Hypercalcaemia in T cell acute lymphoblastic leukaemia: report of two cases

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SUMMARY Two young adults presenting with acute lymphoblastic leukaemia (ALL) associated with hypercalcaemia and osteolytic lesions were both found to have T cell ALL. Hypercalcaemia is a rare feature of ALL and has not previously been related to T cell disease. Both cases, in some respects, resembled (age between 10 and 20 years and low white cell count) the few other previously reported cases. In one of our cases increased concentrations of vitamin D3 seemed to have a role in the pathogenesis of the hypercalcaemia.

Hypercalcaemia and severe osteolytic lesions are rare complications of acute lymphoblastic leukaemia (ALL), and only a few cases with this as a presenting feature have been reported.¹⁻³ Radiographic bone changes, such as prominent transverse metaphyseal lucent bands, intramedullary osteolytic mottling, and periosteal reaction are more common, occurring in 21% of childhood cases at diagnosis,⁴ but these do not correlate with bone pain or prognosis. The low incidence of hypercalcaemia in ALL contrasts with the high incidence in some other lymphoid malignancies, such as myelomatosis and adult T cell leukaemia/lymphoma (ATLL). Normal lymphocytes are known to produce lymphokines that can modulate osteoclast proliferation and activity.⁵ The mechanisms of hypercalcaemia in these malignancies, however, and their implications for normal bone metabolism have so far been poorly understood. We report two unusual cases of ALL with severe bone disease and hypercalcaemia, in whom marker studies showed that the blasts were of T cell lineage. In one case the hypercalcaemia was associated with an increased concentration of vitamin D3.

Case reports

CASE 1

A man aged 17 years presented with haematemesis after two weeks of vomiting and weight loss. Physical examination yielded normal results except for dehy-

dration. Investigations showed a haemoglobin concentration of 11.2 g/dl, a white cell count $6.8 \times 10^9/l$ of (normal differential), platelets $156 \times 10^9/l$, serum sodium 136 mmol/l (136 mEq/l), serum potassium 4.8 mmol/l (4.8 mEq/l), serum urea 31 mmol/l (86 mg/100 ml), serum creatinine 316 $\mu\text{mol/l}$ (3.6 ng/100 ml), serum calcium 3.01 mmol/l (12.1 mg/100 ml), and serum phosphate 1.2 mmol/l (3.6 mg/100 ml). Abdominal ultrasonography, chest, abdominal, and hand x-rays all yielded normal results. Endoscopy showed gastritis and duodenitis. He was treated with rehydration and discharged one week later when calcium concentration and renal function had returned to near normal. He was readmitted a week later with vomiting and was once again found to be hypercalcaemic: calcium concentration was 3.01 mmol/l (12.18 mg/100 ml), haemoglobin was 8.3 g/dl, and white cell count $5.1 \times 10^9/l$. He was again treated with rehydration, and 10 days later his haemoglobin had fallen to 6.5 g/dl. A bone marrow aspirate showed ALL (more than 90% lymphoblasts) and he was transferred to Hammersmith Hospital for treatment.

The blasts were Sudan black, periodic acid Schiff negative, and acid phosphatase positive with localised reaction product. Cell markers (terminal transferase (TdT) and OKT17) were positive and the monoclonal antibodies B4 and anti-HLA-Dr were negative. T-cell ALL was diagnosed. Biochemical tests on admission were: calcium concentration 3.2 mmol/l (12.9 mg/100 ml), serum phosphate 1.16 mmol/l (3.48 mg/100 ml), serum urea 9.3 mmol/l (25.8 mg/100 ml), serum creatinine 124 $\mu\text{mol/l}$ (1.45 ng/100 ml), alkaline phosphatase activity 106 IU/l, serum albumin 39 g/l.

Fig 1 Lateral skull x-ray of case 1 showing multiple osteolytic lesions.

Chemotherapy with daunorubicin, vincristine, and prednisolone was started, according to the UKALL X trial protocol. Three days later the serum calcium and renal function had returned to normal. Serum taken at the time of his admission showed parathyroid hormone activity to be $0.32 \mu\text{g/l}$ (within the normal range as in other cases of hypercalcaemia in malignancy); vitamin D3 concentrations were grossly increased at 187 pg/l (normal range $20\text{--}40 \text{ pg/l}$). Skeletal survey showed multiple lytic lesions in the skull (fig 1), pelvis, and femora.

