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A Diagnostic Dilemma In An Elderly Patient With Bone Pains

D H C Wong, P Sivaraman, T C Liu, S Das De

ABSTRACT

A 61-year-old patient presented with multiple bone pains. Biochemical, haematological and radiological investigations initially suggested a diagnosis of osteomalacia because of the presence of hypocalcaemia and looser zones. There were also multiple lytic bone lesions and bone scan showed multiple hot spots suggesting multiple bone secondaries. The key investigation in this case was examination of the bone marrow.

Keywords: Bone pain, osteomalacia, lytic bone lesions.

CASE DISCUSSION

History: A 61-year-old Malay man was referred from the Polyclinic with a complaint of right hip pain. He gave a history of chronic back pain of 10 years duration. For the past few years he also had pain in the right thigh and the right foot. The right thigh pain was worse on getting up from the sitting position.

Clinically the patient appeared to be in good general condition. There was slight back pain on extension of the spine. The SLR was 90/90 and there was no neurological deficit. Examination of the hips were normal.

The initial clinical diagnosis was spinal stenosis. Radiographs of the lumbosacral spine was done (Figs 1a and 1b).

Department of Orthopaedic Surgery
National University Hospital
5 Lower Kent Ridge Road
Singapore 119074

D H C Wong, MBBS, FRCS (Glas)
Registrar

S Das De, FRCS (Engl), FRCS (Orth), (Edin), Mch (Orth)
Associate Professor

Department of Medicine
National University Hospital

P Sivaraman, MBBS, MRCP, M Med
Registrar

Department of Laboratory Medicine
National University Hospital

T C Liu, MBBS, MRCP, MRCPath
Senior Registrar

Correspondence to:
Dr D H C Wong

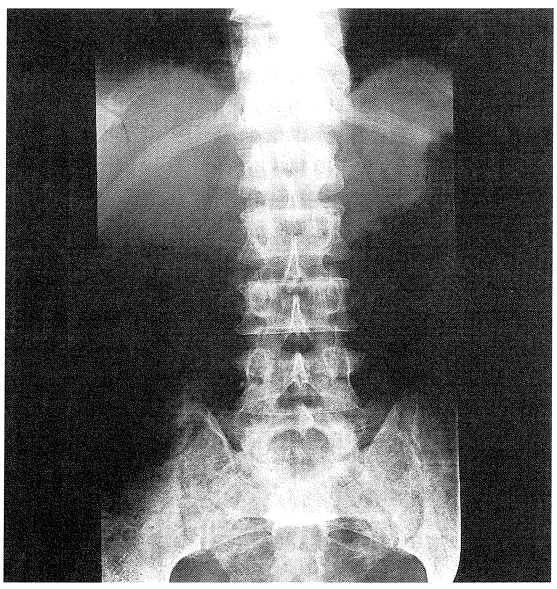

Fig 1a - Radiograph of the lumbosacral spine (AP)

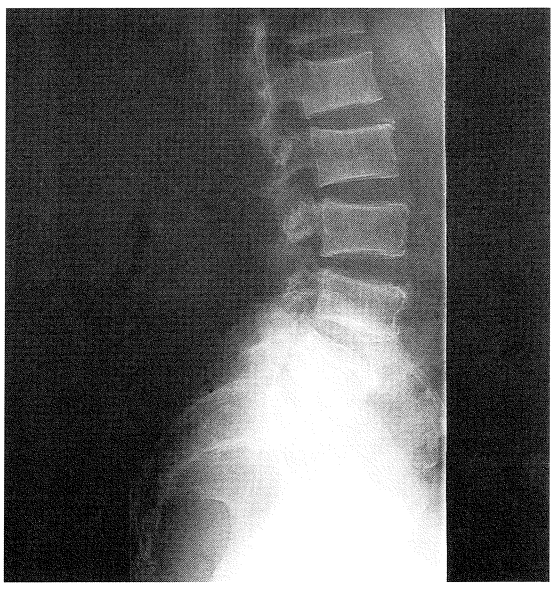

Fig 1b - Radiograph of the lumbosacral spine (lateral)

Question: How would you describe the radiological findings?

Answer: The alignment of the spine appears satisfactory. Osteophytes are present in the lower thoracic spine and in the lumbar vertebral bodies, compatible with spondolysis. What is striking are the multiple areas of osteopenia and a pseudofracture of the right 11th rib. This would suggest osteomalacia.

