Physicians, paraproteins and progress: diagnosis and management of myeloma

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 relapse. Physicians who do not work in haematology are therefore more likely than ever before to be consulted by a patient with myeloma, either for an unrelated condition or with a side effect of myeloma or its treatment. Myeloma is also the cancer most likely to be diagnosed in accident and emergency departments 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 summarizes the presenting features of disease, diagnostic criteria for myeloma and related plasma cell disorders, and discusses current management.

Myeloma and other plasma cell disorders can present to accident and emergency departments and general physicians in a variety of different ways. Of all cancers myeloma is the most likely to be diagnosed in accident and emergency 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 patient comorbidities. The latter is increasing in likelihood as patients with myeloma live longer with their disease. As such, general physicians should be aware of the disease, its presentation, diagnostic tests and pathways to haematology referral along with commonly used treatments and their side effects.

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 5700 patients in the UK each year, representing approximately 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 ageing. 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 very rarely is an identifiable underlying precipitant found. Familial and genetic factors have been implicated and single nucleotide polymorphisms 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 facilitated by genetic editing processes such as class switch recombination and somatic hypermutation, allowing the diversity of antibody production required to fight pathogens. However, these processes are 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 in approximately half of cases or the acquisition of a hyperdiploid karyotype in the other half, with additional 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 it 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 at diagnosis.

Stages of disease and early detection

Myeloma can be divided into three stages:

1. Monoclonal gammopathy of uncertain significance
2. Smouldering myeloma – disease that reaches a significant burden threshold but does not require treatment
3. Myeloma that requires treatment.

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

Dr Charlotte Pawlyn, NIHR Clinical Lecturer in Haematology, The Institute of Cancer Research, London and The Royal Marsden Hospital, London SM2 5NG

Professor Graham H Jackson, Professor of Haematology, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne

Correspondence to: Dr C Pawlyn (charlotte.pawlyn@icr.ac.uk)

and preventing damage to organs at the point of diagnosis. Patients with monoclonal gammopathy of undetermined significance can be risk stratified (Kyle et al, 2010) and those at low risk monitored in the community, as the risk of progression to myeloma is only approximately 1% per year.

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 labelled with this stage of disease. Numerous ongoing trials are therefore examining the potential benefit of starting treatment for patients with smouldering myeloma at high risk of progression. As the ability to determine risk factors for progression advances it is likely that this group will cease to exist and disease will be described as either requiring treatment or monitored like monoclonal gammopathy of undetermined significance.

Patients with myeloma often report having felt non-specifically unwell for several months before 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. back pain. More amenable to intervention is the fact that patients will often have been reviewed by several medical specialties regarding their symptoms before 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.

Table 1. Causes of renal impairment

Cause	Comments
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 drugs*
	Antibiotics
	Bisphosphonates
	Anti-myeloma therapies

**Patients are advised to avoid these once a diagnosis is made but will often have been given them for back pain or other musculoskeletal pains before diagnosis*

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 monoclonal gammopathy of undetermined significance and therefore how far advanced the disease is at diagnosis. The numbers quoted are from historical disease cohorts (Kyle et al, 2003; Ramsenthaler et al, 2016; Howell et al, 2017).

Pathological fracture or bone pain

Myeloma destruction of the bone cortex causing a lytic lesion detectable by skeletal survey is present in around 70% of patients at diagnosis. Destruction is often present at a lower level, however, and this can be detected by different imaging modalities such as whole body computed tomography or magnetic resonance imaging. 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 increased osteoclast and decreased osteoblast activity thought to be caused by 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 from 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 of, 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 multidisciplinary cord compression pathway involving the neurosurgeons, but surgery can often be avoided by the use of rapid acting anti-myeloma therapies or radiotherapy.

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 approximately 5% requiring dialysis at diagnosis. The inclusion of paraprotein or light chain analysis in screens for acute kidney injury 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*) (Dimopoulos et al, 2008; Davenport and Merlini, 2012; Yadav et al, 2016). The most common cause is cast nephropathy where free light chain excess exceeds the capacity of tubular cell catabolism or tubular cell reabsorption and the light chains appear in the tubular fluid of distal nephrons. There, light chains form complexes with uromodulin (Tamm–Horsfall protein) resulting in

aggregates and casts leading to 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, particularly 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.

