Missed Diagnosis

Hypercalcaemia in a patient with non-secretory myeloma

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Summary: A case of severe hypercalcaemia associated with a non-secretory multiple myeloma in the absence of skeletal deposits is described. The importance of considering this condition in the differential diagnosis of hypercalcaemia in the elderly is discussed.

Introduction

Multiple myeloma is a relatively common cause of hypercalcaemia in the elderly and most clinicians would attempt to exclude this possibility by screening serum and urine for abnormal monoclonal immunoglobulin secretion. Occasionally diagnosis is complicated by myeloma cells not secreting monoclonal immunoglobulin in serum or urine. It has been recognized that this so called non-secretory myeloma can cause hypercalcaemia.^{1,2} Radiographs of the skeleton have, however, always previously shown the typical lytic lesions of multiple myeloma in these circumstances.

We report a case of severe hypercalcaemia associated with a non-secretory myeloma in which the only radiological abnormality was a severe osteopenia. Although multiple myeloma was considered, the absence of serum markers and lytic lesions on radiographs caused the diagnosis to be missed in life and this potentially treatable condition was only discovered at post-mortem.

Case report

A 71 year old retired male marine engineer presented with a 3-month history of increasing confusion, unsteadiness and constipation. In the 12 months prior to admission he had four episodes of cystitis and a solitary episode of painless haematuria. He had been treated for pulmonary tuberculosis 35 years previously and for many years had suffered from chronic airways limitation which had caused his early retirement from work.

On examination he was thin, dehydrated, extremely confused, disorientated and agitated. General examination was otherwise normal. Rectal examination revealed a large hard right lobe of the prostate gland which felt neoplastic. Initial investigations showed haemoglobin 14.0 g/l, ESR 69 mm/h, blood glucose, serum sodium and potassium were normal, blood urea 25.5 mmol/l, creatinine 225 μ mol/l, plasma calcium 3.82 mmol/l (normal range 2.20-2.70 mmol/l), plasma phosphate 0.97 mmol/l (normal range 0.80-1.4 mmol/l), alkaline phosphatase 19 U/l, albumin 36 g/l and globulins 41 g/l. Serum immunoelectrophoresis on two occasions showed no abnormal monoclonal band, serum immunoglobulin levels were, IgG 10.36 g/l (normal range 5.00-14.00 g/l), IgA 2.55 g/l (normal range 1.00-4.00 g/l), IgM 0.90 g/l (normal range 0.50-2.00 g/l) and when repeated were again within normal limits. No light chains were detected by immunoelectrophoresis of the urine. Serum parathyroid hormone levels were 65 pmol/l and 35 pmol/l (reference range 29-85 pmol/l), plasma calcium levels taken simultaneously were 3.82 mmol/l and 3.05 mmol/l respectively.

A chest X-ray showed extensive pulmonary calcification caused by healed tuberculous lesions but no other abnormality. Radiographs of skull, thoraco-lumbar spine, pelvis, wrists and fingers showed a diffuse osteopenia suggestive of severe osteoporosis. A technetium-99m isotope bone scan showed no evidence of increased uptake. Technetium-pertechnetate subtraction scan of the parathyroid glands showed no abnormal uptake. An ultrasound scan of the kidneys showed a normal left kidney but a right hydronephrosis and hydroureter with a small lower pole calculus. Intra-

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venous urogram confirmed the right hydronephrosis, the right kidney functioned poorly; in addition a large filling defect of the right side of the bladder suggestive of an enlarged prostate gland was revealed.

Trucut biopsies of the prostate gland were performed, histology showed a poorly differentiated keratinizing squamous cell carcinoma of the prostate.

The hypercalcaemia was treated initially with intravenous saline and frusemide. On which regime his plasma calcium fell to 2.97 mmol/l after 5 days, with improvement in clinical condition. Blood urea and creatinine returned to normal values.

