Differential Diagnosis of Hypercalcemia and Cancer

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There has been considerable interest in hypercalcemia recently, in part because this biochemical abnormality touches upon a wide variety of disciplines: to the endocrinologist, it poses a problem in differential diagnosis; to the oncologist, a problem related to tumor growth or function; to the internist, it often demands prompt treatment; to the radiologist, it means a radiographic evaluation of the skeleton; to the neurologist, it necessitates consideration of metabolic encephalopathy in his appraisal of the central nervous system; and to the clinical scientist, it poses many questions regarding pathogenesis. Hypercalcemia in patients with cancer was reported sporadically in the past, but has been described with increasing frequency over the last 20 years as a result of increased recognition and, perhaps to a major extent, because of the remarkable increase in the availability of serum calcium measurements.

There are, of course, a number of other disturbances of calcium homeostasis in cancer patients such as hypercalcemia, hyper- and hypoparathyroidism, Vitamin D-resistant osteomalacia and osteoporosis. Although these abnormalities are of substantial interest in themselves, the current review is limited to a discussion of the hypercalcemic syndrome in the adult with cancer from the standpoint of clinical manifestations, diagnostic evaluation, pathogenesis and treatment.

Clinical Manifestations
Cancer hypercalcemia occurs most often in patients with carcinoma of the breast and, usually, associated bone metastases. The frequency of hypercalcemia in this group may be due to the large number of patients with breast cancer, but obviously this is not the only reason, since patients with colorectal cancer, also a common tumor, rarely develop hypercalcemia. Another factor linking breast cancer with hypercalcemia is that treatment of the cancer with androgens, estrogens and progestins may induce hypercalcemia. In our experience, hypercalcemia associated with solid tumors occurs, in decreasing order of frequency, as follows: cancers of the breast, lung,
kidney, head and neck, cervix, prostate, neuroblastoma, melanoma, and a wide variety of miscellaneous tumors. It is also frequently found in the hematological neoplasms (lymphomas, leukemia, myeloma). The incidence, however, varies from institution to institution depending on referral patterns. In a retrospective review of 430 patients with cancer and hypercalcemia, 86 percent of those who had bone surveys (334/390) had X-ray evidence of bone metastases. It has been stated that hypercalcemia in the absence of bone metastases on X-ray most often occurs in patients with squamous cancer of the lung, but we have seen this association even more frequently in those with lymphomas. Of course, skeletal surveys can not in themselves rule out bone metastases; autopsy studies have revealed the presence of metastases to the bone in about one-third of patients with negative skeletal radiographs.

Patients with cancer who have hypercalcemia, hypophosphatemia, hypercalciuria and negative bone surveys or scans may have the syndrome of ectopic hyperparathyroidism, due solely to the cancer, or they may have coexistent primary hyperparathy-

| General: | Somnolence, lethargy, weakness |
|---------|--------------------------------|
| Gastrointestinal: | Anorexia, nausea, vomiting, constipation, abdominal pain, peptic ulcer, pancreatitis |
| Renal: | Polydipsia, polyuria, nephrolithiasis, nephrocalcinosis, renal failure |
| Neurological: | Hyporeflexia, myopathy, stupor, coma, occasionally localizing signs, modest increases in CSF protein, visual abnormalities, psychotic behavior |
| Cardiac: | Shortened QT interval, bradycardia, tachycardia, digitalis sensitivity, arrhythmias, hypertension |
| Skeletal: | Fractures, pain, skeletal deformities, loss of height |
| Associated Endocrinopathies: | Symptoms and signs of Zollinger-Ellison syndrome, pituitary and adrenal tumors, pheochromocytoma, medullary carcinoma of the thyroid |
| Miscellaneous: | Poor skin turgor, calcinosis, band keratopathy, hypercoagulability |
roidism. In a review of 100 consecutive patients with primary hyperparathyroidism seen at Memorial Hospital over a 35-year period, one-third had cancers that occurred either before, coincident with, or subsequent to the discovery of a benign parathyroid adenoma, and 10 of these had breast cancer. The presence of a breast mass and hypercalcemia does not necessarily mean that the two are related, but may well indicate the coexistence of cancer and hyperparathyroidism.

