The Differentiation of Primary Hyperparathyroidism From the Hypercalcemia of Malignancy

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The presence of hypercalcemia in patients with known cancers may be due to the cancers themselves, or to co-existing primary hyperparathyroidism. The differentiation of primary hyperparathyroidism from the hypercalcemia of malignancy is important since the relief of distressing symptoms and prevention of hypercalcemic crises and renal failure can be accomplished relatively easily by parathyroid surgery in the former condition, and only with difficulty, at times, with fluids and drugs in the latter condition. The histories of three recent patients are presented, which demonstrate the difficulties inherent in the differentiation of these conditions. These patients were ultimately found at operation to have primary hyperparathyroidism in addition to malignancies of the cervix, adrenal gland and kidney. In our experience the following have been helpful in establishing a diagnosis: history of hypercalcemia prior to development of cancer, the type of cancer itself, the effect of cancer therapy on the hypercalcemia, and selective venous sampling with radioimmunoassay for parathyroid hormone.

IN THE MANAGEMENT OF PATIENTS with hypercalcemia one must differentiate between parathyroid adenoma or hyperplasia and a variety of other diseases that can cause elevations in serum calcium. It is known that certain cancers can produce hypercalcemia in individual patients and this has been termed the hypercalcemia of malignancy, pseudohyperparathyroidism or ectopic hyperparathyroidism. The differential between primary hyperparathyroidism and hypercalcemia of malignancy can be very difficult since the carcinoma may be occult. This differential diagnosis must be considered even in patients with a known cancer. In other words, in the patient with an active cancer and hypercalcemia, is the elevated calcium due to the cancer or to a coexisting parathyroid adenoma? This is not merely an academic question. The symptoms caused by the high calcium levels may cause the patient great discomfort and may actually be more immediately life threatening, at times, than the cancer itself. There are reports of patients with neoplastic diseases dying as a result of hyperparathyroid crises due to uncontrollable hypercalcemia.

The management of hypercalcemia of malignancy and primary hyperparathyroidism is obviously very different. In the former, fluid and drug therapy are often successful in managing the hypercalcemia, but in many patients management is extremely difficult. In the latter, operative exploration for primary parathyroid disease is generally successful and there are relatively few complications. With the low risks involved, operative explorations can be performed even in patients with debilitating diseases and in those in the later stages of cancer. We have had three patients recently with active cancers and coexisting primary hyperparathyroid disease. The management of these patients illustrates the problems involved in these conditions as well as an approach to the differential diagnosis.

Case Reports

Case No. 1: This 57-year-old female was admitted to the hospital on December 19, 1971 with a 5 month history of vaginal bleeding. Biopsies taken in the out-patient clinic several weeks earlier established the diagnosis of carcinoma of the cervix, Class II-B. The patient was also noted to be hypertensive. Among her other laboratory studies, the serum calcium was >15 mg%, phosphate was 1.4 mg%, and the alkaline phosphatase was 92.* An SMA-12 two months earlier in the clinic also showed a calcium of >15 mg%, a phosphate of 2.2 mg% and an alkaline phosphatase of 107. The carcinoma was treated by radium implantation.

The patient was re-admitted to the hospital on September 15, 1972 with a complaint of low back pain, easy fatiguability, and constipation. She also

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* Normal values at this hospital: calcium 8.5 to 10.5 mg.%, phosphate 2.5 to 4.5 mg.%, alkaline phosphatase 30 to 85 International units.

