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An Unusual Presentation of MEN-1

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MEN-1 is a rare autosomal dominant disorder characterized by the occurrence of tumors, both benign and malignant, of the parathyroid glands, the pancreas, and the anterior pituitary gland. Its incidence varies and it can occur as a sporadic event or as a familial trait. Multiple other associated tumors and disorders are associated with the familial trait, which should be considered as each patient and their laboratory values are evaluated by their family physician.

Case Presentations

The chart on the door had a set of vital signs and a single chief complaint: "Personal." As I entered the room, a young woman I had known for years looked up and said, "Doc, I can't get pregnant." It had been nearly a year since her last annual examination, at which time we discussed her desire to start a family and stop her oral contraceptives. In that ensuing period, she had had only a single scant menstrual period. She also related drainage from her breasts that had started shortly after her birth control pills were stopped.

Her clinical examination was unremarkable except for clear drainage from both breasts. Laboratory studies were drawn and were normal except for a prolactin level of 113 ng/mL (normal: 3.0–18.6 ng/mL). A computed tomography (CT) scan of her brain revealed a pituitary macroadenoma.

She and her husband sat down with me to discuss this finding and to review treatment options. They both elected to pursue surgery, because the tumor was quite large, and a referral was made to a tertiary center where she underwent a successful transsphenoidal pituitary resection.

Upon her return, she related that a medical student had taken a great deal of interest in her case and had asked her if she could have Wermer's syndrome. She asked that of her attending physicians on her discharge date and they laughed.

Several years later, at age 27, she presented with right upper quadrant pain, vomiting, and dehydration. Her admission labs revealed serum calcium of 12.6 mg/dL (normal: 8.0–10.2 mg/dL) and ionized calcium of 7.65 mg/dL (normal: 4.8–5.7 mg/dL). Parathyroid hormone levels were elevated at 93.0 pg/mL (normal: 15–65 pg/mL) and a sestamibi scan revealed gross enlargement of three of her four glands. Surgery was consulted and she underwent a successful parathyroidectomy with an autotransplant of a small remnant of parathyroid tissue to her nondominant forearm. She recovered quickly and was discharged on calcium carbonate 1,500 mg and calcitrol 0.5 mg three times daily to maintain a normal level of calcium.

A deeper review of her family history revealed that her maternal grandfather had died of pancreatic cancer, type unknown, at 46 years of age. Her mother within the past two years had been diagnosed with multiple superficial and visceral lipomas, two of which were intra-atrial, requiring resection and septal reconstruction. Because she now had two of the three tumors needed for diagnosis, as well as a positive family history, it appeared that the suspicions of the

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medical student were correct and she did have Wermer's syndrome, now known as MEN-1.

Topic Review

Multiple endocrine neoplasia type 1 (MEN-1) is a hereditary autosomal dominant disorder characterized by parathyroid neoplasia (95–100%), benign and malignant pancreatic islet cell neoplasia (35–76%), and anterior pituitary neoplasia (15–40%), with a penetrance of 95% for at least one entity by age 40 to 50 years.[1-3] In other studies, the reported prevalence varies from 2 to 20 per 100,000 to 1 per 30,000.[3,4]

Other, less frequent conditions associated with MEN-1 include thymic carcinoid; bronchial carcinoid; gastric and duodenal carcinoid; nonfunctioning gastric enterochromaffin-like tumors; subcutaneous, visceral, or retroperitoneal lipomas; facial angiofibroma; truncal collagenoma; leiomyoma; meningioma; adrenal cortical tumors; pheochromocytoma; testicular teratoma; and melanoma.[4-9]

The MEN-1 gene has been located at chromosome 11q13 and generates a 610 amino acid protein known as *menin* that was thought to reside primarily in the nucleus.[2,4,8] Immunofluorescence, Western blot analysis, and epitope tagging with enhanced green fluorescent protein (EGFP) have confirmed that menin is indeed located in the nucleus.[10] It has been hypothesized that tumorigenesis could likely be caused by a dysfunction of menin.[10] Further observations indicate that menin serves as either a repressor or activator by interacting with activator protein-1-family transcription factor (JunD), changing it from an oncoprotein to a tumor suppressor protein.[11] Immunologic staining of pancreaticoduodenal neuroendocrine tumors (PET) of malignant potential revealed a marked reduction in immunostaining for menin when compared with normal surrounding islets.[12] It is now recognized that menin is a tumor suppressor and transcriptional regulator controlling proliferation and apoptosis of cells.[13] Inactivation of one copy of the menin protein-coding alleles allows neoplasia to occur after an inactivating somatic mutation of the remaining allele.[1]

