Plasma cell neoplasms

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Abstract

Plasma cell neoplasms encompass a spectrum of diseases related to clonal expansion of neoplastic plasma cells and/or their precursors. These include essential monoclonal gammopathy, plasma cell myeloma, solitary plasmacytoma of bone or soft tissue, primary amyloidosis and immunoglobulin chain deposition diseases. Plasma cell myeloma is the prototype of a plasma cell neoplasm that occurs as generalized disease involving primarily bone marrow with associated serum monoclonal protein and lytic bone lesions. This review first focuses primarily on plasma cell myeloma and its variants, and then discusses other plasma cell neoplasms.

Keywords Plasma cell myeloma; MGUS; M-protein

Plasma cell myeloma

Plasma cell myeloma (PCM), or multiple myeloma, is the most common haematological malignancy, accounting for 10% all haematological malignancies in the USA. The annual incidence is approximately 19,920 with an estimated annual death of 10,690 in the United States. PCM affects mostly older people with a median age of approximately 70 years. There are no confirmed genetic or environmental risk factors, although blacks are more likely to be affected than whites (2:1).[1]

Clinical findings and diagnostic criteria

Patients usually present with bone pain and pathological fractures. Anaemia, recurrent infections and renal failure are other frequent findings. Less common symptoms include hyperviscosity syndrome, hypercalcaemia and spinal cord compression due to vertebral body fracture or epidural mass. Most patients have a monoclonal serum protein (M-protein). IgG is most common (53%), followed by IgA (22%), light chain only (20%), non-secretory (3%), IgD or IgE (1.5%) and IgM (0.5%). Bence Jones protein can be detected in 80% of patients.

The diagnosis of PCM generally requires detection of 10% or greater of monoclonal plasma cells and M-protein in the serum or urine. In most symptomatic patients, the serum M-protein levels are usually 3 g/dl or greater or Bence Jones protein 1 g/day or greater. However, cases meeting these criteria are not necessarily symptomatic and require intervention. Historically, major or minor criteria, largely defined by the extent of marrow plasmacytosis, lytic lesions and levels of M-protein, were used to divide patients into symptomatic, indolent and smoldering myeloma subgroups.

In 2003, the International Myeloma Working Group (IMWG) proposed a simplified scheme for the diagnosis of symptomatic myeloma.[2] Recognizing that a subset of symptomatic patients may present with marrow plasmacytosis less than 10% and M-protein less than 3 g/dl, a minimal level of marrow plasmacytosis or M-protein is no longer required for the diagnosis of myeloma as long as both are present in patients with evidence of related end-organ or tissue impairment, defined as hypercalcaemia, renal insufficiency and anaemia or bone lesions (CRAB) (Table 1). The IMWG further retained the category of smoldering myeloma, which is still reserved for patients who meet the minimal diagnostic criteria but are asymptomatic clinically.[2] The IMWG scheme has been adopted by the new World Health Organization (WHO) classification published in 2008.[3]

Imaging

Imaging studies are an essential part of the myeloma work up. Standard skeletal survey may detect multiple 'punched-out' lytic lesions within the skull, spine and/or pelvis (Figure 1). Computerized tomography (CT) is usually unnecessary except in

World Health Organization diagnostic criteria of myeloma and monoclonal gammopathy of unknown significance

Symptomatic plasma cell myeloma

- M-protein in serum and/or urine
- Bone marrow (clonal) plasma cells or plasmacytoma
- Related organ or tissue impairment (end-organ damage, including bone lesions):
  - Serum calcium > 0.25 mmol/l (1mg/dl) above the upper limit of normal or > 2.75 mmol/l (11 mg/dl)
  - Renal insufficiency: creatinine > 173 mmol/l (1.96 mg/dl)
  - Anaemia: haemoglobin 2 g/dl below the lower limit of normal or haemoglobin < 10 g/dl
  - Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
  - Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

Asymptomatic (smouldering myeloma)

- M-protein in serum > 30 g/litre and/or
- Bone marrow clonal plasma cells > 10%
- No related organ or tissue impairment (no end-organ damage, including bone lesions) or symptoms

Monoclonal gammopathy of undetermined significance (MGUS)

- M-protein in serum < 30 g/litre
- Bone marrow clonal plasma cells < 10% and low level of plasma cell infiltration in a trephine biopsy (if done)
- No evidence of other B-cell proliferative disorders
- No related organ or tissue impairment (no end-organ damage, including bone lesions)

Table 1

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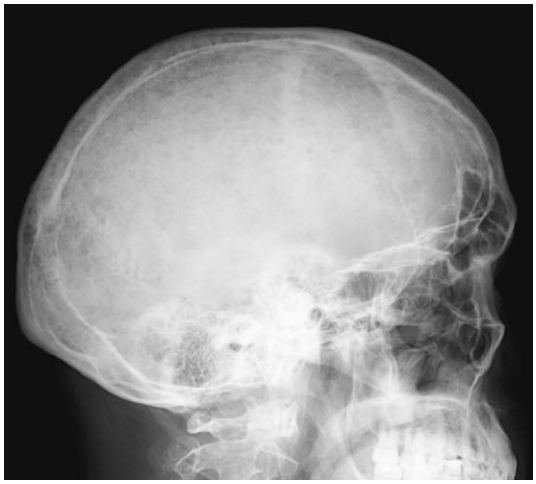

Figure 1 Skeletal survey of the skull showing multiple 'punched out' osteolytic lesions characteristic of plasma cell myeloma.

cases with a negative skeletal survey. Magnetic resonance imaging (MRI) is useful in assessing for spinal cord compression and for extramedullary diseases.

