Hypercalcaemia in chronic lymphatic leukaemia

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Summary: A 75 year old woman with a 13 year history of classical chronic lymphatic leukaemia (CLL) developed hypercalcaemia. Unlike previous reports, this was not associated with blastic transformation, hyperparathyroidism or features of multiple myeloma, but was due to classical CLL *per se*.

Introduction

Hypercalcaemia is a well recognized complication of several B lymphoproliferative disorders including multiple myeloma, non-Hodgkin's lymphoma and Burkitt's lymphoma. It is however rarely seen in classical B cell chronic lymphatic leukaemia (CLL). I report such a case.

Case report

A 75 year old woman was found to have Rai stage O CLL, lymphocytes $38.3 \times 10^9/l$, (Rai *et al.*, 1975) in 1969 but did not require therapy until 1982, when she had progressed to stage II (hepatosplenomegaly, lymphocytes $160 \times 10^9/l$, haemoglobin 10.1 g/dl, platelets $230 \times 10^9/l$). The lymphocytes expressed surface IgM of restricted κ light chain type. She responded to

intermittent chlorambucil returning to stage O and therapy was discontinued in June 1983.

In May 1984 she developed bone pain, lymphadenopathy, splenomegaly and anaemia, haemoglobin 10.3 g/dl, platelets $150 \times 10^9/l$. The lymphocyte count had risen to $42 \times 10^9/l$. She was noted to be hypercalcaemic, calcium 2.74 mmol/l (normal 2.2–2.55 mmol/l); alkaline phosphatase 282 IU/l (normal 100–280 IU/l), creatinine 105 $\mu\text{mol/l}$. The plasma albumin remained between 36 and 40 g/l throughout the period of observation. Chlorambucil was re-started but she was admitted 3 weeks later with severe bone pain, nausea and general malaise. On examination she was dehydrated and had widespread bony tenderness over the thorax and pelvis. The splenomegaly and lymphadenopathy were unchanged. There were no thyroid, breast or abdominal masses palpable. Inves-

Figure 1 Effect of chemotherapy on serum calcium and alkaline phosphatase concentrations. C=cyclophosphamide; O = vincristine; P = prednisolone; V = vinblastine.

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tigation showed lymphocytosis $160 \times 10^9/l$ with smear cells, haemoglobin 9.3 g/dl, direct Coomb's test negative, platelets $111 \times 10^9/l$, calcium 4.02 mmol/l, phosphate 1.47 mmol/l, alkaline phosphatase 418 IU/l, creatinine 169 $\mu\text{mol/l}$, urea 15.4 mmol/l, serum immunoelectrophoresis showed immune paresis but no monoclonal protein and urinary light chain excretion was not detected. Chest X-ray was normal as was skeletal survey, with no evidence of lytic lesions or osteoporosis, but ^{99}Tc bone scan showed widespread areas of increased uptake, compatible with metabolic bone disease. Serum parathyroid hormone was <40 pg/ml on three occasions (normal <120 pg/ml), serum 25 (OH) vitamin D 8.7 ng/ml (normal 3–35 ng/ml), serum 1,25 (OH) $_2$ vitamin D 34 pg/ml (normal 20–65 pg/ml). Bone marrow examination showed 75% small mature lymphocytes. Combination chemotherapy (vincristine 1.4 mg/m 2 intravenously (i.v.) days 1 and 8, cyclophosphamide 750 mg/m 2 i.v. days 1 and 8, oral prednisolone 10 mg/day, days 1–8) was started with resolution of the bone pain and hypercalcaemia. The alkaline phosphatase was raised on admission, fell with resolution of the hypercalcaemia but then showed a second, more pronounced but temporary rise following chemotherapy (Figure 1). During remission the bone scan showed considerable regression of involved areas, the serum parathyroid hormone rose to 50 pg/ml. She remained stage 0 for 6 months on a modified oral regime but became hypercalcaemic once more on stopping the vincristine because of a peripheral neuropathy. Introduction of vinblastine rendered her normocalcaemic and reduced the lymphocyte count from $60 \times 10^9/l$ to $12 \times 10^9/l$ but her general condition deteriorated and she died. There

was no morphological evidence of prolymphocytoid or lymphoblastic transformation of the disease, but the lymphocytes no longer expressed surface immunoglobulin.

Discussion

Hypercalcaemia is rarely seen in CLL (Laugen *et al.*, 1979) and previous reports have emphasized its association with raised serum parathyroid hormone levels (Laugen *et al.*, 1979), lymphoblastic transformation (Benvenisti *et al.*, 1969) or features suggestive of multiple myeloma. The latter includes osteolytic bone lesions (McMillan *et al.*, 1980) and monoclonal protein production (Redmond *et al.*, 1983) and is classically associated with a normal alkaline phosphatase reflecting the lack of osteoblastic response. This patient had a classical clinical course with no morphological evidence of transformation. The raised alkaline phosphatase and widespread increased uptake on bone scan despite a normal skeletal survey are suggestive of metabolic bone disease or metastatic solid tumour. The low serum parathyroid hormone, normal vitamin D metabolites, absence of any demonstrable solid tumour and response to chemotherapy would, however, suggest that the hypercalcaemia was due to the CLL *per se*. I report this to emphasize that hypercalcaemia can be caused by classical CLL.

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