Hypercalcemia and Cancer

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Case Report: A 67-year-old man with a five-month history of anorexia, constipation, polyuria, polydipsia and associated 35-pound weight loss was referred to the Mayo Clinic in October, 1969. Prior laparotomy was negative for cancer. Gallstones were found and a cholecystectomy performed. The surgeon reported that the liver was slightly enlarged and possibly "fatty," but liver biopsy was not done. Subsequently, hypercalcemia and hypophosphatemia were documented and the diagnosis of primary hyperparathyroidism was considered.

Physical examination at our institution confirmed the obvious weight loss and liver enlargement; the liver was palpable four cm. below the right costal border. The patient was not anemic. Serum calcium values were 14.2 and 13.9 mg./100 ml. and the inorganic phosphorus, 2.2 mg./100 ml.; the 24-hour urine excretion of calcium was 483 mg. The BSP dye retention was 10 percent in one hour but the alkaline phosphatase level and the serum protein electrophoretic pattern were normal, as was the excretory urogram. Roentgenograms of the hand showed demineralization of the phalanges but no classical subperiosteal resorptive changes. The serum iPTH level was 14 μeq./ml. (upper limit of normal with the assay used here is 40 μeq./ml.). A radioisotope liver scan showed a large area of decreased uptake in the upper portion of the right lobe. A celiac axis arteriogram demonstrated two vascular masses in the right upper lobe of the liver. Needle biopsy of the right lobe of the liver revealed a Grade 2 malignant epithelial tumor. Exploration of the abdomen confirmed the presence of a large hepatoma.

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A high level of serum calcium (15 mg./100 ml. or greater) must always be considered a medical emergency. Data from many medical centers that use biochemical screening procedures document the fact that hypercalcemia is far more common than has hitherto been suspected.1-4

The clinical manifestations of hypercalcemia are protean and may involve many organ systems. (Table 1.) In cases of extreme hypercalcemia, a catastrophic syndrome may develop, characterized by abdominal pain, intractable vomiting, profound weakness and severe dehydration with rapid deterioration of renal function. Progression of the disorder may result in coma and death. Sudden death, probably cardiogenic, has also been observed in patients with hypercalcemia. It must be stressed, however, that some patients with a serum calcium of 14 mg./100 ml. or greater may present with minimal or no findings attributable to hypercalcemia per se.

When hypercalcemia is discovered, confirmation by repeated measurements is important before proceeding to extensive laboratory and X-ray studies. In this way, possible sources of laboratory error, including mislabeling of serum, contamination of the blood specimen from unclean glassware or test-tube stoppers and other factitious causes of hypercalcemia, may be excluded.

The normal range of serum calcium varies depending on the method of measurement. At the Mayo Clinic, we use atomic absorption spectrophotometry (normal range, 8.9 to 10.1 mg./100 ml.). Reliable measurement of the ionized calcium concentration in the plasma using ion-specific electrodes can now be done.5 Measurement of ionized calcium has no general advantages over measurement of total calcium for diagnosis, though some investigators have suggested that "normocalcemic hyperparathyroidism" may result from a disproportionate increase in the ionized fraction.6

Electrophoretic analysis of serum proteins is important in all hypercalcemic patients, as variations in the concentration of serum proteins may directly affect the serum calcium level. For each increment in serum albumin or globulin of one gm./100 ml., the serum calcium value may increase by approximately 0.8 mg./100 ml. An increase in the level of alpha-2 and beta globulins has been reported in some patients with hyperparathyroidism. Serum protein studies may additionally prove to be helpful in excluding a diagnosis of myeloma or sarcoidosis.

The most common cause of hypercalcemia is cancer, either with or without osseous metastases. Normal radiographs do not always exclude the presence of osseous metastases. In a series of

Table 1. Clinical Picture of Hypercalcemia

| Gastrointestinal | Genitourinary | Neurologic | Psychiatric | Metastatic calcification |
|------------------|---------------|------------|-------------|--------------------------|
| Anorexia, constipation, nausea, vomiting, peptic ulcer pain, acute pancreatitis | Polyuria, renal insufficiency, calculi, nephrocalcinosis, polydipsia | Fatigue, muscle weakness, depressed tendon reflexes, disorientation, stupor, coma, death | Apathy, depression, psychotic behavior | Ocular keratopathy, nephrocalcinosis, vascular calcification, periarticular calcification, chondrocalcinosis |
autopsies, Bachman and Sproul found that only half of the cases with histologically documented skeletal metastases had radiographic findings indicative of metastatic cancer. Confirming the original postulate by Albright in 1941, recent studies have shown that one cause of hypercalcemia in cancer patients without apparent skeletal metastases is the synthesis and secretion of a parathyroid hormone-like substance by the malignant tumor.9

