CASE REPORTS

Hypercalcaemia in malignant lymphoma

M. GREAVES
M.B.Ch.B., M.R.C.P.

B. W. HANCOCK
M.D., M.R.C.P., D.C.H.

Department of Medicine, University of Sheffield, Royal Hospital, Sheffield

Summary

Three patients with malignant lymphoma complicated by hypercalcaemia without radiological bone abnormality are described. The medical literature has been reviewed and the possible underlying mechanisms discussed. The early diagnosis of this potentially fatal complication is important since this may respond (together with the underlying disease) to appropriate chemotherapy.

Introduction

The occurrence of hypercalcaemia secondary to malignant lymphoma has been described previously (Herrmann, Kirsten and Krakauer, 1949; Plimpton and Gellhorn, 1956; Kabakow, Mines and King, 1957; Moses and Spencer, 1963; Powell *et al.*, 1973; Singer *et al.*, 1973; Canellos, 1974) although the incidence of this complication (less than 2% of cases of advanced lymphoma have elevated serum calcium levels at presentation [Canellos, 1974]) is lower than might be predicted from the relative frequency of bone marrow involvement in this condition.

The majority of cases described in the literature had bone involvement by lymphomatous tissue and all patients had disseminated disease.

The authors have recently seen 3 patients with disseminated malignant lymphoma who developed hypercalcaemia. One was found to have raised serum calcium level at the time of presentation; the other 2 developed the abnormality during the course of their disease. In 2 cases the hypercalcaemia may have been a major factor in the death of the patient.

Case 1

A 55-year-old female presented with sore throat cervical lymphadenopathy and loss of 12 kg body weight over a period of one month. Examination revealed ulceration of the right tonsil and generalized lymphadenopathy. Biopsy of the tonsillar lesion was reported as showing large non-cleaved follicular

centre cell non-Hodgkin's lymphoma. Chest radiograph and biochemical indices were all normal (serum calcium 2.21 mmol/l). The haemoglobin level was 11.5 g/dl, WBC $9.5 \times 10^9/l$ (lymphocytes $7.0 \times 10^9/l$, neutrophils $2.4 \times 10^9/l$), platelets $270 \times 10^9/l$, ESR 21 mm/hr (Westergren). Serum immunoglobulin levels were normal but cellular immunity was depressed. Abdominal lymphography demonstrated possible lymphomatous changes in the para-aortic nodes, the intravenous pyelogram being normal. Bone marrow trephine showed involvement by non-Hodgkin's lymphoma. The patient was thus in Stage 4B (Ann Arbor criteria) and she began treatment with the 'COPAD' regime (intravenous cyclophosphamide 400 mg/m² and vincristine 1.4 mg/m² on days 1 and 8; oral prednisolone 40 mg/day for 14 days; intravenous adriamycin 40 mg/m² on day 1; 28 days between the start of each course). Her lymphadenopathy resolved and she remained well until her sixth course of combination chemotherapy when she was admitted to hospital with a history of gradual onset of mental confusion and showing features of paranoid psychosis. She had also lost weight and had developed night sweats. Serum biochemical screen now revealed a grossly elevated serum calcium level (3.75 mmol/l) with low normal inorganic phosphate (0.85 mmol/l), slightly raised urea (12.6 mmol/l). The alkaline phosphatase level was slightly elevated (112 u./l). Skeletal radiography was normal but lymphogram follow-up films suggested the presence of active lymphoma. The patient was hydrated via the intravenous route and given oral prednisolone 40 mg/day and oral phosphate with dramatic clinical and biochemical improvement. Within 24 hr the blood urea, serum uric acid and serum calcium levels were normal (6.8, 0.14, 2.13 mmol/l respectively); the serum phosphate was low (0.60 mmol/l). These values remained satisfactory over the ensuing 7 days and in particular the serum calcium level remained well within the normal range. The oral phosphate was therefore discontinued and the prednisolone reduced to 10

mg/day and the patient allowed home. Two days later the patient was re-admitted in a semi-comatose state with a history of rapid mental deterioration, vomiting and urinary incontinence. She was again dehydrated and had developed bronchopneumonia. The serum calcium level was now markedly elevated at 5.0 mmol/l with blood urea of 10.7 mmol/l and there was severe hypokalaemic alkalosis. Resuscitative measures, including intravenous fluids, hydrocortisone, phosphate infusion and broad spectrum antibiotics were unsuccessful and the patient died 24 hr after admission. Post-mortem was not performed.