Primary hyperparathyroidism (PHT) is the most common endocrinopathy associated with MEN-1 occurring in 87 to 100% of the cases reported.[6,7,14,15] It is characterized by asymmetric multiglandular enlargement, hypercalcemia, and renal colic, but is asymptomatic in the early stage of the disease and frequently found during screening studies.[1,7,16] Histopathology of the glandular tissue reveals diffuse or nodular hyperplasia and adenomas with difficulty distinguishing between the two.[1,7,14,17] No clear-cut differences have been found, either clinically or immunocytochemically, between parathyroid hyperplasia and adenoma.[7]

Hypercalcemia secondary to PHT can lead to the development of the Zollinger-Ellison syndrome (ZES), with resultant increase in the serum gastrin level, increased acid secretion, diarrhea, and abdominal pain.[14,18] In addition, bone mass, particularly in females because of the long-standing unrecognized nature of the disease, decreases and leads to early osteoporosis.[14]

Treatment of PHT in the setting of MEN-1 requires a careful neck dissection, with removal of all four parathyroid glands.[14,17] Some recommend leaving a remnant of parathyroid tissue in the neck or an auto transplant to the nondominant forearm, but neither strategy yields ideal results.[1] The resultant hypoparathyroidism and hypocalcemia can be treated with vitamin D analogs and calcium replacement. During the parathyroidectomy, it is important to perform a prophylactic thymectomy because thymic neuroendocrine tumors, which occur at a rate of 1.3 to 5.5% by age 40, have a very poor prognosis in MEN-1.[14,19] After parathyroidectomy with associated ZES, it is important to continue to monitor serum gastrin and gastric acid output to be certain that a gastrinoma has not developed.[16,18]

Pancreaticoduodenal neuroendocrine tumors (PET) appear to arise as a somatic mutation of the MEN-1 gene in the foregut.[20] These tumors can be secretory (functional) or nonsecretory and include pancreatic polypeptide secreting, gastrinomas, insulinomas, and vasoactive intestinal polypeptide secreting (VIPoma).[1,14,16] Additional nonpancreatic neuroendocrine tumors include carcinoids of the gastric or duodenal mucosa, bronchus, and thymus.[4,5,14,16]

Pancreatic polypeptide–secreting tumors are the most common, occurring in 80 to 100% of MEN-1 patients.[1,7,14] These tumors generally cause symptoms only as a result of the mass of the tumor itself and thus often present when tumor growth is far advanced.[1] Treatment when identified by obstructive symptoms involves surgical resection.

Gastrinoma, the second most common PET associated with MEN-1, is one of the leading causes of morbidity and mortality, occurring in 21 to 70% of recorded cases.[16] Pancreatic gastrinomas are rare because most arise in the duodenum and are frequently metastsatic at the time of diagnosis. These functioning tumors may be multiple and may also be smaller than 2 mm, making detection very difficult. Treatment involves the use of gastric acid–suppressing agents and surgical resection of identified tumors.[7,16,17,21]

Insulinomas, glucagonomas, and VIPomas are identified much less frequently, 1 to 3% of the time, and are generally solid tumors.[1] They are primarily diagnosed by associated constitutional symptoms and, because medical control is difficult, usually require surgical resection.

Nonfunctioning islet cell tumors of the pancreas are small but associated with significant mortality and have been recognized as the most frequent cause of death, particularly in young individuals, in association with MEN-1. These tumors are generally diagnosed when constitutional symptoms from metastatic disease present.[1,3,12,20,22]

Nonpancreatic neuroendocrine tumors include foregut carcinoids of the bronchus and thymus, and gastric and duodenal mucosa. Bronchial carcinoids are estimated to occur in 0 to 8% of patients with MEN-1 and, although they can at times be aggressive, they generally pursue a benign course. Thymic carcinoids, which occur in 1.3 to 5% of

MEN-1 patients, are aggressive tumors associated with early metastatic disease and subsequent early death. Gastric and duodenal carcinoids occur in 10% of MEN-1 patients, but with MEN-1/ZES that percentage rises to 21%. In that setting, 18 to 33% will be metastsatic to regional lymph nodes and 0 to 10% metastatic to the liver at the time of diagnosis.[4,5,14,16]