The clinical picture of patients with hypercalcemia may vary from no symptoms at all (i.e., an unexpected biochemical abnormality) to a full-blown hypercalcemic crisis manifested by nausea, vomiting, abdominal pain, lethargy, coma, dehydration and renal failure. The symptoms and signs, listed in Table 1, are notable for the wide range of organ systems that may be involved. Most patients, of course, do not present with the full spectrum but rather with one or another cluster of findings. The most common presenting complaints are anorexia, nausea, constipation, polydipsia and polyuria. However, it must be stressed that a particular organ system may be involved to the virtual exclusion of the others so that patients may be misdiagnosed as having, for example, diabetes insipidus (polydipsia, polyuria), brain metastasis (localizing neurological signs, mild increases in CSF protein) or an acute abdominal illness (nausea, vomiting, abdominal pain). The symptoms and signs of hypercalcemia are not per se indicative of its cause, and the physician must look for supporting evidence of various diseases. Thus, the common causes of hypercalcemia—cancer (with and without bone metastases), hematological neoplasms (myeloma, leukemia, lymphoma), hyperparathyroidism, sarcoidosis, vitamin D intoxication and thiazide administration—may be revealed only by associated information and not by the symptoms of hypercalcemia. The symptomatology of hypercalcemia probably depends in part on the rapidity of onset, the prior general condition of the patient and the presence or absence of underlying disease, particularly of the kidneys and central nervous system.

**Diagnostic Evaluation**

The evaluation of a patient with hypercalcemia, shown in Table 2, follows a "first things first" approach, and the clinician should attempt to arrive at a diagnosis using the minimum number of studies. The initial diagnostic effort includes at least two determinations of serum calcium, phosphorus and alkaline phosphatase activity, in order to avoid an incorrect decision based on possible laboratory or other error. It is useful to be familiar with the normal ranges of the laboratory making these determinations. For example, the former range of 9 to 11 mg./dl. for serum calcium cannot be safely applied any longer, since many laboratories now report lower normal ranges such as 8.8 or 8.9 to 10.3 or 10.4 mg./dl. Analysis of the serum protein is necessary to interpret fully the serum calcium (calcium is about 50 percent protein-bound) and as an initial step in the detection of dysproteinemias.

The presence of hypophosphatemia is supporting evidence for hyperparathyroidism but it may also occur in ectopic hyperparathyroidism, which is most commonly seen in patients with carcinomas of the lung, kidney, head and neck and non-Hodgkin's lymphoma. Hypophosphatemia is not usually found in breast cancer and, in fact, its occurrence in these patients should lead to the suspicion of coexistent hyperparathyroidism. Serum alkaline phosphatase activity is often
| Priority | Blood | Urine | X-rays | Other |
|----------|-------|-------|--------|-------|
| **First level evaluation** | Complete blood count Calcium X 2 Phosphorus X 2 Alkaline phosphatase X 2 Blood urea nitrogen Creatinine Total protein and A/G Na, K, CO₂, Cl Radio immunoassay for parathyroid hormone | Urinalysis Calcium (24-hour urinary Ca or Ca excreted per gram of creatinine in morning sample) Creatinine | Chest X-ray Flat film of abdomen X-rays of skull, hands X-rays of abnormal areas on bone scan or symptomatic areas | Bone scan Electrocardiogram Check for history of ingestion of milk, absorbable alcalis, thiazides and Vitamin D |
| **Second level evaluation** | Serum protein electrophoresis Serum thyroxin Uric acid Magnesium Plasma cortisol | Urinary 17 hydroxycorticosteroids | Intravenous pyelogram X-rays of esophagus and stomach | Marrow aspiration Bone biopsy Biopsy of abnormal tissue |
| **Third level evaluation** | Plasma ionized calcium Blood pH, pCO₂ Serum levels of gastrin and calcitonin Vitamin D | Urinary metabolite of prostaglandin E₂ (PGE-M) Urinary catecholamines | Special X-rays as indicated by history and clinical findings | Further endocrine studies for tumor markers as indicated by history and clinical findings |
elevated in cancer patients with hypercalcemia and may in part reflect associated liver disease. If it is elevated and the bone films do not show evidence of osteitis fibrosa, hyperparathyroidism is an unlikely cause of the hypercalcemia. Determinations of serum bicarbonate and chloride may be useful in the differential diagnosis in that the former generally tends to be slightly depressed and the latter somewhat increased in hyperparathyroidism, while the reverse occurs in cancer hypercalcemia. The chloride:phosphate ratio has been suggested as an index for differentiating between patients with hyperparathyroidism and those with hypercalcemia from other causes (i.e., CI/PO₄ > 33 in hyperparathyroidism and < 33 in hypercalcemia due to other causes). However, since patients with ectopic hyperparathyroidism (those with hypercalcemia, hypophosphatemia, cancer and no bone metastases) often have ratios in the hyperparathyroid range and patients with primary hyperparathyroidism may have ratios less than 33, this measurement has not proved to be the discriminating index it was once considered.

