CASE REPORT

Multiple myeloma presenting with bilateral ankle pain (microangiopathy) and complicated by streptococcal meningitis and *Pneumocystis carinii* pneumonia

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SUMMARY

Multiple myeloma is characterised by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow, resulting in extensive skeletal destruction with osteolytic lesions, osteopenia and pathological fractures. Additional disease-related complications include hypercalcaemia, renal insufficiency, anaemia and infection. We present the case of a 64-year-old woman presenting with rapid onset, painful distal symmetrical lower limb weakness and an acute kidney injury. Owing to her IgG κ paraprotein (kappa light chain 4620, kappa:lambda ratio 826), she was diagnosed with probable plasma cell myeloma. This diagnosis was confirmed following a trephine biopsy. She required renal replacement therapy, inotropic support and a percutaneous tracheostomy. She became acutely confused with a Glasgow Coma Scale score of 10/15 and a CT head showed no acute pathology. Further investigation with a lumbar puncture confirmed the diagnosis of streptococcal meningitis. She was treated with intravenous acyclovir, ceftriaxone and fluconazole. Her non-bronchoalveolar lavage revealed a diagnosis of *Pneumocystis carinii* pneumonia and she required treatment with co-trimoxazole. This case report discusses the clinical presentation, diagnostic algorithm and treatment of myeloma. This manuscript offers an important clinical reminder to consider myeloma in the differential diagnosis in patients presenting with bone pain and acute kidney injury.

CASE PRESENTATION

A 64-year-old female UK resident was referred from Wexham Park Hospital to the Department of Intensive Care Medicine at the Royal Berkshire Hospital with end organ damage attributable to a suspected underlying plasma cell disorder. She presented to the emergency department at Wexham Park Hospital with a 3-day history of rapid onset painful distal symmetrical lower limb weakness leading to impaired mobility. Respiratory, cardiovascular and abdominal examinations were unremarkable. Neurological examination confirmed decreased power of both legs (4/5). There was no sensory level. Her reflexes were normal. Biochemistry revealed an abnormal renal function: urea 41.1 mmol/L, creatinine 966 μ mol/L and estimated glomerular filtration rate 4 mL/min/L. Furthermore, a low haemoglobin (79 g/L) with a

mean corpuscular volume of 97.8 fL was observed. She had an elevated white cell count (11.50×10^9 /L) and a neutrophilia (10.19×10^9 /L) with a raised C reactive protein (235.3 mg/L). She was also hyponatraemic (sodium 127 mmol/L). Her serum B₁₂ was 1151 ng/L (197–771) and her serum folate was 6.0 μ g/L (4.6–19.7) (table 1).

Owing to her IgG κ paraprotein (κ light chain 4620, κ : λ ratio 826), she was diagnosed with probable plasma cell myeloma. A urine dip was negative for leucocytes, but positive for blood (200+++) and protein (300+++). She required inotropic support with norepinephrine to maintain a mean arterial pressure >65 mm Hg. She developed new onset atrial fibrillation and was loaded with amiodarone.

INVESTIGATIONS

On the 2nd day of her admission, a chest radiograph confirmed bilateral consolidation and she started treatment with intravenous amoxicillin (figure 1). Her influenza swabs for influenza A (H1N1) and influenza B were negative. Furthermore, her urinary pneumococcal antigens were negative. Three days postadmission, she developed severe headache, confusion and vomiting, with a Glasgow Coma Scale score of 10/15 requiring intubation and ventilation. However, a CT head showed no evidence of acute intracranial pathology, acute infarct or space occupying lesion. Slight dilation of the temporal horn of the right lateral ventricle of uncertain significance was noted (figure 2). A lumbar puncture was performed and her opening pressure was 33. Macroscopically, clear yellow fluid was observed. Her cerebrospinal fluid (CSF) indicated a dense neutrophilic infiltrate with ~10% of cells consisting of monocytes and foamy macrophages; 90% were polymorphs (table 2).