Morphology

Morphological evaluation is essential for the diagnosis and management of PCM. Although plasma cell enumeration is usually performed on Wright–Giemsa stained bone marrow aspirate smears using a differential count of 200–500 cells, it may underestimate plasmacytosis if the infiltrate is patchy or associated with fibrosis. Bone marrow trephine biopsy should be performed, at least in the initial evaluation, to assess the extent and pattern of plasmacytic infiltration, as well as the presence of amyloid deposition and bone changes. There is usually increased osteoclastic activity and microvascular density.[4]

Plasma cells comprise 1–4% of nucleated cells in normal marrow and are of the mature 'Marschalko' type with abundant basophilic cytoplasm, perinuclear hof and 'spoke-wheel' nuclear chromatin pattern. Neoplastic plasma cells often show a variable degree of immaturity or anaplasia. Asynchronous maturation of the nucleus and cytoplasm, high nuclear-to-cytoplasmic ratio and prominent nucleoli are features of immaturity. Bizarre nuclear shapes and marked variation in nuclear size are evidence of anaplasia. Plasma cell immaturity and anaplasia are strong evidence of malignancy that support the diagnosis of myeloma when the percentage of plasma cells is less than 10% or light chain analysis fails to demonstrate monoclonality, as in cases of non-secretory myeloma. Binucleation or even trinucleation are not reliable indications of malignancy. Accumulation of cytoplasmic immunoglobulin can lead to the formation of Russell bodies or crystalline rods. Cells containing multiple immunoglobulin inclusions are described as grape cells, flame cells, Mott cells, Gaucher-like cells and thesaurocytes. Dutcher bodies are nuclear immunoglobulin inclusions.

Two major grading systems commonly used to describe the morphological spectrum of myeloma cells are the Greipp system and the Bartl system.[5] The Greipp system consists of four subtypes: mature, intermediate, immature and plasmablastic. The Bartl system consists of seven subtypes. Examples of different Bartl grade tumours are illustrated in Figure 2. Bartl also described six patterns of infiltration: interstitial, interstitial with paratrabecular sheets, interstitial/nodular, nodular, packed and sarcomatous.

The plasmablastic subtype appears be the only one that predicts an adverse prognosis.[6] However, recognition of other subtypes helps distinguish myeloma from mimics. For example, the asynchronous or blastic subtype may resemble monoblastic leukaemia. The polymorphous subtype is frequently associated with fibrosis and can be confused with primary myelofibrosis or acute panmyelosis with myelofibrosis. The small cell variant may resemble low grade B-cell lymphoma or leukaemia with plasmacytic differentiation.

Laboratory studies

M-protein is detectable in most cases of myeloma by serum/urine protein electrophoresis (SPEP/UPEP) as a narrow peak in the densitometer tracing or a distinct band on agarose gel. However, in light chain only myeloma, hypogammaglobulinaemia may be the only finding. SPEP may be completely negative in IgD or IgE myeloma. Immunofixation (IFE) determines the type of M-protein and will detect a serum M-protein of 0.2 g/litre or greater and a urine M-protein of 0.04 g/litre or greater. IFE is the gold standard for detection of M-protein. Serum immunoglobulin quantification shows suppression of non-myeloma immunoglobulin. Serial quantification of M-protein allows easy assessment of tumour load reduction as an indication of response to treatment.[7]

Serum- or urine-free immunoglobulin light chain (FLC) ratio (κ/λ) is considered to be most useful in monoclonal gammopathy of unknown significance (MGUS), AL amyloidosis, light chain deposition disease (LCDD) and non-secretory multiple myeloma (NSMM) when the M-protein levels are low. Recently, it has been shown that the FLC ratio at initial diagnosis predicts prognosis or risk for asymptomatic PCM to evolve to symptomatic multiple myeloma.[8,9] However, the sensitivity and specificity of FLC analysis in comparison to SPEP and IFE are still controversial. In many instances, FLC analysis cannot replace SPEP and IFE.

Serum level of β2 microglobulin (β2 M) reflects tumour turnover and renal function. C-reactive protein (CRP) regulated by interleukin (IL)-6 is a reliable marker for myeloma activity. Serum carboxy-terminal telopeptide of type-1 collagen (ICTP) is a specific and sensitive marker for bone resorption.[10] Lactate dehydrogenase (LDH) is usually elevated in patients with extensive disease and is associated with a poor prognosis. The plasma cell labelling index (PCLI) measures synthesis of DNA by using a monoclonal antibody (BU-1). BU-1 reacts with bromodeoxyuridine that is incorporated into DNA by cells in S phase. PCLI is usually greater than 1% in symptomatic myeloma or greater than 5% in advanced disease.[2]

Immunophenotype

Flow cytometry (FCM) is not required for the diagnosis of myeloma, however it is useful in recognizing morphologically challenging or non-secretory myeloma cases, and in identifying aberrantly expressed markers to be used as potential therapeutic targets or detection of minimal residual disease.[11] Myeloma cells are positive for CD138 (syndecan-1), CD38 (bright) and