Case 2

A 49-year-old male presented with autoimmune haemolytic anaemia thought to be associated with chronic lymphocytic leukaemia. He responded to prednisolone but 7 months later he required admission to hospital with acute renal failure. At this time his serum calcium, phosphate, alkaline phosphatase and uric acid levels were all normal (2.27, 1.1 mmol/l, 64 u./l, 0.43 mmol/l respectively). He was treated with peritoneal dialysis and made a good recovery from his renal failure. Renal biopsy, however, showed infiltration by malignant lymphoma. Diagnostic laparotomy one month later revealed infiltration of the liver with non-Hodgkin's lymphoma of a large cleaved follicular centre cell type, with normal spleen histology. He was treated initially with chlorambucil but developed weight loss and the chest radiograph revealed changes consistent with pulmonary involvement from lymphoma. Bone marrow trephine also demonstrated involvement by malignant lymphoma although skeletal radiographs were normal. Haemoglobin at this stage was 11.3 g/dl, white cell count $12.0 \times 10^9/l$ with $7.0 \times 10^9/l$ lymphocytes many of which were of abnormal morphology. The platelet count was $250 \times 10^9/l$ and ESR 26 mm/hr (Westergren). At this time the patient was dehydrated and feverish and the serum biochemical screen revealed elevated levels of urea, uric acid and calcium (10.0, 0.53, 3.59 mmol/l respectively). Oral fluids were increased and treatment with COPAd regime begun, together with allopurinol. The serum calcium level had fallen to 3.16 mmol/l at 48 hours and 2.48 mmol/l by 7 days. The blood urea rose to 30.0 mmol/l before falling to 9.3 mmol/l by 7 days. Clinical improvement was dramatic and marked regression of the pulmonary deposits was noted. The patient has since completed 6 courses of combination chemotherapy and appears to be in complete remission. His serum biochemical screen remains normal and the serum calcium level in particular is 2.22 mmol/l.

Case 3

A 73-year-old male presented with a 3-month history of anorexia, weight loss and ill health. He was found to have generalized lymphadenopathy and biopsy of a left cervical node showed non-Hodgkin's lymphoma of the large non-cleaved follicular centre cell type. Chest radiograph revealed multiple lung deposits but no bone deposits were demonstrated. Bone marrow biopsy was normal as was routine haematology. (Hb 14.8 g/dl, white cell count $5.5 \times 10^9/l$ with normal differential). The ESR was 35 mm/hr. Biochemical screening revealed elevated levels of serum calcium (3.01 mmol/l, corrected) and blood urea (24.7 mmol/l). The uric acid level (0.26 mmol/l) was normal. He was staged 4B and treated with COPAd. He did not respond to chemotherapy and rapidly deteriorated, dying of bronchopneumonia. Post-mortem was not performed.

Discussion

The rapidity of the changes in serum biochemical values following treatment in Case 1 is remarkable; the serum calcium level returned to normal within 24 hr with associated clinical improvement. The recurrence of the hypercalcaemia, with hypokalaemic alkalosis, was also very rapid. Other cases of hypercalcaemia in malignant lymphoma described in the literature have shown a similar response to treatment with corticosteroids (Kabakow *et al.*, 1957; Mundy *et al.*, 1976).

In Case 2 hypercalcaemia developed insidiously with associated widespread disease. In this case response to oral hydration and cytotoxic chemotherapy (including prednisolone) was less rapid, although the serum calcium level had fallen significantly by 48 hr. The serum calcium has continued at a normal level whilst the non-Hodgkin's lymphoma has been in remission.

The third case showed hypercalcaemia at the time of presentation with advanced malignant lymphoma and his biochemical abnormalities may well have contributed to his rapid deterioration; there was no clinical or biochemical improvement in this case with cytotoxic chemotherapy (incorporating prednisolone).