Her glucose was low (<1.1) and her protein was high (>6). There was no evidence of myelomatous meningitis or fungal spores. Enterovirus was not detected and there was no bacterial growth after 48 hours incubation. In addition, John Cunningham (JC) virus DNA was not detected. Since JC virus DNA is detected in CSF in only about 80% of patients with progressive multifocal leukoencephalopathy (PML), this result did not exclude the JC virus. Both the meningococcal screening polymerase chain reaction (PCR) test and the cryptococcal antigen test were negative. As well

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Table 1 Biochemistry confirmed hyponatraemia (sodium 127 mmol/L) and an elevated CRP 253.5 mg/L

Complete blood count		Liver function	
WCC	11.50×10 ⁹ /L	ALT	23 iu/L
Differential count		Globulins	39 g/L
Neutrophils	10.19%	Bilirubin	11 µmol/L
Lymphocytes	0.63%	Total protein	68 g/L
Haemoglobin	79 g/L	CRP	253.5 mg/L
MCV	97.8 fL	Adjusted calcium	2.07 mmol/L
Renal		Total calcium	1.77 mmol/L
Sodium	127 mmol/L	Serum B ₁₂	1151 ng/L
Potassium	4.3 mmol/L	Serum folate	6.0 µg/L
Urea	41.1 mmol/L		
Creatinine	966 µmol/L		

ALT,alanine transaminase; CRP, C reactive protein; MCV,mean corpuscular volume; WCC, white cell count.

as this, Listeria and polyoma BK virus were not detected. However, on serology, her pneumococcal antigen was positive for streptococcal pneumonia. Serology was negative for HIV, hepatitis B surface antigen and hepatitis C. She started treatment with intravenous ceftriaxone, acyclovir and fluconazole. A renal ultrasound scan revealed no hydronephrosis. On day 4, a vascath was inserted via a femoral approach and she started renal replacement therapy (RRT), with improving renal function noted. Since her clotting parameters were normal, a bone marrow aspirate and biopsy were performed from the right posterior superior iliac spine under local anaesthesia. A partially dilute particulate aspirate with small hypercellular fragments yielding hypocellular trails were noted. Two bony cores measuring 31 mm were yielded by trephine biopsy and sections were examined at three levels. Reticulin was generally not increased. Congo red was negative for amyloid. The features were consistent with plasma cell myeloma, International Classification of Diseases 0 code (box 1). Dexamethasone was switched to the intravenous route due to concerns about absorption, 33 mg intravenous being the equivalent of 40 mg orally. Ten days post-admission, following a haematology review, her treatment was started with bortezomib (velcade). Her β glucan was negative (<30 pg/mL) but her non-bronchoscopic broncho-alveolar lavage was positive for *Pneumocystis carinii* pneumonia and she started treatment with co-trimoxazole. A skeletal survey was also performed and no focal myeloma deposits were observed.

Figure 1 Chest radiograph. A chest radiograph confirmed bilateral consolidation.

Figure 2 CT head. A CT head showing no evidence of acute intracranial pathology, acute infarct or space-occupying lesion.

TREATMENT

She remained on RRT with improving renal function. Sedation hold revealed improved neurology, but her ankle pain limited her wean; hence, she required a percutaneous tracheostomy. Further investigation with an MRI spine (axial images obtained between L1 and S1) revealed preserved vertebral height and alignment (figure 3). There was no evidence of malignancy, with no marrow deposit or infiltration. Multilevel degenerative disc changes were present with no intra or extra-axial mass or surface collection. Review by Neurology confirmed preserved knee jerks and absent ankle jerks. Impaired vibration below her knees and temperature below her upper calves were noted (slightly asymmetric pattern). The working diagnosis was of confluent painful mononeuritis multiplex affecting her lower limbs, most likely giving rise to axonal injury, a pattern typically seen in vasculitic neuropathies. It was thought likely that the underlying pathology was a microangiopathy. At present, it was thought to be clinically stable and a slow recovery was anticipated over weeks to months (perhaps an incomplete recovery). Anteroposterior and lateral radiographs of her feet and ankles showed no acute bony injury (figures 4 and 5). An electromyography was thought worthwhile when she was medically suitable and less oedematous to guide prognosis, although a demyelinating neuropathy was deemed unlikely. Her neurological signs were monitored closely for any evidence of new nerve involvement which would prompt further investigation.

Table 2 Macroscopically, clear yellow fluid was evident.

CSF bottle 1		CSF bottle 3	
Clear yellow fluid		Clear yellow fluid	
WCCs	290/mm ³	WCCs	976/ mm ³
RBCs	320/mm ³	RBCs	745/ mm ³
		90% polymorphs	
		No organisms seen	

Ninety per cent polymorphs were present.
CSF, cerebrospinal fluid; RBCs, red blood cells; WCC, white cell count.

Box 1 Bone marrow biopsy results

<1 megakaryocyte per low power field
 Normal trabecular bone
 Significant interstitial plasmacytosis
 Immunohistochemistry: CD18 positive and CD20 negative
 κ light chain restricted
 tumour burden of 60%
 CD5 and CD3 showed a moderate interstitial reactive response

Figure 3 MRI spine. Further investigation with an MRI spine (axial images obtained between L1 and S1) revealed preserved vertebral height and alignment.