gave a history, as this time, of duodenal ulcer disease five years earlier. While she continued to have vaginal discharge, pelvic exams revealed only that which was considered a mild fibrosis of the vaginal cuff, felt to be due to radiation. Repeated serum calcium determinations during this time ranged 14.3–15 mg% and serum phosphate levels ranged 1.2–2.1%. With the presumptive diagnosis of primary hyperparathyroidism in this patient, a neck exploration was performed on September 28, 1972. A parathyroid adenoma weighing 1.2 gm was found at the lower left pole of the thyroid gland and was excised. Serum calcium levels rapidly dropped to the normal range, and when the patient was seen in the out-patient clinic during the next few months the serum calcium levels varied from 8.8 to 9.4 mg%. The patient noted improvement of the back pain and generally felt better. However, two months after parathyroid surgery she was re-admitted because of an obvious rectovaginal fistula. An abdominal exploration was carried out and considerable fibrosis and scarring were present in the pelvis. Numerous biopsies revealed only inflammed collagenous connective tissue, although a recurrence of the malignancy was strongly suspected. A diverting colostomy was performed. The patient was discharged in relatively good condition but returned to the hospital two months later in a moribund condition and expired. The patient's abdomen was markedly distended at the time of death, and although no autopsy was performed, it was obvious, clinically, that the patient had succumbed to her recurrent carcinoma. Serum calcium at the time of death was 7.4 mg%.

Comment

This patient lived for only four months after the parathyroid operation but had significant improvement of symptoms to justify this procedure. The presumptive diagnosis of primary hyperparathyroidism rather than hypercalcemia of malignancy was made because the patient had carcinoma of the cervix which does not commonly cause hypercalcemia, although there are several known instances of this occurring. In addition, the serum calcium levels did not drop to normal or near normal levels during the course of treatment of the cancer. At the time of the parathyroid operation, the cervical cancer appeared to be well controlled, but the calcium levels remained in an elevated range. Serum calcium levels of 14 or 15 mg% are potentially dangerous and parathyroid surgery could be justified even if the patient had been asymptomatic.

Case No. 2. This 36-year-old woman was admitted to the hospital on January 20, 1973 because of persistent hypertension. She had a 8 month history of diabetes and her weight had increased during the past few years from 135 to 200 pounds. On examination, her blood pressure was 240/160 and she appeared to have truncal obesity with a moon facies. Of significance in her laboratory tests was a generally low serum potassium, and elevated 17-hydroxy and17-ketosteroid levels. Repeated serum calcium determinations during this time ranged from 9.2 to 10.8 mg% and phosphate from 2.8 to 4.5 mg%. Elevated plasma cortisol levels, lack of suppression of steroid values with dexamethasone administration, unresponsiveness to ACTH stimulation, and evidence of an enlarged left adrenal gland on arteriography suggested Cushing's syndrome secondary to an adrenal tumor.

She was discharged from the hospital after this workup and was re-admitted on April 15, 1973 for further testing and definitive surgery. Adrenal venography was performed and the left adrenal vein appeared to be markedly enlarged with hypervascularity of the adrenal. Attempts to catheterize the right adrenal vein were unsuccessful. Two of three serum calcium determinations at this time were elevated slightly, as high as 10.8 mg%. On April 25, 1973, an abdominal exploration was performed revealing bilateral adenocarcinoma of the adrenals. A bilateral adrenalectomy was performed and a solitary metastatic nodule was excised from the liver. The patient tolerated surgery well and serum cortisol levels dropped below normal, postoperatively, although there was still serum cortisol present without administration of exogenous steroids. One serum calcium determination was obtained postoperatively and was 8.4 mg%. The patient was discharged on the thirteenth postoperative day, on medications including cortisone, 50 mg per day, which was later changed to prednisone, 10 mg per day.

The patient was re-admitted to the hospital on May 20, 1973 for a trial of therapy on o p' DDD. One serum calcium determination at this time was 10.4 mg%. She was discharged in 11 days but readmitted on June 27, 1973 because of vomiting, weakness, malaise, pain in her shoulder and a marked depression. Serum calcium levels at the time of this admission were >15 mg% and the alkaline phosphatase was also elevated. Plasma cortisol levels were at the upper limit of normal initially, but were found to be elevated later during this admission. Repeated serum calcium levels ranged from 11.5 to 15.2 mg% but gradually returned to normal levels of 9.9 mg% without therapy at time of discharge on August, 1973. A review of the patient's past records, revealed that she had high serum calcium levels intermittently over the previous four years, including a level of 11.7 mg% in April 1969.

