

Malignant hypercalcaemia and leucocytosis associated with carcinoma of the bronchus

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Malignancy is a common cause of hypercalcaemia and may account for 60% of hospital cases of raised serum calcium concentration.¹ Leucocytosis associated with malignancy is rarely seen. We report a case of leucocytosis and hypercalcaemia associated with a bronchial squamous carcinoma. The factor or factors causing hypercalcaemia and leucocytosis were probably being produced by the tumour.

Case report

A 63-year-old man, with an eight-year history of rheumatoid disease, was admitted after the development over four weeks of a large painful swelling above the right shoulder. In addition, he complained of anorexia, night sweats, and constipation. He was a non-smoker. His treatment consisted of prednisolone 5 mg daily and indomethacin 100 mg twice daily. Clinical examination showed him to be ill but afebrile. The swelling, measuring 12 × 6 × 8 cm, was red and tense. The chest was normal. The results of laboratory investigations included the following: haemoglobin 9.8 g/dl, erythrocyte sedimentation rate 99 mm in one hour, serum sodium concentration 137 mmol (mEq)/l, potassium 4.3 mmol (mEq)/l, chloride 97 mmol (mEq)/l, urea 12.0 mmol/l (72.3 mg/100 ml), creatinine 0.14 mmol/l (1.6 mg/100 ml). The white cell count on admission was $34 \times 10^9/l$ (75% neutrophils, 21% lymphocytes, 2% monocytes, 1% eosinophils, 1% metamyelocytes). Blood, urine, and sputum specimens were sent for culture. In view of the possibility of a septic arthritis masked by steroid treatment, aspiration of the cyst was carried out and 2000 ml of straw-coloured fluid was obtained. No organisms were seen or cultured. Treatment was commenced empirically with amoxicillin 250 mg thrice daily.

The patient deteriorated five days after admission, becoming confused and paranoid. A radiograph showed erosion of the lateral half of the right clavicle. A chest radiograph showed an opacity in the left upper zone and fractures of the fourth right rib and the third left rib. A diagnosis of metastatic carcinoma of the bronchus was made. The serum calcium concentration was 3.60 mmol/l (14.4 mg/100 ml) uncorrected (serum albumin 26 g/l), serum phosphate 1.11 mmol/l (3.4 mg/100 ml), serum alkaline phosphatase 338 ml/l, and serum parathormone less than 0.3 ng/l (normal range 0.2-0.7 ng/l). Bone marrow examination six days after admission showed an

increase in the myeloid series with giant metamyelocytes but no evidence of malignancy.

A central venous line was inserted and the patient was given 5% dextrose and normal saline along with intravenous frusemide in an attempt to lower the serum calcium concentration. After an initial fall the concentration rose to 3.59 mmol/l (14.4 mg/100 ml) uncorrected. He was treated with intravenous mithramycin (25 µg/kg) on four consecutive days, after which he became rational. The serum calcium concentration became normal. Throughout the treatment period the neutrophil leucocytosis persisted, the count rising to $100 \times 10^9/l$ when the serum calcium concentration was at its maximum. The white cell count fell as the serum calcium fell but the former showed a secondary rise. The patient died 14 days after admission.

At necropsy the body was that of a well-built man, with pallor of the mucous membranes and a swan-neck deformity affecting predominantly the right hand. A tumour (3 × 2 cm) in the left upper-lobe bronchus showed central necrosis. The lung distal to the tumour consisted of white fibrous tissue along with consolidation. On the outer surface of both lungs were small white tumour nodules. In the right lung there was evidence of pulmonary oedema, small pulmonary emboli, and foci of secondary tumour. The subcarinal lymph nodes were replaced by tumour. The heart showed biventricular hypertrophy (total weight 575 g; weight of left ventricle 240 g and right ventricle 100 g). There was moderate atheroma of the left anterior descending coronary artery. There was a benign gastric ulcer measuring 3 × 2 cm, which had bled and perforated to give surgical emphysema affecting the gall bladder serosa. The liver was enlarged (weight 3310 g) with a cavity in the right lobe measuring 17 × 7 cm. This contained altered blood due to necrosis of tumour tissue. There were other discrete tumour nodules in the liver. In the pancreas there was a nodule of tumour in the tail and in the head of the pancreas there were enlarged lymph nodes replaced by tumour. Secondary tumour was present in the kidney; left adrenal; T7, T8, T9, T12, L3, and L4 vertebrae; and the third left and fourth right ribs. The lateral half of the right clavicle was replaced by necrotic tumour. There were no cerebral metastases.

