

## Concurrent Parathyroid Adenomas and Carcinoma in the Setting of Multiple Endocrine Neoplasia Type 1: Presentation as Hypercalcemic Crisis

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We describe a patient with multiple endocrine neoplasia type 1 characterized by the simultaneous occurrence of parathyroid cancer, parathyroid adenomas, and pancreatic gastrinoma, who presented with an episode of acute hypercalcemia. The rapid parathyroid hormone assay provided a basis for the diagnosis of parathyroid hyperfunction. Mediastinal metastasis of the parathyroid carcinoma was found at autopsy. However, the staining of pancreatic and gastric tissue for parathyroid hormone-related protein does not make it possible to exclude completely the contri-

bution of this peptide in mediating the hypercalcemia. To our knowledge, this is the first reported case of parathyroid carcinoma as part of the multiple endocrine neoplasia type 1 syndrome.

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HPT = hyperparathyroidism; MEN 1 = multiple endocrine neoplasia type 1; PTH = parathyroid hormone; PTHrP = PTH-related protein; ZES = Zollinger-Ellison syndrome

Multiple endocrine neoplasia type 1 (MEN 1) is a syndrome associated with up to 20 different endocrine and nonendocrine tumors. Recent cloning of the *MEN 1* gene provided additional information in our understanding of this syndrome. MEN 1 is defined as the presence of 2 of 3 MEN 1-related endocrine tumors (parathyroid adenomas, enteropancreatic endocrine tumors, and pituitary tumors).<sup>1-3</sup> Hyperparathyroidism (HPT) is the most frequent and earliest expression of MEN 1, and up to 20% of patients with familial isolated HPT may have the *MEN 1* mutation.<sup>4</sup> In patients with MEN 1, primary HPT is the most common endocrinopathy, reaching nearly 100% penetrance by age 50 years.<sup>5</sup> Typical age at onset is 20 to 25 years, and often there is simultaneous HPT and Zollinger-Ellison syndrome (ZES).

The cause of hypercalcemia in MEN 1 is HPT secondary to independent clonal parathyroid adenomas.<sup>3</sup> Hypercalcemia increases the secretion of gastrin from gastrinomas, and successful parathyroidectomy lowers blood calcium and can decrease gastrin release in MEN 1.<sup>6</sup> Screening for MEN 1 in a given kindred is usually performed by assessment of serum calcium levels. Thus, understanding the cause of hypercalcemia may prevent additional surgical interventions in these patients.

To our knowledge, no patient has been reported in whom the finding of a parathyroid carcinoma was part of the syndrome. The possible malignant transformation of the parathyroid glands in this setting has not been documented. We describe a patient with MEN 1 characterized by the simultaneous occurrence of parathyroid cancer, parathyroid adenomas, and pancreatic gastrinoma, who presented with acute hypercalcemia.

### REPORT OF A CASE

A 35-year-old man was admitted to the Department of Clinical Sciences, University of Rome La Sapienza in December 1999 because of clinical suspicion of acute pancreatitis. Laboratory tests showed a significant increase of both serum amylase levels (1464 U/L; reference range, 35-115 U/L) and lipase levels (1000 U/L; reference range, 3-73 U/L) and severe hypercalcemia (total calcium, 15.7 mg/dL; reference range, 8.9-10.1 mg/dL; ionized calcium, 2.30 mmol/L; reference range, 1.17-1.33 mmol/L). The clinical history was remarkable for a previous diagnosis of MEN 1 based on the coexistence of ZES, primary HPT, and subcutaneous lipomas.

The patient was initially hospitalized in August 1994 because of a gastric hemorrhage and severe anemia (serum hemoglobin, 3.5 g/dL; reference range, 13.5-17.5 g/dL). A duodenal ulcer was diagnosed on the basis of esophagogastroduodenoscopy and conventional radiography with barium; the latter examination also revealed thickened duodenal walls, and the patient subsequently underwent abdominal computed tomography. This showed an expansive oval mass at the level of the pancreatic tail, which was imaged by octreotide scintigraphy.

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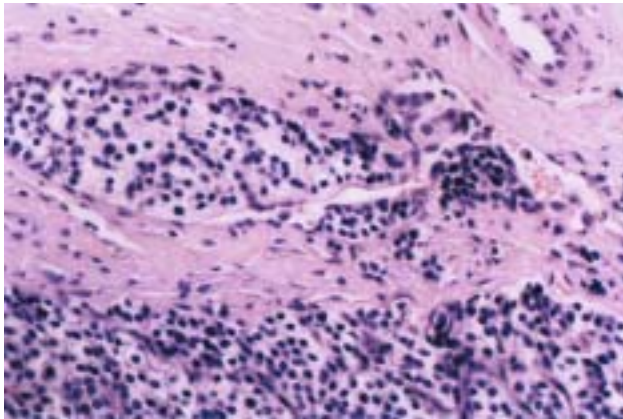


Figure 1. Ectopic parathyroid removed at surgery. Note vascular invasion of the parathyroid carcinoma. Nuclear pleomorphism together with moderate nuclear changes are also apparent (hematoxylin-eosin, original magnification  $\times 100$ ).