She was again admitted to the hospital on August 21, 1973 because of continued nausea and vomiting, pain in the right shoulder, temporal headaches, general malaise and weakness, and extreme depression. Serum calcium at time of admission was 14.7 mg% and phosphate was 2.6 mg%. The serum alkaline phosphatase was again elevated. During the subsequent days, calcium levels rose as high as 17.4 mg%. These levels were controlled at first, with great difficulty, using massive infusions of fluids and sodium phosphate solutions. Although calcium levels dropped as low as 8.4 mg% during therapy, normal levels were extremely difficult to maintain. Because of the possibility of primary hyperparathyroidism, a neck exploration was performed on September 13, 1973. A small parathyroid tumor weighing 98 mg was discovered at the inferior pole of the right thyroid lobe, and was excised. Postoperatively, the calcium and phosphate levels returned to normal, although the alkaline phosphatase remained elevated. The patient had a dramatic response clinically, with marked relief of symptoms. Whereas preoperatively she had been emotionally depressed to the extent of becoming almost totally uncommunicative, postoperatively, within a few days, the patient was alert and cheerful. When seen in the out-patient clinic on January 29, 1974, the serum calcium level was 10.1 mg% and the phosphate level was 5.0 mg%.

Comment

This patient presented us with a difficult diagnostic problem. Although this is a rare tumor, there has been one report of a patient with adenocarcinoma of the adrenals, causing hypercalcemia.[21] In addition, it is very likely that this patient had additional metastatic cancer at the time of adrenalectomy. The decision to explore the neck for parathyroid disease was made, in part, on the history of elevated serum calcium levels as early as four years before discovery of her adrenal carcinoma. We were also impressed that there was only a transient response of the elevated calcium levels to the adrenal tumor surgery, at which time the bulk of the malignant tissue was removed. We felt that although the adrenal operation was not curative, all of the apparent tumor, including one liver nodule was removed and that a drop in calcium level, for a moderate period of time, would have been expected if the tumor was directly responsible for the hypercalcemia. In addition, there is

another somewhat confusing factor involved. Adrenal steroids are often used to control hypercalcemia due to pseudohyperparathyroidism. This patient was producing, endogenously, high levels of adrenal steroids, but still maintained exceptionally high levels of serum calcium. Patients with Cushing's syndrome, even when caused by adrenal carcinoma, generally have normal or low serum calcium levels.[11] In fact, an acute fall in steroid levels after adrenalectomy in Cushing's syndrome may give rise to hypercalcemia. Primary hyperparathyroidism usually does not respond to the administration of adrenal steroids. We felt that there was a strong possibility that a parathyroid gland was hypersecreting independently, causing the elevated serum calcium levels. The operation was successful and the symptomatic response was remarkable.

An additional factor concerning this patient should be mentioned. Paloyan has suggested that the chronic use of thiazide preparations for treating hypertension may encourage the development of hyperparathyroidism.[16] This patient was treated with hydrochlorothiazide; however, she ultimately developed symptoms commonly seen in hyperparathyroidism, particularly musculoskeletal pain and depression, and these responded well to the excision of the parathyroid tumor. In Paloyan's experience, patients with prolonged thiazide administration and hypercalcemia did not suffer from the common complications of hyperparathyroidism.

This patient has already had adrenal and parathyroid diseases, possibly representing components of the multiple endocrine adenomatosis syndrome. She has not manifested signs of other endocrine disease up to this time.

