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Short reports

Severe hypercalcaemia in B-cell lymphoma: combined effects of PTH-rP, IL-6 and TNF

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Summary

Hypercalcaemia as the only manifestation of B-cell lymphoma is seen very rarely. Its pathophysiology is heterogenous and not well understood. We report a 73-year-old man who presented with severe hypercalcaemia before any signs of malignancy became evident. He was diagnosed with a B-cell lymphoma on bone marrow trephine biopsy. The hypercalcaemia was associated with high plasma concentrations of parathyroid-hormone-related protein, interleukin-6 and tumour necrosis factor. Our patient had markedly increased osteoclast and osteoblast activity as a result of synergistic effects between these factors, with consequent severe hypercalcaemia. This is the first reported example of such combined effects of these factors in humans.

Keywords: hypercalcaemia; lymphoma; parathyroid-hormone-related protein; tumour necrosis factor; interleukin-6

A 73-year-old Caucasian man was admitted to hospital with a 5-day history of lethargy, confusion, nausea, abdominal pain, and constipation. This was preceded by weight loss of about 6 kg over a 6-week period. Previously he had been well, apart from benign colonic polyps kept under regular colonoscopy review and a recent chest infection that was treated. On admission he was dehydrated and confused, but had no other signs. Initial investigations revealed an adjusted calcium of 4.27 mmol/l (normal range 2.2–2.6 mmol/l), phosphate 1.76 mmol/l (0.70–1.40), urea 22.5 mmol/l (2.5–7.0), creatinine 391 μmol/l (50–130), alkaline phosphatase 241 IU/l (35–125), erythrocyte sedimentation rate 40 mm/h, haemoglobin 11.4 g/dl, mean corpuscular volume 87 fl (80–100), white cell count 11.3×10^9/l (neutrophils 9.6×10^9/l , lymphocytes 0.6×10^9/l), platelets 407×10^9/l . Chest X-ray was normal. He was treated with 0.9% saline intravenously and although his condition improved (calcium concentration returned to within reference range after 2 weeks and kidney function after 5 weeks), alkaline phosphatase of bony origin (confirmed by electrophoresis) increased to 777 IU/l on day 8 raising a strong possibility of bony metastases. Bone scintigraphy, however, did not reveal any localised increased activity but was suggestive of diffuse metabolic disease (there was prominent lung and kidney uptake due to microcalcification, but no evidence of neoplastic deposits). The prostatic specific antigen was normal and myeloma screen (serum and urine immunoelectrophoresis) was negative. Abdominal ultrasound was also normal. Screening investigations for metabolic causes of hypercalcaemia (thyroid-stimulating hormone/thyroxine, vitamin D, magnesium, angiotensin-converting enzyme concentrations, short synacthen test) were all normal or within reference range. Parathyroid hormone level was found to be low at 0.8 pmol/l (1.1–6.9). Colonoscopy confirmed the presence of benign polyps only.

On day 9 the patient developed pain in both knees. X-Rays revealed multifocal osteopenic peri-articular areas raising again the possibility of metastases or myeloma (figure). Similar abnormalities were later found throughout the radius and ulna of both arms. X-Rays of the skull and hands (apart from degenerative changes) were normal. Parathyroid hormone related protein (PTH-rP) was found to be elevated at 1.3 pmol/l (Diasorin, Stillwater,

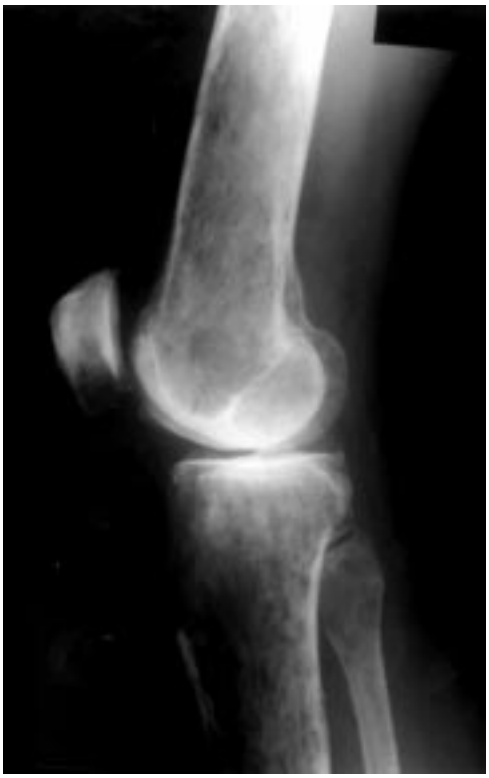

Figure X-Ray of patient's knee showing multifocal areas of peri-articular osteopenia

