction and bone marrow failure. There is also overproduction of a monoclonal antibody (immunoglobulin or ‘paraprotein’) by the malignant plasma cells, detectable in serum and/or urine. It is also characterised by osteolytic bone lesions, renal disease and immunodeficiency.

Myelomas are subclassified by the type of antibody they produce. Immunoglobulin G (IgG) myeloma is the most common type.

Aetiology

- Neoplastic plasma cells accumulate in the bone marrow and produce a monoclonal protein that causes organ or tissue impairment. It appears to be preceded by monoclonal gammopathy of undetermined significance (MGUS).
- Myeloma arises because of genetic changes that occur during the terminal differentiation of B lymphocytes into plasma cells. In around half of cases, a chromosomal translocation occurs, which places an oncogene into the immunoglobulin heavy chain gene on chromosome 14. The remaining cases are characterised by trisomies of several chromosomes (hyperdiploidy).
- As myeloma develops, further genetic events, such as RAS mutations, occur.
- Imbalanced bone remodelling (increased osteoclast and reduced osteoblast function) causes unopposed osteolysis and hypercalcaemia.
- Plasma cells produce varying amounts of monoclonal free light chains. Light chains in the urine (Bence Jones’ proteins) are filtered in the glomeruli and reabsorbed in the proximal tubules. When the light-chain load exceeds the re-absorptive capacity, light chains precipitate out as casts in the distal tubule, causing tubular obstruction and tubulo-interstitial inflammation and acute kidney injury.
- Other causes of renal impairment in patients with myeloma include amyloid deposition, dehydration, hypercalcaemia, hyperviscosity and nephrotoxic drugs.

Epidemiology

- Multiple myeloma is the second most common haematological cancer. It is responsible for 15-20% of deaths from haematological cancer and about 2% of all deaths from cancer.
- The incidence in Europe is 4.5-6.0/100,000/year with a mortality rate of 4.1/100,000/year.
- Generally affects older people: median age at presentation is 70 years.
- More common in Afro-Caribbeans than in Caucasians.
- More common in men.

Presentation

Multiple myeloma can present with a wide variety of symptoms including hypercalcaemia, anaemia, renal impairment and bone pain. Presenting features include:

- Bone pain, particularly backache.
- Pathological fractures.
- Spinal cord/nerve root compression.
- Lethargy (due to anaemia).
- Anorexia.
• Dehydration (due to proximal tubule dysfunction from light-chain precipitation).
• Recurrent bacterial infection.
• Bleeding and/or bruising.
• Features suggesting amyloidosis (eg, cardiac failure, nephrotic syndrome).
• Signs and symptoms of hypercalcaemia (eg, thirst, constipation, nausea, confusion).
• Dizziness, confusion, blurred vision, headaches, epistaxis, cerebrovascular event - due to hyperviscosity.

Blood testing may be carried out for other reasons and show:

• Impaired renal function.
• Anaemia: normochromic, normocytic.
• Leukopenia.
• Thrombocytopenia.
• Hypercalcaemia.
• Persistently raised plasma viscosity or erythrocyte sedimentation rate (ESR).

If there are signs of spinal cord compression, acute kidney injury or hypercalcaemia, the patient should be admitted to hospital immediately. If a paraprotein is found on routine testing, the patient should be referred to an haematologist or oncologist. Multidisciplinary care should follow.

Initial tests for myeloma

If symptoms or the results of routine investigations suggest that a patient may have myeloma, then the following investigations should be performed[6]:

• FBC; ESR or plasma viscosity.
• U&Es and creatinine.
• Calcium, albumin, uric acid.
• Serum protein electrophoresis: shows the type of paraprotein.
• Urine protein electrophoresis: looks for the presence of Bence Jones’ protein.
• Quantitative immunoglobulin levels (eg, IgG, IgA, IgM levels): non-myelomatous immunoglobulin can be suppressed. The level of the myeloma paraprotein can also be used to assess response to treatment.
• Plain X-ray of symptomatic areas.

