CASE REPORT

Coexistent osteoporosis and multiple myeloma: when to investigate further in osteoporosis

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SUMMARY

Osteoporosis commonly causes vertebral collapse fractures. We present a patient with multiple vertebral fractures in the context of severe osteoporosis, who, in the course of investigation for intractable spine and hip pain, was found to have an IgA myeloma. At 2 months post diagnosis, she was discharged home to continue outpatient chemotherapy.

BACKGROUND

While osteoporotic fractures can cause severe spinal pain, failure of the pain to resolve over the expected time course should prompt further investigation. IgA myeloma is often not apparent on serum electrophoresis which can significantly delay the diagnosis of this condition. Even when patients have severe bone pain due to myeloma, other features of this may be absent early in the condition.

CASE PRESENTATION

A previously fit and well 74-year-old pub landlady presented to her local accident and emergency department, with an episode of acute back pain. X-ray of the lumbar spine showed a vertebral fracture at L3 (figure 1). Treatment with vitamin D, calcium supplements and alendronic acid were started, and follow-up with her general practitioner (GP) advised. However, she had ongoing back pain and after 2 months this prompted her GP to refer her on to rheumatology for further investigation and treatment. Dual-energy X-ray absorptiometry (DEXA) at this time showed osteoporotic bone density (left neck of femur T -2.1 and anteroposterior (AP) spine mean L1-L4 T -3.4).

Five months after the acute episode, the patient was seen in a rheumatology outpatient clinic. By then her back pain was much improved, although she was still taking oxycodone and naproxen analgesia. Risk factors for osteoporosis included gender, age, Caucasian ethnicity, early total abdominal hysterectomy and high alcohol consumption. Baseline bloods were normal apart from a mild hypercalcaemia (table 1); myeloma screen with serum electrophoresis did not show a monoclonal band and urinary Bence-Jones protein was negative. In clinic, the vitamin D was stopped due to concerns it may exacerbate the hypercalcaemia.

Four weeks later, the patient developed worsening back pain and MRI of the spine confirmed acute vertebral fractures at T9, T11 and T12, with persistent loss of height at L3, but no other pathological features were seen (figure 2). All images

Figure 1 Plain film of the lumbar spine at initial presentation.

were reviewed by a musculoskeletal radiologist and no secondary causes were identified. A repeat DEXA scan was requested with a view to starting teriparatide (a parathyroid hormone analogue). This showed deterioration of bone density in the intervening 6-month period (left neck of femur T score -3.0, AP spine mean L2-L4 of T -3.4) despite bisphosphonate therapy. Following further blood testing, teriparatide was introduced, 10 months after the initial fracture occurred.

A screen for malignancy with CT of the chest and abdomen, and a colonoscopy, was clear. During this time, the patient also developed a very severe pain in her right hip; plain films were normal; CT of the hip showed no fracture and MRI of the pelvis demonstrated only mild bone marrow oedema (figure 3).

Following persistent severe thoracic pain and hip pain the patient was admitted to hospital from clinic for further management, 12 months after her first vertebral fracture was identified.

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Table 1 Comparison of biochemical, haematological and renal values to institutional laboratory reference ranges at baseline May 2013, and on admission June 2014

