ONCOLOGY

Edited by Jerome B. Block, M.D.

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Preface

Cancer is among the most common and therapeutically complex diseases encountered by internists today. This volume has been developed as part of the UCLA School of Medicine's current postgraduate education program for internists. It discusses cases of clinical cancers and lymphomas in which the informed internist can have an important and useful impact on the diagnosis and management of the patient. Throughout the volume considerable information and attention is given that should be useful to the reader in deciding whether a specific patient has been adequately evaluated or "staged" so that a correct therapeutic decision can be made. Also considered are those areas in which no specific useful anticancer treatment is available; in such instances the internist's role may be critical to good patient advice and further responsible care.

Cancer therapy today benefits from numerous educational efforts in journals, books, and at national meetings often geared to the cancer specialist or to the generalist. It is the intent of this publication to offer current approaches in cancer management that are focused in scope and relevant to today's internist. A CME post-test is included for self-assessment purposes, which should reflect, in part, the value of the book for its readers.

Trends in cancer care today seem increasingly concerned with informed patient decisions and therapeutic choices. Certainly these choices are increasingly broad and often extend beyond orthodox therapies by trained cancer specialists. In this atmosphere the internist may be anticipated to have a "neutral" but increasing role in the responsible advice given to the patient with cancer as to the merits, goals, and deficiencies of modern cancer therapy. This book will offer clear information in these areas.

J.B.B.

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Production of Ectopic Hormones by Tumors

INTRODUCTION

The association of hormonal syndromes with cancer was recognized in the late 1800s and early 1900s; later it became known that neoplasms arising from a variety of tissues could produce conventional hormones. The term *ectopic* was applied to the production of a hormone by a neoplasm derived from tissue that does not normally produce that hormone. The number of hormones now reported to be produced by nonendocrine tumors is large, yet the list remains incomplete (Table 1-1). Except for prostaglandins, those listed in the table are all peptide hormones. In addition, in many apparently humoral syndromes that are associated with cancer, the etiology remains unclear. Current evidence suggests that neoplasms not only produce hormones that cause symptoms but even more commonly elaborate biologically inactive peptides that go unrecognized. Probably all peptide hormones (and possibly other peptides) evolve during synthesis, storage, secretion, and degradation through what we have termed a peptide cascade.

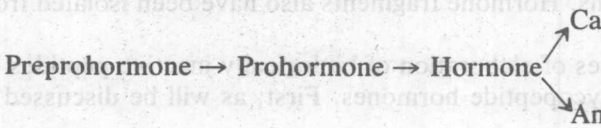

Table 1-1 **Hormones Reportedly Produced by Nonendocrine Neoplasms**

Adrenocorticotropic hormone, adrenocorticotropic prohormone
Lipotropins
Human chorionic gonadotropin (intact and β-subunit)
α-Glycopeptide chain
Vasopressin
Parathormone
Prostaglandins
Osteoclast-activating factor
Somatomedins
Hypoglycemia-producing factor(s)
Insulin
Erythropoietin
Gastrin
Secretin
Vasoactive intestinal polypeptide
Gastric inhibitory polypeptide
Glucagon
Somatostatin
Thyroid-stimulating factor
Hypophosphatemia-producing factor
Calcitonin
Corticotropin-releasing hormone
Prolactin
Growth hormone
Chorionic somatomammotropin

A preprohormone is synthesized at the messenger ribonucleic acid (RNA). It usually begins with methionine, which is followed by an additional hydrophobic amino-acid sequence that may be important in channeling the peptide to the Golgi apparatus for packaging into storage form. The preprohormone is rapidly cleaved to the prohormone. Except for progastrin (which is biologically active), prohormones are biologically inactive or only weakly active. In some endocrine tissues, the prohormone is the major storage form of the hormone. At the time of secretion, the prohormone is cleaved to the bioactive hormone, which is the major form secreted into the blood. The degree of degradation of the bioactive hormone within the cell prior to secretion into the blood is not known. In the blood, the hormone is degraded into fragments, either by peripheral tissues or by circulating peptidases; the carboxyl fragment is, in general biologically inactive, but the amino fragment may retain bioactivity.

