*ABC of clinical haematology***Multiple myeloma and related conditions**

Charles R J Singer

The plasma cell dyscrasias represent a heterogeneous group of conditions characterised by disordered proliferation of monoclonal plasma cells, most of which produce monoclonal immunoglobulin (M protein or paraprotein) in the serum or urine. The clinical phenotype is determined by the rate of accumulation and the biological properties of the abnormal cells and the monoclonal protein.

Multiple myeloma

The incidence of myeloma is about 4 per 100 000 in Britain. It is more than twice as high in African Americans as in white Americans and Europeans, although it is much lower among Chinese and Japanese Asians. Myeloma is extremely rare in people aged under 40 years, but its incidence increases to over 30 per 100 000 in those aged over 80. The median age at diagnosis is 69 years, with slight male predominance.

Pathogenesis and clinical features

Myeloma is due to unregulated, progressive proliferation of neoplastic monoclonal plasma cells that accumulate in the marrow, leading to anaemia and marrow failure. The cell of origin is probably a memory B lymphocyte, and neoplastic cells home to the bone marrow, where the environment rich in interleukin 6 stimulates proliferation of plasma cells.

Myeloma cells produce and secrete a monoclonal protein, usually intact immunoglobulin. IgG paraprotein is present in 60% of cases and IgA in 20-25%, and in 15-20% of cases free immunoglobulin light chains alone are produced. Myelomas whose cells secrete IgD, two clonal proteins, IgM, or no protein are rare. Free light chains are detectable in urine as Bence Jones protein.

Accumulation of M protein may lead to hyperviscosity (especially IgA and IgM polymers) or deposition of the protein in renal tubules, resulting in renal failure. Production of normal immunoglobulin is often depressed (immune paresis) and contributes to the patient's susceptibility to infection.

Bone destruction is characteristic, and the associated bone pain a major cause of morbidity in myeloma. Myeloma is associated with abnormal bone remodelling due to increased osteoclastic bone resorption and inhibition of osteoblastic bone formation. This results in pronounced bone loss and the characteristic osteolytic lesions predisposing to pathological fractures. Widespread bone destruction may lead to hypercalcaemia, resulting in a vicious cycle of dehydration, worsening hypercalcaemia, and renal failure.

The most common presenting complaint is bone pain, commonly affecting the back. Symptoms of anaemia, renal failure, or infection are also frequent. Less common are symptoms of hyperviscosity (impaired central nervous system, impaired vision, purpura, and haemorrhage), acute hypercalcaemia, spinal cord compression, neuropathy, or amyloidosis. About 20% of patients are asymptomatic, and diagnosis results from routine investigations.

Investigations and diagnosis

Myeloma should be suspected in anyone aged over 40 years with unexplained bone pain or fracture, osteoporosis, osteolytic

Conditions associated with M proteins*Stable production*

- Monoclonal gammopathy of undetermined significance
- Smouldering multiple myeloma

Progressive production

- Multiple myeloma (IgG, IgA, free light chains, IgD, IgE)
- Plasma cell leukaemia
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Waldenström's macroglobulinaemia (IgM)
- Chronic lymphocytic leukaemia
- Malignant lymphoma
- Primary amyloidosis
- Heavy chain disease

Clinical features of myeloma*Common*

- Bone pain and pathological fractures
- Anaemia and bone marrow failure
- Infection due to immunoparesis and neutropenia
- Renal impairment

Less common

- Acute hypercalcaemia
- Symptomatic hyperviscosity
- Neuropathy
- Amyloidosis
- Coagulopathy

Radiograph showing multiple lytic lesions and pathological fractures of humerus.

lesions, lethargy, anaemia, red cell rouleaux, raised erythrocyte sedimentation rate or plasma viscosity, hypercalcaemia, renal dysfunction, proteinuria, or recurrent infection. It is characterised by the classic triad of infiltration of the bone marrow by plasma cells, lytic bone lesions on skeletal radiology, and the presence of M protein in the serum or urine, or in both.

