

Practical radiology of plasmacytoma and multiple myeloma

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Abstract

The traditional approach to diagnosis and staging in myeloma, based on haematologic and biochemical criteria, can be improved by inclusion of new forms of imaging. Standard radiographs have limited value but are still required because the majority of patients present with disease readily detected by this means. Also rapid extensive skeletal coverage is possible. Scintigraphy is limited by its poor sensitivity. CT is restricted to a region of interest but is however more accurate than DXA for demonstrating trabecular bone loss and density so that it emerges as valuable in the evaluation of therapy. MRI is currently the best choice for revealing marrow infiltra-

tion and, in ideal circumstances, the most sensible combination includes spine, pelvis and proximal femur MRI with skull, chest and rib X-rays. Furthermore MRI is finding a place in documenting prognosis when these individuals are treated.

Introduction

Localised or disseminated monoclonal proliferation of plasma cells produces a wide range of symptoms and signs primarily in the skeleton. Prominent among the latter is discomfort due to generalised osteoporosis, solitary or multiple lytic lesions¹ in addition to pathological fracture.² Associated is synthesis of a paraprotein which can typically be detected in serum and as Bence-Jones proteins in urine although the more primitive variants may not secrete and occasionally not even produce the aberrant immunoglobulin molecule.³ Metabolic consequences are increases in blood calcium and urate that are risk factors for kidney failure.⁴ Invasion of the bone marrow impairs haematopoiesis⁵ with both humoral and cell-mediated immunity being compromised.⁶ The cause is unknown although the natural history is well described with median survival of only 7 months.⁷ In contrast modern

management improves quality of life by optimum support and combinations of alkylating agents with corticosteroids while investigational approaches centre on haematopoietic stem cell transplantation and thalidomide.^{8,9}

Clinical features

Presentation may be protean and with the increasing use of routine biochemical screening, as part of health care management, diagnosis can be made when only biochemical changes are reported incidentally from the laboratory.

Prominently pain is axial reflecting demineralisation that may be severe, is often aggravated at night and is characteristically responsive to biphosphonates.¹⁰ Areas of destruction vary in number and size. Strong correlations exist with cytokines that alter both osteoclastic and osteoblastic activity.¹¹ Myelomatous masses may erode the cortex and give rise to large subcutaneous swellings, underlie breaks, predispose to vertebral compression and occasionally present as tumours in breast, stomach or adjoining the spinal column.

Haematologically there are varying degrees of normochromic and normocytic anaemia pathophysiologically attributed to the chronic inflammatory state and associated with a marked increase in erythrocyte sedimentation rate. Until late in the course leucocyte and platelet counts are preserved.¹² Bone marrow aspiration reveals increased numbers of plasmacytes many of which may be pleomorphic and, together with their extent and distribution seen in the trephine, are included in some staging procedures.¹³ Biochemical consequences are

increases in calcium and urate with a distinctive spike in the gamma region on serum protein electrophoresis. Free light chains, filtered at the glomerulus, are then deposited in the tubules so contributing to renal dysfunction with polyuria and dehydration culminating in a self-perpetuating cycle that is, however, initially reversible.

Sometimes profound degrees of immune compromise reduce polyclonal antibodies and predispose to sinopulmonary infection. Approximately 10% of patients develop amyloidosis that has widespread effects typically producing nephrotic syndrome but perhaps more ominously restrictive cardiomyopathy. A wide range of other features exist to trap the unwary diagnostician and a high degree of awareness will often lead to an early diagnosis.¹⁴

Laboratory evaluation

There is no substitute for a carefully taken history followed by meticulous examination, maintaining a high degree of awareness and simple bedside tests of which urinalysis remains invaluable.¹⁴

The next stage is confirmation and since a number of the findings are mimicked by other disorders it is wise to combine as many abnormal findings as possible to secure the diagnosis but primarily rely on the presence of the serum paraprotein designated an M-peak and intramedullary plasmacytosis.

Staging defines anticipated outcome and provides a practical means for monitoring management. The most widely used of these is that described by Durie and Salmon

(Table I).¹⁵ Recent studies support the use of β_2 microglobulin and C-reactive protein.¹⁶

An approach to imaging

Plain film radiography

Approximately 80% of individuals have abnormalities at presentation and this remains a logical first step in studying the skeleton.¹⁷ However no systematic approach appears to have been described for the integration of these changes into established staging systems^{15,16} although there is, not surprisingly, a loose correlation implicit between advancing tumour and skeletal damage. To provide a more structured approach to this risk factor a new grading is proposed (Table II).