Precursor forms of hormones—probably prohormones—are commonly elaborated by neoplasms. Hormone fragments also have been isolated from tumor extracts.

Two other examples of elaboration of biologically inactive peptides by tumors relate to the glycopeptide hormones. First, as will be discussed in

the section on gonadotropin production, the glycosylation of human chorionic gonadotropin (hCG) is important for its biologic action; the removal of sialic acid residues results in a virtually complete loss of in vivo bioactivity because the half-life of the peptide in blood is shortened to <1 minute. Studies from our laboratory have shown that although all extracts of a variety of carcinomas contained hCG, in many tumors the hCG had a reduced carbohydrate content. This hCG with reduced carbohydrate content would be expected to have little biologic potency in vivo.

Second, the synthesis of biologically inactive peptides by tumors is illustrated by the elaboration of only one of the two chains composing the bioactive glycopeptide hormones. These hormones, including hCG, luteinizing hormone, follicle-stimulating hormone, and thyrotropin, are composed of an α-chain and a β-chain, neither of which has bioactivity alone. The α-chain is identical for luteinizing hormones, follicle-stimulating hormone, and thyrotropin; for hCG it differs only by a two-residue amino-acid inversion and an additional three residues at the amino terminus. Biochemical differences in the β-chain of each hormone confer immunologic and biologic specificity. Combination of the α-chain with a β-chain results in a bioactive molecule whose bioactivity relates to the β-chain. Carcinomas have been shown commonly to secrete only the α-chain and, less commonly, only the β-chain.

The evidence demonstrating the frequency of production of these biologically inert peptides by tumors led us to postulate and test the hypothesis that ectopic synthesis of peptides is a universal concomitant of neoplasia. Data so far have supported this hypothesis.* While these biologically inert peptides may prove to be useful tumor markers, they produce no clinically recognizable syndrome.

Ectopic synthesis of peptides by neoplastic cells appears to result from increased translation of genetic data present in every cell of the organism. It is estimated that over 90% of the genetic data coded in nuclear deoxyribonucleic acid (DNA) are repressed in the differentiated cell. Activation of the repressed DNA during cell replication may result in "new" protein synthesis. Some data indicate that the genomes for hormones such as hCG and calcitonin in humans and adrenocorticotropin (ACTH) in rats and in smoking dogs are not completely suppressed in various noncancerous tissues—i.e., lung, colon, and liver. The mechanisms for control of activation or regulation of protein synthesis are not fully understood. Normal cell replication and the process of neoplasia may affect these controls. Peptide synthesis may be activated randomly in neoplasia, or (as enzyme studies indicate) there may be an ordered, neoplasia-linked reprogramming of gene expression. The distinction between ectopic peptide elaboration by replicating normal cells and that by neoplastic cells is obviously important; if

* Supported by National Cancer Institute Contract No. NOI-CB-43903.

these peptides are to be useful as tumor markers, they must be quantitatively or qualitatively specific for the neoplastic process. To date, evidence supports the belief that "ectopic" peptide synthesis occurs in all carcinomas; those tumors associated with a clinical syndrome of ectopic hormone production process more ubiquitous, biologically inactive peptides to bioactive hormones.

HYPERCALCEMIA

For more than 50 years, the association of hypercalcemia with cancer has been recognized. In 1923, one report described a man with hypercalcemia in whom a locally extended carcinoma of the gallbladder was discovered at autopsy, with no abnormality of the parathyroid glands. In 1936, another author described a 57-year-old man with elevated levels of calcium in serum (16 to 18 mg/100 ml), decreased concentrations of phosphates in serum (2.1 to 2.4 mg/100 ml), incidental Paget's disease of bone, and bronchogenic carcinoma. The cases of these patients served as the background for discussion in still another report of a 50-year-old man with severe hypercalcemia, renal carcinoma metastatic to the ilium, and no parathyroid abnormality detectable by surgical exploration. The investigator pointed out that if the hypercalcemia had been attributable to bony dissolution, it would have been associated with hyperphosphatemia, whereas these patients had hypophosphatemia. It was suggested for the first time that carcinomas may elaborate a substance with parathormone-like activity.