History and examination should be followed by a full blood count and film; erythrocyte sedimentation rate or plasma viscosity; urea and creatinine concentrations; calcium, phosphate, and alkaline phosphatase concentrations; uric acid concentration; serum protein electrophoresis; measurement of serum immunoglobulins; routine urine analysis; urine electrophoresis for Bence Jones protein; skeletal survey; and bone marrow aspirate and biopsy.

Protein electrophoresis strip showing (1) normal plasma, (2) polyclonal hypergammaglobulinaemia, (3) serum M protein, and (4) urine M protein (Bence Jones proteinuria) and albuminuria.

Normochromic normocytic anaemia is often present; neutropenia and thrombocytopenia suggest advanced disease. Rouleaux are usually seen in the blood film, and plasma cells may also be present in about 5% of cases. The erythrocyte sedimentation rate and plasma viscosity are often noticeably increased but are normal in 10% of cases. The serum calcium concentration is increased in 30% of cases, with normal alkaline phosphatase concentration. Raised urea and creatinine concentrations occur in 20% of cases. Low serum albumin concentration reflects advanced disease. Skeletal radiology shows lytic lesions or generalised bone rarefaction in 80% of cases. Bone scans are typically negative in multiple myeloma despite extensive bone damage.

The most important differential diagnosis is between multiple myeloma and monoclonal gammopathy of undetermined significance (for which no treatment is indicated). No single test differentiates the two conditions reliably. A serum IgG concentration >30 g/l or IgA concentration >20 g/l suggests a diagnosis of myeloma rather than monoclonal gammopathy of undetermined significance. Some patients have “smouldering multiple myeloma,” in which M protein and bone marrow criteria exist for the diagnosis of myeloma, but anaemia, renal impairment, and skeletal lesions do not develop and the M protein and plasma cells remain stable. Here too a “watch and wait” policy is appropriate.

Management and clinical course

Without treatment a patient with multiple myeloma is likely to experience progressive bone damage, anaemia, and renal failure. Infection is the most common cause of death. Initial treatment should consist of (a) adequate analgesia—opiates often, and local radiotherapy to fractures or osteolytic lesions may have dramatic benefit; (b) rehydration—patients are often dehydrated at presentation, even without hypercalcaemia or renal impairment; (c) management of hypercalcaemia if

Bone marrow aspirate showing infiltrate of abnormal plasma cells (medium power).

Minimal diagnostic criteria for myeloma

- ☆ 10% Plasma cells in bone marrow or plasmacytoma on biopsy
- Clinical features of myeloma
- Plus at least one of:
 - Serum M band (IgG >30 g/l; IgA >20 g/l)
 - Urine M band (Bence Jones proteinuria)
 - Osteolytic lesions on skeletal survey

If myeloma is suspected a urine sample should always be analysed for Bence Jones proteinuria as solitary free light chains are commonly undetected by routine serum electrophoresis

Laboratory findings at diagnosis (proportion of cases)

• Normochromic normocytic anaemia	60%
• Increased erythrocyte sedimentation rate or plasma viscosity	90%
• Serum M protein	80%
• Urine M protein only	20%
• Raised serum calcium concentration	20%
• Raised serum creatinine concentration	25%
• Proteinuria	70%

Blood film rouleaux and abnormal plasma cell (medium power).

present—rehydration, diuresis, and if necessary bisphosphonate therapy; (d) management of renal impairment—rehydration and treatment of any hypercalcaemia often have a pronounced effect on abnormal serum chemistry in myeloma, though in some patients only careful chemotherapy or dialysis, or both, is effective; (e) treatment of any infection—most infections at diagnosis are bacterial and respiratory and respond to broad spectrum antibiotics, though later in the disease antifungal treatment may be necessary; and (f) chemotherapy.