Bone mineral density

As part of an ongoing evaluation, (Jacobs, Wood, Hitchcock and du Toit — unpublished data) this is quantitated initially and followed serially seeking to define the influence of different interventions, particularly the use of biphosphonates.¹⁸ We have found that the much favoured DXA often underestimates trabecular thinning which is readily evident on computerised axial tomography.¹⁹

Scintigraphy

Radionuclide scanning using technetium-99m labelled diphosphonate is typically normal or shows areas of decreased uptake. The explanation for this relative insensitivity is that the osteoblastic activity in these tumours is outweighed by the aggressive

Table I. Classification of myeloma (modified from Durie and Salmon¹⁵). The best predictors are degree of anaemia, quantitation of paraprotein and serum calcium level

Stage	Criteria
I: All must be present	<ul style="list-style-type: none"> • Haemoglobin value > 100 g/l • Serum calcium < 2.2 mmol/l • Radiographically <ul style="list-style-type: none"> Normal bone structure Solitary bone plasmacytoma • M-component <ul style="list-style-type: none"> IgG < 50 g/l IgA < 3 g/l Urine light chain < 4 g/24 hours
II	Fitting neither Stage I nor Stage III
III: One or more only needed	<ul style="list-style-type: none"> • Haemoglobin value < 85 g/l • Serum calcium value > 2.2 mmol/l • Advanced osseous destruction • M-component <ul style="list-style-type: none"> IgG > 70 g/l IgA > 50 g/l Urine light chain > 12 g/24 hours

Subclassification
 A = Serum creatinine < 120 μ mol/l
 B = Serum creatinine > 120 μ mol/l.

Table II. Constantiabergrading of skeletal changes (Jacobs, Wood and du Toit — unpublished data). Uncertainty exists as to whether the total amount of cortical damage reflected in multiple small defects has different value to a smaller number of much larger areas of destruction

Grade	Criteria
0	Normal
I	Diffuse demineralisation
II	Less than 10 lytic lesions
a.	Maximum 1 cm
b.	2 - 4 cm
c.	Greater than 5 cm
III	More than 10 bony defects
IV	Associated pathological fracture

destruction of the hypertrophic osteoclasts.²⁰

Computerised tomography (CT)

Although not routinely used it may nevertheless demonstrate early trabecular bone destruction within a vertebral body where other imaging modalities are negative.

Magnetic resonance imaging (MRI)

Support derives from a greater sensitivity in revealing otherwise occult invasion which is seen in about 50% of asymptomatic patients with normal X-rays.¹⁷ Representative areas are full spine, pelvis and proximal femora because these contain the normal haematopoietic tissue that harbours the neoplasm. Three patterns are discernable (Table III).²¹ Focal accumulations exhibit low-T1 and

low or high T2 signal in approximately equal numbers of untreated cases. The variegated or salt and pepper appearance has small nodules on T1 and is sometimes best appreciated in the pelvis. A diffuse involvement has similar intensity to the isolated deposits with homogenous replacement resembling other intramedullary proliferative disorders. Mixed pictures occur depending on the status of the immunoproliferative neoplasm. This variable appearance results from relatively even neoplastic distribution throughout the haematopoietic tissue in widespread disease contrasting with the small or large nodules composed entirely of tumour in localised patterns. Compounding factors are increasing age with conversion of red to yellow marrow that influences both detection and character of the image produced by the myeloma. Thus, although nor-

mal haematopoiesis is impaired with replacement of the former, the relative increase in the adipocytes gives an enhanced signal, which offsets reduction from areas of infiltration, and so the scan may look normal. Contrast enhancement with gadolinium is often marked but neither specific nor essential if any abnormality has already been demonstrated. Similarly medullary invasion may be patchy although widespread overall so that an adequate trephine biopsy will invariably demonstrate the aetiology. Hence MRI is not usually required to direct the aspiration site.

Vertebral fractures are seen with significant osteoporosis, which is frequent, and approximately 60% of compression fractures look benign. Thus in 37 patients with 224 fractures, 67% had this appearance, 33% appeared malignant and, interestingly, 14 of these or 38% had no sinister features.²² The distribution of such radiological changes was similar to that observed in non-myelomatous demineralisation predominantly in the lower dorsal and upper lumbar regions. In contrast ominous features are low T1 signal extending from the vertebral body into the pedicles and posterior elements, diffuse body involvement, multiple level involvement and extension outside of bone to form a soft tissue mass.²³ The anatomical site may be helpful in detecting malignancy since those above T4 are usually pathological.

A prognosis on therapeutic outcome can be correlated with Durie and Salmon stage III where four groups are defined; normal, fewer or more than 10 focal sites and widespread infiltration.²⁴ It is notable that with apparently solitary lesions MRI will typically reveal other deposits.

Table III. Magnetic resonance imaging in myeloma (modified from Kaplan *et al.*²¹)

Pattern	Signal	
	T1	T2
Focal	Low	High or low
Variegated or salt & pepper	Low	Mild high
Diffuse	Low	High or low

Following therapy those with lower grades based on both biopsy and radiological criteria experienced significantly longer fracture-free survival than where more extensive changes were present.

It is also useful to forecast response. In Durie and Salmon stage I invasion is associated with subsequent progression.²⁵ Stage III patients with normal images (24%) achieve better results with therapy and survive longer than those where this is abnormal.²⁶ When coupled with CRP this pair were the best independent prognostic indicators for survival. This method can be refined using contrast when complete response is defined as resolution of the baseline abnormality and is superior to persistence of any change even if this is only peripheral rim enhancement.²³

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