History: Blood investigations were done and the patient was reviewed after one week. The results of the investigations were as follows:

Full blood count:	Total white	5.81 x 10^9/L	
	Haemoglobin	13.1 g/dL	
	Platelets	144.0 x 10^9/L	
	ESR	15 mm/hr	
Renal panel:	Urea	6.5 mmol/L	(2.5 - 7.5)
	Sodium	140 mmo/L	(135 - 150)
	Potassium	3.6 mmol/L	(3.5 - 5.0)
	Chloride	106 mmo/L	(95 - 105)
	Creatinine	228 µmo/L	(65 - 125)>
Bone panel:	ALP	418 u/L	(40 - 130)>
	Calcium	2.05 mmol/L	(2.15 - 2.55)<
	Ca++	0.84 mmol/L	(1.15 - 1.35)<
	Phosphate	0.81 mmol/L	(0.85 - 1.45)<

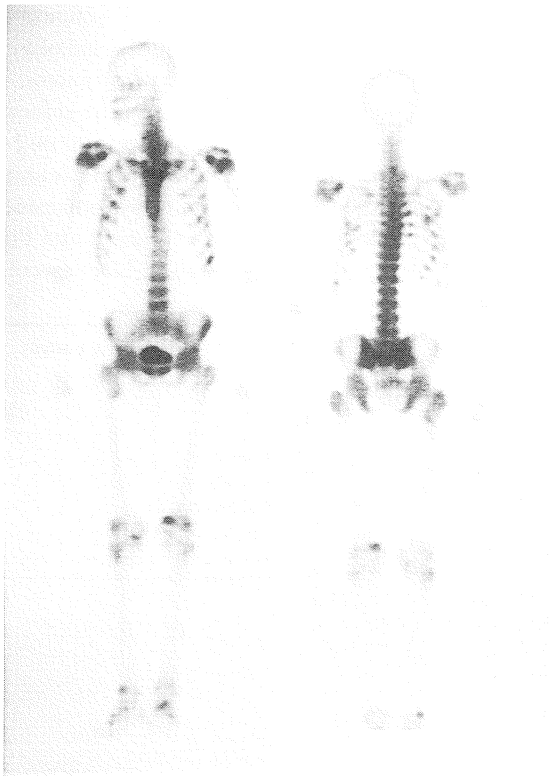

Fig 2 - Bone Scan

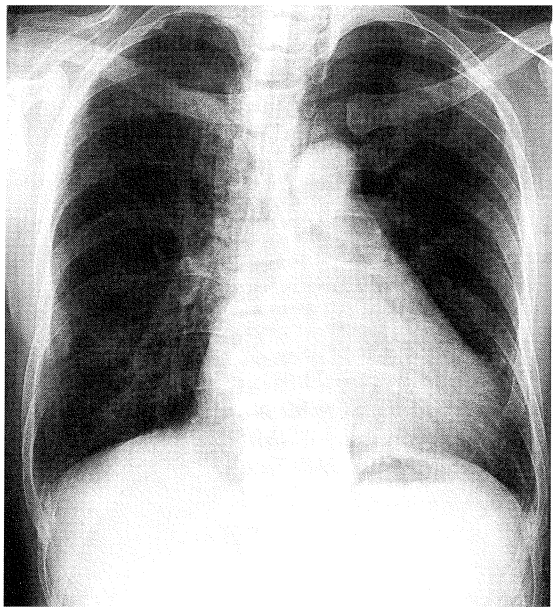

Fig 3 - Radiograph of the chest

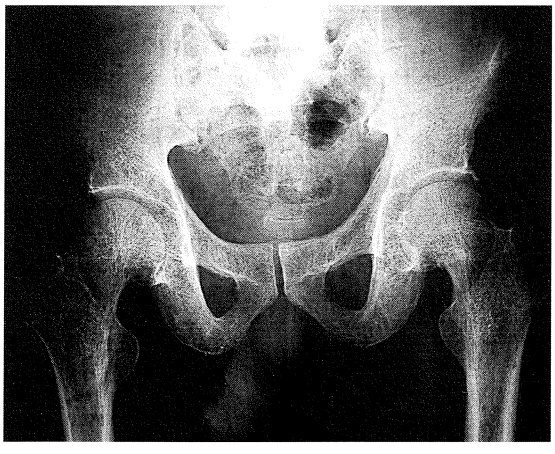

Fig 4 - Radiograph of the pelvis and proximal femur

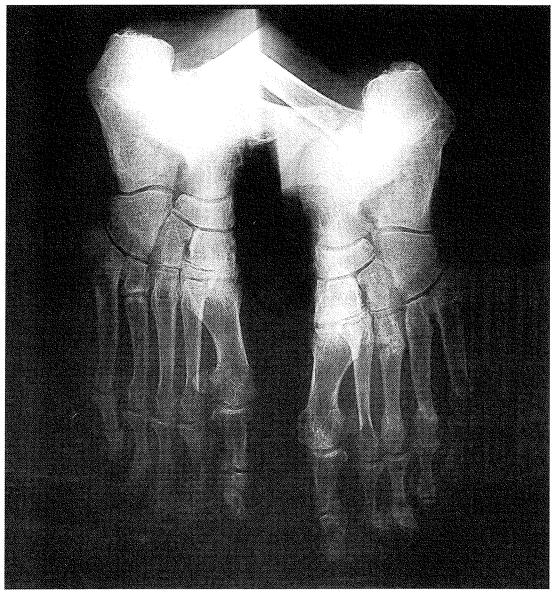

Fig 5 - Radiographs of the feet

Question: Can you comment on the blood investigations?

Answer: This patient has several abnormal results. The elevated serum creatinine level would suggest mild to moderate degree of renal insufficiency though serum urea is not elevated. It is difficult at this stage to tell whether it is acute or chronic renal insufficiency and further history, examination and investigations would be helpful. Serum alkaline phosphatase (ALP) is about 3 to 4 times above the upper limit of normal. It would be useful to do GGT (gamma-glutamyl transferase) and bilirubin levels to exclude hepatic pathology for the raised ALP. However, based on clinical grounds the elevation is probably of bone origin. This patient has severe hypocalcaemia (ionised) and low serum phosphate levels. This is not compatible with the degree of renal impairment. In depressed renal function when the creatinine falls below 30 to 50mm ml/min the production of 1,25 dihydroxyvitamin D3 would be impaired. There would usually be phosphate retention. The degree of hypocalcaemia is also not expected usually with the degree of renal function. Furthermore, hypophosphatemia is not usual in renal impairment unless there is significant proximal renal tubular acidosis. All of these would point to an etiology other than renal osteodystrophy causing the hypocalcaemia and hypophosphatemia.

