# Physicians, Paraproteins and Progress

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## Abstract
Myeloma outcomes have improved dramatically over the last decade as a result of novel therapies, several of which are now commonly continued to disease progression. Physicians outside the haematology specialty are therefore more likely than ever before to be consulted by a myeloma patient either for an unrelated condition or due to a side effect of their myeloma or its treatment. Myeloma is also the cancer most likely to be diagnosed in A+E or by the acute physician and so an awareness of its presentation and management is especially important in these settings to enable early diagnosis and limit the morbidity associated with end organ damage. This review summarises the presenting features of disease, diagnostic criteria for myeloma and related plasma cell disorders and discusses current management.

## Key points
- Early diagnosis and treatment of myeloma can improve outcomes
- Myeloma is the cancer most likely to be diagnosed in A+E or by the acute physician and so an awareness of its presentation and management is especially important in these settings
- Progress in therapies and supportive care over the last few decades makes myeloma the cancer with the most rapidly improving prognosis of all major cancer types, with more than a third of UK patients now alive at ten years from diagnosis
- Myeloma patients are living longer with their disease and may present to other clinical specialities with the complications of their disease or its treatment

## Short Introduction

We aim to address why all physicians should be interested in myeloma and other plasma cell disorders. We discuss the presenting features of disease, diagnostic criteria and summarise the progress that has been made in treatment over recent years.

## Introduction

Myeloma and other plasma cell disorders can present to A+E and general physicians in a variety of different ways. Of all cancers myeloma is the most likely to be diagnosed in A+E or by the acute physician. Once a patient is diagnosed, and undergoing treatment under the care of a haematologist, physicians of other specialties may again become involved in their care as a result of complications, the side effects of treatment or due to patient co-morbidities. The latter is increasing in likelihood as myeloma patients live longer with their disease. As such, awareness by general physicians of the disease, its presentation, diagnostic tests and pathways to haematology referral along with treatments and side effects are imperative.

## Pathophysiology

Myeloma is a bone marrow cancer of terminally differentiated B cells, which are antibody-secreting plasma cells. It is the second most common haematological cancer and a new diagnosis occurs in over 5,700 patients in the UK each year, representing 2% of all new cancer cases. Myeloma is predominantly a disease of older people with median age at diagnosis of around 70 years and as such the incidence is increasing with population aging. It is more common in males by a ratio of 1.4:1 and has an increased incidence in those of black ethnicity. Myeloma aetiology has been associated with radiation, agricultural and other chemical use and combustion fuel products such as benzene but only rarely is an identifiable underlying precipitant found. Familial and genetic factors have been implicated and there are single nucleotide polymorphisms that have been associated with an increased relative risk, although the difference in absolute risk is small.

The normal function of a plasma cell, the production of antigen specific immunoglobulin, is enabled by genetic editing processes such as class switch recombination and somatic hypermutation, allowing the diversity of antibody production required to fight pathogens. These processes are, however, error-prone and can lead to an oncogenic proliferation advantage and the production of clonal plasma cells. (Morgan et al., 2012) The clone is initiated by chromosomal translocations or the acquisition of a hyperdiploid karyotype in approximately half of cases respectively, with further genetic lesions such as point mutations, secondary translocations and chromosomal copy number abnormalities driving further clonal evolution. A plasma cell clone usually secretes an intact immunoglobulin monoclonal protein termed a paraprotein although may secrete only the light chains from the immunoglobulin molecule which will be of either lambda or kappa subtype. Asecretory myeloma (secreting neither a paraprotein or serum free light chains) is very rare, around 1% of all cases.

## Stages of disease and early detection

Retrospective studies of serial stored serum have shown that myeloma is almost always preceded by the pre-malignant stage monoclonal gammopathy of undertermined significance (MGUS). (Landgren et al., 2009) This stage of disease will often not be clinically detectable but if it is this enables patient monitoring,

allowing early detection of progression and preventing damage to organs at the point of diagnosis. Patients with MGUS can be risk stratified (Kyle et al., 2010) but those with low risk can often be monitored in the community, as there is a relatively low risk (1% per year) of progression to myeloma.

