CASE REPORT

Acute lymphocytic leukaemia presenting as a metabolic bone disease

Suja P Sukumar, Karthik Balachandran, Jaya Prakash Sahoo, Sadishkumar Kamalanathan

Department of Endocrinology,
Jawaharlal Institute of Post
Graduate Medical Education &
Research, Puducherry, India

Correspondence to
Dr Sadishkumar Kamalanathan,
sadishkk@gmail.com

SUMMARY

A 7-year-old boy presented with the acute onset of low backache of 2 months duration. An x-ray of thoracolumbar spine revealed multiple vertebral fractures, and biochemical evaluation showed hypercalcaemia with a suppressed parathyroid hormone which raised the possibilities of malignancy, granulomatous conditions or vitamin D toxicity. Despite the absence of blast cells in his blood, the bone marrow biopsy was unequivocally diagnostic of acute lymphoblastic leukaemia.

BACKGROUND

Hypercalcaemia is often a clue to the presence of an unsuspected illness. A great majority of patients with elevated serum calcium have been found to have either primary hyperparathyroidism or malignancy among other causes. Adult malignancies commonly present with parathormone independent hypercalcaemia (5–20%). In paediatric population, however, presentation of malignancies with hypercalcaemia is extremely rare (0.5–1.5%). Acute lymphoblastic leukaemia (ALL) is one of the commonest malignancies causing hypercalcaemia in this age group. Often, it presents only with radiographic skeletal abnormalities mimicking a metabolic bone disease. Recently, we encountered a patient who presented to us with multiple vertebral compression fractures and hypercalcaemia without any blasts in peripheral smear initially but was later diagnosed to have ALL upon bone marrow examination.

CASE PRESENTATION

A 7-year-old previously healthy boy with a 2-month history of low backache was referred to the endocrinology department from a private hospital for metabolic abnormalities. There was worsening of his symptoms for past 2 weeks. He had no history of trauma or involvement of bowel and bladder. There was no polydipsia or polyuria. Upon examination, tenderness was present diffusely over his back and shoulders. He had mild pallor with bilateral enlarged non-tender, firm axillary, cervical and epitrochlear lymph nodes. Moderate splenomegaly was present.

INVESTIGATIONS

Investigations revealed a raised serum calcium of 3.1 mmol/l (normal range (NR) 2–2.5), normal serum albumin of 44 g/l (NR 31–43), high serum phosphorus of 2.1 mmol/l (NR 1.45–1.78), urea nitrogen 3.2 mmol/l (NR 2.1–7.1) and creatine 52.8 µmol/l (NR 46–115), uric acid 321.3 µmol/l

(NR 120–320) and alkaline phosphatase of 104 IU/l (NR 38–126). He had a 24 h urine calcium–creatinine ratio of 0.55. His 25-hydroxy vitamin D was 54.8 nmol/l (NR 50–250) thereby ruling out vitamin D toxicity as a cause of hypercalcaemia. The intact parathormone level was 0.01 ng/l (NR 10–55) which ruled out a diagnosis of primary hyperparathyroidism. Hence, the possibilities of malignancy or granulomatous condition-induced hypercalcaemia were entertained. Parathyroid hormone (PTH)-related peptide (PTHrP) assay was considered but it was very expensive and was not easily available. His 1,25-dihydroxy vitamin D (1,25(OH)₂D) was 33.8 pmol/l (NR 40–160) thus ruling out enhanced 1-α-hydroxylase activity and extrarenal production of 1,25(OH)₂D by lymphoma cells and granulomas.

His haemoglobin was 9.2 g/l and the total leucocyte count was 3800/mm³ with 60% lymphocytes. Chest x-ray revealed no hilar or mediastinal mass. CT scan showed a normal liver, a mildly enlarged spleen, diffuse osteoporosis and mild compression fracture of multiple vertebral bodies (figure 1). Bone scan showed lesions involving left humeral head, thoracic and lumbar vertebrae which raised the possibility of neoplastic infiltration (figure 2). Because of suspicious blood picture, a bone marrow biopsy was performed to rule out a haematological malignancy. It showed acute leukaemia with 85% blasts and immunohistochemistry was conclusive for precursor B-cell lymphoblastic leukaemia.

DIFFERENTIAL DIAGNOSIS

The boy had parathormone-independent hypercalcaemia and its differential diagnosis is mainly grouped as follows:

- ▶ Malignancies
 - Haematological malignancies like multiple myeloma, lymphomas and leukaemias.
 - Non-haematological malignancies like renal cell carcinoma, non-small cell lung cancer and breast cancer.
- ▶ Granulomatous diseases (tuberculosis, sarcoidosis).
- ▶ Vitamin D intoxication

TREATMENT

The patient was initially managed with intravenous fluid and frusemide for hypercalcaemia and was then referred to paediatric haemato-oncologist for chemotherapy.

To cite: Sukumar SP, Balachandran K, Sahoo JP, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-008758

Figure 1 CT chest showing compression fracture of multiple vertebral bodies.

Figure 2 Anterior and posterior whole body planar images reveals areas of abnormal increased uptake in multiple dorsolumbar vertebrae, ribs anteriorly and left humeral head suggestive of skeletal infiltration.

