Nonparathyroid Hypercalcemia

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The hypercalcemia of malignancy is important in differential diagnosis, since the physician must know whether a given patient who presents with hypercalcemia has malignancy as the cause or a more benign disorder, such as hyperparathyroidism or sarcoidosis. Hypercalcemia can be life-threatening and must often be treated by general measures even before the diagnosis is known. More definitive therapy, however, requires a firm diagnosis. Clinically, malignancy is often evident due to a variety of systemic symptoms and obvious signs and manifestations of the tumor, but occasionally the presence of the malignancy is not obvious. There may be an occult tumor with a slow clinical course, such as hypernephroma. Alternatively, in an individual with chronic obstructive pulmonary disease, radiological detection of a lung tumor may be difficult, and the symptoms of chronic disease difficult to distinguish from the presence of malignancy.

In many cases of hypercalcemia and malignancy, the biologically responsible agent is not parathyroid hormone. Studies of the chemical and biological nature of the tumor-derived factors responsible for the hypercalcemic syndrome(s) may provide clues to the physiological roles of the substances (assuming overproduction of naturally occurring factors) and may contribute to the knowledge of basic mechanisms of oncogenic transformation. Current theories of oncogenesis suggest that overproduction of substances normally produced in cells occurs as a “downstream” effect of excessive action of promotors or enhancers. In this regard, the association of hypercalcemia with certain types of tumor may reveal interesting features of genetic translocation in tumor cells responsible for hypercalcemia.

Clinical observations of tumor hypercalcemia have a long and sometimes confusing history. In 1941, Albright called attention to the peculiar “parathyroid-like” features of tumor hypercalcemia. Fifteen years later, Lafferty defined the syndrome of pseudohyperparathyroidism in his excellent 1966 review. Around 1972 Arnaud and his colleagues found detectable or slightly elevated immunoreactive PTH in most malignancies. However, a year or two later, Powell and his colleagues in our group found that immunoreactive PTH was not detectable in blood or tumor extracts in most patients with malignancy and hypercalcemia. This confusing situation is still unresolved today. Parathyroid hormone is frequently detected in the circulation of many patients, despite the growing...
evidence that the responsible tumor-derived agents are not biologically identical to active parathyroid hormone in the blood. Hence, parathyroid hormone levels might have been expected to be undetectable.

Several decades have elapsed since the initial clinical interest in the etiology of the hypercalcemia of malignancy. Only recently have certain clinical tests (1,25(OH)2D, fasting urinary calcium and bone biopsies) begun to clarify the confusion surrounding this problem. Twenty years ago, Sherwood performed studies with Aurbach, O'Riordan, and myself to indicate that some tumors contained parathyroid hormone. Tashjian and Munson had similar findings. Today, Singer, et al (pp. 288 ff.) reviewed evidence about the frequency with which immunoreactive PTH can be detected in tumor extracts. Despite this evidence, many clinical and laboratory features noted in hypercalcemic patients with cancer suggest that parathyroid hormone is not the responsible mediator of the hypercalcemia. Hence, attention has begun to focus on identification and isolation of tumor-derived agents distinct from parathyroid hormone that act as bone resorbing factors.

Clinically, Stewart and Broadus and their colleagues (pp. 284 ff.), as well as other groups, have made useful advances in differential diagnosis by simultaneous application of hormonal assays and related biochemical techniques. Useful distinctions have been found between patients with hypercalcemia of malignancy and those with hypercalcemia due to hyperparathyroidism. Disagreements about certain findings among groups exist; these must reflect variations in patient populations or differences in techniques.

In 1983, one can say with greater confidence that parathyroid hormone is not biologically responsible for tumor hypercalcemia in most cases. The normal or even slightly increased circulating immunoreactive PTH detected by many laboratories may mean that inactive or incomplete PTH is being secreted as a type of tumor marker. Alternatively, low levels of hormone may still be secreted by suppressed glands at concentrations detectable by some assays. Finally, abnormalities in blood proteins associated with malignancy may affect immunoassay results in a totally nonspecific fashion. Goltzman and colleagues (pp. 6 ff.) indicated that this confusion about the nature of circulating “PTH-like” material in patients with malignancy is evident even in the cytochemical bioassay.

No clear consensus exists among groups about the practical usefulness of applying a battery of special assays, such as nephrogenous cyclic DMP, 1,25(OH)2D3, renal tubular clearance of mineral ions, and other tests, because of continuing disagreement about certain results with these tests as used by different groups. Cost effectiveness of the approach is not clear. The best future direction may derive from present efforts to isolate and chemically characterize the responsible nonparathyroid tumor substances. Specific assays for these tumor factors should be useful.

The evidence seems to point to multiple factors distinct from one tumor to another. Different groups have identified tumor-derived growth factors, peptides of molecular weight several times larger than parathyroid hormone, and peptides also distinct from parathyroid hormone but similar in molecular size. Certain evidence points to action of the factor through the parathyroid hormone receptor with stimulation of cyclic AMP as central to the mechanism of action of the tumor-derived hypercalcemic factors. However, others, as summarized by Brinshurst and colleagues, (pp. 295 ff.) find bone resorbing activity in the absence of increased cyclic AMP production at the levels of the substance required to resorb bone in in vitro assays. Hence, even in basic studies of tumor factors, a single direction of research findings is not yet evident.