Myeloma can be divided into smouldering myeloma, disease that reaches a significant burden threshold but does not require treatment and myeloma that requires treatment. Classically smouldering myeloma has been described as having a risk of progression to myeloma of 10% per year although in reality there is a broad range of risk among patients classically labeled as smouldering. As our ability to determine risk factors for progression advances it is likely that this group will cease to exist and disease described as either requiring treatment or monitored like MGUS.

Myeloma patients will often report having felt non-specifically unwell for several months prior to their emergency presentation. This poses the potential opportunity to intervene early by attempting to lower the threshold for GPs to perform screening blood tests such as a paraprotein in the community. The majority of GPs, however, will have only a handful of patients diagnosed with myeloma through their whole career and patients present with symptoms of low predictive value e.g. musculoskeletal/back pain. More amenable to intervention is that fact that patients will often have been reviewed by several medical specialties with regard to their symptoms prior to diagnosis and meeting a haematologist. There is currently no evidence to support a screening programme for paraproteinaemia, as there is no early intervention that can prevent progression to myeloma.

## Presenting symptoms of myeloma

Systemic symptoms such as fatigue are highly prevalent but other symptoms vary between patients and are discussed below. The spectrum of presenting symptoms of myeloma will change in frequency depending on the ability to put in place mechanisms for early detection of myeloma and/or monitoring of MGUS. The numbers quoted are from historical disease cohorts. (Kyle et al., 2003, Ramsenthaler et al., 2016, Howell et al., 2017).

### *Pathological fracture/bone pain*

Myeloma destruction of the bone cortex causing a lytic lesion detectable by skeletal survey was present in around 70% of patients at diagnosis. Patients may present with a pathological fracture or with sites of bony pain. Vertebral crush fractures are common at diagnosis and associated back pain and deformity can be relieved by vertebroplasty or kyphoplasty procedures. Bone destruction is caused by increase osteoclast and decreased osteoblast activity thought to be due to cytokines and other factors produced by the myeloma cells.

Myeloma can also present as cord compression, a medical emergency. In the undiagnosed setting, this will most often require emergency neurosurgical intervention with the diagnosis made as a result of diagnostic tissue taken at the time of surgery. Concurrent diagnostic tests

from serum and/or urine should be sent to enable rapid confirmation of the diagnosis potentially in advance or concurrent with histology results being available. In a previously diagnosed patient actual or impending cord compression remains a medical emergency and should always be urgently discussed via a multi-disciplinary cord compression pathway involving the neurosurgeons, but surgery can often be avoided by the use of rapid acting anti-myeloma therapies.

### *Renal failure*

Almost half of patients with myeloma will present with at least some degree of acute kidney injury, 20% with severe kidney injury and 5% requiring dialysis at diagnosis. The inclusion of paraprotein/light chain analysis in screens for AKI is recommended especially in patients of an age with a higher incidence of disease (>60 years) to enable early diagnosis. There are multiple mechanisms by which myeloma can cause renal failure (**Table 1**). (Yadav et al., 2016, Davenport and Merlini, 2012, Dimopoulos et al., 2008) The most common cause is cast nephropathy where free light chain excess exceeds the capacity of tubular cell catabolism/tubular cell reabsorption and the light chains appear in the tubular fluid of distal nephrons. Light chains form complexes with uromodulin (Tamm-Horsfall protein) resulting in aggregates and casts leading to tubular obstruction of the distal tubule and thick ascending loop of Henle. Renal function often improves with myeloma treatment especially in the majority with mild to moderate impairment especially if therapy is started promptly.

### *Hypercalcaemia*

Hypercalcaemia of malignancy is present in around 15% of patients presenting with myeloma as a result of bone destructive lesions. This requires urgent intervention with hydration and bisphosphonates, considering appropriate dose reductions based on renal impairment.

### *Infections*

Immune deficiency in myeloma results from plasma cells in the bone marrow displacing normal white cell precursors and also as a result of the paraprotein causing immuneparesis and suppression of normal immunoglobulin production. Around 15% of patients will present with recurrent or severe infection, which may be their only manifestation of disease. Unusual features such as prolonged recovery, associated anaemia or other cause for concern should prompt investigation for myeloma in general medical patients presenting with infections.