Oral melphalan and prednisolone administered in four day pulses at intervals of four to six weeks produces >50% reduction in the M protein concentration in 50% of patients. The treatment is well tolerated, but complete responses are rare. The median survival is about three years. During the plateau phase clinical and laboratory results should be reviewed at regular intervals to identify progression at the earliest opportunity. Further treatment (with melphalan) may then induce another plateau phase.

Combination intravenous chemotherapeutic regimens may produce higher response rates (up to 70%) and may improve survival. Combination regimens may be more effective in younger patients with high tumour loads, though they may be more toxic in elderly patients.

High dose melphalan and autologous stem cell transplantation after initial treatment produces a complete response in up to 75% of patients and prolongs survival but is not curative. It is applicable only to younger patients.

Allogeneic bone marrow transplantation may cure the condition but with considerable treatment related morbidity and mortality.

Plateau phase

In most patients a stable partial response is achieved in which at least a 50% reduction in the M protein has occurred but chemotherapy fails to produce a further fall over a three month period. A plateau phase may occur in which cessation of chemotherapy may not be followed by a rise in the M band or further signs of progression for many months. Maintenance interferon alfa may prolong the plateau phase by six to 12 months, but little evidence exists of an effect on survival. Bisphosphonate treatment reduces the rate of further bone damage and may have an additive analgesic effect in patients with pre-existing damage and a survival benefit.

Disease progression

With regular follow up, serological detection of disease will allow chemotherapy to be restarted before new bone damage develops, and in many patients several separate periods of plateau phase may be re-induced by chemotherapy. Inevitably myeloma becomes resistant to melphalan; oral dexamethasone may achieve further responses, and oral low dose cyclophosphamide daily is often effective palliative treatment in combination with local radiotherapy to sites of bone pain.

Conditions related to multiple myeloma

Monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance is defined by the presence of an M protein in a patient without multiple myeloma, Waldenström's macroglobulinaemia, amyloidosis, lymphoma, or other related disease. The prevalence of monoclonal gammopathy of undetermined significance is about 20 times greater than that of multiple myeloma, and the incidence increases with age (1% at over 50 years; 3% at over 70).

Features of poor prognosis at diagnosis

- Low haemoglobin concentration (<85 g/l)
- Hypercalcaemia
- Advanced lytic bone lesions
- High M protein production rates (IgG >70 g/l; IgA >50 g/l; Bence Jones protein >12 g/24h)
- Abnormal renal function
- High plasma cell proliferative index
- Low serum albumin concentration (<30 g/l)
- High β_2 -microglobulin concentration (>6 mg/ml)

Treatment considerations in myeloma

- Analgesia
- Rehydration
- Treatment of any hypercalcaemia
- Treatment of any renal impairment
- Treatment of any infection
- Local radiotherapy if required
- Chemotherapy
- Prevention of further bone damage

Bone pain from mechanical effects of myeloma damage (as in spine shown here) often necessitates long term treatment with strong analgesia despite response to chemotherapy.

Options for initial chemotherapy in myeloma

- Melphalan with or without prednisolone
- Infusional chemotherapy—vincristine and adriamycin infusion plus either dexamethasone or methylprednisolone
- Combination therapy—for example, adriamycin, carmustine, cyclophosphamide, and melphalan
- Weekly cyclophosphamide ("C weekly")

Diagnostic criteria for monoclonal gammopathy of undetermined significance

- No unexplained symptoms suggestive of myeloma
- Serum M protein concentration <30 g/l
- $\leq$ 5% Plasma cells in bone marrow
- Little or no M protein in urine
- No bone lesions
- No anaemia, hypercalcaemia, or renal impairment
- M protein concentration and other results stable on prolonged observation

Multiple myeloma, macroglobulinaemia, amyloidosis, or lymphoma ultimately develops in 26% of patients with monoclonal gammopathy of undetermined significance, with an actuarial rate of 16% at 10 years.

Solitary plasmacytoma

About 5% of patients have a single bone lesion at diagnosis with no evidence of disseminated bone marrow involvement.