History: The patient was admitted on 17 May 1996 for further investigations. He complained mainly of right thigh pain for the past 3 years with difficulty getting up from squatting or sitting position. He also had bilateral rib pains for the past 5 years. He had no night pains or fever but had gradual weight loss of 15kg over the past 10 years. His bowel and urinary functions were normal.

He has a history of diabetes for the last 13 years. He also has mitral stenosis with atrial fibrillation and ischaemic heart disease with myocardial infarct 10 years ago. Clinical examination was essentially normal. The bone scan and radiographs of the chest, pelvis and feet were shown on Figs 2, 3, 4 and 5.

Question: Based on the radiological findings, what is your diagnosis?

Answer: The bone scan showed multiple hot spots in the ribs, proximal humeri, pelvis, bilateral proximal femur and the foot. These hot spots correspond to areas of pseudofractures (Looser zones) in the ribs and both feet. These findings are pathognomonic of osteomalacia. However, the multiple lytic lesions in the pelvis and bilateral proximal femur are suggestive of malignancy, possibly multiple secondaries or myeloma.

History: The patient was referred to the endocrinologist for assessment and results of further blood investigations done were as follows:

Full blood count:	WBC	7.56 x 10^9/L	
	Hb	12.5 g/dL	
	Platelet	161 x 10^9/L	
	ESR	19 mm/hr	
Thyroid function:	Free T4	10.8 pmol/L	(12.0 - 24.0)
	TSH	2.10 mU/L	(0.40 - 4.00)
	Calcitonin	<4.7 pmol/L	(4.7 - 14.6)
	PTH	84.4 pg/mL	(10 - 65)
Bone panel:	ALP	341 U/L	(40 - 130)
	Calcium	1.97 mmol/L	(2.15 - 2.55)
	PO_4	0.90 mmol/L	(0.85 - 1.45)
Liver function:	Normal		
	Serum Albumin	46 g/L	
24 Hr Urinary Study:	Creatinine Clearance	23.31 ml/min	
	24 Hr urine calcium	1.62 mmol/day	
	24 Hr PO_4	2.40 mmol/day	
	24 Hr UTP	4.5 g/day	

Question: How would you interpret these laboratory results?