### *Symptoms of anaemia or pancytopenia*

Around a third of patients will present with anaemia, usually normocytic normochromic. This is a result of bone marrow infiltration by plasma cells displacing red cell precursors.

### *Other modes of presentation*

Other organ systems may be involved at presentation and although these are less common myeloma should be considered in cases of diagnostic

uncertainty. Patients may present with peripheral neuropathy or with symptoms of hyperviscosity such as headaches, visual disturbance and mucosal bleeding. Myeloma is not always confined to the bone marrow and extramedullary lesions can be found in other organs such as the liver. CNS involvement is rare, especially at first diagnosis but associated outcomes are poor. Deposition of light chains or paraprotein has been recognised as a cause of corneal keratopathy presenting to ophthalmologists. Skin manifestations are uncommon but reported.

## Diagnostic work-up

The diagnostic criteria for myeloma were updated in 2014 and the current version does not require evidence of end organ damage (**Figure 1A**). (Rajkumar et al., 2014) The criteria now incorporate biomarkers of malignancy that suggest impending end organ damage based on prior studies suggesting patients with such features would have a greater than 80% chance of developing myeloma within 2 years.

At a minimum a patient with suspected myeloma under the care of a general physician should have a full blood count, renal profile, bone profile, serum paraprotein analysis (by electrophoresis +/- immunofixation) and free light chain analysis. Serum free light chain analysis is the most sensitive methods for detecting free light chain secretion but urine bence jones protein analysis can be performed if this is not available. If there is evidence of a paraprotein or light chain imbalance then discussion/referral to a haematologist is recommended. A haematologist will perform a bone marrow aspirate and trephine, except in cases that can confidently be diagnosed as low risk MGUS. In order to distinguish between myeloma and smouldering myeloma whole body imaging with whole body low dose CT and MRI is also required. Skeletal surveys are now rarely performed as to detect bone lysis on x-ray requires more than 30% of the bony cortext to have been eroded. CT imaging techniques are better able to pick up earlier stages of bone destruction and the benefit of MRI is that it can detect intramedullary focal lesions of myeloma before bone damage has occurred. (Dimopoulos et al., 2015)

## The spectrum of plasma cell dyscrasias

There is a wide range of other plasma cell dyscrasias characterized by clonal plasma cell proliferation and these are shown in **Figure 1B**. Perhaps the most important of these to the general physician is light chain amyloidosis as this can present with a very wide spectrum of seemingly unrelated symptoms affecting virtually every organ system and therefore present to any clinical specialty. (Merlini et al., 2011) Particular situations that should raise the possibility of amyloidosis include unexplained cardiomyopathy, nephrotic syndrome, sensorimotor or autonomic neuropathy and macroglossia. In primary AL amyloidosis there is a low-level plasma cell clone producing abnormally folded light chains, which deposit to cause organ damage. A clone size meeting the diagnostic criteria for myeloma can also produce light chains causing

amyloid deposits and this may even evolve from previously non-amyloidogenic light chains earlier in the disease course.

Cryoglobulinaemia (mostly type I), a circulating immunoglobulin that precipitates with cold temperature, may be associated with either MGUS or myeloma. This may present with skin manifestations, glomerulonephritis and/or neurological involvement.(Muchtar et al., 2017) Amyloid, POEMS and cryoglobulinaemia are all examples of conditions where an 'MGUS-sized' clone is far from being of 'undetermined significance' and may require therapy. (Fermand et al., 2018)

