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 ethinyloestradiol 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.

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.

¹ Galasko, C S B, and Burn, J I, *British Medical Journal*, 1971, **3**, 573.

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.

(Accepted 27 September 1976)

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

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 $\approx$ 1.16 mg/g creatinine. Urinary calcium: 1 mmol/24 h $\approx$ 40 mg/24 h. Serum calcium: 1 mmol/l $\approx$ 4.0 mg/100 ml.

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

mouth. Electroencephalography and brain scanning showed a focal lesion in the left temporal region. At the same time she developed conjunctivitis and her plasma calcium was found to be 3.4 mmol/l (13.6 mg/100 ml). Intravenous treatment restored the plasma urea to normal without correcting the hypercalcaemia. She remained drowsy, confused, and hypotensive, and had light, generalised pigmentation. Her plasma sodium concentration remained normal, plasma phosphate was 1.2 mmol/l (3.7 mg/100 ml), alkaline phosphatase 7 KA units, and urinary calcium 10 mmol/24 h (400 mg/24 h). Radiography showed erosions in the phalanges of the hands and feet (see figure). The leucocyte count was $7.1 \times 10^9/l$ (7100/mm³), with 12 % eosinophils.

Subperiosteal erosions on radial side of proximal and middle phalanges of right index finger and middle phalanges of middle and ring fingers.

We thought that the patient was in hypercalcaemic crisis. To allow time to determine its cause we gave her phosphate and prednisolone by mouth. The plasma calcium fell to 2.4 mmol/l (9.6 mg/100 ml) in four days and she improved. Further investigation showed no evidence of sarcoidosis, leukaemia, paraproteinaemia, or other malignant disease or of vitamin D deficiency. The radiological findings seemed to indicate hyperparathyroidism.

Phosphate and prednisolone were stopped and the patient went to a surgical ward for neck exploration. With induction of anaesthesia she was given 100 mg hydrocortisone because of the recent exposure to steroids. Exploration of the neck and mediastinum showed four parathyroid glands that were normal on microscopy of frozen sections. After surgery she remained well for 24 hours but then developed mild fever and tachycardia. Plasma calcium, urea, and electrolyte values were normal. Deterioration continued over the next 10 days with increased fever, hypotension, tachycardia, and confusion. We diagnosed adrenocortical insufficiency because of the hypotension, pigmentation, and eosinophilia and the improvement when treated with prednisolone, which was earlier attributed to the phosphate treatment. At this stage the plasma chemistry was: Na⁺ 122 mmol(mEq)/l, K⁺ 6.6 mmol(mEq)/l, Cl⁻ 88 mmol(mEq)/l, HCO₃⁻ 17 mmol(mEq)/l, and urea 15.7 mmol/l (94.6 mg/100 ml). The plasma 11-hydroxycorticosteroid concentration was 196 nmol/l with no rise after tetracosactrin. Treatment was started with intravenous saline and hydrocortisone, and within 12 hours her temperature, pulse, and blood pressure were normal. She remained well on hydrocortisone and fludrocortisone with no neurological symptoms and normal electroencephalograms and brain scans. The radiological abnormalities healed in two years. Her serum contained adrenal autoantibodies.

Comment

We know of no case of adrenocortical insufficiency presenting with hypercalcaemic crisis. Our case is also unique because the bone lesions seen on radiography resembled the typical erosions of hyperparathyroidism. Bone resorption has not been noted previously in

adrenocortical insufficiency. Indeed, increased bone resorption is characteristic of cortisol excess.⁴ A wide range of neurological and psychiatric symptoms occur in hypercalcaemia.¹ EEG abnormalities are well known⁵ but the abnormal brain scan is difficult to explain.

Several features of our case might have made us question the diagnosis of hyperparathyroidism. These included the eosinophilia and the normal plasma phosphate and plasma alkaline phosphatase values in a patient with bone lesions. The presenting symptoms, however, were those of severe hypercalcaemia of any cause, and the diagnosis of hyperparathyroidism was apparently confirmed by the radiological findings. Though our case is exceptional, we feel that adrenocortical insufficiency should be remembered as an important treatable cause of hypercalcaemia.

We thank Professor J Crooks for his support, and Miss M C K Browning for help with the investigations.

¹ Paterson, C R, *Metabolic Disorders of Bone*. Oxford, Blackwell Scientific, 1975.

² Siegler, D I M, *British Medical Journal*, 1970, **2**, 522.

³ Jørgensen, H, *Acta Medica Scandinavica*, 1973, **193**, 175.

⁴ Jowsey, J, and Riggs, B L, *Acta Endocrinologica* (Copenhagen), 1970, **63**, 21.

⁵ Swash, M, and Rowan, A J, *Archives of Neurology*, 1972, **29**, 218.

(Accepted 5 October 1976)

Ninewells Hospital and Medical School, Dundee DD1 9SY

W W DOWNIE, MRCP, lecturer in therapeutics (present address: Clinical Pharmacology Unit, Royal Bath Hospital, Harrogate HG1 2PS)

A GUNN, FRCS, senior lecturer in surgery

C R PATERSON, DM, MRCPATH, senior lecturer in biochemical medicine

G F A HOWIE, MD, FRCR, consultant radiologist

Neonatal septicaemia due to group A beta-haemolytic streptococcus

Streptococcal septicaemia in neonates is usually associated with strains of Lancefield's group B.^{1,2} Though no longer the scourge of maternity units, group A streptococci may still cause severe neonatal infection.³ I report a case of group A streptococcal septicaemia in a 2-week-old boy in which the probable source of infection was the mother or grandmother.

Case history

A full-term baby boy was delivered with forceps at St Luke's Hospital, Guildford, on 24 April 1976. He weighed 4080 g. Apart from mild, transient jaundice the immediate neonatal period was uneventful and both mother and child were discharged home the third day after delivery.

Ten days later the child developed an erythematous lesion on his left cheek, which spread to the trunk during the next two days. The lesion was slightly raised but not typical of erysipelas. The cheek became swollen and the eyelid oedematous. The baby, who had been breast-fed since birth, began to take feeds poorly.

On admission to hospital the erythematous rash covered the left half of the face, the neck, the trunk, and the legs up to the knees. The rash was indurated over the neck but not elsewhere. The rectal temperature was 39°C. The white cell count was $9.3 \times 10^9/l$ (9300/mm³) with 35 % polymorphs and 61 % lymphocytes. No cells or bacteria were seen in a urine specimen. Nose and throat swabs were taken and blood was cultured.

During the next 24 hours the child deteriorated rapidly and the rash became confluent. As a β -haemolytic streptococcus had been isolated from the nose and throat swabs, intravenous penicillin 125 000 U six-hourly was given. He continued to worsen and developed a generalised petechial rash. Septicaemia was diagnosed and ampicillin and gentamicin were given in addition to the penicillin. Hydrocortisone treatment was also started. Progress was stormy, with many episodes of respiratory arrest.

On the second day a group A β -haemolytic streptococcus was isolated from the blood cultures. Penicillin was continued at an increased dose of 250 000 U four-hourly and ampicillin and gentamicin were withdrawn. The penicillin was given for 14 days. The child made an uneventful recovery and was discharged four weeks after admission.

The peripheral white cell count rose from $9.3 \times 10^9/l$ on admission to $44.3 \times 10^9/l$ (44 300/mm³) in seven days with 74 % polymorphs and evidence