

## Extensive Calcinosis Cutis in Relapsed Acute Lymphoblastic Leukaemia

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### Abstract

**Introduction:** Hypercalcaemia with calcinosis cutis occurring at relapse of acute lymphoblastic leukaemia (ALL) is rare and unusual. **Clinical Picture:** A 19-year-old lady with B precursor ALL presented with extensive waxy, verrucous, tender plaques over the flexures of her arms and legs a week after relapse of leukaemia. She was found to have hypercalcaemia, hyperphosphataemia, hyperuricaemia and acute renal impairment. Skin biopsy was consistent with calcinosis cutis. There was no evidence of metastatic calcification in other organs. **Treatment:** Hypercalcaemia was treated with aggressive hydration and intravenous pamidronate. High doses of analgesics were required for partial pain relief. **Outcome:** Cutaneous lesions proved resistant to early calcium lowering and were a source of constant pain. She succumbed to leukaemia four months later. **Conclusion:** Treatment of calcinosis cutis was unsatisfactory and would have been dependent on the successful treatment of the underlying leukaemia.

Ann Acad Med Singapore 2004;33:107-9

**Key words:** Hypercalcaemia, Metastatic calcification, B-cell leukaemia

### Introduction

Calcinosis cutis is characterised by the aberrant deposition of calcium salts in the skin. In metastatic calcinosis cutis, calcium salts are precipitated in normal tissue as a result of an underlying defect in calcium and/or phosphate metabolism. Calcification in these cases may be widespread, affecting skin as well as blood vessels, muscle and internal organs. Hypercalcaemia is a complication of many malignancies. We report an unusual case of extensive and refractory calcinosis cutis secondary to hypercalcaemia in B-cell lymphoblastic leukaemia.

### Case Report

A 19-year-old lady from the haematology ward was referred to the dermatologist for a painful eruption over both arms and legs lasting two weeks. She had been admitted for a relapse of B precursor acute lymphoblastic leukaemia (ALL) which was diagnosed four months earlier with cytogenetic studies demonstrating t(1;19) translocation. She had completed four cycles of chemotherapy with the HyperCVAD regimen (alternating cyclophosphamide, adriamycin, vincristine and dexamethasone with high-dose cytarabine and methotrexate)

and achieved haematological and cytogenetic remission with the first cycle of treatment. There was no transplant option. Thereafter, maintenance chemotherapy was given. The serum calcium and phosphate levels were also normal.

Upon relapse of her leukaemia, she developed acute renal impairment with a serum creatinine of 305 µmol/L as well as hypercalcaemia (corrected serum calcium of 4.77 mmol/L, normal <2.6 mmol/L), elevated phosphate levels (1.96 mmol/L, normal <1.38 mmol/L) and marked hyperuricaemia with a serum uric acid level of 2148 µmol/L (normal <340 µmol/L). Radiographs of the chest, abdomen and lumbosacral spine did not show any osteolytic lesions nor any unusual sites of calcification. No cutaneous lesions were noted. There were no crystals on urine microscopy. She was treated with intravenous pamidronate and aggressive intravenous hydration, as well as oral dexamethasone and allopurinol, with recovery of renal function and normalisation of the serum calcium, phosphate and uric acid levels.

A week later, the serum calcium level again increased to 4.4 mmol/L with normal phosphate levels and renal function. She was readmitted and similarly given intravenous pamidronate, hydrocortisone and hydration, together with

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frusemide. On this occasion, pigmented plaques were found distributed over both thighs and popliteal fossae. These were initially asymptomatic and flat. Over the next two weeks, the skin lesions became more widespread and painful, and were also found on the bilateral axillae, arms and back. Radiographs of the elbows did not reveal any unusual calcification. She was treated with systemic and topical antifungal agents, but showed no improvement. She received salvage chemotherapy and the serum calcium levels remained low over the next month. There was morphological remission of leukaemia on repeat marrow studies, but the cytogenetic abnormality persisted.