## Prognostic factors

Myeloma prognostic biomarkers have been refined in recent years. It is often confusing for patients that myeloma is not staged similarly to solid organ tumours with spread to other organs or the bone marrow being associated with adverse outcomes. Given that the disease starts in the bone marrow a different classification is clearly required and the current staging system, the Revised International Staging System (R-ISS) relates certain factors to outcome. (Palumbo et al., 2015) It includes factors relating to both patient organ function and condition (albumin and beta-2-microglobulin, B2M) and tumour factors (genetic changes in the tumour known to associate with outcome). Within the score tumour cytogenetic factors, which are identified using fluorescence in-situ hybridization on plasma cells isolated from diagnostic bone marrow biopsies, considered high risk are del(17p), t(4;14) and t(14;16). Risk is categorized into three groups, from low-risk R-ISS group I with ISS Stage I; no high-risk cytogenetic abnormality (CA) and normal LDH level; to high-risk R-ISS group III with ISS Stage III and high-risk CA or high LDH level. More recently further modifications to this score have been suggested such as the incorporation of next generation sequencing date with features such as bi-allelic disruption of *TP53* and amplification of 1q associated with the most adverse outcomes. As sequencing technologies become available in routine clinical practice these are likely to be incorporated more routinely. Other features of disease associated with adverse outcome include the presence of extramedullary disease, circulating plasma cells, renal failure and blastic plasma cell morphology. (Chng et al., 2014)

## Current treatments and their complications

Progress in outcomes for myeloma patients over the last decade has been dramatic. This is, at least in part, due to the fact that since 2007 8 new agents for the treatment of myeloma have become available in the UK under NHS funding (NICE/CDF) with 3 of these in the last 2 years. These agents are shown in **Table 2** with their mechanism of action. Their use in the UK is limited under NHS funding to specific time points of disease. It is usually possible to obtain a good remission following initial treatment that can last for several years, however myeloma will almost inevitably relapse at which point the clone is likely to have become more aggressive, having evolved to have features of more high risk

disease. (Pawlyn and Morgan, 2017) Following re-induction therapy subsequent remission duration tends to be shorter than the previous. (Yong et al., 2016) Standard first line treatment for myeloma is with the combination of a proteasome inhibitor (bortezomib) and immunomodulatory agent (thalidomide/lenalidomide depending on funding) with steroid (dexamethasone). This is followed by high dose melphalan alkylating agent consolidation with autologous stem cell rescue in patients' young and fit enough to withstand this treatment. Ongoing maintenance therapy has been demonstrated to be effective in clinical trials. Older patients should be assessed for co-morbidities and frailty prior to commencing treatment. Whether up-front frailty adjusted dosing can improved outcomes is currently being studied.

There are side effects associated with anti-myeloma agents that may lead to a presentation to a specialty other than haematology and as myeloma patient survival increases this is likely to occur more commonly. Several agents are also now continued until disease progression or as 'maintenance' type therapies meaning patients may be in remission from their myeloma but continue on therapy, making them more likely to present elsewhere on therapy. These side effects, along with the specialty they most commonly present to are shown in **Table 3**.

Other interventions recommended for myeloma patients include the institution of bisphosphonate therapy. This is primarily for the prevention of skeletal related events but there is evidence from some studies it may also prolong overall survival. (Morgan et al., 2013, Mhaskar et al., 2017) Patients are advised to maintain a good fluid intake (2-3 litres per day). Prophylaxis against viral reactivation, pneumocystis and fungal infections is routinely used along with anticoagulants to prevent venous thrombosis with immunomodulatory agents. Recent trial data suggest that antibiotic prophylaxis with levofloxacin may reduce febrile episodes and death early in treatment.

Myeloma patients in the UK are often taking part in clinical trials as there is a strong network of clinical trials centres around the UK and motivated physicians working to enroll patients wherever possible, enabling patients to access new therapies not available via usual funding routes. There are also an increasing number of new agents with novel mechanisms of action being studied from antibody-drug conjugates and chimeric antigen receptor T cells to spindle kinase inhibitors and nuclear export protein inhibitors. Clinical trials are also underway to try and find therapeutic combinations that may benefit patients with adverse risk disease as with current regimens their outlook remains poor and has improved much less over recent decades than patients with standard risk disease. Trial drugs will have class and drug specific side effects and so patients on trials should always be discussed with a haematologist urgently if presenting to another specialty.