Diagnostic tests for myeloma[1]

Further tests are then needed to confirm the diagnosis:

• Bone marrow aspirate and trephine biopsy, with plasma cell phenotyping.
• Immunofixation of serum and urine to confirm and show the subtype of the paraprotein.
• A skeletal survey.

Tests to estimate tumour burden and prognosis (to be performed by a haematologist):

• Fluorescence in situ hybridisation analysis of bone marrow aspirate.
• Serum beta-2 microglobulin concentration.
• Serum albumin concentration.
• Quantification of monoclonal proteins in serum and urine.

Diagnostic criteria

• Because there is a high prevalence of MGUS and because serum protein electrophoresis is frequently carried out, most people who have serum monoclonal proteins detected will not have myeloma but will have MGUS.
• Diagnostic criteria have been set to distinguish MGUS from myeloma.
• The criteria also separate asymptomatic and symptomatic myeloma.
Asymptomatic myeloma is basically myeloma with no signs of organ or tissue impairment. It was previously referred to as indolent or smouldering myeloma. Patients with MGUS and asymptomatic myeloma require monitoring but no immediate treatment. Patients with symptomatic myeloma need immediate treatment because there is organ impairment.

**International Myeloma Working Group diagnostic criteria** [1]

**Symptomatic myeloma**
All three criteria needed for diagnosis:

- Monoclonal plasma cells in marrow $\geq 10\%$.
- Monoclonal protein in serum or urine (unless non-secretory; if so, need $\geq 30\%$ monoclonal plasma cells in bone marrow).
- Evidence of myeloma-related organ or tissue impairment:
  - Hypercalcaemia (>10.5 mg/dL (2.6 mmol/L) or upper limit of normal).
  - Renal insufficiency (serum creatinine $>$ 2 mg/dL (176.8 $\mu$mol/L).
  - Anaemia: haemoglobin $<$ 100 g/L or 20 g below normal range.
  - Lytic bone lesions, osteoporosis, or pathological fractures.

**Asymptomatic myeloma**
Both criteria needed for diagnosis:

- Monoclonal protein $\geq 30$ g/L or monoclonal plasma cells in marrow $\geq 10\%$.
- Absence of myeloma related organ or tissue impairment.

**MGUS**
All three criteria needed for diagnosis:

- Monoclonal protein $<$ 30 g/L.
- Monoclonal plasma cells in bone marrow $<$ 10%.
- Absence of myeloma-related organ or tissue impairment.

**Other investigations**

- CT scanning: can be used to detect small lytic lesions that may not be visible on plain X-ray. Consider if bony symptoms are present but plain X-rays are negative. It can show soft tissue disease and can be used to guide biopsy and plan radiotherapy or surgery.
- MRI scanning: can be used to assess soft tissue disease. It is the investigation of choice if spinal cord compression is suspected. It can also show pattern of bone marrow involvement.
- Chromosome analysis: this can be carried out using karyotyping and fluorescence in situ hybridisation (FISH). This can detect chromosome abnormalities that have been associated with a poorer prognosis. However, how much this information can be used to direct patient management is unclear.
- Beta-2 microglobulin levels: used for staging and to predict prognosis (see below).
- Serum viscosity: should be assessed if there is epistaxis, and when there are neurological symptoms or very high paraprotein levels.

**Differential diagnosis**

A monoclonal protein can also be present in:

- MGUS: a paraprotein is found in the blood but there are no other symptoms or signs of myeloma.
- Amyloid light-chain (AL) amyloidosis.
- Solitary plasmacytoma.
- B-cell non-Hodgkin's lymphoma (including Waldenström's macroglobulinaemia).
- Chronic lymphocytic leukaemia.