A few short years ago the inclusion of the serum iPTH (immunoreactive parathyroid hormone) in the first level of work-up of hypercalcemia would have been impossible. Now, this measurement is available through several commercial laboratories and although it has problems (laboratory-to-laboratory variations, different antisera “reading” different portions of the polypeptide molecule, immunoheterogeneity of circulating hormone, etc.), serum iPTH determinations are clinically useful and represent a great advance in the evaluation of patients with hypercalcemia. Serum concentrations of iPTH should be evaluated in relation to the concentration of serum calcium, since hypercalcemia should normally cause a reduction in the secretion of endogenous parathyroid hormone. Thus, a value could be in the normal range in an absolute sense but regarded as abnormal if considered in conjunction with an elevated serum calcium. In addition, a number of studies have shown a decreased quantity of biologically inactive COOH-terminal fragments of iPTH in ectopic hyperparathyroidism, in contrast to primary hyperparathyroidism.³ This difference has formed the basis for separating the two entities with a minimal overlap. Hence hypercalcemia with a relatively low value of serum iPTH (in the normal range or slightly above) would be more consistent with ectopic hyperparathyroidism, and hypercalcemia with high values of serum iPTH would favor the diagnosis of primary hyperparathyroidism. This distinction obviously depends on the use of an antiserum with specificity for the COOH-terminal portion of the PTH molecule. It would be well for the physician to be aware of some of these details regarding the laboratory method being used in order to fully interpret the serum iPTH results.

Urinary calcium may be measured on a 24-hour collection (normal is usually about 70-200 mg. calcium per 24 hours on a restricted calcium diet) or, more conveniently, on a morning random sample measuring both calcium and creatinine and expressing the results as mg. of calcium per gram of creatinine (normal urinary creatinine is 15-25 mg/kg. body weight per 24 hours; normal urinary calcium for a 50 kg. patient is 70-200 mg. per gram of creatinine). Since parathyroid hormone suppresses the renal clearance of calcium, the excretion of urinary calcium tends to be lower (for the same elevation of serum calcium) in patients with primary hyperparathyroidism
than in those with other forms of hypercalcemia. However, increased tubular reabsorption of calcium has been reported in some patients with cancer hypercalcemia, so that urinary calcium measurements may not be of help in the differential diagnosis. In addition, patients who are salt depleted may have spuriously low urinary calcium. Nevertheless, it has been our general impression that for equal degrees of hypercalcemia, patients with cancer tend to have higher urinary calcium values than those with primary hyperparathyroidism. Urinary calcium data may also provide a useful parameter of response to subsequent treatment and, for these reasons, such measurements are usually useful in the evaluation of patients with hypercalcemia.

X-rays are invaluable in the differential diagnosis of hypercalcemia. Chest films may suggest sarcoidosis, lymphoma or primary lung cancer, as well as possibly showing resorptive changes of the acromioclavicular joints, a radiographic sign of hyperparathyroidism. A flat film of the abdomen may reveal nephrolithiasis, which virtually never occurs in cancer hypercalcemia and, if present, is more consistent with primary hyperparathyroidism. An X-ray of the hands indicating subperiosteal resorption is virtually pathognomonic of hyperparathyroidism. Bone scans have been substituted for skeletal radiographs in surveys of the skeleton for bone metastases, with films reserved for abnormal areas of uptake or for symptomatic areas. In this connection it is well to remember that bone scans may not reveal increased uptake over a myeloma lesion; if this disease is suspected, X-rays of the skeleton should be taken.