Answer: This patient has longstanding diabetes mellitus which could account for his renal dysfunction but there are severe inconsistencies. Before I comment on that let us look at the ALP again which is probably of bone origin as the GGT (LFT) is normal. To my understanding calcitonin is only useful if the levels are high when one suspects medullary carcinoma of the thyroid. Thus a low level is difficult to interpret.

The elevated parathyroid hormone with low calcium and phosphate would be compatible with a metabolic bone disease like osteomalacia. What is interesting is the heavy proteinuria (in the nephrotic range) and the impaired creatinine clearance. This patient has diabetes mellitus for more than 10 years and this could cause diabetic nephropathy explaining the heavy proteinuria. However, it is unusual to get a normal high albumin in the context of nephrotic range proteinuria from diabetic nephropathy. This would suggest that the proteinuria is not due to a generalised protein loss via the kidneys but a semi-selective loss. Tubular proteinuria (from increased secretion) per se would not cause such levels. The only explanation would be 'overflow proteinuria' and multiple myeloma would be an important differential. Generally in multiple myeloma, the ESR would be elevated and low or normal ESR is unusual but can be seen in light chain disease. Either multiple myeloma or amyloidosis can cause renal dysfunction with severe proximal renal tubular acidosis and osteomalacia explaining most of this patient's problems. However, I would favour amyloidosis of the kidney associated with light chain disease. A renal biopsy would be interesting but probably avoided because of the bleeding risks.

History: A myeloma panel was done and the result is shown as Table I and Fig 6. Bone marrow aspirate and trephine biopsy were also done (Fig 7).

Table I - Myeloma panel

IgA	1.07	(0.80 - 4.00)
IgG	18.8	(5.00 - 15.00)>
IgM	0.40	(0.80 - 2.00)<
Kappa	23.00	(5.50 - 13.50)>
Lambda	2.16	(2.90 - 8.90)<
Kappa/Lambda	10.62	(1.30 - 2.60)>
Serum electrophoresis	distinct band gamma zone	
Urine electrophoresis	dark beta-1 zone	

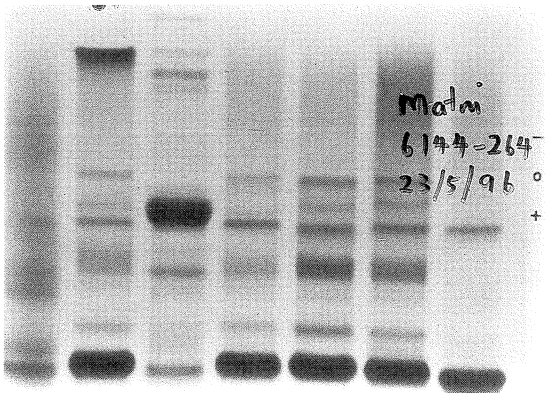

Fig 6 - Immunophoresis result

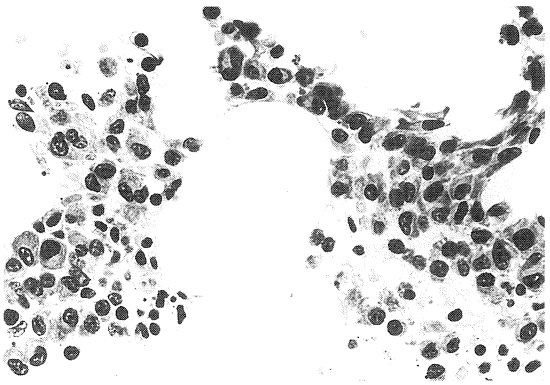

Fig 7 - Bone marrow biopsy

Question: What is your diagnosis based on these results?

Answer: The major diagnostic clue is the presence of multiple lytic bone lesions. The differential diagnosis is largely between metastatic bone disease and myeloma. The key investigations are an examination of the bone marrow aspirate as well as a trephine biopsy for the presence of plasma cells or other malignant cells.