**Management** [3]
Myeloma is currently seen as an incurable disease that is chronic, relapsing and remitting. Treatment is aimed at controlling the disease, prolonging survival and maximising quality of life\[6\]. Emotional and psychological support for patients, carers and relatives should not be forgotten.

Patients with MGUS and asymptomatic myeloma are observed under the supervision of a consultant haematologist but not treated until they develop symptomatic myeloma. No intervention has been found to delay or prevent the progression of MGUS to myeloma\[1\].

**Symptomatic myeloma**

Treatment should be initiated in all patients with active myeloma: hypercalcaemia >11.0 mg/dL, creatinine >2.0 mg/mL, anaemia (Hb <10 g/dL), active bone lesions, and in those symptomatic due to the underlying disease.

**Elderly patients (non-transplant setting)**

- Oral combinations of melphalan and prednisone (MP) plus novel agents - eg, melphalan/prednisone/thalidomide (MPT), or bortezomib/melphalan/prednisone (VMP).
- Bendamustine plus prednisone is also approved in patients who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib.
- Cyclophosphamide/thalidomide/dexamethasone (CTD) has also been compared with MP and is superior in terms of response rates, but does not induce a clear survival advantage over MP.

The National Institute for Health and Care Excellence (NICE) recommends that\[7\]:

- Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.
- Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contra-indications to thalidomide.

**Younger patients (<65 years or fit patients in good clinical condition)**

- Induction followed by high-dose therapy with autologous stem cell transplantation (ASCT) is the standard treatment.
- Bortezomib-dexamethasone has been the most used induction therapy. The addition of a third agent (eg, thalidomide, doxorubicin, lenalidomide or cyclophosphamide) has shown higher response rates.
- Bortezomib is recommended by NICE as an option, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation\[8\].
- Peripheral blood progenitor cells are the preferred source of stem cells, rather than bone marrow.
- Allogeneic stem cell transplantation should only be carried out in the context of a clinical trial and only in patients with good response before transplant\[9\].

**Consolidation**

There is still not enough evidence that consolidation therapy should be systematically used for elderly patients or for young patients following ASCT.

**Follow-up**

FBC, serum and urine electrophoresis, creatinine and calcium should be carried out every 2-3 months. In the case of bone pain, skeletal X-ray, MRI or CT scan should be carried out to detect new bone lesions.

**Treatment of relapsed and refractory disease**

The choice of therapy depends on several parameters - eg, age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy.
Approved options include lenalidomide in combination with dexamethasone, and bortezomib either alone or in combination with pegylated doxorubicin. However, bortezomib is mostly used in combination with dexamethasone in the relapse setting. In young patients, a second ASCT may be considered, provided the patient responded well to the previous ASCT.

Lenalidomide in combination with dexamethasone is recommended by NICE as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies\[10\].

Bortezomib monotherapy is recommended by NICE as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, but only if the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (reduction in serum M protein of 50% or more)\[11\].

Pain control

- Analgesics: a variety of drugs may be used for pain relief, including ranging from simple analgesics such as paracetamol to potent opioids. Use the analgesic ladder. Non-steroidal anti-inflammatory drugs (NSAIDS) should be avoided where possible (renal effects and gastric irritation).
- Adjuvant drugs: amitriptyline, carbamazepine or gabapentin can help in neuropathic pain.
- Corticosteroids: these can help to relieve bone pain in late stages.
- Alternative techniques: for example, relaxation, aromatherapy, and hypnotherapy may be helpful.
- Radiotherapy: this can be used in bone and soft tissue disease.
- Chemotherapy: if the underlying disease is treated, this should help pain as treatment response occurs.
- Surgery: for example, stabilisation of fractures, treatment of vertebral collapse.

Bisphosphonates

These inhibit bone resorption, but might also inhibit proliferation of multiple myeloma cells. They can help to prevent bone pain, hypercalcaemia and pathological fractures.