If the diagnosis has not been arrived at with the above studies, additional studies are undertaken at the second level of evaluation (Table 2), including serum protein electrophoresis (M spike of multiple myeloma, diffuse hyperglobulinemia of sarcoidosis, increased alpha-2 and beta globulins in hyperparathyroidism). Searches for some of the rarer causes of hypercalcemia, such as hyperthyroidism and adrenal insufficiency, are also performed. Hyperuricemia has been reported in hyperparathyroidism (as has splenomegaly), but in general its occurrence should lead one to suspect cancer, especially lymphoma. Patients with hypercalcemia, whatever the cause, may have associated hypokalemia and hypomagnesemia; these are included in the diagnostic evaluation primarily for therapeutic reasons.

Other useful laboratory studies include intravenous pyelography (renal neoplasms), X-rays of the esophagus (displacement of the esophagus by a parathyroid adenoma) and stomach (ulcer, neoplasm) and bone marrow aspiration and biopsy for extrinsic cells or for evidence of leukemia, lymphoma or myeloma. Finally, biopsy of a subcutaneous nodule or lymph node may be the critical diagnostic step in the study of a patient with hypercalcemia.

The third level of evaluation (Table 2) includes more esoteric analyses used to detect associated endocrinopathies (multiple endocrine adenomatosis) and to appraise the possible role of prostaglandins (vide infra). Blood pH and pCO₂ may be helpful since systemic alkalosis in a hypercalcemic patient can be considered as evidence against hyperparathyroidism and more in favor of carcinoma or other non-parathyroid causes of hypercalcemia.

Although plasma ionized calcium measurements are now available, and although some clinicians have cited their usefulness in detecting normocalcemic hyperparathyroidism, it is reasonable to say that, almost without exception,
problems in the differential diagnosis of hypercalcemia can be resolved without these determinations.

Pathogenesis of Cancer Hypercalcemia

Available evidence indicates that enhanced bone resorption is the fundamental event in the production of cancer hypercalcemia. Radioisotope kinetic studies have shown that patients with cancer, bone metastases and normalcalcemia have normal skeletal accretion and resorption rates of calcium; when such patients become hypercalcemic, they have a markedly enhanced resorption rate of skeletal calcium and a slightly increased accretion rate. Since enhanced resorption rates were also observed in patients without bone metastases, it appears that increased bone resorption occurs in cancer hypercalcemia whether the cancer is intraskeletal or extraskeletal. (Figure.)

How do cancers produce these effects on bone? The subject has been a matter of considerable interest and a variety of physiologically active substances, possibly released by the tumor or caused by its presence, have been studied, including citrate, lactate, hydrogen ion, collagenases and sterols. However, three humoral substances have recently received most attention: parathyroid hormone, prostaglandins and osteoclast activating factor.

Parathyroid Hormone

The possibility that parathyroid hormone (PTH), ectopically produced by the tumor, may play a role in cancer hypercalcemia was raised a number of years ago by Albright, and has since been suggested by many clinical studies. Pre- and postoperative studies have revealed that removal of a non-parathyroid cancer can entirely reverse hypercalcemia, hypophosphatemia, hypercalciuria and hyperphosphaturia—the biochemical hallmarks of hyperparathyroidism. It has also been shown that, at least in some patients, increased levels of immunoreactive PTH may occur in the blood and tumor tissue. The inference has been drawn that the tumor is able to synthesize PTH ectopically, and that this is responsible for the observed hypercalcemia. Lung and kidney tumors have most often been implicated. However, recent studies have clearly shown that cancer hypercalcemia may be seen in these patients without any evidence of ectopic production of PTH. Some investigators have considered the possibility that tumors can elaborate a substance which stimulates the patient's own parathyroid glands to overactivity, but there is no evidence that such a substance exists. Histologic studies of parathyroid glands in cancer hypercalcemia have, almost without exception, failed to show signs of parathyroid hyperplasia. In addition, parathyroidectomy does not ameliorate the hypercalcemia of cancer.