Case No. 3. This patient, a 43-year-old female, was admitted to the hospital on February 10, 1973 with a complaint of headaches, hypertension, and a right abdominal mass. An intravenous pyelogram performed before the patient was admitted to the hospital revealed a markedly enlarged right kidney. The serum calcium level at time of admission was 12.1 mg% and the phosphate was 2.8 mg%. A repeat serum calcium was 12.4 mg% several days later. A right renal arteriogram showed a huge right renal mass with tumor staining and stretching of the vessels, suggesting a carcinoma. A metastatic roentgenographic survey and brain, lung, and liver scans were all normal. A right nephrectomy was carried out on February 15, 1973. While there was no evidence of capsule invasion or any lymph nodes invasion, and the renal vein was free of tumor, microscopic sections of this well-differentiated adenocarcinoma demonstrated some tumor cells in the small blood vessels and one small renal calyx showed some invasion. On the day after surgery the serum calcium dropped to 9.7 mg% but rose on the following day to 11.0 mg% and ranged during the next week from 11.0 to 12.3 mg.%

The patient remained well, without therapy, for about eight months but again was admitted to the hospital on October 24, 1973 because of a 4 cm mass in the subcutaneous area of the right flank, in the site of the previous incision. The metastatic x-ray survey was negative at this time. A repeat liver scan was interpreted as questionable for metastatic disease. Serum calcium on admission was 12.4 mg% and serum phosphate was 2.6 mg%. On October 25, 1973, the mass was excised and histologic examination showed a local recurrence of the same tumor. The serum calcium levels remained elevated postoperatively, ranging from 10.9 to 12.1 mg%.

Although the patient remained essentially asymptomatic in relation to her hypercalcemia, several radioimmunoassays for parathyroid hormone were performed during the next few months. An assay performed on October 29, 1973, using peripheral blood revealed a parathyroid hormone level of 180,° which was considered to be inappropriately elevated in relation to the serum calcium level. Selective venous sampling was carried out in December 1973 and revealed increased concentrations of parathyroid hormone in the superior vena cava and right innominate vein compared to other sites.

On February 20, 1974, the patient was admitted for the third time because of another recurrent mass in the right flank and also for an explorative operation of the neck for primary parathyroid disease. The serum calcium level at admission was 12.0 mg% and the serum phosphate was 2.6 mg%. On the following day, February 21, 1974, a parathyroid exploration was performed and a 1.6 gm parathyroid adenoma was removed from the left lower pole of the thyroid gland. In addition the nodule in the right flank, measuring 5 × 4 × 4 cm was excised. This again proved to be recurrent renal tumor. The patient has done well postoperatively and serum calcium levels have remained normal since the day after surgery, ranging from 8.7 to 9.9 mg%.

Comment

This patient also presented us with a difficult diagnostic problem. On the one hand, renal cell carcinomas are one of the two most common tumors known to produce hypercalcemia of malignancy. However, we were influenced by the fact that there was no response in the calcium level to nephrectomy, which at the time was felt to be a curative operation. At the second operation, with removal of the known metastatic lesion, there was again no response in the serum calcium levels. Finally, radioimmunoassayable parathyroid hormone was elevated in the peripheral blood and, of even greater importance, the highest concentration of parathyroid hormone appeared to be in the veins draining the neck region. We felt these findings justified exploration of the neck, even in a patient who was asymptomatic. Serum calcium levels of over 12 mg% are potentially dangerous and acute rises may lead to hypercalcemic crisis in such patients. In addition, we were concerned with protecting her remaining kidney from the development of nephrocalcinosis or nephrolithiasis, which could ultimately result in renal failure.

