

CLINICAL VIGNETTE

Multifocal Pancreatic Neuroendocrine Tumors in MEN1 Syndrome

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Case Report

A 52-year-old woman was incidentally found to have lesions in her pancreas on a CT of the chest, abdomen, and pelvis, ordered by an outside physician for unclear reasons. There was a 2.4 x 2.5 cm enhancing mass in the pancreatic tail and a 7 mm faintly enhancing lesion in the pancreatic body. She underwent a CT guided biopsy of the pancreatic tail mass. Pathology showed benign pancreatic tissue without diagnostic alterations. She was referred to oncology for further evaluation. She underwent an endoscopic ultrasound and fine needle aspiration of the two pancreatic lesions. Pathology revealed pancreatic neuroendocrine tumor (PNET) in both lesions. She was referred to a hepatobiliary surgeon who performed distal pancreatectomy and splenectomy. Pathology showed neuroendocrine tumor, well differentiated (grade 1), measuring 2.5 cm in the pancreatic tail. There were 3 additional separate foci of neuroendocrine tumor, low grade, measuring 0.6 cm, 0.1 cm, and 0.1 cm. The margins were clear. 7 peripancreatic lymph nodes were negative for tumor. Ki-67 was <2%. Pathologic stage was pT3 N0.

Given the multifocal nature of the pancreatic NET, the possibility of MEN 1 syndrome was raised. Although she did not provide the following history at the time of initial oncology consultation, direct questioning revealed she had a history of hyperparathyroidism and underwent removal of a parathyroid adenoma in 2010. Her paternal cousin died of metastatic neuroendocrine tumor. With this information, she met clinical criteria for familial MEN 1 syndrome. She was referred to genetic counseling and was confirmed to have a pathogenic mutation in the MEN 1 gene. MRI of the pituitary showed a tiny right pituitary cyst but no evidence of microadenoma or macroadenoma.

Discussion

Multiple endocrine neoplasia 1 (MEN1) was first described as an autosomal dominant inherited syndrome characterized by parathyroid, pituitary, and pancreatic adenomas (classical “P-triad”) by Paul Wermer in 1954.¹ Since then, the genetic basis for MEN1 has been elucidated and linked to germline mutations in the MEN1 gene, which encodes for a tumor suppressor protein called menin.² Menin interacts with proteins involved with transcription regulation, genome stability, and cell proliferation. The prevalence of MEN1 is 2-3 per 100,000.³

The initial clinical manifestation of MEN1 is most commonly hyperparathyroidism caused by parathyroid hyperplasia, which is found in 95-100% of MEN1 patients. Anterior pituitary tumors are found in 54-65% of MEN1 patient and pancreatic/duodenal neuroendocrine tumors (PNETs) in 20-70%.⁴

The diagnosis of MEN1 is made by one of the following criteria:

1. The presence of two or more MEN1 associated tumors.
2. The presence of one MEN1 associated tumor and a first degree relative with MEN1.
3. Diagnosis of a germline MEN1 mutation.² Other than the classic P-triad, MEN1 has been found to be associated with tumors in the following: adrenal gland, thyroid, central nervous system, skin (angiofibromas, collagenomas), smooth muscle, and foregut (carcinoids of the thymus, stomach, and lung).⁴

PNETs are of particular importance in MEN1 as they are the leading cause of mortality.³ PNETs have varying malignant potential and can metastasize to the regional lymph nodes and liver. PNETs are discovered at an earlier age in MEN1 cases compared to sporadic cases³ and are typically detected between the third and fifth decade of life.⁴ They can be divided into functional and nonfunctional subtypes. Nonfunctional PNETs are more common than functional PNETs and can secrete hormones but do not manifest with a clinical syndrome. Among functional PNETs, gastrinoma is the most common, followed by insulinoma, then glucagonoma, VIPoma (vasoactive intestinal peptide), GRFoma (growth hormone releasing factor), and somatostatinoma. Clinical manifestation of gastrinoma is Zollinger Ellison syndrome, characterized by hypersecretion of acid leading to recurrent peptic ulcer disease and diarrhea. Gastrinomas are much more commonly found in the duodenum than in the pancreas and can be malignant. Insulinomas present with the Whipple triad of hypoglycemic symptoms, low blood glucose, and relief of symptoms with glucose intake in patients without diabetes. Clinical manifestations of glucagonomas include necrolytic migratory erythema, weight loss, and anemia. Patients with VIPomas have severe diarrhea.

