Commentary

The hypercalcaemia of malignancy: changing hypotheses

H. M. Docherty and D. A. Heath

Over the past years the explanation of the hypercalcaemia associated with malignancy has changed repeatedly. Theories have come and gone and, in some cases, come again. The search for new hypercalcaemic factors is gaining momentum and major new breakthroughs seem imminent.

The original explanation of the hypercalcaemia of malignancy was that it was due to bone metastases physically causing the release of calcium from bone. This simple theory, though widely believed, was not supported by any evidence. Many patients with extensive bone disease had normal serum calcium values, many were hypercalcaemic in the absence of bone metastases, and certain malignancies had high or low incidences of hypercalcaemia despite similar rates of bone metastases, c.f. squamous cell and small cell carcinoma of the lung. That certain malignancies might produce a humoral factor was suggested by the work of Gordan, Cantino, Erhardt et al. (1966) who claimed to have isolated vitamin D-like sterols from breast cancer. Subsequent work, however, failed to confirm this, but the hunt for humoral mediators of hypercalcaemia was on. Breast cancer remains the principle example of a malignancy in which hypercalcaemia is virtually never seen in the absence of bone secondaries; however, it seems likely that the cancer cells stimulate osteoclastic bone resorption at endostial surfaces by releasing prostaglandins or other, locally acting, bone resorptive factors (Mundy, DeMartino & Rowe, 1981).

Evidence began to emerge that the hypercalcaemia associated with non-metastatic malignancy could, occasionally, be completely corrected by treatment of the primary tumour. Furthermore, the biochemical changes present in such patients closely resembled those of primary hyperparathyroidism (Stewart, Horst, Defts et al. 1980). This information suggested the production of a humoral agent by the primary tumour, and the possibility that it might be parathyroid hormone (PTH) was raised. There followed much conflicting evidence on circulating PTH levels in patients with hypercalcaemia of malignancy, with some findings appearing to confirm the ectopic production of PTH. Recent work, however, which includes the application of greatly improved immunological and biological means of detecting PTH in serum and tumour extracts, as well as recombinant DNA techniques for the detection of RNA encoding PTH in tumour cells, has cast considerable doubt on those early findings, and it is now believed that no case of ectopic PTH production has been adequately demonstrated (Skrabeneck, McPartlin & Powell, 1980). Despite this, the term ‘ectopic PTH syndrome’ refuses to disappear, although the term humoral hypercalcaemia of malignancy (HHM) is to be preferred.

In recent years the number of tumour-derived factors displaying bone-resorbing properties which have been suggested as mediators of HHM has increased considerably. These are most readily dealt with in groups. Cells associated with the immune system produce numerous factors capable of inducing bone resorption. During the 1970s these were classed together under the title of osteoclast-activating factor but are now known to comprise, at least, tumour necrosis factors α and β (Bertolini, Nedwin, Bringman et al. 1986). The hypercalcaemia associated with some haematological malignancies may be due to the local activation of osteoclasts by these factors produced by myeloma cells in the marrow cavity. Unrelated to osteoblast-activating factors but again immune system derived, the monokine interleukin 1 has demonstrable bone-resorbing activity (Gowen, Wood, Ihrie et al. 1983). The production of this factor was recently demonstrated in cultured cells derived from squamous cell carcinomas, which cause hypercalcaemia when transplanted into nude mice (Sato, Fujii, Kasono et al. 1987).

In 1984 conclusive reports were made that HTLV type-1 associated T-cell lymphomas, most common in oriental subjects and universally associated with osteolytic bone lesions and hypercalcaemia, produce 1,25-dihydroxy-vitamin D (Breslau, McGuire, Zerwekh et al. 1984). Thus vitamin D returned to the list of causes of malignant hypercalcaemia.

The transforming growth factors (TGF) constitute the second major group of bone resorbers implicated in the aetiology of HHM. Both TGFα and TGFβ have been isolated from tumours used as experimental...
models of HHM. Platelet-derived growth factor has been shown to enhance the bone-resorptive effects of TGFα and TGFβ in vitro (Assoian, Grotendorst, Miller & Sporn, 1984) and may be a common product of HHM tumour cells (Deuel, Huang, Strobant & Waterfield, 1983). Although epidermal growth factor and TGFα, which share a receptor, have been shown to produce hypercalcaemia when infused into mice (Tashjian, Voelkel, Lloyd et al. 1986), it still remains for the clinical significance of these growth factors in HHM to be established.

The third and final group of putative mediators of HHM comprise the PTH-like factors. These have largely been characterized by their ability to activate adenylate cyclase via PTH receptors on osteoblastic or kidney cells in culture, or on renal membranes. The PTH-like biological activity generated by the tumour factors was consistently found to be inhibited in the presence of the PTH receptor-binding antagonist bovine PTH (3–34), but unaffected by saturating concentrations of antisera to PTH known to inhibit PTH bioactivity. Although biologically similar to PTH, these factors are both immunologically (Powell, Singer, Murray et al. 1973; Gottlieb, Rude, Sharp & Singer, 1982; Loveridge, Kent, Heath & Jones, 1985) and genetically (Simpson, Mundy, D’Souza et al. 1983; Docherty & Heath, 1987) distinct from the hormone. Several groups have demonstrated the presence of the PTH-like factors in tumours associated with HHM, and there is general agreement over their published characteristics, however their chemistry remains to be fully determined. Our own work shows that up to four distinct molecular forms of the active peptide can be extracted from a single human tumour (Docherty & Heath, 1987). Last year Rabbani, Mitchell, Roy et al. (1986) published the purification of PTH-like factors from human and rat sources, so it seems that the full identity of this agent or agents will be known within the next year. The evidence for the role of PTH-like factors in HHM is again largely circumstantial, but the isolation of tumour products with PTH bioactivity from a patient who had overt ‘parathyroid’ bone disease is highly suggestive that the PTH-like factors were the aetiological agents in that patient’s metabolic disorder (Loveridge et al. 1985). Of particular relevance to this argument is the discovery of a PTH-like factor produced by non-transformed, human keratinocytes in culture (Merendino, Insogna, Milstone et al. 1986). Our own work confirms this finding and our preliminary results show that the major active component has a molecular weight of around 9000 daltons, similar to one of the factors isolated from a tumour in our laboratory. Should the two be shown to be related, or identical, it would suggest that the factor is produced by normal epithelial cells at some stage in their development, presumably for a paracrine function. This may explain why tumours of epithelial origin are among the commonest to be associated with hypercalcaemia.

The past 20 years have seen numerous developments in the understanding of the hypercalcaemia of malignancy. It seems clear that no one factor or mechanism will be implicated, but a number which will vary in importance depending on the type of tumour and its environment. One thing seems certain, the explosion of interest in this area ensures that many of the important questions about HHM will be answered in the very near future.

REFERENCES


Department of Medicine,
Queen Elizabeth Hospital,
Edgbaston,
Birmingham B15 2TH.