CASE REPORT

Increase in serum 1,25-dihydroxyvitamin D and hypercalcaemia in a patient with inflammatory myofibroblastic tumour

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Hypercalcaemia complicates the clinical course of a substantial number of patients with advanced cancer. This report describes a patient with an inflammatory myofibroblastic tumour in soft tissue who developed an inflammatory reaction, hypercalcaemia, and a high serum concentration of 1,25 dihydroxyvitamin D. Serum concentrations of 25-hydroxyvitamin D, parathyroid hormone, and parathyroid hormone related protein were normal. Histological examination of the tumour revealed fibrosarcoma with abundant macrophage infiltration. mRNA for 25-hydroxyvitamin D-1 α -hydroxylase was identified in the tumoral tissue. In view of this case, inflammatory myofibroblastic tumour should be added to the list of diseases that are responsible for vitamin D mediated hypercalcaemia.

Parathyroid hormone related protein (PTHrP) is the main mediator of hypercalcaemia in solid tumours,¹ whereas the extrarenal synthesis of activated vitamin D sterols has a central causative role in the hypercalcaemia associated with various granulomatous diseases, such as tuberculosis and sarcoidosis.² We describe a case of fibrosarcoma associated with a pronounced inflammatory reaction and hypercalcaemia. High circulating concentrations of 1,25 dihydroxyvitamin D (1,25(OH)₂D), probably caused by tumoral tissue, contributed to the hypercalcaemia.

CASE PRESENTATION

A 69 year old man presented with a five year history of enlarging soft tissue mass of the left inguinal region, recent weight loss, and general fatigue. Imaging studies showed an ill margined tumour, measuring 15 × 20 cm, surrounding femoral vessels and invading the pelvic cavity (fig 1). A computed radiogram of the thoracic, abdominal, and pelvic cavity and endoscopic examinations of the gastrointestinal tract revealed that there were no abnormal lesions except for the inguinal tumour. Laboratory tests revealed leucocytosis (21 000/ μ l), thrombocytosis (51 000/ μ l), anaemia (haemoglobin, 66 g/litre), increased erythrocyte sedimentation rate (139 mm/hour), increased C reactive protein concentration (94 mg/litre), and hypercalcaemia (albumin corrected total calcium, 3.6 mmol/litre; normal range, 2.1–2.6). Hormone investigations showed suppressed PTH values (< 5 pg/ml; normal range, 10–60), normal PTHrP (< 0.2 pmol/litre; normal value, <1.1), normal 25-hydroxyvitamin D (12.9 ng/ml; normal range, 9.0–33.9), and raised concentration of 1,25 (OH)₂D (78 pg/ml; normal range, 20–60). Histological examination of the tumour revealed an inflammatory myofibroblastic tumour, which consisted of fibroblastic tumour cells, plasma cells, granulocytes, and CD68 positive macrophages (fig 2A–C). The

Figure 1 Computed tomography scan showing a large soft tissue tumour in the left groin.

tumour cells were positive for vimentin and smooth muscle actin, but negative for desmin, S100 protein, cytokeratin, epithelial membrane antigen, and anaplastic lymphoma kinase. The patient occasionally developed disorientation probably because of hypercalcaemia.

The hypercalcaemia was treated successfully with hydration and an infusion of bisphosphonate (incadronate disodium, 10 mg/1–3 weeks), and the disorientation resolved. The patient refused surgical treatment and was given two courses of chemotherapy, consisting of carboplatin, etoposide, and cisplatin. However, the tumour continued to enlarge and the inflammatory reaction did not resolve. The patient continued to deteriorate and died of pneumonia nine months after presentation.

