SHORT REPORTS

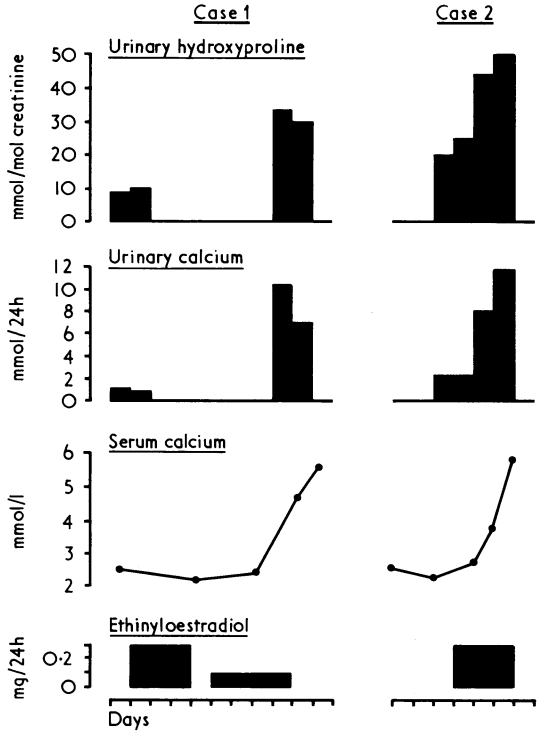
Fatal irreversible hypercalcaemia in breast cancer

Osteolytic bone metastases may cause excessive release of calcium from the skeleton and result in progressive, fatal hypercalcaemia.[1 2] Oestrogen treatment for metastatic disease may precipitate this.[3] We describe two patients who developed fatal hypercalcaemia within days of starting oestrogen treatment.

Case reports

Case 1—A 73-year-old woman was admitted to hospital with carcinoma of the breast, lymph node and liver metastases, and bilateral pleural effusions. She had no pain, and marrow aspirate and skeletal *x*-ray appearances were normal, but the bone scan showed multiple bone metastases. Serum calcium was 2·4 mmol/l (9·6 mg/100 ml) and serum alkaline phosphatase 145 IU/l. Ethinyloestradiol 0·3 mg/day caused nausea, malaise, and drowsiness but the serum calcium remained normal (2·15 mmol/l; 8·8 mg/100 ml). She recovered after withdrawal of the hormone, which was restarted at 0·1 mg/day. Three days later she was asymptomatic but her serum calcium had risen to 4·76 mmol/l (19 mg/100 ml). Oestrogen treatment was stopped but despite a diuresis of 5 l in 24 hours, intramuscular hydrocortisone 100 mg six-hourly, and intravenous mithramycin 1 mg, the serum calcium rose to 5·5 mmol/l (22 mg/100 ml) and she died (see figure). Necropsy showed metastatic deposits in viscera, lymph nodes, ovaries, and bone marrow. Parathyroid glands were normal.

Case 2—In 1971 a 57-year-old woman had a mastectomy for carcinoma of the breast. From 1974 to August 1975 she was treated with nandrolone for bone metastases with good symptomatic results. In November 1975 she was admitted to hospital for further hormone treatment. Serum calcium was 2·25 mmol/l (9 mg/100 ml) and serum alkaline phosphatase over 500 IU/l. *X*-ray examination showed widespread osteolytic metastases, and bone marrow contained malignant cells. After three days' treatment with ethynil-oestradiol 0·1 mg three times daily she remained well but her calcium was 3·57 mmol/l (14·3 mg/100 ml). Despite intramuscular hydrocortisone 200 mg four-hourly, intravenous mithramycin 1·25 mg, a diuresis of 4 l in 12 hours, intravenous neutral phosphate (400 ml), and finally plasma exchange, serum calcium rose in 24 hours to 5·6 mmol/l (22·4 mg/100 ml) and she died (see figure). Multiple lung and bone metastases were seen at necropsy. The parathyroid glands were normal.



Changes in concentrations of urinary hydroxyproline, urinary calcium, and serum calcium in two patients during treatment with ethinyloestradiol.

Conversion: SI to traditional units—Hydroxyproline: 1 mmol/mol creatinine ≈ 1·16 mg/g creatinine. Urinary calcium: 1 mmol/24 h ≈ 40 mg/24 h. Serum calcium: 1 mmol/l ≈ 4·0 mg/100 ml.

Discussion

Ethinyloestradiol (0·3-1·5 mg/day) is commonly used for treating metastatic breast cancer. It may cause hypercalcaemia of gradual onset, with nausea, vomiting, constipation, polyuria, and dehydration. This usually responds to withdrawal of medication, rehydration, and corticosteroid or mithramycin injections or both.

Our two patients were carefully monitored in the metabolic ward because they were in a study of hydroxyproline excretion with hormone treatment. The asymptomatic hypercalcaemia was detected by accident. Despite early diagnosis we could not reverse the process and both patients died rapidly. If serum calcium had not been measured the correct diagnosis in both cases would probably have been missed. This sequence may therefore be a more common complication than had previously been thought.

The rise in serum calcium, together with the increased excretion of calcium and hydroxyproline, indicates that osteolysis was stimulated by oestrogen. This does not occur in patients without cancer, suggesting that osteolysis produced by tumour cells had occurred. It has been reported that osteolysis might be caused by the synthesis and release of osteolytic substances from breast tumours,[4] and therefore oestrogens may cause hypercalcaemia by activating this metabolic process.

We thank Sister Sheila Lynch and Staff Nurse Ruth Grabow, who cared for these patients in the metabolic ward, and Mr J C Gazet and Mr A G Nash for referring them to the division of medicine.

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[2] Kleinfeld, G, *Journal of the American Medical Association*, 1962, **13**, 1137.
[3] Parsons, V, *et al*, *British Medical Journal*, 1967, **4**, 658.
[4] Powles, T J, *et al*, *Lancet*, 1976, **1**, 608.

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Division of Medicine and Ludwig Institute for Cancer Research, Royal Marsden Hospital, Sutton, Surrey
M CORNBLEET, BSC, MRCP, senior house officer
P K BONDY, MD, FRCP, professor of medicine
T J POWLES, PHD, MRCP, senior lecturer and honorary consultant physician

Hypercalcaemic crisis as presentation of Addison's disease

Addison's disease is an uncommon but well-recognised cause of hypercalcaemia.[1-3] We report a case of severe hypercalcaemia that was difficult to diagnose correctly.

Case report

A 32-year-old housewife presented with a one-week history of vomiting. For several months she had been listless and losing weight. She was dehydrated and hypotensive (90/60 mm Hg). The plasma chemistry was: Na^+ 137 mmol(mEq)/l, K^+ 5·1 mmol(mEq)/l, Cl^- 88 mmol(mEq)/l, HCO_3^- 27 mmol(mEq)/l, and urea 15 mmol/l (90 mg/100 ml). Three days later she developed dysarthria, nystagmus, and paraesthesiae around the