Nonfunctioning PNETs (NF-PNETs) are typically discovered later in the natural history due to lack of hormone related symptoms, although improved screening techniques for MEN1 patients are allowing for increasingly earlier detection.

Although NF-PNETs are usually indolent, early detection is important as they have malignant potential and are associated with worse prognosis compared to functional PNETs. Estimated 10 year survival for patients with NF-PNETs and MEN1 ranges from 23-62%, although one recent study reported 100%.³ Data from the Groupe des Tumeurs Endocrines (GTE) series revealed patients with NF-PNETs and MEN1 had a 43% chance of having liver metastases when the primary tumor was >3 cm, an 18% chance when the primary was 2.1-3 cm, a 10% chance when the primary was 1.1-2 cm, and only 4% chance when primary was 1 cm or less.⁵ The correlation between size of NF-PNET and liver metastasis was statistically significant.

A hallmark feature of PNET in MEN1 cases is the presence of multiple pancreatic tumors compared to solitary tumors found in sporadic cases.^{3,4,6,7} Microadenomatosis, defined as the presence of multiple neuroendocrine tumors measuring up to 0.5 cm, is present in almost all MEN1 cases. Microadenomas are frequently mixed with macroadenomas (>1 cm). Therefore, at the time of surgery, multiple tumors are found in the pancreas of MEN1 patients. This is an important fact to know since the presence of multiple tumors may be the initial clue for clinicians to suspect MEN1 syndrome. Studies have shown that PNET can be the first clinical manifestation of MEN1 and diagnosed before hyperparathyroidism. These PNETs can be mistaken for sporadic cases. Therefore, in a patient without any other clinical manifestations of MEN1, multifocal PNET should alert to the possibility of MEN1 syndrome, allowing for earlier diagnosis and management.^{6,7}

Management of PNETs in MEN1 generally aims at both treating hormone-excess states and treating the tumors that have malignant potential. Medical therapy of hormone-excess states includes treatment of acid hypersecretion with proton pump inhibitors in patients with gastrinomas. For other functioning PNETs, long-acting somatostatin analogues can be used for control of symptoms before surgery or in those not cured by surgery. Surgical resection of PNETs can also potentially treat hormone-excess states and remove the tumors that have malignant potential. Surgery is recommended for most functional PNETs.

The challenges with PNETs in MEN1, however, are finding which of the multiple tumors are responsible for the functional syndrome and the likelihood of recurrent tumors when partial pancreatectomy is performed.⁴ Most of the controversy in surgical management involves NF-PNETs. Some experts recommend aggressive resection upon diagnosis of NF-PNETs due to their malignant potential while others recommend partial pancreatectomies at different thresholds of tumor size. Triponez et al⁸ reported more than 10 year follow up data of 46 patients with MEN1 and NF-PNETs less than or equal to 2 cm who did not have surgery at the time of diagnosis. 28 patients (61%) had stable disease and 16 patients had progression, requiring surgery in 7 patients. One patient died of metastatic disease, but none of the living patients at last follow-up had evidence of metastatic disease. The authors concluded that conservative management without surgery in patients with MEN1 and NF-PNETs measuring 2 cm or smaller results in low disease specific mortality.

Currently, most guidelines recommend conservative management of tumors 1 cm or less and surgery for tumor greater than 2 cm. There are mixed recommendations for tumors 1.1 to 2 cm. National Institutes of Health (NIH), National Comprehensive Cancer Network (NCCN), and GTE recommend conservative management of tumors 2 cm or less. Patients that are managed conservatively should be followed closely for evidence of disease progression, including rapid growth on imaging or development of hormone-excess states. Most experts agree that management of these patients with MEN1 and PNETs should be discussed in multidisciplinary tumor boards.

In conclusion, pancreatic neuroendocrine tumor is an important manifestation of MEN1 syndrome, contributing to significant morbidity and mortality. Although hyperparathyroidism is the most common initial presentation, patients may present with multifocal PNETs, a feature that should raise suspicion for MEN1 syndrome and is in contrast to sporadic solitary PNETs. Optimum management of nonfunctioning PNETs in MEN1 patients is debated, but tumors greater than 2 cm should be considered for resection due to a higher risk of metastasis, which is in accordance with most guidelines.

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