## Conclusions

Plasma cell disorders are very relevant to the physician but can be difficult to diagnose if the appropriate investigations are not considered. The

modes of presentation discussed above should trigger investigation with referral to haematology where appropriate. Myeloma can cause devastating problems that are largely avoidable or reversible with prompt diagnosis. With new therapies prognosis for myeloma patients is improving rapidly with numerous new therapies being developed.

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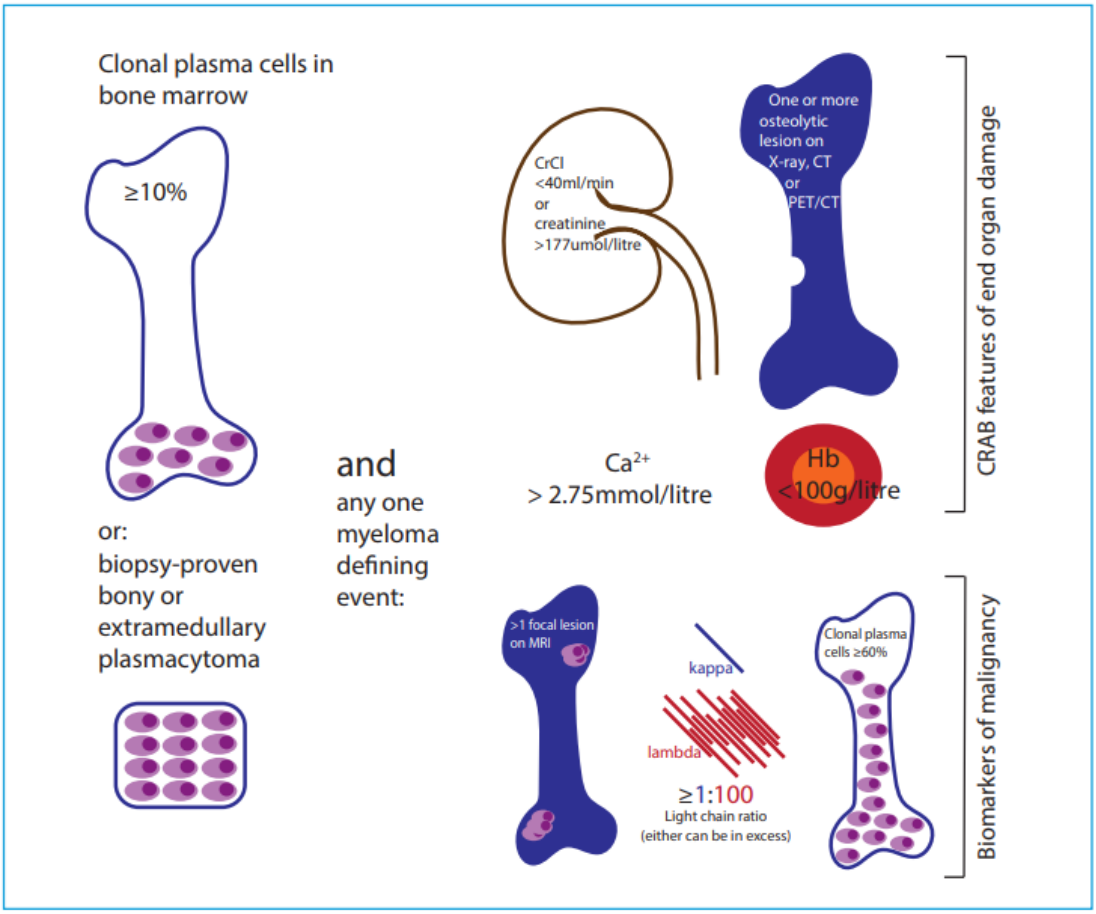


Figure 1. Paraproteinaemias. Myeloma diagnostic criteria. Based on Rajkumar et al (2014). CRAB = hyperCalcaemia, Renal impairment, Anaemia and Bone disease; CrCL = creatinine clearance; CT = computed tomography; Hb = haemoglobin; MRI = magnetic resonance imaging; PET/CT = positron emission tomography– computed tomography.