The clinical syndrome of a non-parathyroid tumor associated with hypercalcemia and hypophosphatemia has been referred to as pseudohyperparathyroidism or ectopic hyperparathyroidism. According to Lafferty, it is only a little less common than primary hyperparathyroidism. Moreover, differentiation of ectopic from primary hyperparathyroidism may be difficult. Patients with ectopic hyperparathyroidism may have all the biochemical characteristics of primary hyperparathyroidism (including elevated concentrations of immunoreactive parathyroid hormone [iPTH]) and the cancer may not be clinically apparent when the patient is first seen.

Although a variety of malignant tumors have produced ectopic hyperparathyroidism, hypernephromas and bronchogenic carcinomas accounted for 60 percent of the cases in Lafferty's series. He concluded that this syndrome is more likely than primary hyperparathyroidism under the following circumstances:

- when the serum calcium exceeds 14 mg./100 ml.;
- when the serum alkaline phosphatase activity is increased and radiographic evidence of osteitis fibrosa is absent;
- when there is a significant degree of anemia.

On the other hand, primary hyperparathyroidism is more likely to occur in patients with a long history of recurrent renal lithiasis or in those with radiographic evidence of osteitis fibrosa. Roof and her colleagues have observed that breast carcinomas rarely produce ectopic hyperparathyroidism.

Because the serum concentration of iPTH in primary hyperparathyroidism, in ectopic hyperparathyroidism, and in some patients with bronchogenic carcinoma without hypercalcemia is reportedly increased, direct measurement of iPTH has been generally considered valueless in differentiating these conditions. However, recent reports in-

| Table 2. Causes of Hypercalcemia |
|-------------------------------|
| **Common**                     | **Uncommon**                |
| Cancer                        | Leukemia                    |
| With metastases              | Hyperthyroidism             |
| Without metastases           | Myxedema                    |
| Hyperparathyroidism           | Hyperparathyroidism         |
| Primary                      | "Tertiary"                 |
| Thiazide therapy             | Addisonian crisis           |
| Myeloma                      | Immobilization              |
| Sarcoidosis                  | Young adults and children   |
| Hypervitaminosis D           | Paget's disease             |
| Milk-alkali syndrome         | Diuretic phase of renal tubular damage |
|                              | Idiopathic hypercalcemia of infancy |
|                              | Acromegaly                  |
dicate that the binding affinity of certain antisera for the PTH-like material in the sera of patients with ectopic hyperparathyroidism is lower than that for the iPTH in the sera of those with primary hyperparathyroidism.\textsuperscript{3,11,14} Hence, for a given serum calcium concentration, iPTH is lower in ectopic than in primary hyperparathyroidism. On the basis of the serum concentrations of calcium and iPTH, Riggs and coworkers\textsuperscript{14} were able to exclude primary hyperparathyroidism as a cause of hypercalcemia in 16 of 18 consecutive patients with the syndrome of ectopic hyperparathyroidism. The usefulness of the measurement of iPTH, using such an antisera, and the subtle difficulties in the clinical differentiation of these syndromes are illustrated by the introductory case report.

Of all the cancers, myeloma perhaps deserves special consideration because of its frequent association with hypercalcemia. The mechanism underlying hypercalcemia in this disease is presumably resorption of bone and release of calcium into the plasma. The specific diagnostic features of "punched-out" skeletal lesions and the finding of myeloma cells in the bone marrow, M-protein in the plasma and Bence-Jones protein in the urine are well known. It should be recognized, however, that generalized demineralization of the skeleton without a localized "punched-out" appearance may also occur in this disease; skeletal involvement may be devastating. Despite the frequent increase in plasma protein concentration, elevation of the total serum calcium generally reflects an increase in the ionized fraction of calcium. As a result, hypercalcemia is often accompanied by nausea, vomiting, anorexia and sometimes stupor or even coma.

Impairment of renal function in multiple myeloma may occur as a consequence of: (1) the myeloma itself (precipitation of protein in the renal tubular lumina); (2) the hypercalcemia; or (3) a combination of the two. It is often difficult to differentiate these possibilities, but careful observation of renal function during therapy of the hypercalcemia may help. This is important, since the nephropathy of hypercalcemia may respond dramatically to appropriate therapy of hypercalcemia and may allow time for more specific treatment of the myeloma.

Other common causes of hypercalcemia are listed in Table 2.

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