Prostaglandins

The observation that prostaglandins may stimulate bone resorption was derived from organ cultures of bone explants, which showed that a tumor product from a transplanted mouse fibrosarcoma could cause bone resorption. Further studies of organ cultures revealed that prostaglandins E1 and E2 (PGE1 and PGE2) caused enhanced bone resorption of the explants. Subsequently, the mouse fibrosarcoma product was identified as PGE2. It was then shown that hypercalcemia occurred in animals bearing this tumor and that it was reversible with the administration of indomethacin, a drug capable of inhibiting prostaglandin synthesis. The relationship between PGE2, hypercalcemia and reversibility with indomethacin
was also found in another animal tumor system—the VX2 carcinoma of the rabbit.

Attention to the prostaglandins in clinical hypercalcemia began at a time when it was becoming increasingly clear that ectopic production of PTH could not explain all instances of hypercalcemia in cancer. Case reports appeared in which hypercalcemia was ameliorated in some patients with cancer as a consequence of treatment with indomethacin. However, such treatment was not universally successful and some investigators observed no correlation between changes in circulating PGE$_2$ induced by indomethacin and serum calcium.$^8$ These differences have apparently been reconciled in studies that measured the excretion of the major urinary metabolite of PGE$_1$ and PGE$_2$, known as 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid or, more simply, PGE-M.$^9$ This urinary metabolite was increased in 12 of 14 patients with cancer hypercalcemia but in none of those with hematopoietic neoplasms or hyperparathyroidism. The response of these patients to indomethacin has varied according to the presence or absence of bone metastases, as determined by X-rays or bone scans. Patients without bone metastases all responded with a decrease to normal serum calcium levels and decreased urinary PGE-M without any change in the normal excretion of cyclic AMP. Those with bone metastases showed only slight decreases in urinary PGE-M and the serum calcium response to indomethacin was minimal. Also of interest is the finding that some hypercalcemic patients who have a normal urinary excretion of PGE-M had an increased urinary cyclic AMP/creatinine ratio and some increase in serum chloride, which suggests ectopic PTH. However, no immunoreactive PTH could be identified in these patients.$^{14}$ Thus, prostaglandins appear to be the responsible humoral agent from tumors in some patients, notably those without bone metastases.

Another interesting development has been the observation that in some experimental tumor systems, pre-treatment of animals with aspirin or indomethacin prevented tumor deposits in bone and hypercalcemia, both of which occurred regularly in non-treated animals.$^{15}$ These studies were extended to patients with breast cancer and it has been reported that some human breast cancers contain and synthesize greater amounts of prostaglandins than normal breast tissue.$^{16}$ In one series of 38 women with operable breast cancer, 23 primary tumors showed in vitro osteolytic activity (presumably due to prostaglandins) and 15 did not. In a three-year follow-up period, seven patients in the former group developed bone metastases (four with hypercalcemia), compared to none in the latter group.$^{17}$ Experimental animal tumor studies have shown that osteolysis in cancer occurs in two steps: an initial step attended by osteoclastic resorption and a second step in which the tumor extensively invades bone and presumably causes destruction by direct action on bone. It appears that prostaglandins may be involved in the first step and that prostaglandin inhibitors might be effective against early osteolysis but not against late destruction.$^{18}$

Precisely how these findings will ultimately fit together depends on further study, but it appears that the prostaglandins, already so widely involved in the physiology of the human organism, may play still another role, this time in the pathogenesis of skeletal metastases and hypercalcemia.

Osteoclast Activating Factor (OAF)

This factor was first reported in cultures of human peripheral blood leuco-
cytes from patients with periodontal disease. Dental plaque antigen stimulated the leucocytes from these patients to elaborate a substance that caused osteoclastic bone resorption in an in vitro organ culture system. This substance has been partially purified and appears to be a polypeptide occurring in big and little forms.

