

**THE INFAMOUS THREE ‘P’S’ – PITUITARY, PARATHYROID, PANCREAS –  
THE BUILDING BLOCKS OF MULTIPLE ENDOCRINE NEOPLASIA TYPE I (MEN I)**

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**QUESTIONS:**

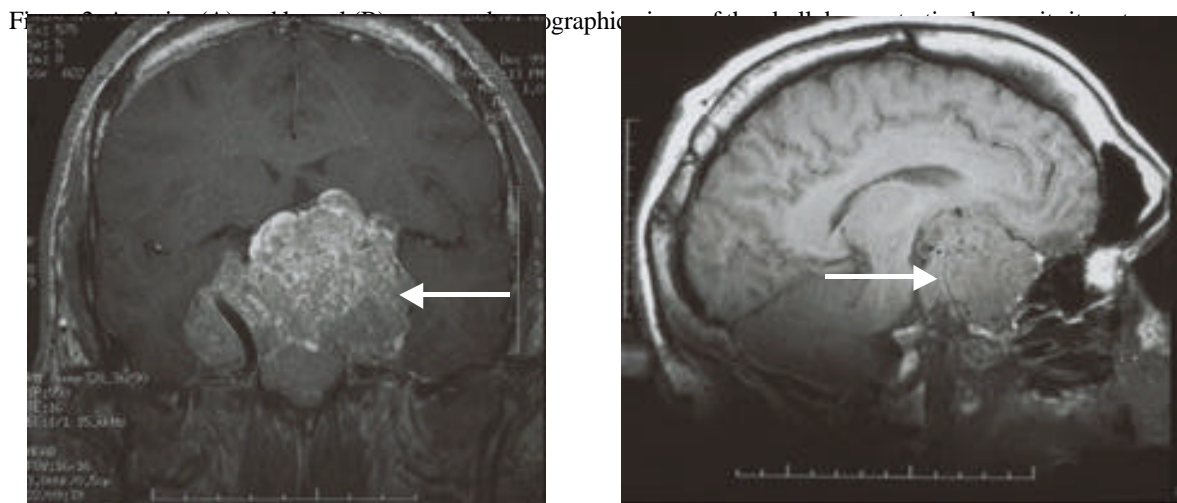
1. Which is the most common endocrine disease in patients with MEN I?
2. What is the anticipated pathology in MEN I patients with primary hyperparathyroidism?
3. What is the most common islet cell tumor of the pancreas encountered in these patients?
4. Name the gene responsible for MEN I.

**CLINICAL ASPECTS:**

A 34-year-old, previously healthy male farmer (Figure 1) presented because of the fairly rapid onset of bilateral, lateral visual field blindness (homonymous hemianopsia). This was confirmed by ocular examination. Computerized tomographic examination (CT) of the head demonstrated a large pituitary tumor (Figure 2A and B) – the obvious cause of his visual field defects due to pressure on the optic chiasma.



Figure 1: Facial appearance of patient



A palliative trans-sphenoidal hypophysectomy was performed. Histology was compatible with a benign prolactinoma, and the patient was started on bromocriptine in view of the residual tumor.

During the postoperative course, he was found to be hypercalcemic. His serum calcium was 11.3 mg/dL (normal = 8.9-10.1) with a concomitant immunoreactive parathyroid hormone (iPTH) level of 9.5 pmol/L (normal < 5.0). A subsequent sestamibi parathyroid scan was highly suggestive of multiglandular disease (Figure 3).

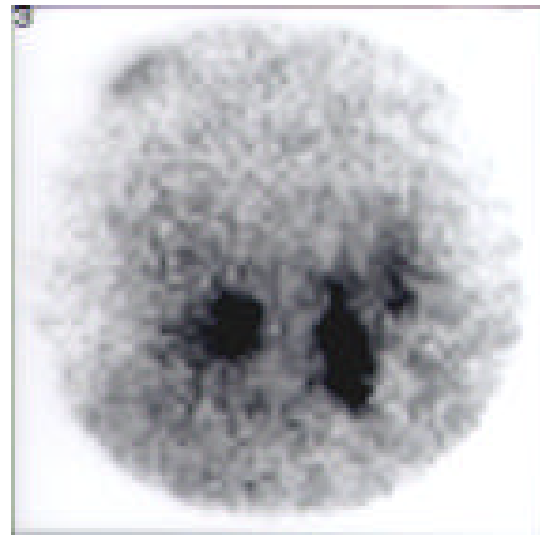


Figure 3: Sestamibi scan showing bilateral uptake suggesting multiglandular disease

At the time of elective cervical exploration, which was performed with intraoperative PTH monitoring, a three-gland parathyroidectomy was performed excising glands weighing 1200, 350, and 2700 mg, respectively (normal < 50 mg). The right inferior gland was never visualized, and a transcervical thymectomy revealed no parathyroid tissue. His postoperative serum calcium/PTH levels were 9.0 mg/dL and 3.2 pmol/L.

During his ongoing evaluation, CT scans of the chest (Figure 4) and abdomen (Figure 5A and B) were obtained, as were appropriate tumor markers (Table 1).

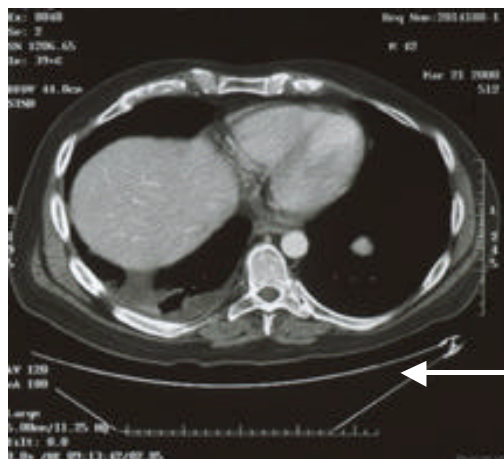


Figure 4: Computed tomographic scan of the chest demonstrating a 2 cm lesion in the lower lobe of the left lung

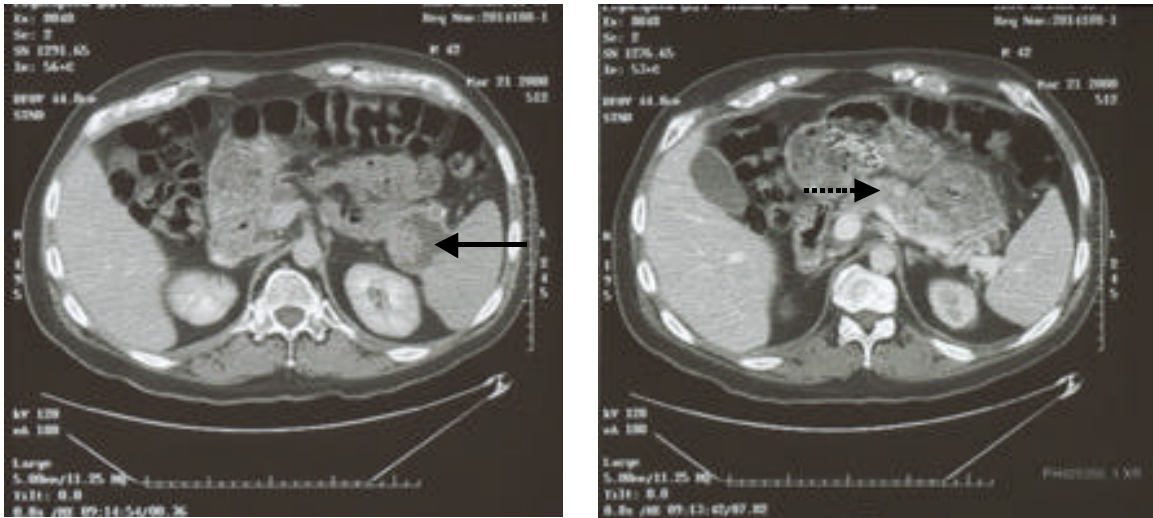


Figure 5A and B: Computed tomographic scan of the abdomen demonstrating a large heterogenous mass in the tail of the pancreas (solid arrow) with evidence of other smaller tumors in the body of the pancreas (dotted arrow)

Table 1: Serum Tumor Markers

	Value (normal)
Glucagon	84 pg/mL (< 60)
hPP	4836 pg/mL (<270)
Serotonin	24 mg/24 hr (0-6.0)
Gastrin	250 pg/mL (< 200)

In sequence, a near-total pancreatectomy and thoracotomy were performed. Histology of the pancreas showed multiple benign islet cell tumors (Figure 6A and B), which stained positive for multiple pancreatic hormones on immunohistochemical staining, while the lung nodule was that of a classical benign carcinoid tumor.

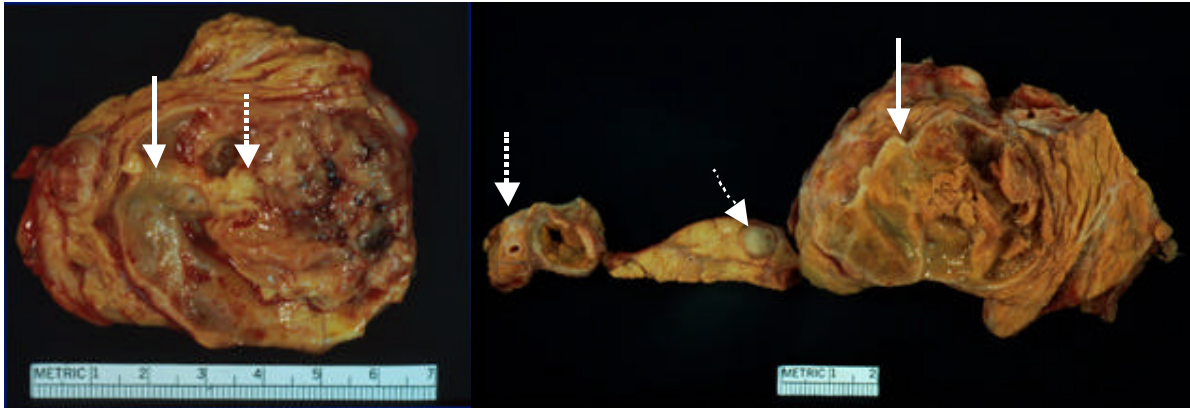


Figure 6A and B: Gross specimens demonstrating large tail of pancreas islet cell tumor (solid arrow) with other smaller tumors clearly seen as well (dotted arrows)

His menin I gene was positive, and extensive family screening was undertaken. He remains well one year after all of the surgical interactions.

#### **DATA SUMMARY:**

Multiple endocrine neoplasia (MEN) syndromes are of special interest to endocrinologists, surgeons, and oncologists because they are among the first group of tumor syndromes to be predicted by genetic testing, detected by biochemical screening, and, in part, subsequently cured by surgical intervention. The syndromes are autosomal dominant traits with high penetrance and variable expressivity. MEN type I (Wermer syndrome) consists of primary hyperparathyroidism (HPT) (90%- 100%), pancreatic islet cell tumors (30% - 80%), and anterior pituitary adenomas (43% - 65%). MEN I occurs in 2-20/100,000 of the general population. For a diagnosis of MEN I, a patient may have at least two of the three listed primary components, or one primary component and a family member with two documented components. The parathyroid and pituitary lesions are almost never malignant, whereas the pancreatic lesions may be malignant (gastrinoma with greater frequency than insulinoma).

### Screening and Predictive Testing

Prospective screening of MEN I detects the onset of excess hormone production and allows early treatment of life-threatening tumor or hormone-excess syndromes. All first-degree relatives of an index case should have yearly physical examinations and biochemical screening beginning at five years of age, unless they are genetically negative in which case no further follow-up is needed. The length of time for testing is not clear, but it should continue to at least 45 years of age. Minimal tests to be done should include serum calcium, PTH, gastrin, insulin, blood glucose, prolactin, growth hormone, and insulin-like growth factor-I (IGF-I). This procedure can reduce the age of diagnosis by almost two decades to an average of 18 years. Predictive genetic testing using DNA markers is beginning to play an important role in this screening procedure. The gene for MEN I (menin) has been localized to chromosomal region 11q11 – q13.

### Primary Hyperparathyroidism (HPT)

Only 2.5% of all patients with HPT have MEN I. Fifty percent of MEN I patients present with HPT as the initial component, however, and 90% to 100% of MEN I patients have HPT. The disease may be mild, with the pathology being diffuse hyperplasia associated with multiple parathyroid gland disease in up to 90% of cases. A plasma factor in patients with MEN I-associated HPT appears to play a role in the stimulation of parathyroid gland hyperplasia. The diagnosis of HPT is not difficult and is based on the presence of elevated serum calcium (total and ionized) and an inappropriate elevation of PTH. The patient should be questioned about nephrolithiasis and symptoms of hypercalcemia.

Surgical treatment of choice is controversial and centers on the need for subtotal resection versus total parathyroidectomy and autotransplantation. HPT in MEN I can recur with

variable frequency. Persistent hypercalcemia is often due to failure to visualize all four glands and inadequate resection at the time of primary surgery. Even though many patients may appear to have “solitary” adenomas or a single enlarged gland, the remaining hyperplastic glands inevitably will lead to recurrence. Our preference is subtotal resection (removal of 3 ½ glands) based on a 94% chance of immediate cure. To perform this resection safely, all cervical parathyroid glands should be visualized prior to resecting any of the glands to ensure preservation of 50 to 100 mg of clearly viable, well-vascularized parathyroid tissue. Surgical principles in MEN I-related parathyroid disease should emphasize the following: 1) identification of all four glands, 2) as a minimum, a subtotal resection in every case, and 3) routine transcervical thymectomy to minimize the problem of supranumerary gland involvement. There is recurrence of up to 16.4% after 10 years with this approach. Total parathyroidectomy with autotransplantation minimizes cervical recurrence but leads to a higher incidence of permanent hypocalcemia and risk of problematic graft-dependent hypercalcemia.

### Pancreatic Endocrine Tumors

A variety of pancreatic endocrine tumors occur in MEN I with the range of expression of 30% to 80% depending upon the series reported. These include gastrinoma in 50% to 67% of patients, insulinoma (9% - 30%), glucagonoma (11%), insulinoma and glucagonoma combined (6%), and the rarer VIPoma, PPoma (pancreatic polypeptide), and somatostatinoma.. These tumors are characteristically multicentric, diffuse, and do have tendencies to metastasize to lymph node or to the liver.

### Pituitary Tumors

Pituitary tumors associated with MEN I appear to mirror the tumor frequency and behavior of the general population except for a higher occurrence of hormone-secreting tumors.

the most common hormone secreted is prolactin alone, followed by growth hormone alone and combined prolactin and growth hormone. Adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and glycoprotein hormone production by tumors is less common.. If the MEN I pituitary tumors do follow the known frequencies, the glycoprotein-secreting tumors will be noticed and reported more frequently. Nonfunctioning tumors do occur. Their major manifestations clinically would be anatomic compression syndromes and hypopituitarism.

### Summary

Patients with MEN syndrome present a unique opportunity to address the treatment of multiple endocrine tumors. Surgery is the primary treatment in most cases for the major components of the MEN syndromes. In MEN I, the parathyroid, pancreatic, and pituitary lesions can each be treated surgically in appropriate cases.

### **ANSWERS:**

1. Primary hyperparathyroidism is the most common endocrine disease in patients with MEN I, occurring in more than 90% of patients.
2. The most commonly encountered pathology is multi-gland disease. There is also a increased incidence of five glands in these patients (approximately 12%). This mandates routine transcervical thymectomy.
3. The Zollinger-Ellison syndrome is the most common islet cell tumor of the pancreas in MEN patients. It too is often multicentric.
4. The recently discovered gene, which is localized to chromosomal region q11, has been named *menin*.

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“Better to remain silent and thought a fool,  
then to open your mouth and remove all doubt.”

-- Mark Twain