Histologically the lungs showed bronchopneumonia and the tumour was a squamous-cell carcinoma with appreciable necrosis. Many tumour cells showed a clear cytoplasm, possibly as a result of the mithramycin. There was no enlargement of the parathyroid glands. The marrow away from the secondary tumour showed features similar to those of the antemortem specimen.

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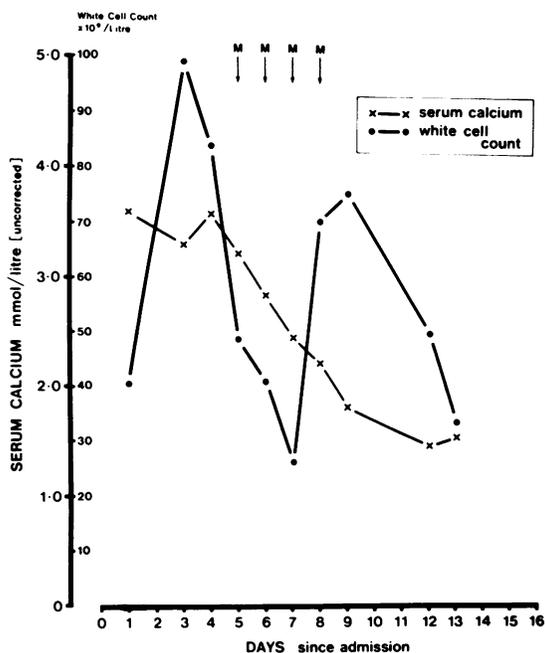
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Discussion

The association between carcinoma, leucocytosis, and hypercalcaemia is uncommon.^{2,3} The presence of hypercalcaemia is well documented and in the lung usually occurs with squamous-cell carcinomas.^{4,5} Why hypercalcaemia should be produced by squamous-cell carcinoma rather than oat-cell carcinoma and adenocarcinoma, both of which metastasise to bone, is unknown. The factors causing the hypercalcaemia have been described in detail by Heath.⁴ One leading contender as the cause of malignant hypercalcaemia is osteoclastic activating factor. This is thought to be produced by peripheral blood leucocytes, probably lymphocytes. In the present case initially there was both neutrophil leucocytosis and lymphocytosis (21%). The neutrophil leucocytosis persisted but the per-

centage of lymphocytes fell to between 4% and 6%. Possibly neutrophil polymorphs are important in the production of osteoclastic activating factor. It is certainly striking that once mithramycin had been given the neutrophil leucocytosis and the serum calcium both fell dramatically, although the fall in calcium concentration began before administration of mithramycin (fig). The secondary rise in the leucocyte count may have been due to tumour necrosis. Though we have no definite proof, the factors causing hypercalcaemia and the leucocytosis would appear to have been produced by the tumour. Alternatively, the drug may have caused tumour necrosis and arrest of further bone destruction, causing the serum calcium concentration to fall. The drug may have directly affected the marrow, leading to a fall in the leucocyte count. There was no evidence of necrosis, however, in the non-tumour sites of the marrow.

Colony-stimulating factor causes leucocytosis. This stimulates granulopoiesis *in vitro* only.⁶ Prostaglandins, especially prostaglandin E₂,⁷ have been thought to cause hypercalcaemia in malignancy. In our patient the rheumatoid disease was being treated with a prostaglandin synthetase inhibitor, indomethacin, and yet the hypercalcaemia still occurred. Although prostaglandin-induced hypercalcaemia is important in experimental animals, it may not be in bronchial malignancy.



Serum calcium level and white cell count in relation to treatment (M—mithramycin). The first dose of mithramycin on day 5 was given four hours after the blood samples were taken.

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