Hypercalcaemia in Hodgkin’s disease related to prostaglandin synthesis

J B Laforga, J Vierna, F I Aranda

Abstract
A case of paraneoplastic hypercalcaemic syndrome is reported in a patient with Hodgkin’s disease. This was detected eight months before widespread lymphadenopathy became apparent. Lymphocyte depleted Hodgkin’s disease was diagnosed. PTH (parathyroid hormone) activity was suppressed and PTHRP (PTH related protein) was less than 5 pmol/l. 1,25(OH)2D3 was in the normal range. Plasma calcium values returned to normal after the administration of indomethacin. Thus the pathogenesis of the hypercalcaemia in this patient could be associated with the synthesis of prostaglandins.

Case report
A 64 year old man was admitted to hospital because hypercalcaemia was detected at routine examination. The serum calcium ranged from 11.2–14 mg/l and remained in this range, with no response to treatment with diuretics. Immunoradiometric assay showed that the parathyroid hormone (PTH) value was suppressed at 10.0 pg/ml (normal range 10.0–65.0 pg/ml). PTHRP measured by radioimmunoassay was under 5.0 pmol/l (reference value: up to 5.0 pmol/l); 1,25 (OH)2D3 was 20.7 mg/24 hours (normal range 6–22 mg/24 hours, for 22–65 year olds. Chest x-ray picture and whole body computed tomogram failed to show lymph node enlargement or any tumour mass. No radiological bone abnormalities were detected. A bone marrow biopsy was performed to detect neoplastic infiltration. The only remarkable finding was the presence of non-necrotising histiocytic granulomas (fig 1). A second bone marrow biopsy was performed in another hospital and was negative. The administration of indomethacin 150 mg daily eventually led to normal calcium values. Three months later cervical, thoracic, and retroperitoneal adenopathy developed. On the basis that these signs might be lymphoma a cervical lymph node biopsy was performed. Immunohistochemical stains with CD15 (Leu M-1; Becton Dickinson), and CD-30 (Ki-1/Ber H2; Dako) were positive in mononuclear Hodgkin’s cells and pleomorphic Reed-Sternberg cells (fig 2). The mixed lymphoid cellularity expressed T cell markers (UCHL-1; Dako), histiocytes (lisozyme; Dako), and a population of residual B lymphocytes (4KB5 and L-26; Dako). The typical histological and immunophenotypical findings suggested the diagnosis of Hodgkin’s disease, of the lymphocyte depleted type.

At the time of writing the patient was clinically stable and had remained normocalcaemic.

Discussion
Some malignant tumours are associated with hypercalcaemia, especially epithelial tumours, such as squamous cell carcinoma of the lung, renal cell carcinoma, and those with neuroendocrine differentiation like small cell carcinoma of the lung, carcinoid and small cell carcinoma of the ovary.1,2 Hypercalcaemia is relatively rare in lymphoproliferative diseases. It has been detected in patients with T cell leukaemia associated with the HTLV-1 retrovirus.2

Since the first publication by Kabakow et al in 1957, describing hypercalcaemia associated

Figure 1 Bone marrow biopsy specimen showing a histiocytic non-caseating granuloma formed by mononuclear cells, lymphocytes, and plasma cells.

Figure 2 Lymph node biopsy specimen. Pleomorphic Reed-Sternberg cell stained with CD-15. Note the sparsely cellular infiltrate of lymphocytes and histiocytes (CD-15).
with Hodgkin's disease, there have been few subsequent reports.\(^4\) When hypercalcemia is present in Hodgkin's disease, it is usually associated with extensive skeletal pathology, and occurs later in the course of the disease.\(^4\) However, in the case under discussion we have no radiographic evidence of bone infiltration by Hodgkin's disease. The first bone marrow biopsy specimen contained histiocytic granulomas without diagnostic Reed-Sternberg cells, and the second one was negative.

Hypercalcemia has been related to excess production of 1,25(OH)\(_2\)D\(_3\) in lymphoid neoplasms and in sarcoidosis. Calcitriol is probably a regulatory hormone in both progenitor and mature haematolymphoid cells. If so, then its production in Hodgkin's disease, lymphomas, and granulomatous diseases may not be coincidental. Thus similarities among granulomatous diseases, Hodgkin's disease, and non-Hodgkin's lymphomas are seen with respect to this mechanism of hypercalcemia.\(^7\)

Interestingly, there are also histological resemblances between the mononuclear cells seen in Hodgkin's disease and those in sarcoidosis. In Hodgkin's disease, besides the neoplastic cells represented by Reed-Sternberg and its variants, there is a mixed cellular infiltrate composed of histiocyte-like cells, epithelioid histiocytes, and multinucleated Langhans-type giant cells. Histological sarcoïd-like features may be present in both affected and non-affected organs of patients with Hodgkin's disease. We draw attention to the fact that many cases of lymphocyte depleted Hodgkin's disease have to be reclassified as T cell non-Hodgkin's lymphoma,\(^8\) and that sarcoidosis may be related to excessive activity of helper T lymphocytes, causing lymphokine activation of monocytes and macrophages, leading to granulomas and local injury.

Karmali\(^9\) reported a patient with Hodgkin's disease and hypercalcemia who was treated with hydrocortisone. The serum 1,25(OH)\(_2\)D\(_3\) decreased rapidly and eventually led to normocalcemia. It seems also that the disturbances of the calcium metabolism are similar to those described in sarcoidosis.

The current case was successfully treated with indomethacin for the normalization of the calcaemia. This agrees with in vitro studies of bone reabsorption activity. According to most of the cases described, Jacobson et al\(^10\) hypothesised that a large tumour burden is a necessary prerequisite for the appearance of hypercalcemia in Hodgkin's disease. However, this does not apply to the case under discussion, in which the development of humoral hypercalcemia preceded the appearance of multiple adenopathy by eight months.

In a recent paper a case of Hodgkin's disease associated with hypercalcemia was investigated for the presence of PTHrP (PTH related protein) in the patient's plasma and in tissue neither was detected.\(^11\) In our case the appearance of hypercalcemia was not explained by the presence of PTHrP nor was 1,25(OH)\(_2\)D\(_3\) detected in plasma. According to the response to indomethacin, we suggest that the hypercalcemia could be explained by prostaglandin synthesis by the tumour cells or the mixed cells present in Hodgkin's disease.

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