CASE 2

A girl aged 15 years presented with intense bone and joint pains, especially in the sternum and long bones. Physical examination yielded normal results. Blood count showed a haemoglobin of 8.9 g/dl , platelets $100 \times 10^9/\text{l}$, and white cell count $4.4 \times 10^9/\text{l}$, with 5% blast cells. Bone marrow aspirate showed complete replacement by lymphoblasts which were periodic acid Schiff and peroxidase negative and positive for acid phosphatase (localised reaction). X-rays showed multiple osteolytic lesions in the skull (fig 2) and no

Fig 2 Bone marrow lymphoblasts from case 2 (May-Grünwald-Giemsa stain.) $\times 1200$.

Fig 3 Lymphoblasts from case 2 showing strong localised acid phosphatase reaction $\times 1200$.

mediastinal mass. Other laboratory investigations showed a raised uric acid, a serum calcium concentration of 2.8 mmol/l (11.3 mg/100 ml); alkaline phosphatase activity, urea, and creatinine concentrations

were normal. She was treated with vincristine, prednisolone, and asparaginase and received consolidation with daunorubicin, cytosine arabinoside, and 6-thioguanine, and later with an intermediate dose of methotrexate given by 24 hour infusion and folinic acid rescue. A remission was achieved after which she received cranial irradiation and intrathecal methotrexate. Twenty weeks after presentation she relapsed and had further transient responses to other drug combinations. During one of the relapse episodes she experienced intense bone pain and was noted to be again hypercalcaemic: calcium concentration was 3.3 mmol/l (13.4 mg/100 ml) with worsening of the osteolytic lesions. She died without further improvement 11 months after initial presentation. The bone marrow blasts formed E-rosettes when studied at diagnosis and at relapse: this was consistent with a diagnosis of T-ALL.

Discussion

The cases presented here were unusual in two respects; firstly, the presentation with hypercalcaemia; and secondly, a clinical picture that was atypical for T-ALL—low white cell count, absence of mediastinal mass, and lymphadenopathy. Both patients probably presented at an earlier stage than

Fig 4 Lateral skull x-ray from case 2 showing multiple osteolytic lesions.

usual because of the bone disease. Although less than 20 cases of ALL and hypercalcaemia have been reported, many show strikingly similar features to those described here—namely, age 10–20 years, severe osteolytic bone lesions, and normal white cell count with rare or absent circulating blasts.² No cell marker data are available on the earlier cases, but one recent case was CALLA (common-ALL antigen) positive.³

Another T cell malignancy, ATLL, is associated with a high incidence of hypercalcaemia, which varies from 50–100% in different series. The negative TdT in the blasts of ATLL characterises them as mature post-thymic cells, distinct from those of T-ALL, which are TdT positive and have a thymic membrane phenotype. Increased concentrations of vitamin D3 have recently been implicated as the cause of hypercalcaemia in ATLL. Breslau *et al*⁵ described three cases of non-Hodgkin's lymphoma with hypercalcaemia and increased vitamin D3 concentrations, one of which was ATLL. Mundy *et al*⁶ subsequently reported that HTLV-I infected lymphocytes could hydroxylate vitamin D2 to the active D3 form. The increased vitamin D3 concentration in case 1 may have resulted from a similar mechanism but this may not have been the only factor contributing to the hypercalcaemia, as other lymphokines are capable of modulating osteoclast activity.

Hypercalcaemia in ALL has not previously been identified as being related to T cell ALL. Case 1 is also the first example of ALL in which increased vitamin D3 concentrations have been shown. In most cases no mechanism for the hypercalcaemia has been found and although one previous case suggested that ectopic

parathormone production was the cause,⁷ this has not been supported by subsequent observations. These cases and the previous reports emphasise that leukaemia, although rare, should be borne in mind as a cause of hypercalcaemia, even when the peripheral white cell count is normal. Raised concentrations of vitamin D3 should be investigated as a cause of hypercalcaemia in other lymphoid malignancies.

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