The type of malignancy most commonly associated with hypercalcemia in patients without bone metastases is carcinoma of the lung. A study of 200 consecutive patients with carcinoma of the lung revealed hypercalcemia in 12.5%. Twenty-three percent of patients with epidermoid carcinoma, 2.5% of those with adenocarcinoma, and 12.7% of those with large-cell anaplastic carcinoma either presented with or developed hypercalcemia. No patients with small-cell carcinoma developed hypercalcemia. Fourteen of the 25 patients with hypercalcemia did not have osseous metastases.

The next type of cancer most frequently associated with nonmetastatic hypercalcemia is renal carcinoma. A study of 118 patients with renal cell carcinoma revealed hypercalcemia in 13% at the time of diagnosis.

Several causes of hypercalcemia associated with malignancy have been well characterized: production of ectopic parathormone, production of prostaglandins or osteoclast-activating factor by tumors, and coexisting primary hyperparathyroidism. The relative frequency of each cause is unclear; estimates vary with the methods used and with the focus of the investigators involved. More then one cause may be implicated in some patients with cancer.

Production of Ectopic Parathormone

Results of reports have supported the idea that production of a parathormone-like peptide by tumors causes hypercalcemia. In studies of patients with cancer and hypercalcemia, parathormone was demonstrated by immunologic techniques in extracts of tumor tissue and by immunofluorescent staining of the tumor. This parathormone-like material, when further characterized chemically, appeared to be identical to endogenous parathormone. In case reports of patients with hypercalcemia associated with breast carcinoma, parathormone was identified in extracts of the tumors; in patients with breast cancer and normal levels of calcium in serum, no parathormone activity was found in tumor extracts.

The most convincing description of ectopic parathormone production involved a patient with renal carcinoma and hypercalcemia. Tumor extracts studied by radioimmunoassay contained parathormone in a concentration of 2,200 ng/g of tissue, while extracts of normal kidney contained no detectable amounts. An increased concentration of parathormone was demonstrated in the venous drainage from the tumor compared to that in arterial blood. After removal of the tumor, the level of parathormone in serum fell to normal.

Ectopic parathormone production was implicated in a patient with hypercalcemia associated with acute myeloblastic leukemia. On six occasions hypercalcemia recurred with relapses of leukemia, and on two of these occasions the serum level of parathormone was abnormally high. Parathormone was released in vitro from the patient's myeloblasts, but not from normal cells.

Results of all of these studies suggest that the production of parathormone by tumors may be a common cause of hypercalcemia associated with neoplasms. It is significant, however, that serum parathormone concentrations were not measured in most of the patients described as having this syndrome.

Urinary adenosine 3′:5′-cyclic monophosphate (cyclic AMP) was studied in order to evaluate secretion of bioactive parathormone associated with hypercalcemia of malignancy. From one third to one half of urinary cyclic AMP is generated in the kidney under the control of parathyroid hormone. In normal subjects, the infusion of calcium in order to increase serum concentrations to 10.5 mg/dl has been shown to suppress urinary excretion of cyclic AMP to <4 μmol/g of creatinine. In patients with hypercalcemia, a urinary level of cyclic AMP >4 μmol/g of creatinine suggests that the hypercalcemia is mediated by parathormone. Primary hyperparathyroidism is associated with an elevated level of urinary excretion of cyclic AMP (average level, 8.5 μmol/g of creatinine). In this study, patients with hypercalcemia associated with malignancy fell into two groups. In one group suppressed urinary excretion of cyclic AMP (≤ 4 μmol/g of creatinine) suggested that

hypercalcemia was not mediated by parathormone; these patients all had evidence of metastatic bone lesions. Six of 10 patients with elevated urinary excretion of cyclic AMP had no evidence of bone metastases; these patients had levels of immunoreactive parathormone in blood that were inappropriately high for the degree of hypercalcemia, but lower than parathormone concentrations in patients with primary hyperparathyroidism. The observation that urinary levels of cyclic AMP did not correlate with the low serum concentrations of parathormone suggests that a nonparathormone substance from the tumor was contributing to the elevation of urinary cyclic AMP levels and to the hypercalcemia. In this study, autopsy of 2 patients with elevated urinary levels of cyclic AMP revealed no pathologic condition of the parathyroid gland.