None of the patients showed radiological evidence of bone involvement, although bone marrow trephine biopsy was positive for lymphoma in 2 cases (Cases 1 and 2). Indeed, bone marrow infiltration or osteolytic bone lesions occur in about 50% of cases of advanced lymphoma (Canellos, 1974; Richmond *et al.*, 1962) but hypercalcaemia is regarded as a relatively rare complication. In contrast, in myelomatosis and in metastatic bone disease from various carcinomas, hypercalcaemia is very

commonly found. In Case 1 the hypercalcaemia was responsible for the patient's stuporous condition and was therefore rapidly identified but in the other 2 cases the high serum calcium level might easily have been overlooked and it may be that the overall incidence of this complication of malignant lymphoma has been underestimated.

Cases of hypercalcaemia with malignant disease, especially where there is an associated low or low normal serum phosphate and an absence of radiological evidence of bone involvement, have been regarded as examples of pseudohyperparathyroidism (Tashjian, Levine and Munson, 1964; Munson, Tashjian and Levine, 1965; Sherwood *et al.*, 1967; Omenn, Roth and Baker, 1969) although adequate parathyroid hormone and radio-immunoassay data have rarely been obtained. It now seems likely that in the majority of cases parathyroid hormone-like activity produced ectopically by the tumour is not the underlying mechanism of the hypercalcaemia (Powell *et al.*, 1972), and other mechanisms have been postulated.

The direct resorption of bone by tumour tissue remains a possibility but this fails to explain the low incidence of hypercalcaemia in haematological malignancies other than myelomatosis in which bone marrow involvement may be very extensive; even in this condition, however, bone resorption appears to be mediated by increased numbers of osteoclasts, rather than by the abnormal plasma cells (Mundy *et al.*, 1974b).

There is some *in vitro* evidence that normal human monocytes can resorb bone by a humoral mechanism (Munday *et al.*, 1977), but the importance of this *in vivo* is not known.

Various humoral agents have been postulated as mediators of hypercalcaemia in malignant and inflammatory disease. In some carcinomas, particularly those of breast (Greaves *et al.*, 1976; Powles *et al.*, 1976; Dowsett *et al.*, 1976; Bennett *et al.*, 1976; Bennett *et al.*, 1977) and kidney (Atkins *et al.*, 1977; Greaves, Atkins and Martin, 1977), large amounts of prostaglandins have been demonstrated and some of these tumours can resorb bone *in vitro* by a mechanism that seems to involve the production of bone-resorbing prostaglandins (particularly prostaglandin E) and the stimulation of osteoclasts. Prostaglandin production has been shown to be important in the genesis of hypercalcaemia in some animal tumours (Tashjian *et al.*, 1972; Powles *et al.*, 1973; Woelkel *et al.*, 1975; Seyberth *et al.*, 1976; Seyberth *et al.*, 1977). There is, however, no evidence that the bone-resorbing agent liberated by lymphoid cell lines in culture is a prostaglandin (Mundy *et al.*, 1974a) or indeed that cultured bone marrow cells from patients with myeloma can elaborate prostaglandins in significant amounts, although

they can produce immunoglobulin (Mundy *et al.*, 1974b; Greaves, 1977, unpublished observations).

The production of vitamin D-like sterols by tumours has been postulated (Gordan, Cantino and Erhardt, 1966), although there is little evidence to support this.

The humoral agent which seems most likely to be of importance in myeloma and lymphoreticular malignancy is the so-called osteoclast activating factor (OAF) which has been shown to be produced by myeloma cells (Mundy *et al.*, 1974b). This appears to be indistinguishable from the bone-resorbing factor produced by phytohaemagglutinin-stimulated human leucocytes in culture (Horton *et al.*, 1972; Luben *et al.*, 1974). It has been demonstrated that the *in vitro* bone resorption induced by this macromolecular compound is inhibited by low concentrations of cortisol (Horton *et al.*, 1972) and it is possible that this may be the mechanism for the response of the hypercalcaemia to prednisolone that was seen in 2 of the patients (Cases 1 and 2).

The inhibition of production of a humoral agent by the malignant cells, rather than interference with the action of such an agent on bone, by corticosteroids remains a possible explanation for the activity of these drugs in hypercalcaemia, although there is no experimental evidence to support this.

This applies particularly to Case 1 where the response was dramatic and rapid; in Case 2 the slower response of the hypercalcaemia may also reflect the reduction in tumour mass by the cytotoxic chemotherapy (including prednisolone).