Anterior pituitary adenomas, as a first manifestation of MEN-1 in familial settings, occur in less than 10% of the cases.[14,16] The total incidence of pituitary tumors in typical MEN-1 has been reported to occur in 54 to 80% of adult cases.[1,4,23,24] Pituitary tumors can be either micro or macroadenomas, secretory or nonsecretory, and are primarily prolactinomas, although rarely every type of pituitary adenoma except for gonadotropinoma has been reported.[1,14,16,23,24] Pituitary adenomas tend to occur at a younger age with a female to male preponderance of 2:1.[25,26] This is an unexpected ratio, but the role of menin and estrogen transcription factor has been proposed as a cause of tumorigenisis because estrogens can amplify tumor growth-promoting factors in pituitary cell lines.[11,24,26,27] Although hyperprolactinemia occurs in all sexes, it is found primarily in females where it is associated with galactorrhea, amenorrhea, and infertility; whereas in males, erectile dysfunction is a frequent occurrence.[1,24,25] Presenting symptoms, other than those caused by hormone excess, are caused by local encroachment and include headache and visual defects.[1,25] Treatment of a pituitary mass depends on its symptoms and size. If large and symptomatic surgical resection will be needed, however, the majority of asymptomatic pituitary masses are managed using dopamine agonist therapy with close follow-up.[1,7] Should surgical resection be performed, it is important to continue to follow the patient's symptoms and laboratory values, administering dopamine agonist therapy as indicated, because recurrence is likely.[1,14]

Diagnosis of MEN-1 requires an index of suspicion on the part of the family physician and the occurrence of two of the three primary tumors.[14] The finding of elevated serum and ionized calcium should be further investigated by an analysis of parathyroid hormone (PTH). Should the PTH levels return elevated, nuclear scanning with sestamibi to delineate the extent of parathyroid involvement followed by surgical referral will be necessary. In addition, serum prolactin and gastrin levels should be drawn to determine whether the patient has PHT or if this event could be an expression of MEN-1.[12] Should these levels return positive, magnetic resonance imaging of the pituitary and endoscopic pancreatic ultrasound, which can detect tumors as small as, or reportedly smaller than, 20 mm will be needed.[14,22] Management of these complex patients should be a joint venture between Family Medicine, Endocrinology, Gastroenterology, Surgery, and Oncology, with each discipline contributing their recommendations for follow-up as well as the need and frequency for further serial studies.[1,3,12]

In familial MEN-1, other family members should receive genetic counseling and periodic laboratory screening.[2,12,14] A number of marker tests are available but because primary hyperparathyroidism (PHP) is the most frequent expression, the most cost-effective screening tests would be the biomedical markers calcium and ionized calcium.[14] There is no need to perform more complex laboratory studies because the expense far outweighs the yield.[16,25] Genetic testing is available but is expensive and not always accurate.[5,6,14,16]

Case Follow-Up

The need for close follow-up was stressed and the patient was very compliant. Serial laboratory studies and yearly CT scans were followed. She continued with episodic right upper quadrant pain, eventually diagnosed as acalculous cholecystitis, and underwent an open cholecystectomy by an experienced surgeon. At that time, a thorough intraabdominal examination was preformed with no abnormalities noted. On July 3rd, one day after her 32nd birthday, she called the office complaining of abdominal pain and swelling. Her examination was consistent with hepatomegaly and ascites. A CT scan done two days later revealed multiple metastatic nodules in her liver that, compared with a previous scan done eight months earlier, had totally changed. A CT-guided needle biopsy was done the next day without incident. The pathology report was consistent with nonsecretory islet cell carcinoma of the pancreas, confirmed by secondary review at the tertiary care center. Chemotherapy by a local oncologist in consultation with the tertiary care center was initiated and for several months her response was excellent, with a decrease in hepatomegaly and ascites, and an improvement in her activities of daily living. She was able to return to her usual part-time job. Her malignancy, however, became resistant to the chemotherapeutic agents and, despite protocol changes, continued to progress aggressively. She ultimately chose hospice care and as co-director of the hospice at that time, I was able to follow her through her last days. She died peacefully at age 33 with her family and me at her side, a little more than a year after she presented with abdominal pain and swelling, and nine years after her initial presentation.

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