We used reverse transcriptase polymerase chain reaction (PCR) to detect the expression of 25-hydroxyvitamin D-1 α -hydroxylase in the tumour sample and cultured tumour cells. Total RNA was extracted from the tissue sample and cultured tumour cells, which showed a fibroblastic appearance. RNA (1 μ g) was converted to cDNA by reverse transcription, using M-MLV reverse transcriptase (Gibco BRL, Gaithersburg, Maryland, USA). The primers for PCR of human 25-hydroxyvitamin D-1 α -hydroxylase were designed according to Cross *et al.*³

We confirmed the expression of 25-hydroxyvitamin D-1 α -hydroxylase in the tumour sample and the normal kidney of an unrelated postmortem case. The cultured tumour cells, established human fibrosarcoma cell line (HT-1080; Health Science Research Resources Bank, Osaka, Japan), and skeletal muscle of the unrelated postmortem case did not express the mRNA (fig 3).

Abbreviations: 1,25(OH)₂D, 1,25 dihydroxyvitamin D; PCR, polymerase chain reaction; PTHrP, parathyroid hormone related protein

Figure 2 (A) High power photomicrograph of the tumour showing spindle fibroblastic cells with numerous inflammatory cells, such as granulocytes, plasma cells, and macrophages. (B) High power photograph of the tumour showing abundant foamy cell proliferations. (C) Immunostaining for CD68 showing numerous macrophage infiltrations.

DISCUSSION

Inflammatory myofibroblastic tumour, a lesion that has also been described as inflammatory fibrosarcoma and inflammatory pseudotumour, is a tumour of intermediate or low grade malignancy. The tumour is frequently associated with fever, weight loss, increased erythrocyte sedimentation rate, anaemia, and thrombocytosis, as in our present case. The tumour consists of myofibroblasts, lymphocytes, plasma cells, and histiocytes.⁴

High serum 1,25 (OH)₂ D concentrations have been reported in hypercalcaemic patients with granuloma forming

Figure 3 Reverse transcriptase polymerase chain reaction reveals expression of 25-hydroxyvitamin D-1 α -hydroxylase mRNA in both tumoral tissue and kidney. Glyceraldehyde-3-phosphate dehydrogenase was used as an internal control.

Take home messages

- We report a patient with an inflammatory myofibroblastic tumour in soft tissue who developed hypercalcaemia and a high serum concentration of 1,25 dihydroxyvitamin D
- The optimal treatment for hypercalcaemia associated with a neoplasm is antitumour therapy, but if the tumour is uncontrollable bisphosphonates may be effective in controlling hypercalcaemia
- Inflammatory myofibroblastic tumour should be added to the list of diseases that are responsible for vitamin D mediated hypercalcaemia

diseases and in patients harbouring lymphoproliferative neoplasms.² Extrarenal expression of 25-hydroxyvitamin D-1 α -hydroxylase has a central role in hypercalcaemia in these patients. To our knowledge, this is the first case of a high serum concentration of 1,25 (OH)₂ D and hypercalcaemia in a patient with mesenchymal tumour. A recent study by Zehnder *et al* has demonstrated the expression of 25-hydroxyvitamin D-1 α -hydroxylase by macrophages in a granuloma and concluded that this was the most likely cause of coexisting hypercalcaemia.⁵ In our present case, the expression of 25-hydroxyvitamin D-1 α -hydroxylase was confirmed in the tumoral tissue, which contained reactive macrophages, but not in the cultured fibroblastic tumour cells. These results suggest that macrophages, but not neoplastic cells, in the tumour tissue are the main source of expression of 25-hydroxyvitamin D-1 α -hydroxylase.

The optimal treatment for hypercalcaemia associated with a neoplasm is antitumour therapy. However, if the tumour is uncontrollable, as in this case, bisphosphonates may be effective in controlling hypercalcaemia.

"These results suggest that macrophages, but not neoplastic cells, in the tumour tissue are the main source of expression of 25-hydroxyvitamin D-1 α -hydroxylase"

Given the findings described here, we believe that inflammatory myofibroblastic tumour should be added to the list of neoplasms that are responsible for 1,25 (OH)₂ D mediated hypercalcaemia.

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