OUTCOME AND FOLLOW-UP

Her rectal swab cultured *Enterococcus faecium*, a strain of enterococcus resistant to vancomycin. She developed loose stools and *Clostridium difficile* was not detected. Cultures were negative for *Salmonella* sp, *Shigella* sp, *Escherichia coli* 0157 and *Campylobacter*. *Giardia* and *Cryptosporidium* were not detected. She was isolated in a side room. Her haemoglobin dropped to 69 g/L and she required a transfusion of 1 unit of packed red blood cells. The pain in her ankles improved with the addition of gabapentin. Following cycle 1 of velcade, she developed abdominal pain. A CT abdomen and pelvis with contrast demonstrated

Figure 4 Radiograph of her left foot. There was no acute bony injury.

Figure 5 Radiograph of her left ankle. No acute bony injury was evident.

pancolitis. The morphology of the colitis indicated pseudomembranous formation suggestive of *C. difficile*. Sigmoid and rectal biopsies were performed and the glandular architecture and goblet cells were preserved. Changes to suggest a pseudomembranous colitis were not seen. However, her stool culture was positive for *C. difficile*. She was refractory to medical management and developed PR bleeding and shock. A repeat CT abdomen and pelvis with contrast demonstrated mucosal thickening throughout the

colon with a little more distension of the transverse colon but no intramural or free gas is seen. There was no perforation. She is waiting to start cycle 2 of her chemotherapy.

DISCUSSION

The first case of multiple myeloma was described in the medical literature in 1884 by Solly.¹ The term 'Kahler's disease' was subsequently introduced to describe myeloma following a report by Professor Kahler of Prague.² Multiple myeloma, a plasma cell malignancy characterised by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin, accounts for 12% of haematological malignancies. Indeed, it is the 17th most common cancer in the UK, occurring more frequently in men and those of African-Caribbean origin.³ The plasma cells proliferate in the bone marrow and often result in extensive skeletal destruction with osteolytic lesions, osteopenia and/or pathological fractures. The median age at presentation is 66 years, with 10% of patients <50 years and 2% <40 years.⁴ Myeloma presents with non-specific symptoms, thus leading to a delay in diagnosis, ultimately resulting in early morbidity and mortality. Although effective treatments have been developed over the past 15 years, myeloma still remains an incurable disease and its management is both complex and challenging. So how does myeloma present? Its clinical presentation covers a wide spectrum of diseases and includes a normocytic, normochromic anaemia in 75% of cases, bone pain in 60% of cases at diagnosis, most commonly affecting the back and chest, with the extremities less frequently involved, fatigue and weight loss.⁴ In 1/5th of cases, renal failure may be the presenting manifestation, as in our reported case, with light chain nephropathy and hypercalcaemia the main causes. Affected individuals are at a high risk of infection, especially from streptococcal pneumonia, as demonstrated in our case, and Gram-negative organisms. Less common but emergency presentations include spinal cord compression and severe hypercalcaemia in one-third of cases. As in our case, peripheral neuropathy affects up to 20% of patients with multiple myeloma at diagnosis, increasing in frequency during the course of treatment, with velcade and thalidomide resulting in 75% of cases. Individuals describe pain, burning and tingling. It is postulated that the monoclonal (M) proteins can damage nerves resulting in peripheral neuropathy as well as metabolic changes resulting from the accumulation of bortezomib in the dorsal root ganglia cells; mitochondrial-mediated dysregulation of calcium homeostasis and dysregulation of neurotrophins may also contribute. However, the aetiology of peripheral neuropathy is multifactorial and may involve hereditary, metabolic, infectious, inflammatory, toxic and traumatic causes. Peripheral neuropathy may also be present in connective tissue and autoimmune diseases such as systemic lupus erythematosus, polyarteritis nodosa and systemic vasculitis. It is important to consider alcohol, HIV, diabetes and uraemic neuropathy in the differential diagnosis. According to the literature, 97% of patients with multiple myeloma will have a monoclonal (M) protein produced and secreted by the malignant plasma cells, which can be detected by protein electrophoresis of the serum and/or of an aliquot of urine from a 24 hour collection. The malignant plasma cells can produce immunoglobulin heavy chains plus light chains, light chains alone, or neither combined with immunofixation of the serum and urine.⁴ Urinalysis for myeloma cast nephropathy is typically negative for protein. Rouleaux formation, seen in patients with a raised protein level, is the most frequent finding on peripheral smear (>50%), followed by leucopenia (20%) and thrombocytopenia (5%). The majority of myeloma tumours have genetic