Investigation	Baseline	Inpatient admission	Institutional reference range
Full blood count			
Hb, g/L	127	84	115–165
MCV, fL	95.4	100.8	80–98
Platelets, $\times 10^9$	118	107	150–400
WCC, $\times 10^9$	5.7	8.5	4–11
Neutrophils, $\times 10^9$	3.2	6.8	2–7.5
Lymphocytes, $\times 10^9$	1.8	1.1	1–4
Haematinics			
B12, ng/L	Not checked	156	200–1000
Folate, $\mu\text{g/L}$	Not checked	5.0	4–18
Endocrine function tests			
Parathyroid hormone, pmol/L	0.8	0.4	1.3–6.8
Free T4, pmol/L	Not checked	15.0	9.19
TSH μL	Not checked	0.77	0.3–5
Biochemical bone profile			
25 OHD, nmol/L	43	55	50–150
Corrected calcium, mmol/L	2.61	3.23	2.2–2.6
Phosphate, mmol/L	1.52	0.63	0.8–1.4
Magnesium, mmol/L	0.78	0.51	0.7–1.0
Albumin, g/L	41	33	38–50
ALP, IU/L*	92	103	25–115
Renal profile			
Urea, mmol/L	5.6	12.1	2–6.6
Sodium, mmol/L	140	146	135–147
Potassium, mmol/L	4.3	3.3	3.4–4.9
Creatinine, $\mu\text{mol/L}$	67	67	60–100
eGFR, mL/min	75	75	
Liver function tests			
GGT, μL	53	38	0–32
Other			
CRP, mg/L	<5	<5	0–10
Kappa:Lambda ratio		15.04	
κ chains		119	
$\beta 2$ microglobulin, mg/L		7.19	0–2.2
LDH		663	

All biochemical tests were conducted by the medical testing laboratory of Homerton University Hospital NHS Foundation Trust, London, UK.

*Significantly raised during admission. Highest value 316 IU/L end of June 2014.

ALP, alkaline phosphatase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; GGT, γ glutamyl transferase; LDH, lactate dehydrogenase; MCV, mean corpuscular volume TSH, thyroid-stimulating hormone; WCC, white cell count; 25 OHD, 25-hydroxyvitamin D.

Figure 2 MRI lumbar spine (T2 weighted) in December 2013.

INVESTIGATIONS

MRI of the whole spine on admission showed no significant change in known T9, T11, T12 and L3 fractures identified 6 months previously (figure 4).

Biochemical investigations on admission identified worsening hypercalcaemia (corrected Ca^{2+} 3.23 mmol/L normal range (NR) 2.2–2.6), stable renal impairment (estimated glomerular filtration rate 75 mL/min) and macrocytic anaemia (haemoglobin 84 g/L, NR 115–165, mean corpuscular volume 100.8 fL NR 80–98), which had worsened considerably in recent months. Serum vitamin B12 was low at 156 ng/L (NR 200–1000) but holotranscobalamin was normal (49.6 pmol/L, NR 35–70), as was the functional marker methylmalonic acid (0.22 $\mu\text{mol/L}$, NR 0–0.29) (table 1).

The hypercalcaemia was attributed to treatment with teriparatide, which was stopped and the calcium initially normalised, but then it elevated again after 3 weeks.

With no clear cause of the patient's deterioration, and no explanation for the right hip pain, previously eliminated

Figure 3 Short tau inversion recovery (STIR) MRI showing bone marrow oedema bilaterally in hip joints. STIR, short tau inversion recovery.

diagnoses were revisited. Myeloma screen at the time of first presentation 7 months earlier showed a reduced γ -globulin region on serum electrophoresis with absent Bence-Jones protein but raised β -2 globulins. Repeat serum electrophoresis during the admission produced an equivocal result and Bence-Jones protein was reported as a possible abnormal band. Serum immunofixation confirmed IgA κ paraprotein (4.0 g/L) in the β -2 globulin region and β 2-microglobulin remained high at 5.49 mg/L (0–2.2 mg/L). This positive myeloma screen prompted a skeletal survey which identified multiple lytic lesions in keeping with a diagnosis of myeloma (figure 5). Retrospective review of MRI light of the possible diagnosis revealed high signal in the right neck of femur, in keeping with a lytic lesion. Finally, bone marrow aspirate findings of 32% plasma cells confirmed the diagnosis of multiple myeloma.

DIFFERENTIAL DIAGNOSIS

- Osteoporotic vertebral fractures with concurrent anaemia.
- Hypercalcaemia secondary to teriparatide.

Figure 4 MRI lumbar spine (T2 weighted) in June 2014.

Figure 5 Lytic lesions seen throughout the humerus on plain film.