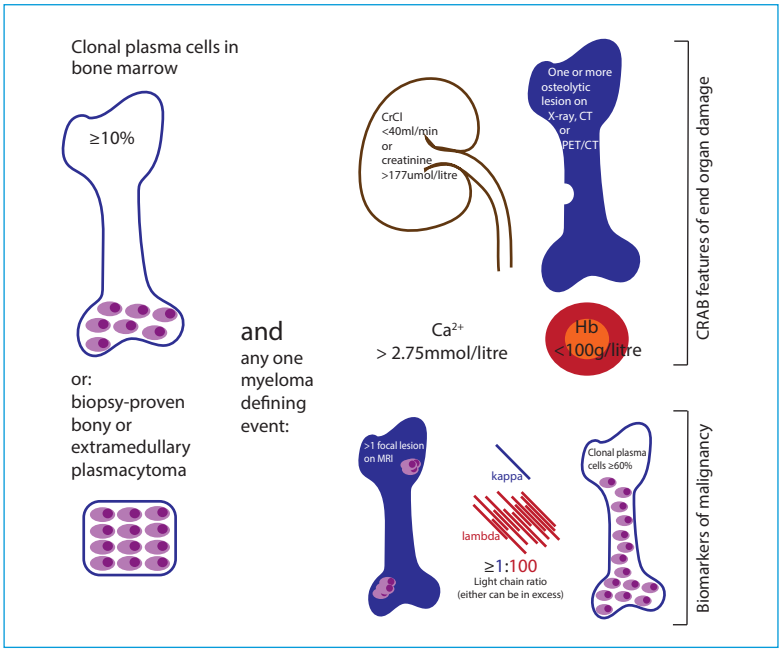
Infections

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 causes 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 anaemia. This is a result of bone marrow infiltration by plasma cells displacing red cell precursors.

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.



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 and associated outcomes are poor. Deposition of light chains or paraprotein has been recognized 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 1*) (Rajkumar et al, 2014). The criteria now incorporate biomarkers of malignancy that suggest impending end organ damage, based on prior studies which indicated that 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 and/or 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, or in cases of diagnostic uncertainty, then discussion with or referral to a haematologist is recommended. A haematologist will usually proceed first to perform a bone marrow aspirate and trephine as well as whole body imaging, except in cases that can confidently be diagnosed as low risk monoclonal gammopathy of undetermined significance. In order to distinguish between myeloma and smouldering myeloma whole body imaging with whole body low dose computed tomography and magnetic resonance imaging is also required. Skeletal surveys are now rarely performed as bone lysis can only be detected on X-ray if more than 30% of the bony cortex has been eroded. Computed tomography imaging techniques are better able to pick up earlier stages of bone destruction and the benefit of magnetic resonance imaging is that it can detect intramedullary focal lesions of myeloma before cortical 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 (*Table 2*), including solitary plasmacytoma. Amyloid, POEMS and cryoglobulinaemia are all examples of conditions where an 'monoclonal gammopathy of undetermined significance-

sized' clone is far from being of 'undetermined significance' and may require therapy (Fermand et al, 2018). 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.

Systemic immunoglobulin light chain amyloidosis is diagnosed in patients with amyloid-related systemic symptoms (e.g. renal, liver, heart, gastrointestinal tract or peripheral nerve involvement), positive amyloid staining by Congo red in any tissue (e.g. fat aspirate, bone marrow or organ biopsy), evidence that amyloid is light chain-related and evidence of a monoclonal plasma cell proliferative disorder.

Cryoglobulinaemia (mostly type I), a circulating immunoglobulin that precipitates with cold temperature, may be associated with either monoclonal gammopathy of undetermined significance or myeloma. This may present with skin manifestations, glomerulonephritis and/or neurological involvement (Muchtar et al, 2017).

POEMS syndrome comprises polyneuropathy and a monoclonal plasma cell proliferative disorder, plus any one of the three major criteria: sclerotic bone lesions, Castleman's disease, elevated levels of vascular endothelial growth factor-A and any one of the six minor criteria: organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilloedema, and thrombocytosis or polycythemia.