The bone marrow in this instance showed scattered clusters of plasma cells. The numbers were not high and comprising of 18% of the nucleated cells present in the bone marrow. A small number of the plasma cells had atypical features.

The moderate level of plasmacytosis does not exclude a reactive state where there is a polyclonal accumulation of plasma cells secondary to a chronic inflammatory state. Clonality assays will be required to exclude this. As the cell in question is a functionally active cell with a readily measurable product, excreted serum immunoglobulins, clonality can be readily determined by regular serum protein electrophoresis and immuno-fixation. Plasma cells from the same clone will secrete identical immunoglobulins carrying the same electrical charge and molecular weight, thus producing a distinct, sharp band on electrophoresis as opposed to a polyclonal gammopathy where a smear is the result. Serum protein electrophoresis in this instance showed the presence of 2 bands which were immuno-fixed to reveal free kappa light chain band and another comprising of a IgG-kappa chain immunoglobulin. Identical bands were present in the urine.

The level of the immunoglobulins were not high and there was relatively more light chain than heavy chain production. This accounts for the normal ESR in the patient. An indolent monoclonal gammopathy referred to as 'Monoclonal Gammopathy of the Unknown Significance (MGUS)' is a relatively common occurrence amongst the elderly. These patients are largely asymptomatic and they remain well for many years to come. Treatment is not indicated. The gammopathy is largely static and only a small percentage of these will progress to a full-fledged myeloma. MGUS is always a consideration especially where the paraprotein level is low. To distinguish between myeloma and MGUS, it is helpful to look for indicators of possible 'malignant' behaviour in the patient:

(1) Is there evidence of bone marrow suppression?
(2) Is there an immune-paresis?
(3) Are there free urinary light-chains (Bence Jones protein)?
(4) Are there lytic skeletal lesions?

Evidence of 3 of the above conditions were present, bone marrow suppression being the only one absent.

The diagnosis present in this patient is therefore a myeloma. The hypocalcaemia and raised serum alkaline phosphatase is unusual. The biochemical evidence is suggestive of osteomalacia, presumably of renal origin. Where the usual manifestation of a myeloma kidney is a slow and progressive failure caused by the accumulation of myeloma casts within the tubules on the basement membrane, other rare forms of renal involvements have been described. In particular a Fanconi's syndrome with proximal tubular dysfunction and even rickets has been described. Amino-aciduria and acidosis are commonly associated. Renal biopsy would have shown abnormalities largely in the proximal tubules. Typically, this group of patients have no or mild skeletal lesions. As with the other forms of myelomatous kidney involvement, it is the free light chain excretion (usually kappa) that has been implicated in the pathogenesis.

Question: What is the prognosis?
Answer: Myeloma is presently an incurable disease. A good level of palliation, especially in the early stages, is however possible. Treatment is principally directed towards the prevention/relief of complications. Prognosis in myeloma had been shown to correlate well with the measured tumour (plasma cell) load. Indicators of this load (paraprotein level, haemoglobin and platelet counts, presence of lytic skeletal lesions) enable the disease to be staged for prognostication. The presence of lytic lesions and renal impairment in this patient categorises him as Stage IIB. Beta-2 microglobulin, a protein also formed during immunoglobulin product provides an alternative and independent means of staging. The expected median survival for Stage II with B_2M levels, 600 μg/L is 33 months.

SUMMARY

Bone pain in the elderly is a common condition encountered in the outpatient clinic and the differential diagnosis are myriad including metabolic bone disease, infection, arthritis and malignancy. Often several conditions may co-exist and a team approach by doctors of various specialities may be required before a definitive diagnosis can be made.

Multiple myeloma is the most common malignancy of bony origin in the elderly. It typically develops during middle age and affects multiple skeletal sites. Symptoms can include bone pain, fever, malaise and weight loss. The typical features of anaemia, hypercalcaemia and raised sedimentation rate may not be present as illustrated in this case. Radiologic findings may include classic osteolytic lesions but generalised osteopenia is a more common presentation.

The diagnosis of multiple myeloma has to be made by conventional examination of the bone marrow for plasmacytosis and demonstration of paraproteinemia by serum and urine immuno-electrophoresis.

FURTHER READING

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