In the quest for humoral factors in cancer hypercalcaemia, it was logical next to investigate lymphoid cell lines from patients with lymphoproliferative diseases known to cause osteolysis clinically. Cultures of lymphoid cell lines from patients with multiple myeloma, Burkitt's lymphoma and malignant lymphoma have been shown to release a bone-resorbing factor into the culture medium. After extensive studies, it was concluded that this factor was OAF, or something similar. Follow-up studies in which myeloma cell lines were cultured directly also revealed bone-resorbing activity in the supernatant medium; the evidence
Tumors, whether intraskeletal or extraskeletal, cause enhanced resorption of calcium from bone apparently through the elaboration of humoral substances such as prostaglandins (PGE₂), parathyroid hormone (PTH), and osteoclast activating factor (OAF). Lymphocytes also appear to be a source of OAF as a consequence of stimulation by tumors. Some of these humoral factors may be responsible for enhanced tubular reabsorption of calcium. Rarely (in myeloma), increased binding of calcium by abnormal proteins may lead to hypercalcemia. The wavy lines surrounding the tumors indicate the elaboration of physiologically active tumor products, including PTH, PGE₂, and OAF again indicated that the substance was similar of analogous to OAF.

It is of course possible that the source of OAF is not the tumor but the lymphocyte, which has been stimulated to produce OAF as part of a cell-mediated immune response to the tumor. In lymphocytes obtained preoperatively from patients with operable breast cancer, we have found in preliminary studies that even those lymphocytes not stimulated by phytohemagglutinin (PHA) produce a substance in the culture medium that causes brisk osteoclast activation in vitro: the osteoclasts are increased in size and number, become vacuolated and cause striking bone resorption in organ cultures of fetal rat bones. Thus, it appears from studies of hematopoietic neoplasms and, more recently, of lymphocytes from women with operable breast cancer, that a factor, presumably OAF, is elaborated that can induce osteoclastic resorption in vitro. The relationship of these findings to
hypercalcemia and the possible ultimate development of bone metastases can only be speculated upon at present.

Other Mechanisms

As shown diagrammatically in the Figure, enhanced renal tubular reabsorption of calcium has been described in some patients with cancer, although this has not been universally true particularly in patients with myeloma. The presence or absence of enhanced tubular reabsorption may well depend on the nature of the humoral substance produced by the cancer, which may or may not have an effect on the renal clearance of calcium. Hypercalcemia may also be intensified, in part, by reduction of the glomerular filtration rate, which, in turn, is often a consequence of increased levels of serum calcium. With respect to calcium and the gastrointestinal tract, balance studies and radiocalcium data have shown neither enhanced calcium absorption nor decreased endogenous secretion in patients with cancer hypercalcemia.

Treatment

Before starting treatment of cancer hypercalcemia, it should be determined whether the patient has a mild, moderate or marked elevation of serum calcium and whether or not he is symptomatic. Mild degrees of hypercalcemia (i.e., less than 13 mg./dl.) in an asymptomatic patient require no treatment other than that indicated for the cancer. In the last analysis, treatment of the cancer is the best treatment for the hypercalcemia. At times, however, the severity of the metabolic complication makes additional measures necessary. Treatment should fit the situation and, obviously, not all of the possible therapeutic modalities should be employed in all patients. The treatment possibilities, outlined in Table 3, are directed against one or another of the pathogenic mechanisms.

Measures Against Dehydration, Reduced Glomerular Filtration Rate and Enhanced Tubular Reabsorption of Calcium

Patients with cancer hypercalcemia are often water depleted from vomiting, poor intake and polyuria. Replacement with fluids, especially saline, will help to correct dehydration and restore intravascular volume and, since increased sodium excretion is accompanied by increased calcium excretion, to induce calciuresis. The usual precautions regarding the patient’s cardiopulmonary status must be observed. Frequent intravenous administration of furosemide (40-80 mg. every four-six hours) may result in significant calcium diuresis by blocking tubular reabsorption, but depletion of sodium, potassium and magnesium may occur as a side-effect if the regimen is administered too vigorously. Thiazide diuretics, of course, are contraindicated because they depress the urinary excretion of calcium. Hemodialysis has been used to control severe hypercalcemia in patients with marked renal disease and azotemia, and peritoneal dialysis has been employed in long-term management. The use of these modalities, however, depends on the overall assessment of the patient’s clinical problem and the therapeutic objectives. Since the source of calcium in cancer hypercalcemia is the skeleton and not abnormal absorption from the gastrointestinal tract, reduction of calcium in the diet is not likely to be of any benefit except that it may at least help to avoid aggravation of the situation.