Generally M protein is absent (up to 70% of cases) or present in low concentration. Plasmacytoma may be cured by local radiotherapy. Patients with solitary plasmacytoma should be monitored for evidence of myeloma, which develops in most cases. Further plasmacytomas may develop, and magnetic resonance imaging may show bone lesions undetectable by conventional radiology. Median survival is over 10 years.

Waldenström's macroglobulinaemia

This condition is the result of proliferation of lymphocytes and plasma cells which produce monoclonal IgM. The median age at presentation is 63 years, and over 60% of patients are male. Many of the clinical features are the result of hyperviscosity due to the raised IgM concentration.

Weakness, fatigue, and bleeding are the most common presenting complaints, followed by visual upset, weight loss, recurrent infections, dyspnoea, heart failure, and neurological symptoms. Bone pain is rare.

The erythrocyte sedimentation rate is greatly raised, and when the plasma viscosity exceeds 4 cP most patients have symptoms of hyperviscosity. Serum protein immunoelectrophoresis shows an IgM paraprotein concentration often exceeding 30 g/l. Monoclonal light chains may be present in the urine. Trephine biopsy often shows extensive infiltration with plasmacytoid lymphocytes.

Symptomatic hyperviscosity is corrected by plasmapheresis. Chlorambucil with or without prednisolone for one week every four to six weeks frequently reduces bone marrow infiltration, the IgM concentration, and plasma viscosity. Median survival is about five years.

Other related conditions

Chronic lymphocytic leukaemia and diffuse low grade non-Hodgkin's lymphoma may be associated with low serum concentrations of monoclonal IgG or IgM. This finding has no prognostic importance for patients with these diseases. Primary amyloidosis is associated with an M protein in 85% of cases. The "heavy chain diseases" are rare lymphoproliferative disorders in which the abnormal cells excrete only parts of immunoglobulin heavy chains (γ , α , or μ).

The slide of the protein electrophoresis strip was provided by Mr D Costello.

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No treatment for monoclonal gammopathy of undetermined significance is indicated, but follow up is necessary

Plasma cell leukaemia

- May be diagnosed when blood plasma cells exceed $2.0 \times 10^9/l$
- May occur as a terminal stage in advanced multiple myeloma or as aggressive disease at diagnosis in under 5% of cases
- Bone involvement is often minimal, and the M protein concentration is often low
- Results of treatment are poor, but intensive treatment can induce responses and prolong survival

Clinical and laboratory features of Waldenström's macroglobulinaemia

- Fatigue and weight loss
- Anaemia
- Hyperviscosity syndrome (may cause chronic oral or nasal bleeding, visual upset, headache, vertigo, hearing loss, ataxia, somnolence, and coma)
- Retinal haemorrhages
- Venous congestion (sausage formation) in retinal veins
- Recurrent infection
- Lymphadenopathy
- Hepatosplenomegaly
- Raised erythrocyte sedimentation rate
- High serum monoclonal IgM concentration
- Lymphoplasmacytoid bone marrow infiltrate

Further reading

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ONE HUNDRED YEARS AGO

Women as veterinary surgeons

An action is likely to be called in the Scotch Courts, asking that decree be pronounced ordaining the Royal College of Veterinary Surgeons to proceed to the examination of a female candidate for the diploma of that College, and if she be found duly qualified, to grant her that diploma, and to confer on her all the rights and privileges thereto accruing. The facts are these: A female candidate had registered herself as a medical student, and has gone through the necessary course at the New Veterinary College. She presents herself for examination, and the Royal College of Veterinary

Surgeons decline to examine her, on the ground that it is contrary to use and wont to examine a woman or to grant her a qualification in veterinary medicine and surgery. To this the authorities of the New College reply that forty-four years are too short a term to constitute a ground for a plea of usage, or use and wont, as is the Scotch phrase. And further, the laws speak of a "student," not "he" or "she." The Council of the Royal College thus far has declined to give way, though, as we understand, by a small majority. (*BMJ* 1897;i:1176.)