Despite treatment with initially intravenous then adequate oral fluids, the plasma calcium gradually rose to 4.12 mmol/l over a period of 14 days. He was treated with an intravenous infusion of mithramycin 1.25 mg and oral phosphate-Sandoz 1 tablet twice daily. On this regime his plasma calcium fell to 2.30 mmol/l after 4 days. On oral fluids the calcium rapidly rose again to 3.5 mmol/l and intravenous mithramycin in the same dose was again infused, plasma calcium levels falling to normal levels. The patient developed bronchopneumonia at this stage and died 2 days later.

Post-mortem revealed that the immediate cause of death was an extensive bilateral bronchopneumonia. A large neoplasm arising from the prostate gland was occluding the right ureter and causing a right hydronephrosis. There were no macroscopic metastatic deposits. On histological examination the prostatic neoplasm was of an anaplastic type with squamous keratinizing features. The lungs contained a number of microscopic metastatic deposits of the prostatic tumour. Examination of the bone marrow from sternum and iliac crest revealed sheets of lymphoplasmacytoid cells typical of multiple myeloma (Figure 1).

Discussion

This man presented with hypercalcaemia, a not uncommon clinical problem in the elderly, and was found to have dual malignancies. He had a multiple myeloma which did not secrete monoclonal immunoglobulin fractions in serum or urine and a squamous carcinoma of the prostate gland. It seems likely that the hypercalcaemia was associated with the multiple myeloma rather than the carcinoma of the prostate, as approximately 20% of patients with multiple myeloma will develop hypercalcaemia at some point during the course of their illness,³ whereas it is rarely associated with neoplasms of the prostate gland.⁴ Squamous carcinoma of the prostate is responsible for between only 0.2% and

Figure 1 Vertebral bone marrow showing hypercellularity due to infiltration with normal and abnormal plasmacytes. The appearance is typical of myeloma. Haematoxylin & eosin: original magnification $\times 600$.

3%⁵ of all prostatic malignancies and there is only one published report of it being complicated by hypercalcaemia.⁶

Non-secretory multiple myeloma was first described in 1958,⁷ and a large review of 869 cases of multiple myeloma in 1975 suggested that only about 1% of cases do not secrete immunoglobulin in serum or urine.³ This indicates that the screening of elderly patients with hypercalcaemia for the presence of multiple myeloma by immunoelectrophoresis of serum and urine is sometimes fallible. Fortunately radiographic studies of the skeleton usually provide evidence of the presence of multiple myeloma by showing the typical punched out lytic lesions seen in the condition. Radiographs of thoracolumbar spine, pelvis, skull and hands of our patient showed evidence of a severe osteopenia but no evidence of lytic lesions or other clues of the presence of multiple myeloma. The technetium labelled isotope bone scan showed no evidence of increased uptake in this patient. Radionuclide imaging is relatively insensitive at detecting myeloma deposits in bone⁸ and radiography remains the primary method of screening for skeletal involvement by myeloma. The negative bone scan does however provide convincing evidence that the prostatic neoplasm has not metastasized to the skeleton.

Diffuse osteopenia has been described in secretory multiple myeloma but rarely in the non-secretory variety. A review of clinically documented cases of non-secretory multiple myeloma found 33 such subjects and described a further 2 cases;⁹ 31 of these had evidence of lytic lesions on skeletal radiographs and only 4 cases were found with

diffuse osteopenia alone; however none of these also had hypercalcaemia.

The presence of hypercalcaemia in association with non-secretory multiple myeloma in the absence of lytic lesions in bone is not surprising, and is explained by the way in which multiple myeloma causes bone resorption. It seems to be caused by the stimulation of osteoclasts by osteoclast activating factor,¹⁰ a group of monokine and lymphokine-like substances which are secreted by the malignant plasma cell¹¹ independently of immunoglobulin manufacture and act generally on the skeleton and not just locally at the site of bone destruction by myelomatous deposits.

This case describes a previously unreported association of hypercalcaemia secondary to non-

secretory multiple myeloma with diffuse osteopenia but more importantly emphasizes the need to consider non-secretory multiple myeloma in the differential diagnosis of hypercalcaemia in the elderly. We would particularly emphasize the need for bone marrow examination if the cause of the hypercalcaemia seems obscure, otherwise a potentially treatable condition may be missed.

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