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 in which spread to other organs or the bone marrow is 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) 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:

1. R-ISS 1: B2 microglobulin <3.5 mg/litre and albumin ≥35 g/litre, no high-risk cytogenetic abnormality and normal lactate dehydrogenase level
2. R-ISS 2: patients not meeting criteria for R-ISS 1 or R-ISS 3
3. R-ISS 3: B2 microgloblin ≥5.5 mg/litre and high-risk cytogenetic abnormality and/or high lactate dehydrogenase level.

More recently further modifications to the definition of high-risk disease have been suggested such as the incorporation of next generation sequencing data 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).

Table 2. Other plasma cell dyscrasias

	Smouldering myeloma	Non-IgM MGUS	Light chain MGUS	Solitary plasmacytoma	Solitary plasmacytoma with minimal marrow involvement
Serum monoclonal protein	≥30 g/litre*	<30 g/litre	Not detected	Low level	Low level
Bone marrow clonal plasma cell	10–60%	<10%	<10%	0	<10%
Light chain ratio	Normal to 100	n/a	<0.26 or >1.65	Normal to 100	Normal to 100
Myeloma defining event	No	No	No	No	No
Other			Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells	

**or urinary monoclonal protein ≥500 mg per 24 hours. Based on Rajkumar et al (2014). MGUS = monoclonal gammopathy of undetermined significance; n/a = not applicable.*

Table 3. Myeloma therapies available in the UK via NHS funding

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

Current treatments and their complications

Progress in outcomes for patients with myeloma over the last decade has been steadily improving. This is, at least in part, because since 2007 eight new agents for the treatment of myeloma have become available in the UK under NHS funding (via the National Institute for Health and Care Excellence and/or the Cancer Drugs Fund), with three of these in the last 2 years. These agents are shown in *Table 3* 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, but 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 or lenalidomide depending on funding) with steroid (dexamethasone). This is followed by high-dose melphalan alkylating agent consolidation with autologous stem cell rescue in patients who are young and fit enough to withstand this treatment. Ongoing maintenance therapy has been demonstrated to be effective in clinical trials but is not currently routinely available. Older patients should be assessed for comorbidities and frailty before commencing treatment. Whether up-front frailty adjusted dosing can improve 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 survival of patients with myeloma 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 while on therapy. These side effects, along with the specialty they most commonly present to, are shown in *Table 4*.

Other interventions recommended for patients with myeloma 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. Patients on immunomodulatory therapies should be risk assessed for appropriate venous thromboembolism prophylaxis.

Patients with myeloma 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 is 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 that of 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. Prognosis for patients with myeloma is improving rapidly with numerous new therapies being developed. BJHM

KEY POINTS

- Early diagnosis and treatment of myeloma can improve outcomes.
- Myeloma is the cancer most likely to be diagnosed in accident and emergency departments 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 10 years from diagnosis.
- Patients with myeloma are living longer with their disease and may present to other clinical specialities with the complications of their disease or its treatment.

Table 4. Common side effects that may present to a specialty other than haematology

Side effect	Speciality to which patients may present or require input from	Mechanism	Agents most commonly responsible	Management
Neutropenic sepsis or other systemic infection	Accident and emergency or acute medicine Infectious diseases Microbiology	Bone marrow suppression leading to cytopenias	Alkylating agents Immunomodulatory agents Proteasome inhibitors Monoclonal antibodies Histone deacetylase inhibitors	Antibiotics (to be administered within 1 hour of presentation in the case of neutropenic sepsis, as per local protocols)
Peripheral neuropathy	Neurology	Unknown	Thalidomide Bortezomib Less commonly other immunomodulatory agents and proteasome inhibitors	In conjunction with haematologist: dose hold and then modification (full cessation not often required) Analgesia
Venous thromboembolism	Accident and emergency or acute medicine	Unknown, contributed to by myeloma itself	Immunomodulatory agents	Anticoagulation
Diarrhoea	Acute medicine Gastroenterology	Bile acid malabsorption	Lenalidomide	If confirmed, bile acid sequestrant, e.g. colesevelam*
		Unknown	Panobinostat	Loperamide once infection excluded
			Alkylating agents	Loperamide once infection excluded
Constipation	Acute medicine Gastroenterology	Unknown	Thalidomide	Laxatives
Cardiac failure, pulmonary oedema, hypertension	Cardiology	Unknown	Carfilzomib	In conjunction with haematologist: dose modification (cessation may be required)
Cataract	Ophthalmology	Unknown	Steroids	Cataract removal
Diabetes	Accident and emergency or acute medicine, endocrine	Beta cell dysfunction Insulin resistance	Steroids	Hypoglycaemic agents, may resolve when steroids cease
Adrenal insufficiency	Accident and emergency or acute medicine, 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 orally administered dose critical medications to avoid a detrimental effect on drug absorption.