Discussion

It is well established that certain types of cancer can cause elevations in the levels of serum calcium (Table 1). There appear to be two mechanisms involved in the hypercalcemia: 1) destruction of bone by metastatic growth, and 2) production of a parathyroid hormone-like substance or Vitamin D-like sterol by the tumor itself. The most common cancer to produce hypercalcemia by bone destruction is cancer of the breast. This is not a rare phenomenon. Davis,[6] in his study encompassing 305 patients with cancer of the breast noted hypercalcemia in 22 patients or 7.2%. The incidence may even be higher, as suggested by Muggia,[14] who quoted a figure of 10–25% of patients with breast

° Normal in this laboratory up to 200 units.

cancer. This can occur relatively abruptly in these patients, sometimes after the administration of hormonal therapy, either androgens, estrogens or both.[12] Multiple myeloma is also known to produce extensive bone destruction with an accompanying hypercalcemia. Hypercalcemia can be seen with other types of cancers in situations where bone metastases are present. This may also be the mechanism of hypercalcemia seen occasionally in lymphomas or leukemias, possibly due to wide-spread bone marrow involvement which may ultimately result in destructive skeletal lesions.

Until recently there has been only indirect evidence of a clinical nature to suspect that cancers are able to produce a hormone-like substance. There are several criteria listed by Sherwood[21] that would suggest the presence of this substance in patients with cancers. These are: 1) absence of skeletal metastases; 2) low serum phosphate; 3) normal parathyroid glands at surgery or autopsy; 4) a fall in serum calcium levels after removal of the cancer; and 5) an increase of calcium levels with recurrence of the cancer. While not all of these criteria must be met, and there is actually some question as to the validity of some, a combination of several of these will strongly suggest the possibility that the cancer itself is responsible for the hypercalcemia.

Cancers of the lung and renal cell carcinomas are by far the most common tumors to produce this effect. These tumors represent at least 60% of the cases producing the syndrome of hypercalcemia of malignancy, as noted by Lafferty.[13] Bender[5] studied 200 patients with lung cancer in a prospective manner and found that 25 patients (12.5%) developed hypercalcemia at some stage of their disease. By cell type, 23% of patients with epidermoid carcinoma had elevated serum calcium levels, 12.7% of patients with large-cell anaplastic cancer, 2.5% of those with adenocarcinoma, and none of those with small cell cancers. Of these 25 patients, 14 had an absence of bone metastases, including 12 with epidermoid carcinoma and 2 with large-cell anaplastic cancer.

A group of 118 patients with renal cell carcinoma were studied by Warren.[23] Of these 15 (13%) had elevated calcium levels before the operation. General summaries of the types of cancers causing hypercalcemia of malignancy have been published in the last ten years by Goldberg,[9] Lafferty,[13] Omenn,[15] and Ariyan.[2] It has been noted by several authors that squamous cell cancers are often responsible for hypercalcemia, including head and neck tumors. A group of nine patients with these tumors and hypercalcemia were recently described by Ariyan[2] and another group of 5 patients was reported by Terz.[22] Other squamous cell carcinomas that have, on occasion, produced hypercalcemia of malignancy include cancers of the bladder, cervix, esophagus, vulva, and penis. There are, in addition, individual case reports of patients with other cancers which have produced the clinical picture of hypercalcemia of malignancy (Table 1).

Considerable efforts have been expended during the past 10 years to isolate a parathyroid hormone-like substance produced by these cancers. The development of the technique for measurement of parathyroid hormones by radioimmunoassay has helped; but the overall picture is still somewhat confused. It appears at this point that the parathyroid hormone circulating in patients with primary hyperparathyroidism is immunoheterogenous. Arnaud[4] believes there is evidence of at least three circulating forms of immunoreactive parathyroid hormones in patients with primary hyperparathyroid disease. He was able to measure serum parathyroid hormone levels in patients with hypercalcemia of malignancy, but these levels were lower than those found in patients with primary hyperparathyroidism. He felt this might be due to an alteration in the ratio of immunoreactive forms of circulating parathyroid hormones in the two conditions.[3] In contrast, Powell and associates[18] were completely unable to detect parathyroid hormones in the blood or tumor tissues of patients with hypercalcemia of