The authors feel that hypercalcaemia in malignant lymphoma, although uncommon, may be important particularly as the resulting clinical state may be mistaken for that of the underlying malignant process in patients with advanced disease.

In one of the patients, the initial response to hydration, oral phosphate and high doses of prednisolone was extremely rapid and in a second patient there was a slower but sustained response to cytotoxic chemotherapy. This indicates that the potentially lethal condition of hypercalcaemia in cases of malignant lymphoma may respond (together with the underlying disease) to appropriate chemotherapy. It is therefore worth-while checking the serum calcium level regularly in such patients so that any abnormality can be treated early and energetically.

Acknowledgments

We are grateful to the consultants under whose care these patients were admitted; to Professor J. Richmond for his critical advice and to the Yorkshire Cancer Research Campaign for financial support.

References

- ATKINS, D., IBBOTSON, K.J., HILLIER, K., HUNT, N.H., HAMMONDS, J.C. & MARTIN, T.J. (1977) Secretion of prostaglandins as bone resorbing agents by renal cortical carcinoma in culture. *British Journal of Cancer*, **36**, 601.
- BENNETT, A., CHARLIER, E.M., McDONALD, A.M., SIMPSON, J.S. & STAMFORD, I.F. (1976) Bone destruction by breast tumors. *Prostaglandins*, **11**, 461.
- BENNETT, A., CHARLIER, E.M., McDONALD, A.M., SIMPSON, J.S., STAMFORD, I.F. & ZEBRO, T. (1977) Prostaglandins and breast cancer. *Lancet*, **ii**, 624.
- CANELLOS, G.P. (1974) Hypercalcemia in malignant lymphoma and leukemia. *Annals of the New York Academy of Science*, **230**, 240.
- DOWSETT, M., EASTY, G.C., POWLES, T.J., EASTY, D.M. & NEVILLE, A.M. (1976) Human breast tumor-induced osteolysis and prostaglandins. *Prostaglandins*, **11**, 447.
- GORDAN, G.S., CANTINO, T.J. & ERHARDT, L. (1966) Osteolytic sterol in human breast cancer. *Science*. New York, etc., **151**, 1226.
- GREAVES, M., ATKINS, D., IBBOTSON, K. & MARTIN, T.J. (1976) Breast tumours, bone resorption and prostaglandins. *Clinical Science and Molecular Medicine*, **54**, 20.
- GREAVES, M., ATKINS, D. & MARTIN, T.J. (1977) Prostaglandins, erythropoietin and renal cortical carcinoma. *Journal of Endocrinology*, **35**, 21.
- HERRMANN, J.B., KIRSTEN, E. & KRAKAUER, J.S. (1949) Hypercalcaemic syndrome associated with androgenic and estrogenic therapy. *Journal of Clinical Endocrinology*, **9**, 1.
- HORTON, J.E., RAISZ, L.G., SIMMONS, H.A., OPPENHEIM, J.J. & MERGENHAGEN, S.E. (1972) Bone resorbing activity in the supernatant fluid from cultured human peripheral blood leukocytes. *Science*. New York, etc., **177**, 793.
- KABAKOW, B., MINES, M.F. & KING, F.H. (1957) Hypercalcemia in Hodgkin's disease. *New England Journal of Medicine*, **256**, 59.
- LUBEN, R.A., MUNDY, G.R., TRUMMEL, C.L. & RAISZ, L.G. (1974) Partial purification of osteoclast activating factor from phytohemagglutinin-stimulated human leukocytes. *Journal of Clinical Investigation*, **53**, 1473.
- MOSES, A.M. & SPENCER, H. (1963) Hypercalcemia in patients with malignant lymphoma. *Annals of Internal Medicine*, **59**, 531.
- MUNDY, G.R., ALTMAN, A.J., GONDEK, M.D. & BANDELIN, J.C. (1977) Direct resorption of bone by human monocytes. *Science*. New York, etc., **196**, 1109.
- MUNDY, G.R., LUBEN, R.A., RAISZ, L.G., OPPENHEIM, J.J. & BUELL, D.N. (1974a) Bone resorbing activity in supernatants from lymphoid cell lines. *New England Journal of Medicine*, **290**, 867.