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Chng WJ, Dispenzieri A, Chim C-S et al; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014 Feb;28(2):269–277. https://doi.org/10.1038/leu.2013.247

Davenport A, Merlini G. Myeloma kidney: advances in molecular mechanisms of acute kidney injury open novel therapeutic opportunities. Nephrol Dial Transplant. 2012 Oct 01;27(10):3713–3718. https://doi.org/10.1093/ndt/gfs449

Dimopoulos MA, Kastritis E, Rosinol L, Bladé J, Ludwig H. Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia. 2008 Aug;22(8):1485–1493. https://doi.org/10.1038/leu.2008.131

Dimopoulos MA, Hillengass J, Usmani S et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol. 2015 Feb 20;33(6):657–664. https://doi.org/10.1200/JCO.2014.57.9961

Fermand JP, Bridoux F, Dispenzieri A, Jaccard A, Kyle RA, Leung N, Merlini G. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018 Oct 04;132(14):1478–1485. https://doi.org/10.1182/blood-2018-04-839480

Howell D, Smith A, Appleton S et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival - findings from a UK population-based study. Br J Haematol. 2017 Apr;177(1):67–71. https://doi.org/10.1111/bjh.14513

Kyle RA, Gertz MA, Witzig TE et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003 Jan;78(1):21–33. https://doi.org/10.4065/78.1.21

Kyle RA, Durie BGM, Rajkumar SV et al; International Myeloma Working Group. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010 Jun;24(6):1121–1127. https://doi.org/10.1038/leu.2010.60

Landgren O, Kyle RA, Pfeiffer RM et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009 May 28;113(22):5412–5417. https://doi.org/10.1182/blood-2008-12-194241

Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. J Clin Oncol. 2011 May 10;29(14):1924–1933. https://doi.org/10.1200/JCO.2010.32.2271

Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochrane Database Syst Rev. 2017 Dec 18;12:CD003188. https://doi.org/10.1002/14651858.CD003188.pub4

Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. Nat Rev Cancer. 2012 May;12(5):335–348. https://doi.org/10.1038/nrc3257

Morgan GJ, Davies FE, Gregory WM et al. Long-term follow-up of MRC Myeloma IX trial: survival outcomes with bisphosphonate and thalidomide treatment. Clin Cancer Res. 2013 Nov 01;19(21):6030–6038. https://doi.org/10.1158/1078-0432.CCR-12-3211

Muchtar E, Magen H, Gertz MA. How I treat cryoglobulinemia. Blood. 2017 Jan 19;129(3):289–298. https://doi.org/10.1182/blood-2016-09-719773

Palumbo A, Avet-Loiseau H, Oliva S et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015 Sep 10;33(26):2863–2869. https://doi.org/10.1200/JCO.2015.61.2267

Pawlyn C, Morgan GJ. Evolutionary biology of high-risk multiple myeloma. Nat Rev Cancer. 2017 Aug 24;17(9):543–556. https://doi.org/10.1038/nrc.2017.63

Rajkumar SV, Dimopoulos MA, Palumbo A et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 Nov;15(12):e538–e548. https://doi.org/10.1016/S1470-2045(14)70442-5

Ramsenthaler C, Kane P, Gao W, Siegert RJ, Edmonds PM, Schey SA, Higginson IJ. Prevalence of symptoms in patients with multiple myeloma: a systematic review and meta-analysis. Eur J Haematol. 2016 Nov;97(5):416–429. https://doi.org/10.1111/ejh.12790

Yadav P, Cook M, Cockwell P. Current trends of renal impairment in multiple myeloma. Kidney Diseases. 2016 Mar 1;1(4):241–257. https://doi.org/10.1159/000442511

Yong K, Delforge M, Driessen C et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016 Oct;175(2):252–264. doi:10.1111/bjh.14213