

Peptic ulcer disease, hyperparathyroidism, and pituitary tumor

WILLIAM J. BUFKIN, MD

A 41-year-old man consulted his physician because of refractory peptic ulcer disease. Routine laboratory studies revealed mild hypercalcemia (10.7 mg/dL). A pituitary tumor was

removed 10 years earlier. Ultrasound and computed tomography (CT) images are shown below (Figures 1–4).

For diagnosis and discussion, see the following page.

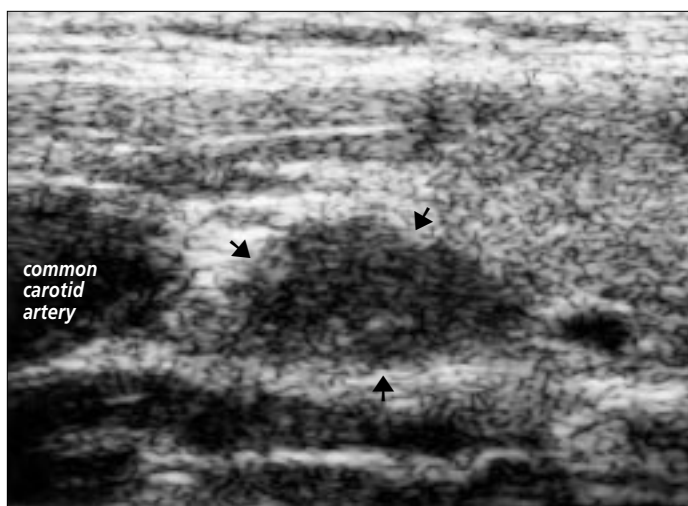


Figure 1. Ultrasound image demonstrates a left superior parathyroid mass (arrows), 12 mm in maximum dimension.

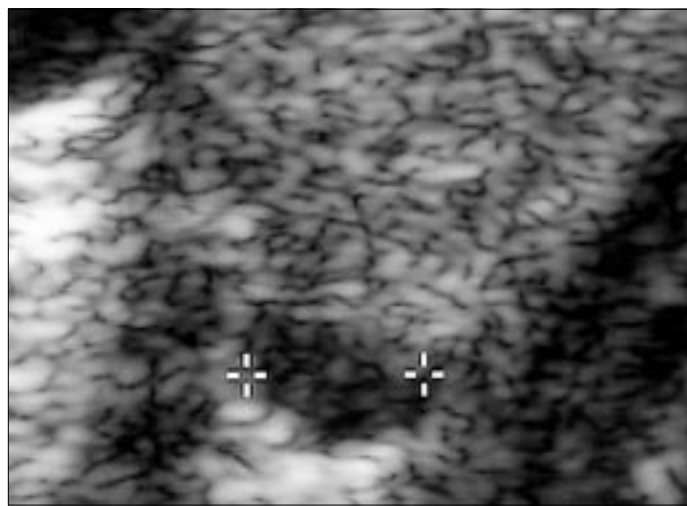


Figure 2. Ultrasound image shows a right superior parathyroid mass (calipers), 8 mm in maximum dimension. A similar right inferior parathyroid mass was present.



Figure 3. Enhanced CT (arterial phase) demonstrates a mass (arrow), approximately 2 cm in diameter, posterior and lateral to the head of the pancreas. The mass is nearly isodense with the head of the pancreas and with the inferior vena cava.



Figure 4. Enhanced CT (arterial phase) shows an enhancing mass (arrows), 1 cm in diameter, in the tail of the pancreas.

From the Department of Radiology, Baylor University Medical Center, Dallas, Texas.

Corresponding author: William J. Bufkin, MD, Department of Radiology, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246.

DIAGNOSIS: Multiple endocrine neoplasia (MEN), type 1.

DISCUSSION

MEN is characterized by the combined occurrence of tumors of 2 or more endocrine glands. Two major forms of MEN are recognized: type 1 and type 2. The development of tumors within specific endocrine glands characterizes each form. MEN 1, also known as Wermer's syndrome, is characterized by tumors of the parathyroids, pancreatic islet cells, and the anterior pituitary. MEN 1 is also associated with adrenal cortical tumors, carcinoid, facial angiofibromas, collagenomas, and lipomatous tumors. MEN 2, or Sipple's syndrome, is characterized by the combined occurrence of medullary thyroid carcinoma (MTC) and pheochromocytoma. Three clinical variants of MEN 2 have been identified: MEN 2A, MEN 2B, and MTC only. The most common variant, MEN 2A, is characterized by MTC occurring with pheochromocytoma and parathyroid tumors. MEN 2B is characterized by MTC and pheochromocytoma in association with a marfanoid habitus, medullated corneal fibers, mucosal neuromas, and intestinal autonomic ganglion dysfunction that causes megacolon. Parathyroid involvement rarely occurs in MEN 2B. In the MTC-only variant, MTC is the only manifestation. MEN 1 and MEN 2 usually occur as separate syndromes, but tumors that are associated with both conditions may occasionally be present.