Omeprazole treatment was initiated, but the patient was again hospitalized for a gastric hemorrhage due to erosive esophagitis and duodenitis. On this occasion, ZES was diagnosed on the basis of increased gastrin levels (720 pg/mL; reference range, 10-100 pg/mL) and a positive secretin test result. Furthermore, laboratory tests revealed increased serum calcium (13.4 mg/dL) and parathyroid hormone (PTH) values (707 pg/mL; reference range, 10-55 pg/mL). A technetium Tc 99m sestamibi scan revealed an area of abnormal tracer accumulation in the superior-anterior mediastinal region. An ectopic parathyroid gland was located in the above-mentioned area and removed surgically, with progressive normalization of serum calcium. The histological examination of the gland (uniform cytology, karyokinesis, fibrous bands, extracapsular extension, vascular invasion) suggested the diagnosis of parathyroid carcinoma (Figure 1).

In April 1996, laboratory tests revealed recurrent hypercalcemia and elevated PTH values. The patient underwent neck surgical exploration, and 3 parathyroid glands were identified and removed. Histological examination revealed that the first gland was 2 cm long and weighed 1.0 g. The second and third glands were of similar size and weight.

Serum calcium levels, which had returned to normal for 6 months, were slightly higher in December 1998. Before admission, the patient underwent computed tomography showing an isodense, 2.5-cm lesion in the anterior mediastinum, an expansive lesion of the pancreatic tail (maximum diameter, 5.0 cm), lymphadenopathy of the gastric lesser curvature, and thickening of the stomach walls. Esophagogastroduodenoscopy revealed widespread polypoid lesions in the fundus, body, and gastric antrum that on histological examination were consistent with microcarcinoids.

Shortly after admission, a rapid PTH assay was performed (1888 pg/mL), which confirmed the parathyroid etiology of the hypercalcemia. In addition, laboratory analysis revealed high serum levels of chromogranin A (331 ng/mL; reference range,  $<30$  ng/mL) and gastrin (220 pg/mL; reference range,  $<40$  pg/mL). The patient received therapy with pamidronate, fluids, and somatostatin and proton pump inhibitors. Although the total calcium level was reduced to 11.1 mg/dL, the patient died during the third day of hospitalization.

The autopsy revealed a lipoma of  $5.0 \times 2.5 \times 2.0$  cm in the peritoneum. An irregular oval tumor (maximum dimension, 3.0 cm) was found in the anterior mediastinum. Histologically, this tumor was composed of monomorphic cellular elements organized in a trabecular growth pattern; some mitotic figures and vascular invasion were noted. Immunohistochemistry revealed a positive reaction to antibodies against PTH; thus, mediastinal metastasis from parathyroid carcinoma was diagnosed. No pituitary abnormality or skeletal metastases were identified.

Two round formations were found in the pancreas, located in the head and in the body-tail (5.0 and 7.0 cm in diameter, respectively). These masses were well circumscribed, not capsulated, and of increased consistency compared with the surrounding tissue. Both pancreatic masses were composed of monomorphic cells, with a round or oval nucleus, with minimum atypia and rare mitotic figures. Cellular elements showed a prevalent trabecular growth pattern with the presence of solid cellular areas or areas formed by cell nests. No mitotic figures, vascular invasion, or infiltration in the surrounding pancreatic tissue was found. Immunohistochemistry revealed no staining of the neoplastic cellular elements with antibodies against glucagon, insulin, pancreatic polypeptide, vasoactive intestinal peptide, or somatostatin. The same cellular elements within the mass stained positively with antibodies against chromogranin A and gastrin. These 2 pancreatic masses were consistent with pancreatic gastrinomas. The normal gastric tissue was totally substituted by numerous polypoids, the majority of which reached as far as 2.5 cm into the gastric lumen. Histology of gastric mucosal samples showed hyperplasia and hypertrophy of parietal cells and hyperplasia of the enterochromaffin-like endocrine cells. Moreover, many carcinoma tumor cells were distributed among the entire gastric mucosa.