No parathormone is detectable in tumor extracts from about 50% of patients with neoplasms and hypercalcemia studied so far. In 1974, Powell et al. studied 11 patients with hypercalcemia, hypophosphatemia, and no bony metastases. In 9 of these patients, surgical ablation or antitumor therapy restored serum levels of calcium to normal. Parathyroid hormone was not detectable either in peripheral blood or in tumor extracts, despite the assessment of these samples with various radioimmunoassays designed to detect intact parathormone as well as parathormone fragments. However, tissue extracts did cause calcium resorption in an in vitro mouse-calvarium bioassay. These data suggest that a nonparathormone substance elaborated by the tumors studied is responsible for the hypercalcemia and that ectopic parathormone production is relatively rare.

Production of Prostaglandins

Mouse fibrosarcoma associated with hypercalcemia has been shown to produce prostaglandins that stimulate bone resorption. This hypercalcemia can be corrected with indomethacin, a potent inhibitor of prostaglandin synthesis. Indomethacin was given to a 54-year-old man with renal carcinoma, hypercalcemia, hypophosphatemia, and no detectable parathormone in serum. This patient responded dramatically, with a return to normal of serum levels of calcium and phosphorus.

Eight human breast carcinomas were reported to cause the release of calcium from mouse calvaria in vitro. A partial suppression of this calcium mobilization by aspirin (16 μg/ml) suggested prostaglandin production. The effects of aspirin and the production of prostaglandins in the patients involved were not studied in vivo.

A study of the urinary prostaglandin metabolite PGE-M in 15 normocalcemic and 14 hypercalcemic patients with cancer revealed increased PGE-M excretion only in patients with solid tumors who either had hypercalcemia or later became hypercalcemic. The level of excretion of PGE-M became normal within 5 days of the initiation of treatment with aspirin or

indomethacin. Serum levels of calcium decreased significantly but did not completely normalize in patients with bony metastases.

Plasma levels of prostaglandin E have also been studied in patients with solid tumors. Fourteen of the 19 patients studied were hypercalcemic, and 10 of these 14 had extensive bony metastases. Eleven of the 14 hypercalcemic patients had elevated plasma PGE concentrations.

Thus, the data indicate that prostaglandin production may be a common cause of hypercalcemia in cancer. According to the highest estimates, prostaglandin production may account for 80% or more of such cases.

Production Of Osteoclast-Activating Factor

A third reported cause of the hypercalcemia of malignancy is the production of osteoclast-activating factor (OAF), a peptide normally produced by white blood cells. This peptide is as potent as parathormone in stimulating bone resorption from fetal rat radius and ulna. Hypercalcemia is common in patients who have multiple myelomas but rare in patients who have diseases associated with an equally packed bone marrow, such as chronic lymphocytic leukemia, acute leukemia, and Waldenström's macroglobulinemia. In vitro, myeloma and lymphosarcoma cells secrete OAF; as a result of OAF elaboration, myeloma and lymphosarcoma may cause hypercalcemia. Other white cell malignancies associated with hypercalcemia (e.g., acute lymphocytic leukemia and acute myeloblastic leukemia) also may elaborate OAF.

The frequency of hypercalcemia associated with hematologic malignancies can be estimated on the basis of one large study, in which 33 patients with lymphoma and 13 patients with leukemia were found among 430 hypercalcemic patients with malignancy. In the previously discussed patient who had acute myeloblastic leukemia and hypercalcemia, whose tumor cells elaborated parathormone in vitro, and whose blood contained an elevated level of parathormone, the tumor cells were not studied for OAF production.

Osteolytic Activity of Tumors

The most common cause of hypercalcemia associated with malignancy is bone metastasis. Breast carcinoma is the type of malignancy most frequently causing hypercalcemia associated with bone metastases. Increased osteoclastic activity has been observed on bone surfaces adjacent to neoplasms. In vitro, the release of calcium[45] from living or devitalized fetal rat long bone increased during incubation with normal monocytes or human breast cancer cells. In the devitalized tissue, this bone resorption was not mediated by osteoclasts (i.e., OAF), but was caused directly by the monocytes and cancer cells themselves.