Measures Directed Against Increased Bone Resorption

Inorganic Phosphate

The oral administration of phosphate
| Measures Directed Against Dehydration, Reduced Glomerular Filtration Rate and Enhanced Tubular Reabsorption of Calcium: |
|---------------------------------------------------------------|
| Fluid replacement with saline (caution re cardiopulmonary status of patient) |
| Diuretics (furosemide) |
| Dialysis |

| Measures Directed Against Increased Bone Resorption |
|------------------------------------------------------|
| Oral phosphate |
| Corticosteroids |
| Mithramycin, actinomycin D |
| Calcitonin |
| Indomethacin |
| IV phosphate |
| Sodium sulfate; disodium ethylenediaminetetraacetate (EDTA) |
| Avoid protracted immobilization |

| Measures Directed Against the Tumor |
|-------------------------------------|
| Surgical removal of tumor |
| Endocrine ablation in breast and prostate cancer |
| Stop treatment with estrogens, androgens, progestins |
| Chemotherapy: tumor specific wherever possible; corticosteroids |
| Radiation therapy |

| Measures Directed Against Associated Problems |
|-----------------------------------------------|
| Correct associated electrolyte abnormalities (low K, low Mg, metabolic alkalosis) |
| Use caution if digitalization becomes necessary |
| Pay attention to pain, fractures, myelophthisic anemia |
effectively controls hypercalcemia of moderate proportions when rapid therapeutic effect is not mandatory. Oral preparations include: Neutra-Phos capsules (each containing 250 mg. of phosphorus, seven mEq of sodium and seven mEq of potassium) and Neutra-Phos-K capsules, which differ only in having 14 mEq of potassium and no sodium. An effective oral dose varies between 1.5 and 3.0 grams of phosphorus daily, with diarrhea as the main limiting factor. Phosphate inhibits bone resorption and its effects may be protracted. The urinary excretion of calcium decreases and it is thought that calcium is precipitated into bone and soft tissues. This latter point concerns in patients with renal impairment and oral phosphate should, therefore, not be used in patients with clearly abnormal renal function, especially if attended by increases in serum phosphorus. One difficulty in assessing the possible causal role of phosphate treatment in metastatic calcification is that hypercalcemia per se may be associated with extensive metastatic calcification. However, renal failure sets the stage for further trouble and its presence should interdict the use of phosphate.

Several problems have been reported with the use of intravenous phosphate: soft-tissue calcification, hypocalcemia, renal failure and hypotension. Some investigators believe it should never be used and others feel it can be used safely, except in patients with renal impairment, at a dose of 50 mM. (1.5 gm.) given intravenously slowly over six-eight hours. The calcium response is dose related: in our hands a dose of 50 mM. caused a mean decrease of serum calcium of 2.44 mg./dl.32

Corticosteroids
The administration of 300 mg. of cortisol intravenously or cortisone or prednisone in equivalent dosage by mouth has been used for many years in the treatment of cancer hypercalcemia with varying results reported by different investigators. In general, it has proved to be most effective in patients with multiple myeloma, non-Hodgkin’s lymphoma and breast carcinoma. The mechanism of action appears to be a dual one: inhibition of bone resorption and of tumor growth. Thus the corticosteroids are listed under both categories in Table 3. The inhibition of bone resorption by corticosteroids may be related, in part, to their antagonism to vitamin D and parathyroid hormone. Usually a trial of seven-10 days should be given before it is concluded that the hypercalcemia is unresponsive.