TREATMENT

On diagnosis of multiple myeloma from peripheral blood and urine investigations, the patient underwent confirmatory bone marrow biopsy and was transferred to a tertiary centre for chemotherapy.

OUTCOME AND FOLLOW-UP

At 2 months from her diagnosis the patient was discharged to her home from the tertiary centre, where she had received dexamethasone and bortezomib for her myeloma alongside radiotherapy to her right hip. Her pain had almost completely resolved.

DISCUSSION

This case further clarifies the unique diagnostic difficulty in frail patients who might have myeloma. Up to 90% of patients with multiple myeloma will develop bone disease, specifically osteoporosis or lytic lesions, and bone pain is one of the commonest presentations of the disease.¹ The principal mechanism for this is thought to be dysregulation of bone turnover via changes in the bone marrow microenvironment. Traditionally, a diagnosis of myeloma requires evidence of a serum and/or urine monoclonal protein band, bone marrow plasma cell population >10%, and evidence of myeloma-related organ/tissue impairment.² Typically, abnormal serum electrophoresis alerts the clinician to the presence of myeloma. However, this may be difficult to interpret in IgA myeloma since IgA migrates on the electrophoresis gel in a region where it may be obscured by other protein bands, particularly in a poorly clotted sample of blood where transferrin, fibrinogen and C3 can be high. In addition to this, IgA myeloma protein bands can be more diffuse than other immunoglobulins because they are often heavily glycosylated.³ Plain films can underestimate diagnosis and staging with a high false negative rate of 30–70%,⁴ and MRI is much more sensitive but findings can be non-specific.^{5 6}

Several case reports to date have identified patients in whom myeloma developed following treatment with teriparatide for

osteoporosis.^{7 8} Use of recombinant parathyroid hormone is contraindicated in patients with known malignant bone disease.⁹ In myeloma there is a continuous imbalance between osteoclast and osteoblast activity, with increased RANKL expression in osteoblasts; this leads to bone resorption. Teriparatide treatment produces a pulsatile influence on RANKL, which causes osteoblast activation and increased bone formation. It is thought that this extra RANKL stimulation in patients with monoclonal gammopathy of unknown significance (MGUS) or smouldering myeloma might be harmful.

It is important to continually review the progress of patients with a 'known' diagnosis. Osteoporosis is extremely common, and one in three women over 50 years of age will experience a fragility fracture,^{10 11} of which vertebral collapse is a common example.¹² While there may be residual pain months after the fracture, the severe initial pain usually resolves in the first few weeks.¹³ If a patient fails to follow their expected course, it is necessary to revisit the initial diagnosis and consider alternatives. In atypical cases where metabolic bone disease is suspected, a bone biopsy may be indicated. Specific to this case, it remains difficult to tell whether myeloma was present from the initial vertebral fractures (despite negative screening tests) or whether it developed superimposed on existing osteoporosis.

Finally, this case highlights the importance of Occam's razor: a single unifying diagnosis is better than multiple individual, but reasonable, hypotheses. In this case, the patient presented with back pain in the face of 'known' osteoporosis. She also had a macrocytic anaemia (without evidence of B12 or folate deficiency), hypercalcaemia (but was being treated with teriparatide) and mild renal impairment, which is not uncommon in this patient group. During the course of her admission, she developed a hospital acquired pneumonia, which was assumed to be related to her immobility and thoracic pain, although it could also be linked to immunocompromise. All of these features can be explained by a diagnosis of multiple myeloma. The vigilant clinician should routinely review the patient holistically as each new problem arises, and be prepared to review the initial diagnosis.

This patient was not involved in a clinical trial.

Patient's perspective

I feel if I had been diagnosed earlier I would have started treatment sooner, and maybe I would not be in a wheelchair now.

Learning points

- In patients with persistent bone pain following osteoporotic fracture, consider concurrent pathology.
- Low-secreting IgA myeloma can cause diagnostic difficulty.
- Use of teriparatide has been linked to higher incidence of myeloma, and this warrants further research.

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Competing interests None declared.

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