TABLE 1. *Cancers Causing Hypercalcemia*

A.	Caused by metastatic destruction of bone
	Breast cancer—most common
	Multiple myeloma
	Lymphoma and leukemia (?)
B.	Caused by parathyroid hormone-like substances
	1. Most common
	Lung cancer—especially epidermoid
	Renal cell carcinoma
	2. Less common
	Head and neck cancer
	Ovarian cancer
	Hepatoma
	Pancreatic cancer
	Bladder cancer
	Endometrial cancer
	Lymphomas
	3. Isolated case reports
	Esophageal cancer
	Colon cancer
	Rectal cancer
	Cervical cancer
	Vulvar cancer
	Uterine Leiomyosarcoma
	Cancer of the penis
	Prostatic cancer
	Adrenal cancer
	Melanoma
	Hemagiopericytoma
	Branchial rest cancer
	Parotid cancer
	Breast cancer
	Mammary dysplasia

malignancy, but they were able to show that extracts of these tumor tissues caused active calcium resorption from bone in vitro. Again, in contrast, Sherwood[21] was able to detect measurable levels of parathyroid hormone in 7 patients but not in an additional 6 hypercalcemic patients with cancer. Measurable levels in the 7 patients were below those of patients with parathyroid adenomas. He felt that a low concentration of hormone was produced by the tumors, but that the generally large size of the cancers would compensate for the low concentration.

Most investigators in this field have felt that the mechanism of calcium elevation is not a simple one. Roof[20] felt that hypercalcemia of malignancy may be associated with two or more types of parathyroid hormones. These include one which cannot be distinguished from normal parathyroid hormone, one which differs immunologically from normal parathyroid hormone, and possibly a third hormone with a higher ratio of immunologic to calcium-increasing activity. Riggs and associates[19] felt that either the parathyroid hormone of hypercalcemia of malignancy may be different from the parathyroid hormone of primary hyperparathyroidism, or more likely, that the immunoreactive material in the serum of patients with hypercalcemia of malignancy is a precursor or an intermediate form of the normally secreted hormone. Powell and associates[18] have suggested the possibility that a humoral substance other than parathyroid hormone, perhaps a Vitamin D-like sterol, may be responsible for the hypercalcemia of malignancy. Obviously, there appears to be more investigative work necessary for complete understanding of the involved mechanisms. Throughout the country, there are considerable differences in laboratories as to the ability to detect measurable hormone levels in patients with hypercalcemia of malignancy. If one uses the services of one of these laboratories, one, therefore, must know the capabilities of the individual laboratory in interpreting the results. Riggs and associates[19] have perhaps been the most successful in distinguishing between hypercalcemia of malignancy and primary hyperparathyroidism, and have been able to diagnose 16 of 18 patients with the former condition by radioimmunoassay.

As pointed out earlier, the establishment of the differential diagnosis between primary hyperparathyroidism and hypercalcemia of malignancy is important clinically, and the problem is not at all rare. Farr and associates[8] at Memorial Hospital have recently written about 100 patients with cancer and primary hyperparathyroidism; of these, 29 patients had active cancer at the same time as primary parathyroid disease. As one becomes more aware of the possibility of hypercalcemia causing moderate and severe symptoms in patients with cancer, undoubtedly more patients with this syndrome will be discovered. Although we would expect that a more highly refined form of radioimmunoassay would ultimately permit differentiation between the two conditions, these tests are still in a developmental stage, and one has to rely on other means of making a definitive diagnosis.