- MUNDY, G.R., RAISZ, L.G., COOPER, R.A., SCHECHTER, G.P. & SALMON, S.E. (1974b) Evidence for the secretion of an osteoclast stimulating factor in myeloma. *New England Journal of Medicine*, **291**, 1041.
- MUNDY, G.R., TURCOFFE, R., BANDELIN, J.C. & RICK, M.E. (1976) Osteoclast activating factor (OAF)—The cause of hypercalcemia in a patient with chronic lymphosarcoma cell leukemia. *Proceedings of the United States Endocrinological Society, Abstr. II*.
- MUNSON, P.L., TASHJIAN, A.H. & LEVINE, L. (1965) Evidence for parathyroid hormone in non-parathyroid tumors associated with hypercalcemia. *Cancer Research*, **25**, 1062.
- OMENN, G.S., ROTH, S.I. & BAKER, W.H. (1969) Hyperparathyroidism associated with malignant tumours of non-parathyroid origin. *Cancer*, **24**, 1004.
- PLIMPTON, C.H. & GELLHORN, A. (1956) Hypercalcemia in malignant disease without evidence of bone destruction. *American Journal of Medicine*, **21**, 750.
- POWELL, D., SINGER, F.R., MURRAY, T.M., MINKIN, C. & POTTS, J.T. (1972) A new syndrome of hypercalcemia with cancer. *Clinical Research*, **20**, 569.
- POWELL, D., SINGER, F.R., MURRAY, T.M., MINKIN, C. & POTTS, J.T. (1973) Non-parathyroid humoral hypercalcemia in patients with neoplastic diseases. *New England Journal of Medicine*, **289**, 176.
- POWLES, T.J., CLARK, S.A., EASTY, D.M., EASTY, G.C. & MUNRO-NEVILLE, E. (1973) The inhibition by aspirin and indomethacin of osteolytic tumour deposits and hypercalcaemia in rats with Walker tumour and its possible application to human breast cancer. *British Journal of Cancer*, **28**, 316.
- POWLES, T.J., DOWSETT, M., EASTY, G.C., EASTY, D.M. & NEVILLE, A.M. (1976) Breast cancer osteolysis, bone metastases and the anti-osteolytic effect of aspirin. *Lancet*, **i**, 608.
- RICHMOND, J., SHERMAN, R.S., DIAMOND, H.D. & CRAVEN, L.F. (1962) Renal lesions associated with malignant lymphomas. *American Journal of Medicine*, **32**, 184.
- SEYBERTH, H.W., HUBBARD, W.C., MORGAN, J.L., SWEETMAN, B.J. & OATES, J.A. (1976) Prostaglandin-mediated hypercalcemia in the VX₂ carcinoma-bearing rabbit. *Clinical Research*, **24**, 370A.
- SEYBERTH, H.W., HUBBARD, W.C., MORGAN, J.L., SWEETMAN, B.J. & OATES, J.A. (1977) Prostaglandin mediated hypercalcemia in the VX₂ carcinoma-bearing rabbit. *Prostaglandins*, **14**, 319.
- SHERWOOD, L.M., O'RIORDAN, J.L.H., AURBACH, G.H. & POTTS, J.T. (1967) Production of parathyroid hormone by non-parathyroid tumours. *Journal of Clinical Endocrinology*, **27**, 140.
- SINGER, F.R., POWELL, D., MINKIN, C., BETHUNE, J.C., BRUKMAN, A. & COBURN, J.W. (1973) Hypercalcemia in reticulum cell sarcoma without hyperparathyroidism or skeletal metastases. *Annals of Internal Medicine*, **78**, 365.
- TASHJIAN, A.H., LEVINE, L. & MUNSON, P.L. (1964) Immunohistochemical identification of parathyroid hormone in non-parathyroid neoplasms associated with hypercalcemia. *Journal of Experimental Medicine*, **119**, 467.
- TASHJIAN, A.W., VOELKEL, E.F., LEVINE, L. & GOLDBERGER, P. (1972) Evidence that the bone resorption-stimulating factor produced by mouse fibrosarcoma cells is prostaglandin E₂. *Journal of Experimental Medicine*, **136**, 1329.
- VOELKEL, E.F., TASHJIAN, A.H., FRANKLIN, R., WASSERMAN, E. & LEVINE, C. (1975) Hypercalcemia and tumor prostaglandins—The VX₂ carcinoma model in the rabbit. *Metabolism*, **24**, 973.