Table 1

| Causes of renal impairment | |
|---|---|
| **Effect of light chains** | Cast nephropathy |
| | Light chain deposition disease |
| | Amyloid |
| | Acquired Fanconi's syndrome |
| | |
| **Effect of myeloma** | Hypercalcaemia |
| | Dehydration |
| | Infection |
| | Hyperuricaemia |
| | |
| **Effect of diagnostic work up** | Contrast media from diagnostic scans |
| | |
| **Effect of therapies** | Non-steroidal anti-inflammatory* |
| | Antibiotics |
| | Bisphosphonates |
| | Anti-myeloma therapies |

*patients are advised to avoid once a diagnosis is made but will often have been given for back pain prior to diagnosis

**Table 2**

| Class / mechanism of action | Name | Current time point of disease at which it is NICE approved / most commonly used |
|---|---|---|
| **Immunomodulatory agents** | Thalidomide | Newly diagnosed |
| | Lenalidomide (Revlimid) | Relapsed (3rd line +) |
| | Pomalidomide (Imnovid) | Relapsed (4th line +) |
| **Proteasome inhibitors** | Bortezomib (Velcade) | Newly diagnosed<br>Relapsed (3rd line +, with panobinostat) |
| | Ixazomib (Ninlaro) | Relapsed (3rd or 4th line with lenalidomide) |
| | Carfilzomib (Kyprolis) | Relapsed (2nd line, if not had bortezomib previously) |
| **Antibody therapies** | Daratumumab (Darzalex, anti-CD38) | Relapsed (4th line only) |
| **Histone deacetylase inhibitor** | Panobinostat (Farydak) | Relapsed (3rd line +, with bortezomib) |
| **Alkylating agents** | Melphalan with autologous stem cell rescue | Newly diagnosed<br>Relapsed |
| | Cyclophosphamide | All |
| | Bendamustine | Relapsed |
| **Steroids** | Dexamethasone | All |
| | Prednisolone | If dexamethasone contraindicated |

Table 3

| Common side effect that may present to a specialty other than haematology | Speciality to which it may present / require input from | Mechanism | Agents most commonly responsible | Management |
|---|---|---|---|---|
| **Neutropenic sepsis** | A+E / Acute medicine<br>Infectious diseases<br>Microbiology | Bone marrow suppression leading to cytopenias | Alkylating agents<br>Immunomodulatory agents<br>Proteasome inhibitors<br>Monoclonal antibodies<br>Histone deacetylase inhibitors | Antibiotics<br>To be administered within 1 hour of presentation, as per local protocols |
| **Peripheral neuropathy** | Neurology | Unknown | Thalidomide<br>Bortezomib<br>Less commonly with other immunomodulatoy agents and proteasome inhibitors | In conjunction with haematologist:<br>Dose hold and then modification (full cessation not often required)<br>Analgesia |
| **VTE** | A+E / Acute medicine | Unknown, contributed to by myeloma itself | Immunomodulatoy agents | Anticoagulation |
| **Diarrhoea** | Acute medicine<br>Gastroenterology | Bile acid malabsorption | Lenalidomide | If confirmed, bile acid sequestrant e.g. colesevelam* |
| | | Unknown | Panobinostat<br>Alkylating agents | Loperamide once infection excluded |
| **Constipation** | Acute medicine<br>Gastroenterology | Unknown | Thalidomide | Laxatives |
| **Cardiac failure, pulmonary** | Cardiology | Unknown, ?endothelial | Carfilzomib | In conjunction with |

| | | | | |
|---|---|---|---|---|
| **oedema, hypertension** | | dysfunction | | haematologist:<br>Dose modification (cessation not often required) |
| **Cataract** | Ophthalmology | Unknown | Steroids | Cataract removal |
| **Diabetes** | A+E / Acute medicine<br>Endocrine | Beta cell dysfunction<br>Insulin resistance | Steroids | Hypoglycaemic agents, may resolve when steroids cease |
| **Adrenal insufficiency** | A+E / Acute medicine<br>Endocrine | Inhibition of corticotropin-releasing hormone from the hypothalamus and adreno-corticotrophic hormone by the pituitary gland that persists after steroids have been stopped | Steroids | Mineralocorticoid replacement |

*Must be given more than 4 hours apart from dose critical medications