Lafferty[13] suggested that certain aspects of the patient's history and certain laboratory tests might be helpful in differentiating between primary hyperparathyroidism and hypercalcemia of malignancy. He observed that the hypercalcemia was of more rapid onset in malignancy than in the primary parathyroid disease. He also noted that renal disease and osteitis fibrosa cystica were more common in patients with primary parathyroid disease. However, none of these are absolutes and they probably have value in only a limited number of patients. Lafferty[13] also noted that the serum calcium levels were more frequently above 14 mg% in patients with hypercalcemia of malignancy, that anemia was more common in these patients, that the serum chloride levels were lower, and that these patients responded to the administration of adrenal steroids to a greater extent than patients with primary hyperparathyroidism. Again, exceptions to these criteria are so frequent that we have felt that they have only limited usefulness. Lafferty[13] admitted that such tests as serum phosphate, serum uric acid levels, tubular reabsorption of phosphorus, and calcium infusion tests had little or no value in differentiating between the two conditions. Others have pointed out that the serum phosphate levels are commonly high in patients with hypercalcemia due to metastatic bone destruction, whereas low normal levels or low levels of phosphate are seen in patients with primary hyperparathyroidism and parathyroid hormone-secreting malignancies.

In establishing a practical modus operandum for making a differential diagnosis in patients with cancer and hypercalcemia we have found the following points to be more useful than the criteria of Lafferty:[13]

1) A history of hypercalcemia prior to the development of the malignancy. With the extensive use of the SMA-12 there are many records of patients with prior serum calcium determinations. In some patients, slight or inconsistent elevations of serum calcium may have been overlooked. This is somewhat similar to the situation of a patient with a pulmonary lesion, where one can compare the findings on present chest x-ray films with those films taken in the past. The presence of one or two slightly elevated serum calcium levels, which might not have been further investigated, may render the diagnosis of hypercalcemia of malignancy less likely.

2) The type of cancer itself is of considerable importance in making the differential diagnosis. If the patient had, for example, a carcinoma of the stomach, the possibility of hypercalcemia of malignancy would be less likely since this cancer has not yet been described as one of those producing this syndrome. If, on the other hand, one is dealing with a patient with a renal cell carcinoma, hypercalcemia of malignancy is more likely, although, as in the case of our third patient, this does not rule out the possibility of a primary hyperparathyroidism. In working with these

patients one should be aware of the types of cancer which are most commonly associated with hypercalcemia of malignancy.

3) The effect of surgery or other types of treatment on the elevated serum calcium levels is of great importance. If the cancer, either the primary or recurrent tumor, is treated adequately, the elevated serum calcium levels should fall significantly in most patients with hypercalcemia of malignancy. This is not an absolute, as noted by Warren[23] in some of his patients with renal cell carcinomas. However, if there is a positive response, one can conclude that hypercalcemia of malignancy was present. If there is no significant or long-lasting response, there is the possibility that either significant metastatic disease is present, which should lead to further investigation, or the patient may have primary hyperparathyroidism.

4) If a diagnosis cannot be made definitively on the basis of the above criteria, specific testing for primary hyperparathyroidism should be performed. As noted recently by Ackerman and Winer,[1] most of the standard tests for localizing primary parathyroid disease have been generally unsuccessful. However, selective venous sampling with radioimmunoassays performed on blood from the large veins of the neck and mediastinum appears to have had a relatively high rate of success recently, as noted by Powell.[17] In these studies, blood from the internal jugular vein, innominate veins, and superior vena cava were obtained and tested. This test may even be more accurate if carried out in combination with superior and inferior thyroid arteriography and venography, and venous sampling of the thyroid veins themselves, as noted by Doppman.[7] These tests require the assistance of an individual skillful in selective angiography and a laboratory equipped to do radioimmunoassay for parathyroid hormone. However, the tests can be extremely helpful in situations where the definitive diagnosis is still ambiguous, as in our third case.

There is one additional situation that is, fortunately, probably quite rare. This is in the patient who has hypercalcemia due to both primary hyperparathyroidism and malignancy occurring simultaneously. A probable situation of this type occurred in the patient described by Hodgkinson,[10] where a parathyroid adenoma was excised and the calcium levels remained elevated. The patient died a month later with a carcinoma of the renal pelvis. It is fortunate that the co-existence of these two syndromes is rare, since merely differentiating between them is itself highly challenging.

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