OUTCOME AND FOLLOW-UP

The patient has shown remarkable improvement with chemotherapy and bone pains have completely disappeared.

DISCUSSION

Hypercalcaemia in paediatric age group is most commonly caused by primary hyperparathyroidism and malignancies. The key to diagnosis in our patient was a suppressed PTH level in spite of hypercalcaemia. This finding reliably excludes primary hyperparathyroidism, the leading cause of hypercalcaemia in which intact PTH level is high normal or elevated.¹ Hypercalcaemia of malignancy can be of two categories—(1) humoral hypercalcaemia of malignancy (HHM) and (2) local osteolytic hypercalcaemia (LOH).

Humoral causes constitute 80% of hypercalcaemia of malignancy and is usually associated with solid malignancies when tumour cells secrete into circulation one or more substances like PTHrP, tumour necrosis factor (TNF), interleukins and cytokines.^{2–5} Serum PTHrP levels are increased in 80–100% of patients with hypercalcaemia owing to solid tumours and this assay may be used in patients in whom the cause of hypercalcaemia is not readily apparent. In the presence of normal renal function, serum phosphate values are low or low normal in HHM, similar to those seen in primary hyperparathyroidism. Serum 1,25-dihydroxy vitamin D measurement is of value in the diagnosis of hypercalcaemia in granulomatous disease, Hodgkin's and non-Hodgkin's lymphomas in which their levels are usually elevated.^{6–8}

LOH constitutes 20% of hypercalcaemia of malignancy and is usually associated with skeletal metastasis, multiple myeloma, lymphoma in adults and leukaemia in children. This generally occurs owing to localised bone destruction by invasive cancer cells by local release of a range of cytokines and other osteoclast-stimulating factors directly onto the surface of bone. The key to diagnosis is demonstration of concomitant suppressed intact PTH with elevated phosphorus.

Patients without a known malignancy should have a complete blood count, serum and urine electrophoresis and bone scan. A bone marrow biopsy should be performed if these studies are not informative. A more recent survey in Japan found an incidence of hypercalcaemia of 4.8% at presentation in children with leukaemia, all of whom had the pre-B cell type.⁹

The ultimate treatment for malignancy-associated hypercalcaemia is the eradication of the underlying cancer. Medical therapy is aimed at prompting renal calcium excretion and inhibiting bone resorption. The first step of therapy is to rehydrate the patient, enhance calciuresis by loop diuretics and administration of bisphosphonates to inhibit osteoclastic bone resorption.^{1 6}

Hypercalcaemia associated with ALL is usually more responsive to treatment than hypercalcaemia associated with paediatric solid tumours.^{5 10} Inukai *et al* reported the largest case series of patients with hypercalcaemia and ALL, which comprised 22 cases treated between 1990 and 2005. Children treated with bisphosphonates achieved a more rapid reduction in serum calcium and more rapid resolution of renal impairment compared with those who did not receive bisphosphonates.^{5 10 11}

Learning points

- ▶ Hypercalcaemia in presence of suppressed parathyroid hormone (PTH) should raise the suspicion of occult malignancy.
- ▶ Absence of malignant cells in peripheral smear does not rule out haematological malignancy.
- ▶ In PTH-independent hypercalcaemia of undetermined origin, a bone marrow aspirate/trephine should be necessary part of work up.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Becker KL. *Principles and practice of endocrinology and metabolism*. 3rd edn. Philadelphia: Lippincott Williams and Wilkins, 2001.
- 2 Camacho PM, Gharib H, Sizemore GW. *Evidence-based endocrinology*. 3rd edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.
- 3 Mundy GR, Ibbotson KJ, D'Souza SM, *et al*. The hypercalcaemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med* 1984;310:1718–27.
- 4 Soni PN. Hypercalcaemia and multiple osteolytic lesions in childhood acute lymphoblastic leukemia. *Postgrad Med J* 1993;69:483–5.
- 5 Trehan A, Cheetham T, Bailey S. Hypercalcaemia in acute lymphoblastic leukemia. *J Pediatr Hematol/Oncol* 2009;31:424–7.
- 6 Yeung SJ, Escalante CP, Gagel RF. *Medical care of cancer patients*. Shelton, CT: People's Medical Publishing House; BC Decker Inc, 2009.
- 7 Hong WK, Holland JF, Frei E. *Holland Frei cancer medicine* 8. 8th edn. Shelton, CT: People's Medical Pub. House, 2010.
- 8 Shimonodan H, Nagayama J, Nagatoshi Y, *et al*. Acute lymphocytic leukemia in adolescence with multiple osteolytic lesions and hypercalcaemia mediated by lymphoblast-producing parathyroid hormone-related peptide: a case report and review of the literature. *Pediatr Blood Cancer* 2005;45:333–9.
- 9 Hibi S, Funaki H, Ochiai-Kanai R, *et al*. Hypercalcaemia in children presenting with acute lymphoblastic leukemia. *Int J Hematol* 1997;66 :353–7.
- 10 McKay C, Furman WL. Hypercalcaemia complicating childhood malignancies. *Cancer* 1993;72:256–60.
- 11 Inukai T, Hirose K, Inaba T, *et al*. Hypercalcaemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. *Leukemia* 2006;21:288–96.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow