Endocrine, *vol. 13, no. 3, 263–266, December 2000* 0969–711X/00/13:263–266/$11.00 © 2000 by Humana Press Inc. All rights of any nature whatsoever reserved.

Large and Asymptomatic Pancreatic Islet Cell Tumor in a Patient with Multiple Endocrine Neoplasia Type 1

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The major phenotypes of multiple endocrine neoplasia type 1 (MEN 1) consist of three lesions characterized by hyperparathyroidism, pituitary tumors, and endocrine pancreatic tumors. The endocrine pancreatic tumors are a significant cause of disease-related mortality in MEN 1. Although symptomatic pancreatic tumors such as insulinoma and gastrinoma should be resected, the management of asymptomatic pancreatic tumors is not established. In asymptomatic pancreatic tumors, the most important factor is the propensity for malignant transformation of the tumors. Although there are no means to foresee it, the size of the pancreatic tumors might be predictive of malignant development in MEN 1. We report here a patient with MEN 1 who had a large asymptomatic pancreatic tumor. The patient (72-yr-old man) was diagnosed with primary hyperparathyroidism and underwent a total parathyroidectomy. Genetic examination showed a germline mutation of the *MEN1* gene (E45G). Abdominal magnetic resonance imaging revealed a large (>6 cm) tumor with a heterogeneous pattern in the tail of the pancreas. No metastases of the tumor were evident. Serum levels of insulin, gastrin, and glucagon were normal, and the patient had no symptoms. Operative resection was performed, and microscopic examination revealed that the tumor was an islet cell tumor stained with multiple hormones. This is a case indicating that asymptomatic pancreatic tumors associated with MEN 1 might be indolent independent of their size.

Key Words: Multiple endocrine neoplasia type 1; asymptomatic pancreas tumor; mutation.

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomally dominant inherited disorder characterized by primary hyperparathyroidism and tumors in the anterior pituitary and pancreas *(1)*. Hyperparathyroidism develops in more than 95% of MEN 1 patients, with onset usually occurring during the second decade of life. Pancreatic tumors are the second most common lesion, and the reported prevalence varies between 30 and 75% *(1–4)*. The *MEN1* gene has been mapped to a limited region of chromosome 11q13 and has recently been cloned *(5)*. Currently, more than 100 germline mutations of *MEN1* gene have been reported in MEN 1 patients *(6–10)*. The diagnosis of MEN 1, therefore, comprises the recognition of MEN 1–related lesions and the detection of *MEN1* gene mutations.

MEN 1 patients with endocrine pancreatic tumors may demonstrate clinical symptoms of Zollinger-Ellison syndrome (ZES) owing to hypergastrinemia and hypoglycemic syndrome due to insulinomas *(11)*. Although these symptomatic patients undergo pancreatic surgery, it is questionable whether asymptomatic pancreatic tumors should be resected. The most important factor is the propensity for malignant transformation of the tumors because endocrine pancreatic cancer is a significant cause of disease-related mortality in MEN 1 *(12)*. A previous report suggested that the size of pancreatic tumors might be predictive of the malignancy in MEN 1 patients with ZES *(13)*. We report in this article an MEN 1 patient who had a large and asymptomatic islet cell tumor, suggesting that the size of the pancreatic tumor might be unrelated to its propensity for malignancy in MEN 1.

Case Report

A 72-yr-old man who had a past history of recurrent urolithiasis was diagnosed with hyperparathyroidism (calcium 12.7 mg/dL; intact parathyroid hormone [PTH], 256 pg/mL) and subsequently underwent a total parathyroidectomy with autoplantation. The pathologic diagnosis was hyperplasia of four parathyroid glands. After the operation, serum calcium and PTH returned to normal levels. Other MEN 1–associated lesions were not evident at that time. At the age of 74, abdominal magnetic resonance imaging

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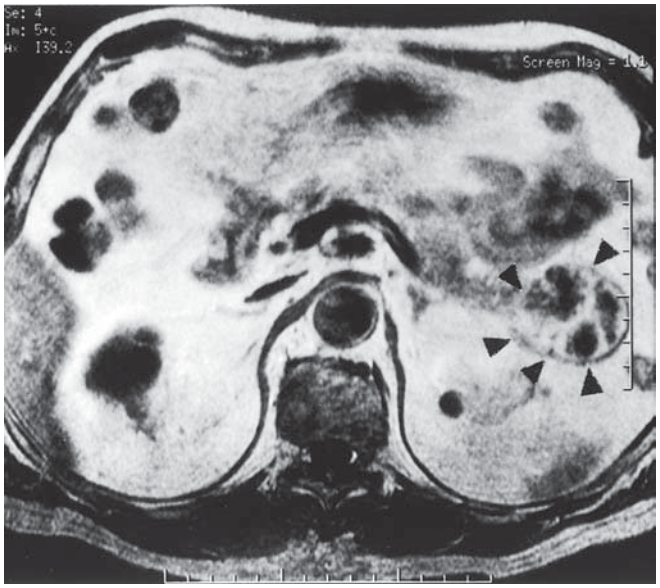

Fig. 1. Image from T1-weighted MRI of the pancreas. MRI revealed a large (>5 cm) mass with a heterogenous pattern in the tail of the pancreas. The arrows indicate the tumor.

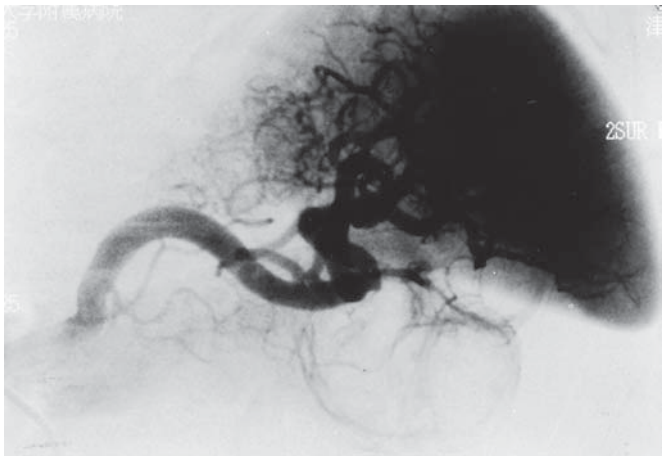

Fig. 2. Selective angiogram of a splenic artery. A looped artery surrounding a pancreatic tumor is shown. Tumor staining is not noted.

(MRI) revealed a large tumor (6 × 6.5 cm) with a heterogeneous pattern in the tail of the pancreas (Fig. 1). Selective angiography of the splenic artery showed a looped artery surrounding the pancreatic tumor (Fig. 2). Tumor staining was not noted in this angiogram. No metastases of the pancreatic tumor were evident. The patient had no symptoms, and serum levels of insulin, gastrin, and glucagon were normal. Pituitary MRI showed no tumor in the pituitary. Sequencing of genomic DNA extracted from the patient's blood showed a germline mutation of the *MEN1* gene (E45G, exon 2) *(10)*. Although we had no chance to examine other family members, the diagnosis of MEN 1 was made because the patient had two MEN 1–related lesions

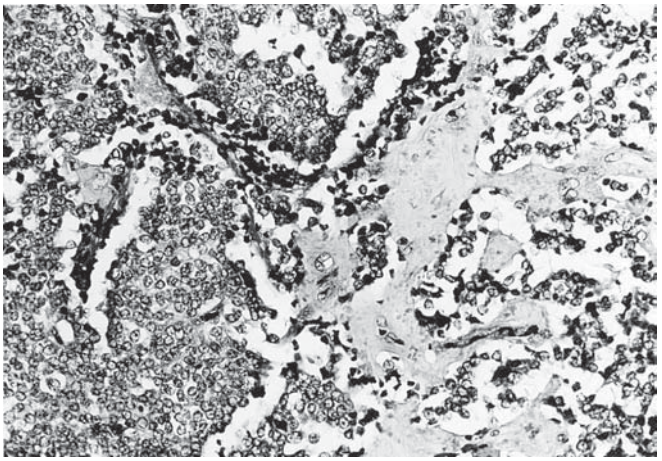

Fig. 3. An islet cell tumors showing a gyroform pattern with ribbons of cells.

Table 1.
Results of Immunohistochemical Study

Insulin	(+)
Glucagon	(+)
Gastrin	(+)
Serotonin	(+)
VIP	(-)
Pancreatic Polypeptide	(-)
Somatostatin	(-)

such as hyperparathyroidism and a pancreatic tumor in combination with a germline mutation of *MEN1* gene. Because the pancreatic tumor was large and pancreatic MRI failed to rule out the malignancy, the patient underwent tumor resection. The microscopic examinination of the tumor revealed typical histologic features of islet cell tumors. These tumors have a gyroform pattern with ribbons of cells passing between vascular sinusoids (Fig. 3). There were no other small multifocal satellite tumors. Although it was extremely difficult to assess the degree of malignancy of the tumor, metastases of the liver and lymph node were not evident, suggesting that the tumor was benign. Immunohistochemical studies showed positive staining for insulin, glucagon, gastrin, and serotonin, as shown in Table 1. Multihormonality was found in most of the cells. The tumor was not stained with antisera to vasoactive intestinal polypeptide, pancreatic polypeptide or somatostatin. A representative result of immunostaining with insulin is shown in Fig. 4.

Discussion

This MEN 1 patient had a large and asymptomatic islet cell tumor in the pancreas. He showed neither ZES nor hypoglycemic syndrome. Pancreatic involvement is the

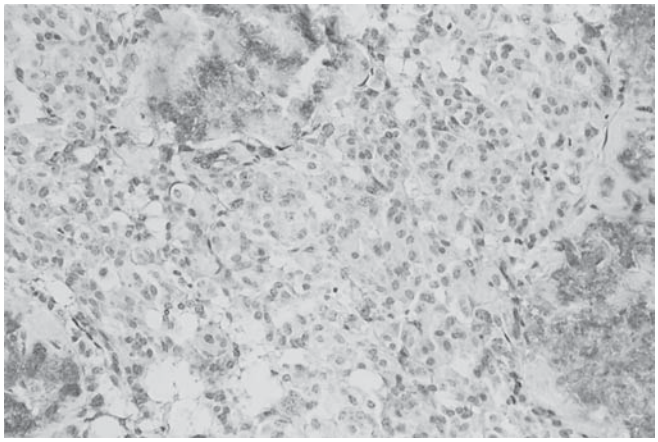

Fig. 4. A representative result of immunostaining with insulin in the islet cell tumor.

second most common lesion in MEN 1, and the reported prevalence in clinical screening varies between 30 and 75% *(1–4)*. Asymptomatic pancreatic tumors are noted in approx 20–50% of patients with pancreatic involvement *(4,14,15)*. The diagnosis of asymptomatic pancreatic tumors chiefly depends on the imaging studies such as computed tomography, MRI, ultrasonography, and angiography. In our patient, MRI was helpful in detecting a large tumor in the tail of the pancreas. The most sensitive biochemical marker is an abnormal serum pancreatic polypeptide response to a meal test *(16)* and an elevated plasma chromogranin A level *(17)*. These tests are reported to detect pancreatic tumors that cannot be detected with imaging studies. We did not perform these tests because the pancreatic tumor was clearly detected with MRI.

There is controversy regarding the treatment of asymptomatic pancreatic tumors in MEN 1 patients. This controversy generally reflects the absence of control studies. A principal therapeutic goal seems to be cancer prevention. However, it is quite difficult to foresee the propensity for malignant transformation of pancreatic lesions. Cadiot et al. *(13)* have reported that large pancreatic tumors (>3 cm) are predictive of the development of liver metastases in patients with ZES in both non–MEN 1 and MEN 1. By contrast, Lowney et al. *(15)* have indicated that the size of pancreatic tumors in MEN 1 does not correlate with metastatic potential. In their study, half of the patients had asymptomatic pancreatic tumors and only 25% of the patients showed ZES. The large pancreatic tumor (>6 cm) observed in our patient showed no evidence of malignancy, suggesting that the size of the pancreatic endocrine tumor might be unrelated to the risk of malignancy in asymptomatic pancreatic tumors of MEN 1, in agreement with Lowney's study *(15)*. This case indicates that asymptomatic pancreatic tumors might be indolent independent of their size in MEN 1. It is also reported that the neuroendocrine neoplasms in MEN 1 are more indolent than their sporadic counterparts *(18)*.

Although the pancreatic tumor in our patient was clinically asymptomatic, immunohistochemical studies of the resected tumor showed positive staining with multiple hormones. These included insulin, glucagon, serotonin, and gastrin. This is compatible with a previous report showing that most asymptomatic and nonfunctioning pancreatic tumors are immunohistochemically stained with various hormones *(14)*. The only difference is that pancreatic polypeptide was negative in our patient although pancreatic polypeptide–cell tumors are known to be common in asymptomatic pancreatic tumors of MEN 1 patients *(14)*. The number of silent tumors (negative staining) is reported to be quite low (7%), i.e., fewer than sporadic single endocrine pancreatic tumors *(4)*. Taken together, the data show that most asymptomatic pancreatic tumors in MEN 1 appear to possess a potential to produce multiple hormones.

A germline missense mutation (E45G) of the *MEN1* gene was identified in our patient. To date, many germline mutations (more than 100) have been reported in the *MEN1* gene *(6–10)*. The mutations include deletions, nonsense mutations, insertions, and missense mutations, of which deletions are the most common. They are scattered on the entire coding region of the *MEN1* gene from exons 2 to 10, depending on the length of each exon. Exons 2 and 3 are the most common regions for the appearence of mutations, probably because they are large, but this does not imply a true "hot spot" as reported in the RET gene of MEN 2 *(19)*. Although there is no direct evidence for the role of *MEN1* gene mutations in the tumorigenesis of MEN 1, the cellular functions of the *MEN1* gene product, menin, are becoming more clear. Guru et al. *(20)* recently reported that menin is a nuclear protein that has at least two independent nuclear localization signals in the C-terminal portion. Recently, Agarwal et al. *(21)* reported that menin interacts with the transcription factor JunD. Menin repressed transcriptional activation mediated by JunD. It was also shown that several types of missense mutations disrupted menin interaction with JunD. Nevertheless, in our patient, the pathogenesis is still unclear because the location of the detected mutations (E45G in exon 2) is separate from the sites of both nuclear localization signals and JunD binding.

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