Mithramycin and Actinomycin D
These cytotoxic agents have been found to inhibit bone resorption at doses lower than anti-tumor doses. It appears that they exert their effects through inhibition of RNA and protein synthesis. Mithramycin causes reversal of hypercalcemia in about 48 hours; its effects may be transitory or may last several days. The usual dose is 25 μg./kg. body weight given intravenously as a direct injection or as a four-hour infusion. If not successful in 48 hours, the dose may be repeated but, if still unsuccessful in correcting the hypercalcemia, it may be well to consider other forms of treatment since thrombocytopenia, hemorrhagic manifestations, renal and hepatic toxicity may all occur with mithramycin (but usually with anti-tumor doses). If these complications exist as a consequence of the underlying cancer, some other method for controlling the hypercalcemia should be used. Actinomycin D in single doses of two mg. has also been advocated in the treatment of hypercalcemia, according to the same rationale as mithramycin.
Calcitonin (CT)
Variable successes have been reported with porcine and salmon CT in the treatment of hypercalcemia. Some investigators have found that two to eight MRC units/kg. of porcine CT given IM every four to six hours resulted in an average decrease of 2.9 mg./dl. while others using approximately equivalent doses of salmon CT have had less success and escape from its effects may occur. The main advantage is the often prompt response and the virtual lack of toxicity. CT acts by inhibiting bone resorption and by promoting calciuresis. Its modest effect may possibly be enhanced by the simultaneous administration of inorganic phosphate, since phosphate loading has been said to increase the hypocalcemic effect of the hormone. Clearly further studies on this point are necessary.

Indomethacin
Since indomethacin inhibits prostaglandin synthesis and has been described as successfully reversing the hypercalcemia of some patients with cancer (presumably by virtue of this effect on prostaglandins), the drug has been used in a variety of neoplasms associated with hypercalcemia. In doses of 75-150 mg. per day, its successes are spotty and the precise indications for its use are not yet known. It may be that indomethacin is primarily indicated for patients with cancer hypercalcemia without bone metastases, who have undetectable levels of serum immunoreactive PTH (vide supra).

Sodium Sulfate; Disodium EDTA
Sodium sulfate has been recommended by some investigators over sodium chloride to induce calciuresis. It also complexes calcium and may therefore augment the sodium effect. However, in our hands, sodium sulfate infusion caused an average maximal decrease of serum calcium of only 1.9 mg./dl. This modest effect taken in conjunction with the adverse effects of a large sodium load and the short-lived responses make sodium sulfate less useful than some of the other therapeutic modalities. Disodium ethylenediaminetetraacetate (EDTA), once a valuable asset in the management of hypercalcemia, has largely given way to more effective forms of treatment.

Avoidance of Protracted Immobilization
Certainly immobilization, which can increase bone resorption, should be prevented when possible. If the patient is immobilized because of pathological fractures or severe bone pain, the hypercalcemic state may be intensified. One recent advance permitting mobilization is the use of intramedullary nails to treat pathological fractures. Ambulation and reduced pain are often a consequence of such treatment.

Measures Directed Against the Tumor
Ultimately those measures that are best suited to control the neoplasm are the best measures to treat the attendant hypercalcemia. This may mean surgical removal of the tumor or treatment with chemotherapy or radiation therapy, alone or in combination; all have been used successfully in treating hypercalcemia. Changing the hormonal environment, whether by stopping androgens, estrogens or progestins or by endocrine ablation, may also be effective. In fact, all of the treatment modalities previously noted are only supportive, pending the successful inhibition of the tumor.

Measures Directed Against Associated Problems
Associated electrolyte abnormalities (hypokalemia, hypomagnesemia) may occur as part of the hypercalcemic syndrome, as well as be a consequence
of vigorous treatment. They should be looked for (as should metabolic alkalosis, which often accompanies cancer hypercalcemia) and treated. Caution regarding rapid digitalization is always a caveat in articles on hypercalcemia. The possible need for digitalization should be anticipated and the patient digitalized slowly by mouth. Attention to skeletal pain and fractures has already been alluded to. Of course, myelophthisic anemia is often a problem that may preclude adequate anti-tumor therapy, and, depending on its extent, may interfere with the proper treatment of hypercalcemia.

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