Complications

These include:

- Hypercalcaemia
- Renal impairment
- Anaemia
- Infection
- Spinal cord compression
- Pathological fractures
- Hyperviscosity
- Peripheral neuropathy
- Bleeding
- AL amyloidosis

More than 80% of myeloma patients suffer from destructive bony lesions, leading to pain, fractures, reduced mobility and neurological deficits\[12\].

Management of complications

- Hypercalcaemia:
  - 30% of people with myeloma develop hypercalcaemia\[6\].
  - Treat mild hypercalcaemia with oral rehydration.
  - Moderate-severe hypercalcaemia may need intravenous (IV) fluids ± furosemide.
  - Start a bisphosphonate (if not already prescribed).
  - IV corticosteroids and calcitonin may be needed in refractory cases.
Renal impairment:
- Can be caused by:
  - Light-chain damage to the proximal tubules.
  - Dehydration.
  - Hypercalcaemia.
  - Hyperuricaemia.
  - Infection.
  - Nephrotoxic drugs.
  - Amyloid.
- Try to avoid by ensuring adequate hydration (3 litres/day) and avoidance of nephrotoxins.
- Treat any underlying cause.
- Plasma exchange or dialysis may be needed.

Anaemia:
- There is a risk of exacerbating hyperviscosity when giving red cell transfusions in people with high paraprotein levels.
- Consider recombinant human erythropoietin therapy (rhEPO) if there is symptomatic anaemia.

Infections:
- Treat any febrile patient with broad-spectrum antibiotics, avoiding aminoglycosides if possible.
- Consider prophylactic trimethoprim-sulfamethoxazole for the first two months when starting chemotherapy.
- Consider influenza, Streptococcus pneumoniae and Haemophilus influenzae vaccination.
- Prophylactic immunoglobulins may be needed in recurrent infections.

Cord compression:
- A medical emergency.
- Affects 10-20% at some point.
- Investigate using MRI.
- Commence dexamethasone.
- Local radiotherapy is the treatment of choice.

Hyperviscosity:
- Treat with plasma exchange.
- Venesection may be needed if plasma exchange is not available.
- Start chemotherapy.

Prognosis

- With the onset of new potential therapies, the prognosis for myeloma is improving.
- The prognosis remains variable. Some patients will live for more than eight years after diagnosis, whereas high-risk disease usually causes death within 24 months.
- The international staging system defines three risk categories based on serum concentrations of beta-2 microglobulin and albumin:
  - Stage I: serum beta-2 microglobulin <3.5 mg/L and albumin ≥35 g/L.
  - Stage II: does not fit criteria for stage I or III.
  - Stage III: serum beta-2 microglobulin ≥5.5 mg/L (regardless of albumin level).
- Specific genetic lesions or gene signatures are associated with worse outcomes. IgH translocations involving chromosomes 4 and 16 are considered high risk and are associated with a worse prognosis.
- Deletion of the short arm of chromosome 17 is also associated with a worse outcome.
- Age and response to treatment are independent prognostic factors. Younger patients who are fit enough for high-dose chemotherapy now have a projected median survival of around seven years.
- Patients who present as an emergency route have a worse prognosis.
Further reading & references

- Supportive care in multiple myeloma; British Committee for Standards in Haematology (October 2010)
- Myeloma: diagnosis and management; NICE Guidance. (February 2016)
- Multiple myeloma: diagnosis, treatment and follow-up; ESMO Clinical Practice Guideline (2017)

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3. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis treatment and follow-up; European Society for Medical Oncology (Aug 2013)
6. The diagnosis and management of multiple myeloma; British Committee for Standards in Haematology (October 2010)
7. Bortezomib and thalidomide for the first-line treatment of multiple myeloma; NICE Technology Appraisals, July 2011
8. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation; NICE Technology Appraisals, April 2014
10. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy; NICE Technology Appraisals, June 2009
11. Bortezomib monotherapy for relapsed multiple myeloma; NICE Technology Appraisals, October 2007

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