Clinically, there were extensive waxy, infiltrated, verrucous, pigmented papules and large plaques predominantly over the flexures, namely, the antecubital fossae, popliteal fossae and axillae (Fig. 1), as well as the chest, scapulae, medial aspects of the upper limbs and lower limbs (Fig. 2). There was no ulceration and no discharge. These lesions were tender, but there was no inflammation. Initial clinical impressions included xanthoma disseminatum and diffuse plane xanthomatosis. Xanthoma disseminatum presents with erythematous, yellow to brown papules and nodules symmetrically distributed on the trunk, face and proximal extremities. These lesions may become



Fig. 1. Hyperpigmented, verrucous plaques in the axillary fold seen from the back.

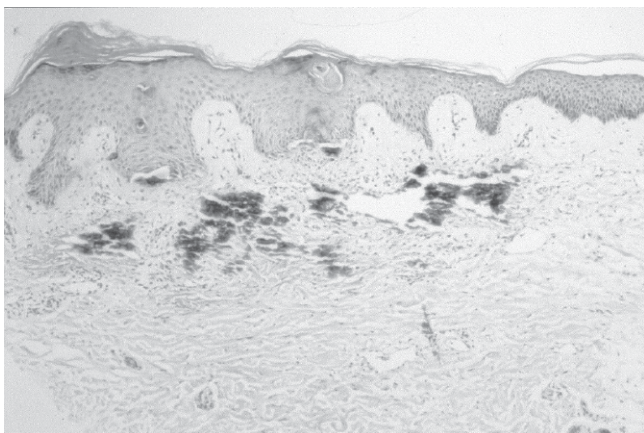


Fig. 3. Epidermal hyperplasia and orthokeratosis. Purple-staining calcium deposits in the superficial dermis (haematoxylin and eosin stain; original magnification  $\times 40$ ).

confluent and verrucous, especially over flexures and skinfolds. Diffuse plane xanthomatosis is associated with myeloproliferative disorders and lymphocytic leukaemias, and presents with large, plaque-like xanthomatous lesions on the upper trunk and flexures. A skin biopsy taken from the right arm showed irregular epidermal hyperplasia, orthokeratosis and diffuse calcification in the upper dermis (Figs. 3 and 4). There were no perivascular deposits. This was consistent with calcinosis cutis. Leukaemic infiltrates were not seen.

The skin lesions progressed despite chemotherapy and normalisation of serum calcium levels. High doses of opioids and tricyclic antidepressants achieved partial pain relief.

Haematological remission was not achieved. Serum phosphate, intact parathyroid hormone levels and N-mid osteocalcin were normal. However, serum beta crosslaps, which is an indicator of high bone turnover from osteolysis, was elevated at  $2.95 \mu\text{g/L}$  (normal values, pre-menopausal  $<0.28 \mu\text{g/L}$ ). 25-hydroxyvitamin D level was low at  $8.7 \mu\text{g/L}$  ( $10.1 \mu\text{g/L}$  to  $40.3 \mu\text{g/L}$ ). Unfortunately, parathyroid hormone-related peptide (PTHrP) could not be measured at our institution. No further chemotherapy was given in compliance with her wishes. She received palliative care with pain relief and



Fig. 2. Hyperpigmented plaques in the popliteal fossae and thighs.

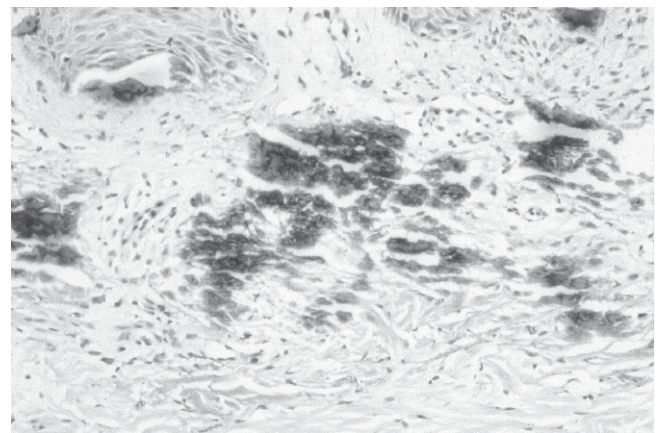


Fig. 4. Dermal calcium deposits (haematoxylin and eosin stain; original magnification  $\times 100$ ).

intermittent doses of pamidronate. The patient finally passed away four months after relapse of her leukaemia, with considerable pain from her skin lesions.