All forms of MEN may be inherited as autosomal-dominant syndromes (1). MEN 1 is produced by a genetic defect on the long arm of chromosome 11 (2). The syndrome may also occur sporadically. The distinction between inherited and sporadic cases is sometimes difficult because the parent may have died before the expected symptoms developed.

The estimated incidence of MEN 1 is 0.25%. Estimated incidences are 1% to 18% in primary hyperparathyroidism, 16% to 38% in gastrinomas, and <3% in pituitary tumors. The reported age range is 5 to 81 years, with 80% of patients developing clinical manifestations of the disorder by the fifth decade. The clinical manifestations of MEN 1 are determined by the location of the tumors and the products of tumor secretion. Familial MEN 1 is present when a patient with MEN 1 has one or more first-degree relatives with at least one of the principal tumors. In >85% of cases, parathyroid tumors are the initial manifestation of MEN 1; in the remaining patients (<15%), the initial manifestation is an insulinoma or a prolactinoma.

The most common clinical manifestation of MEN 1 is primary hyperparathyroidism, which occurs in 95% of patients. Adenomas or hyperplasia usually affect all 4 parathyroid glands (1). Hypercalcemia is present in at least 80% of patients with MEN 1 (2). Increased circulating parathyroid hormone is usually present in these cases, and the hypercalcemia is usually mild (as in this case). In patients with MEN 1, primary hyperparathyroidism begins at an earlier age (20–25 years) than in patients without MEN 1 (55 years).

Pancreatic islet cell tumors occur in 30% to 80% of cases of MEN 1. The excessive amounts of hormone (gastrin, insulin, glucagon, or vasoactive intestinal polypeptide) produced by most of these tumors are associated with distinct clinical syndromes. Some tumors, however, may remain nonfunctional or non-secretory. Patients with MEN 1 have an earlier age of onset of pancreatic islet cell tumors than patients without MEN 1.

Zollinger-Ellison syndrome is characterized by recurrent peptic ulceration, marked gastric acid production, and non-beta islet cell tumors (gastrinomas) of the pancreas. These gastrin-secreting tumors constitute >50% of all islet cell tumors in patients with MEN 1. Gastrinomas are the major source of morbidity and mortality in these patients. They are frequently multiple and may occur in either the pancreas or the duodenal mucosa. Most gastrinomas in MEN 1 are malignant, and metastatic disease is usually present at the time of diagnosis. The pancreatic tumors are associated with a worse prognosis. Approximately 20% of patients with gastrinomas have MEN 1.

Insulin-secreting beta islet cell tumors constitute 10% to 30% of pancreatic tumors in patients with MEN 1. Gastrinomas occur in association with insulinomas in 10% of patients with MEN 1, and the tumors may be metachronous. In patients with MEN 1, insulinomas usually occur in patients <40 years of age, and many occur in patients <20 years of age. In patients without MEN 1, insulinomas usually occur in patients older than 40. In 10% of patients, insulinomas are the initial manifestation of MEN 1. Approximately 4% of patients with an insulinoma have MEN 1. Most insulinomas are small and multiple, and clinical features are usually hypoglycemic symptoms produced by fasting or exertion that improve with glucose intake.

Glucagonomas, or glucagon-secreting alpha islet cell tumors, occur in <3% of patients with MEN 1. The characteristic clinical findings are rash, anemia, weight loss, and stomatitis, although many of these tumors are discovered incidentally. Glucagonomas occur most frequently in the tail of the pancreas, and 50% to 80% of patients have metastatic disease at the time of diagnosis (1).

VIPomas, PPomas, somatostatinomas, and GHRHomas also occur in patients with MEN 1 (1). VIPomas secrete vasoactive intestinal peptide that primarily causes diarrhea (2). The clinical picture has been referred to as VIPoma syndrome; Verner-Morrison syndrome; and watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome. The PPomas secrete pancreatic polypeptide and produce no pathologic sequelae. Although they secrete somatostatin, somatostatinomas do not produce the somatostatinoma syndrome in MEN 1 patients. GHRHomas secrete growth hormone-releasing hormone, and the diagnosis is established by the detection of elevated serum concentrations (1).

Thirty percent of patients with MEN 1 have a tumor of the anterior pituitary (3). Symptoms are determined by the type of hormone secreted and the size of the pituitary tumor (1). Prolactinomas are the most common and occur in approximately 60% of patients (3). These tumors may cause amenorrhea, galactorrhea, or infertility in women and impotence in men (1). Somatotrophinomas are the next most common tumor and have an incidence of approximately 20% in patients with MEN 1. Corticotrophinomas and nonfunctioning tumors constitute <15% of cases (3).

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