abnormalities that can be detected with sensitive molecular genetic techniques, such as interphase fluorescent in situ hybridisation (FISH). National Institute for Health and Care Excellence (NICE) advises performing FISH on CD138-selected bone marrow plasma cells to identify the adverse risk abnormalities t(4;14), t(14;16), 1q gain, del(1p) and del(17p)(TP53 deletion). These abnormalities should be used alongside the International Staging System scores to identify people with high-risk myeloma.³ The following laboratory studies are recommended as an initial screen for myeloma: complete blood count including a peripheral smear, serum calcium, creatinine, albumin, lactate dehydrogenase, β 2 microglobulin and C reactive Protein. Serum-free monoclonal light chain analysis and serum protein electrophoresis are required as well as routine urinalysis and a 24-hour urine collection for electrophoresis and immunofixation. Furthermore, bone marrow aspiration and biopsy, with immune phenotyping, cytogenetics and FISH, are advocated. It is important to request morphology to determine plasma cell percentage and flow cytometry to determine plasma cell phenotype.³ NICE also advocates performing immunohistochemistry (including Ki-67 staining and p53 expression) on the trephine biopsy to identify plasma cell phenotype and give an indication of cell proliferation, to provide further prognostic information.³ A metastatic bone survey with plain radiographs should be performed. The International Myeloma Working Group criteria for the diagnosis of multiple myeloma emphasise the importance of end organ damage, often recalled by the acronym CRAB (calcium, renal insufficiency, anaemia and bone lesions; table 3).⁴ End organ damage is suggested by increased plasma CRAB.⁵ Conventional skeletal surveys reveal punched-out lytic lesions (60%), osteopenia, osteoporosis or fractures (80%). The most frequent sites of involvement include areas with active haematopoiesis, such as the vertebral bodies, skull, thoracic cage, pelvis, proximal humeri and femora. It is now established that positron emission tomography (PET), combined with low dose CT, exhibits a higher diagnostic sensitivity and specificity over the conventional radiographic skeletal survey.⁵ PET/CT is indeed a valuable imaging tool for the assessment of extra-medullary involvement. Regelink's systematic review supports the International Myeloma Working Group guidelines, which recommend that whole body CT can replace whole body X-ray.⁶ However, additional radiographs of the skull and ribs are advised as they are often underdiagnosed by modern imaging.⁷ The differential diagnosis of multiple myeloma includes monoclonal gammopathy of undetermined significance, smouldering multiple myeloma, Waldenstrom macroglobulinemia, solitary plasmacytoma, primary amyloidosis and metastatic disease. In the late 1960s, mephalan-prednisolone was introduced for the treatment of multiple myeloma. In the subsequent 30 years, small increases in the overall response rate were

Table 3 End organ damage is suggested by increased plasma calcium, renal insufficiency, anaemia and bone lesions

Anaemia	Haemoglobin <10 g/L
Hypercalcaemia	Serum calcium >2.75 mmol/L
Renal insufficiency	Estimated or measured creatinine clearance <40 mL/min
Bone lesions	One or more osteolytic lesions > 5 mm in size on skeletal radiography, MRI, CT or PET/CT.
Presence of a biomarker	>60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of 100 or more or MRI with more than one focal lesion.

PET, positron emission tomography.