## Discussion

Hypercalcaemia with calcinosis cutis, occurring at relapse of ALL, is rare and unusual. Although hypercalcaemia is a well-described paraneoplastic manifestation of various malignancies, including the leukaemias, the incidence in B-cell ALL is, however, low and has been reported to be between 2.5% to 4.8% at diagnosis.<sup>1</sup> The incidence of hypercalcaemia manifesting only at relapse of disease is not known. To our knowledge, this is the first case of extensive calcinosis cutis secondary to hypercalcaemia in relapsed B-cell ALL.

Both humoral and local mechanisms have been implicated in the pathogenesis of hypercalcaemia in ALL.<sup>2</sup> PTHrP has been variously shown to be responsible for hypercalcaemia via a humoral effect,<sup>3</sup> and this is the likely mechanism in this patient. The high level of beta crosslaps found indicate a high rate of bone turnover, but there was no evidence of osteolysis on the radiological survey. While measurements of PTHrP and cytokines could not be done for this patient at our institution, circumstantial evidence suggested a predominant humoral mechanism for the hypercalcaemia. Elevated level of 1,25-hydroxyvitamin D has been reported to be associated with leukaemia and lymphoma, but was not demonstrated in this patient. The concomitant occurrence of primary hyperparathyroidism was not suggested by parathyroid hormone levels.

A consequence of marked hypercalcaemia in this young lady was the development of extensive metastatic calcinosis cutis. Calcinosis cutis is characterised by the deposition of calcium salts in the skin. Calcium salts are recognised as fine granules or small deposits, which stain deep blue with haematoxylin and eosin, and black with von Kossa stain. Cutaneous calcinosis may be divided into several main categories: dystrophic, metastatic, idiopathic and iatrogenic. Dystrophic calcification is the most common type of calcinosis cutis and is associated with a variety of disorders. It occurs as a result of local tissue injury or abnormalities. There are no abnormalities of calcium metabolism. In metastatic calcification, precipitation of calcium salts occurs in normal tissues as a result of an underlying defect in calcium and/or phosphate metabolism.<sup>4</sup> Metastatic calcification may be associated with neoplasms such as lymphoma, leukaemia, multiple myeloma and metastatic carcinoma, chronic renal failure, hyperparathyroidism, hypervitaminosis D and sarcoidosis.

Although hypercalcaemia is a common complication of malignancies, aberrant cutaneous calcium deposition – as a result of this – is relatively uncommon. The combination of high calcium and phosphate levels at relapse of disease was likely to have precipitated calcinosis cutis in this patient.

Cutaneous leukaemic infiltrates are a potential triggering factor for dystrophic calcification in the skin, as suggested in a case of congenital leukaemia.<sup>5</sup> There was, however, no histological evidence of leukaemia cutis in this patient.

A combination of intravenous bisphosphonates, corticosteroids and hydration proved to be adequate in rapidly lowering the patient's calcium levels. Sustained control of hypercalcaemia would have required a successful re-induction of remission of leukaemia with chemotherapy. The cutaneous lesions, however, proved resistant to early measures of calcium reduction. The pain and discomfort of these lesions were the main cause of morbidity to this patient prior to her demise. Adequate analgesia for these painful skin lesions was difficult to achieve and largely unsatisfactory. The extensive distribution of these lesions resulted in both resting and mechanical pain, and adequate relief was only obtained after a cocktail of morphine and tricyclic antidepressants were used with non-steroidal, anti-inflammatory agents. Cases of calcinosis cutis have been described to resolve over a period of time with adequate control of the calcium and phosphate levels.<sup>6,7</sup> This would only have been possible with successful treatment of the patient's underlying leukaemia. Unfortunately, it proved to be refractory.

## Conclusion

This case recognises the unusual manifestation of hypercalcaemia at relapse of B-cell ALL, leading to the development of calcinosis cutis. The extent of calcinosis cutis, as well as the predominantly flexural distribution, was unusual. Furthermore, metastatic calcification restricted to the skin is rarely observed. Treatment of these cutaneous lesions is directed at control of the hypercalcaemia and the prognosis is dependent on the underlying malignancy.

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