Cells from both the gastric mucosa and the pancreatic pathological tissue showed intense reactivity to the immunohistochemistry performed with antibodies against PTH-related protein (PTHrP) (Figure 2). Gastric tissue control sections were stained with use of Vectastain Elite ABC Kit

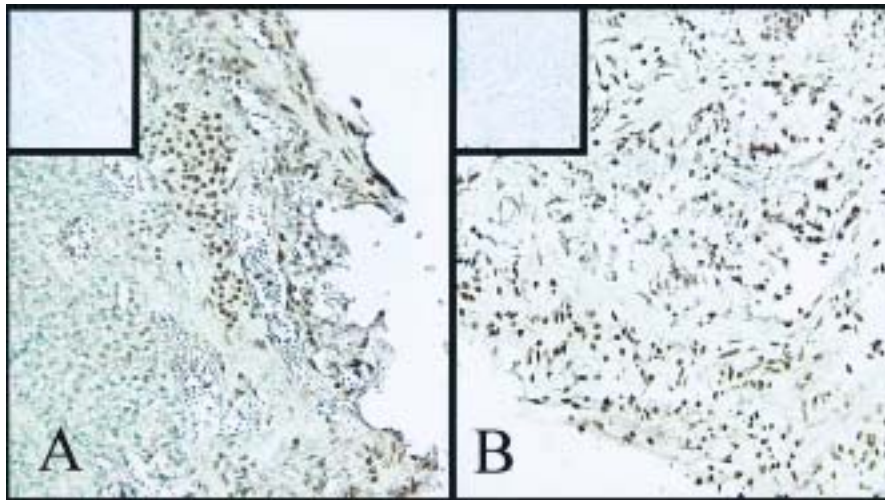


Figure 2. Positive parathyroid hormone–related protein (PTHrP) staining in tissue sections derived from cells of gastric mucosa and pancreas. A, Pancreatic tissue stained for PTHrP; Inset, pancreatic tissue negative control. B, Gastric tissue stained for PTHrP; Inset, gastric tissue negative control.

(Vector Laboratories, Burlingame, Calif). Primary antibody was rabbit anti-PTHrP (human) IgG (Peninsula Laboratories, San Carlos, Calif).

## DISCUSSION

Bearing in mind the medical history of our patient, 3 diagnostic hypotheses are proposed to explain his hypercalcemia.

Patients with MEN 1 generally have involvement of all 3 or 4 parathyroid glands. The glands are asymmetrical in size and are independent clonal adenomas.<sup>1</sup> In our patient, although 3 enlarged parathyroid glands and 1 ectopic parathyroid carcinoma had been removed, the diagnosis of recurrent primary HPT could not be excluded. In MEN 1 patients, 50% will have a recurrence of HPT 8 to 12 years after successful subtotal parathyroidectomy.<sup>1</sup> In the presence of parathyroid carcinoma, hypercalcemia often recurs because of local spread of tumor or distant metastases.<sup>7</sup>

The prevalence of enteropancreatic islet tumors in MEN 1-affected individuals varies from 30% to 75% in clinical series. The enteropancreatic lesions found in MEN 1 are usually multicentric and range from microadenomas to invasive and metastatic carcinomas. Pancreatic islet tumors may contain chromogranin A or B, pancreatic polypeptide, glucagon, insulin, proinsulin, somatostatin, gastrin, vasoactive intestinal peptide, serotonin, calcitonin, growth hormone–releasing factor, and neurotensin.<sup>8</sup> Gastrinomas are present in about two fifths of patients with MEN 1 and often contain a malignant component. Prognosis is worse in patients with pancreatic primary lesions, metastases, ectopic Cushing syndrome, or extremely high gas-

trin levels. Less commonly, thymic carcinoid or type II gastric enterochromaffin-like cell carcinoids are present in MEN 1. Adrenal cortical lesions are common and are usually nonfunctional.

A paraneoplastic origin of the hypercalcemia, mediated by PTHrP production by the pancreatic endocrine tumor, was another possible cause of hypercalcemia. Recently, a case of hypercalcemia due to PTHrP secreted by a pancreatic endocrine tumor in the setting of MEN 1 was described.<sup>9</sup> Furthermore, hypercalcemia has been included among the specific clinical syndromes associated with functional neuroendocrine tumors of the pancreas, possibly due to PTHrP production.<sup>10</sup> The possibility of PTHrP secretion by the microcarcinoids of the stomach could not be excluded.<sup>11</sup>

Finally, hypercalcemia could have been ascribed to osteolytic metastasis of the neuroendocrine tumor. It is well known that from about 60% to 80% of gastrinomas are malignant, and 25% behave aggressively with metastasis to skeletal tissue.<sup>10</sup>

In our case, the rapid PTH assay allowed the diagnosis of HPT, augmented by the discovery of mediastinal metastasis of parathyroid carcinoma. However, the positive PTHrP staining of pancreatic and gastric tissue does not completely exclude the possible contribution of this peptide to hypercalcemia. Unfortunately, peripheral serum measurement of PTHrP was not obtained; thus, a definitive answer cannot be provided. However, it is important to emphasize that PTHrP is commonly expressed in pancreatic tissues of eucalcemic patients with cancer.<sup>12</sup>

The most relevant finding in the present case derives from the coexistence of parathyroid adenoma and carci-

noma in a patient with MEN 1. According to existing literature, primary HPT in MEN 1 is usually manifest by individual clonal parathyroid adenomas. The concurrence of parathyroid carcinoma and hyperplasia has been sporadically reported within the same gland<sup>13,14</sup> in cases of secondary hyperplasia and renal failure, but never in the setting of MEN.<sup>15</sup>

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