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USA) (reference range <0.5 pmol/l, established on 88 normal volunteers who were fit, healthy, ambulant subjects, normocalcaemic and not on medication affecting calcium metabolism; mean age 51 years, range 33–88). After 3 weeks in hospital hypercalcaemia recurred and disodium pamidronate intravenously with calcitonin subcutaneously were required as there was no response to saline diuresis only. Significantly elevated pyridinium crosslinks: urinary free pyridinoline (UfPyr)/creatinine 67.7 (5.0–21.8 nmol/mmol), urinary free deoxypyridinoline (UfDPyr)/creatinine 21.5 (0.4–6.4 nmol/mmol), and a UfPyr/UfDPyr ratio of 3.14 (3.3–5.2), confirmed very high bone resorption. Although computed tomography (CT) of brain, chest and abdomen was normal (the axial skeleton, apart from degenerative changes, appeared intact), CT review of both tibiae showed ill-defined lytic lesions suggestive of myeloma.

Bone marrow aspiration and trephine from the iliac crest was carried out. The aspirate was normal but the trephine biopsy showed lymphoid aggregates consistent with a diffuse large B-cell lymphoma, high grade (immunohistochemical profile: leucocyte common antigen positive, cytokeratin and prostate antigens negative, B-cell markers positive, T-cell markers negative). At that stage plasma tumour necrosis factor (TNF) was significantly elevated at 83.2 pg/ml (<15). Also, levels of interleukin-6 (IL-6) and C-reactive protein were increased at 20.7 pg/ml (<12) and 37 mg/l (<5), respectively (table). The patient was treated with CHOP regime (cyclophosphamide, doxorubicin, vincristine, prednisolone) to which he responded well. His progress was complicated by a pathological fracture of left distal radius. After two courses of CHOP he was discharged home feeling well, with a view to further chemotherapy. His adjusted calcium concentration decreased gradually after the treatment with disodium pamidronate and calcitonin to a nadir of 1.83 mmol/l and subsequently normalised.

Table Changes of C-reactive protein, IL-6, TNF, and calcium over time. Hypercalcaemia responded at first to rehydration, but later required disodium pamidronate and calcitonin. IL-6 and TNF normalised after CHOP

Day	*CRP (mg/l)*	*IL-6 (pg/ml)*	*TNF (pg/ml)*	*Adj Ca^{2+} (mmol/l)*
Normal range	<5	<12	<15	2.2–2.6
1				4.27
0.9% Saline				
10	14	14.0	39.8	2.79
14				2.50
21				2.95
26	16	16.2	63.0	3.53
31	27	19.6	65.4	3.71
Pamidronate and calcitonin				
32	22	14.7	72.9	3.51
33	21	13.1	75.8	
34	19	8.9	75.5	2.41
35	18	11.2	76.5	2.30
46	37	20.7	83.2	2.12
CHOP				
53	16	5.8	9.2	1.83
59				2.23

Abbreviations: CRP = C-reactive protein, IL-6 = interleukin-6, TNF = tumour necrosis factor, Adj Ca^{2+} = calcium adjusted for albumin, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone

Discussion

Hypercalcaemia is most commonly associated with primary hyperparathyroidism and malignancy.[1] In haematological neoplasms it often occurs in the course of multiple myeloma (about 33% of cases) and is nearly always associated with extensive osteolytic skeletal involvement.[1 2] Only 1–2% of patients with lymphoma and leukaemia[3 4] develop this complication (except with adult T-cell leukaemia in which it is common). In non-Hodgkin's lymphoma the finding of hypercalcaemia at presentation is extremely rare (less than 3% of cases),[4] although in advanced disease with skeletal involvement the incidence may be as high as 34%.[5] To the best of our knowledge, there has been only one case of isolated hypercalcaemia as the presenting feature of a B-cell lymphoma reported in the English literature up to now.[6] In that case, hypercalcaemia was attributed to elevated PTH-rP.