observed with vincristine, doxorubicin, dexamethasone and cyclophosphamide. The next step forward in the treatment armamentarium was the use of high-dose mephalan followed by autologous stem cell transplant in young patients, with mephalan-prednisolone remaining the standard of care in the elderly.⁸ Significant developments have occurred in recent years with the availability of novel agents including arsenic trioxide and farnesyltransferase inhibitor 2-methoxyestradiol.⁹ Over the past decade, with the introduction of immune-modulating drugs such as thalidomide, lenalidomide, pamlidomide and protease inhibitors such as bortezomib and carfilzomib, the treatment of myeloma has been transformed. Like all therapeutic agents, appropriate dosing based on metabolism and clearance is important to maintain efficacy while avoiding toxicity. The first-in-class protease inhibitor, bortezomib (Velcade), is commonly used in all myeloma disease settings. It has been extensively studied either alone or in combination with other agents for the treatment of myeloma and can be recommended for both previously treated and relapsed/refractory cases. Scott performed a systematic review and meta-analysis to assess the clinical benefits and side effects of bortezomib. Their analysis demonstrated that patients with myeloma receiving standard bortezomib benefit in terms of overall survival, progression-free survival and response rates.¹ However, further evaluation of protease inhibitors and more studies on quality of life are required. Indeed, randomised controlled trials have demonstrated enhanced survival outcomes and delayed disease progression with immune-modulatory drug-based maintenance therapy.⁴ Using meta-analysis, Wang X compared novel-based regimens using bortezomib, thalidomide and lenalidomide in patients with myeloma for safety and efficacy. This study showed greater benefit in terms of progression-free survival of all subgroups, irrespective of whether the patient received autologous stem-cell transplantation.⁶ However, compared to the control group, a higher proportion of adverse events including neutropenia, thrombocytopenia, peripheral neuropathy and thrombosis occurred in the novel agent groups.⁶ According to Lyu⁸, thalidomide, an immune-modulatory and antiangiogenic 4 drug, appears to improve the overall survival of elderly and/or transplant-ineligible patients with multiple myeloma when it is added to standard mephalan and prednisolone therapy. Gao conducted a meta-analysis of two randomised, double-blind, placebo-controlled studies involving 691 patients. Their results indicated that single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous haematopoietic stem cell transplantation was effective in the improvement of progression-free survival. However, a higher rate of peripheral neuropathy was recorded.⁷ In 2015, Wang performed a meta-analysis of the antitumour effect and safety of bisphosphonates in the treatment of multiple myeloma. All bisphosphonates were effective at reducing skeletal-related events and were tolerated well. Only zoledronic acid showed a clear advantage regarding overall survival.¹⁰ Geng performed a meta-analysis of RCTs to evaluate the efficacy of ibandronate in the treatment of skeletal-related events and bone pain in metastatic bone disease or myeloma. The incidence of adverse renal events was significantly lower in the ibandronate group and a reduction in the incidence of skeletal-related events and bone pain relative to placebo was observed.¹¹ As recently as 2015, Yu *et al* conducted a meta-analysis to quantitatively evaluate the clinical efficacy of chemotherapy with or without plasmapheresis in the treatment of myeloma. Their results showed that plasmapheresis used as an adjunct to chemotherapy had a benefit in the management of dialysis-dependent patients with multiple myeloma with renal

failure, with a lower 6-month dialysis-dependent ratio observed (15.6% vs 37.2%).¹² Cytogenetic abnormalities have emerged as the major novel prognostic factors in myeloma. Yu and co-workers performed a meta-analysis investigating the association between three chromosomal abnormalities t(4;14), del (17p) and Amp (1q21). The aforementioned cytogenetic abnormalities had low overall survival and progression-free survival, providing globally quantifiable confirmation of their adverse prognostic value.¹³ According to the British Committee for Standards in Haematology (BCSH), in 2006, guidelines on the diagnosis and management of multiple myeloma were published.⁵ NICE published guidance (NG35) in February this year on the diagnosis and management of myeloma.³ Knopf states that bortezomib retreatment is well tolerated and appears efficacious in relapsed patients.² Bortezomib, in combination with dexamethasone, or with dexamethasone and thalidomide, is recommended by NICE for the induction of treatment for adults with previously untreated myeloma.³ Furthermore, thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if: high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.³ If a bortezomib-based combination regimen is unsuitable for people with untreated, newly diagnosed, myeloma-induced acute renal disease, consider immediately starting a thalidomide-based and dexamethasone-based combination regime.³

Learning points

- ▶ Multiple myeloma is characterised by the neoplastic proliferation of immunoglobulin-producing plasma cells.
- ▶ The importance of considering multiple myeloma in the differential diagnosis in patients presenting with bone pain with lytic lesions on routine skeletal films, hypercalcaemia, acute renal failure due to cast nephropathy and negative protein on urinalysis, unexplained anaemia and an increased total serum protein concentration and/or the presence of a monoclonal protein in the urine or serum.
- ▶ Furthermore, as in our reported case, peripheral neuropathy may be a presenting symptom in 20% of patients at diagnosis.
- ▶ Serum protein electrophoresis along with immunofixation and a serum free light chain assay should be performed.
- ▶ chain assay should be performed. If a diagnosis of myeloma is rendered, a 24-hour urine collection for electrophoresis and immunofixation must be carried out.
- ▶ The most frequent findings on peripheral smear are rouleaux formation (>50%), leucopenia (20%) and thrombocytopenia (5%).
- ▶ A bone marrow aspirate and biopsy with immunophenotyping, conventional cytogenetics and in situ hybridisation (FISH) are key components to the diagnosis of multiple myeloma.

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