The pathophysiology of hypercalcaemia in haematological malignancies may involve factors produced by the malignant cells: PTH-rP, TNF, IL-1, IL-6, and 1,25-dihydroxyvitamin D, which stimulate osteoclast-mediated bone resorption.[7] In some cases, activated host immune cells may produce TNF or IL-1[7] and in turn these cytokines can induce IL-6 production by T-cells. Most reports of hypercalcaemia associated with malignancy have identified single factors that are thought to cause the elevated calcium. Our patient is the first reported case of a malignancy resulting in high circulating plasma concentrations of three osteoclast-stimulating factors: TNF, PTH-rP and IL-6. Their production in combination may demonstrate synergism, resulting in the severe recurrent hypercalcaemia. Animal models have shown that such synergism occurs when TNF is combined with PTH-rP[8] or IL-6.[9] This is thought to be due to an enhanced effect of two factors on production of early osteoclast precursors with subsequent increase in osteoclastic bone resorption. PTH-rP mediated bone resorption coupled with bone formation is increased two-fold by TNF.[8] In our patient, this potent combination of factors resulted in widespread skeletal effects with biochemical and radiological findings suggestive of multiple myeloma or disseminated carcinoma, but not lymphoma (although sclerotic lesions would have been expected in carcinoma and it would be unusual to find myeloma involving distal bones). Unlike myeloma, our patient had an elevation of bone alkaline phosphatase which increased three-fold following treatment of the hypercalcaemia, and also had generalised increased activity on bone scintigraphy, which reflected increased osteoblast activity, most probably secondary to the systemic effect of the combination of TNF and PTH-rP. It is also possible that the very high osteoclast activity was releasing a factor such as transforming growth factor β (TGFβ) which is a potent regulator of osteoblast activity. TGFβ

is released in increased amounts by osteoclasts that are stimulated by factors such as PTH-rP in bone cultures.[10]

Despite bone marrow involvement and anaemia, the peripheral blood picture on presentation was relatively normal and a trephine bone marrow biopsy was required to establish the diagnosis. In hypercalcaemia of undetermined origin, haematological malignancies should be considered a possibility. The significant systemic effects may be due to production of a number of local and systemically active factors. This case casts a new light on the understanding of the complex pathophysiology that may arise in hypercalcaemia of malignancy.

Learning points

- in hypercalcaemia of undetermined origin, haematological malignancies should be considered a possibility and a bone marrow aspirate/trephine performed
- in B-cell lymphoma the tumour cell–bone micro-environment can result in the production of factors which can stimulate both osteoclasts and osteoblasts
- there is increasing evidence that the systemic synergism between PTH-rP, TNF and/or IL-6 results in significant osteoclast stimulation which may be responsible for hypercalcaemia of malignancy

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Verrucous carcinoma of the female breast

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Summary
Verrucous carcinoma is a rare skin malignancy of squamous cell origin. It is characterised by negligible cellular atypia and a low mitotic rate. These are reflected in slow locally invasive behaviour and very infrequent metastatic spread. The tumour is also recognised in oral and anogenital sites. Cutaneous lesions present most commonly on the sole of the foot. We report a unique case occurring in the female breast.

Keywords: verrucous carcinoma; breast

A 75-year-old woman presented at the breast clinic with an alleged one-year history of an enlarging lesion of her right breast. On examination, the lateral aspect of the breast was replaced by an exophytic and superficially necrotic lesion measuring 120 × 110 mm (figure 1). This was thought clinically to represent advanced breast carcinoma. Two incisional biopsies were taken on separate occasions under local anaesthesia, however, and the lesion was pathologically reported as a benign viral wart. The patient proceeded to wide local excision of the lesion, and frozen section examination at the time of operation was reported as a well-differentiated benign squamous lesion. Examination of paraffin sections from this specimen (figure 2) revealed an acanthotic and hyperkeratotic lesion with both endophytic and exophytic components. There was minimal nuclear pleomorphism and mitoses were confined to the basal layers. The appearances were typical of a verrucous carcinoma, and immunocytochemistry was positive for human papilloma virus. Local excision of the lesion was complete, and the patient made a good clinical recovery. She remains well on follow-up.