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MORNING REPORT

A 59-Year-Old Man with Fatigue and Abdominal Pain

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Abstract

Morning Report is a time-honored tradition where physicians-in-training present cases to their colleagues and clinical experts to collaboratively examine an interesting patient presentation. The Morning Report section seeks to carry on this tradition by presenting a patient's chief concern and story, inviting the reader to develop a differential diagnosis and discover the diagnosis alongside the authors of the case. This report examines the story of a 59-year-old man with a history of nephrolithiasis and gastroesophageal reflux who sought evaluation for fatigue and abdominal pain. Using questions, physical examination, and testing, an illness script for the presentation emerges. As the clinical course progresses, the differential is iteratively refined until a final diagnosis is made.

Pierre O. Ankamah, M.D., Ph.D.,
Editor

Reason for presentation: fatigue and abdominal pain

Part 1: The Patient's Story

History of Present Illness: A 59-year-old man with a history of nephrolithiasis presented to a primary care clinic with fatigue, intermittent upper abdominal pain, and cognitive difficulties. His symptoms began 2 years ago, prompting an evaluation that led to a diagnosis of gastroesophageal reflux disease (GERD). Despite treatment with omeprazole, the abdominal pain only occasionally improved. Over time, he experienced frequent constipation, with bowel movements occurring approximately once every 2 days. During the past year, his fatigue worsened, and he also had a persistent sensation of mental fog. He reported increasing difficulty following multistep instructions and episodes of forgetfulness, which ultimately led him to seek medical evaluation. He reported no fevers, chest pain, vomiting, or diarrhea. Additional information about the patient is provided in [Box 1](#).

PHYSICAL EXAMINATION

The patient's vital signs are presented in [Box 2](#).

He was alert and oriented to person, place, and time. The extraocular movements were intact, and his pupils were equal in size and reactive to light. The ventilatory effort was normal, with no adventitious lung sounds heard during lung auscultation. The heart was in a regular rhythm,

Box 1: Medical and Surgical History, Medications, Allergies, and Social History

Medical and Surgical History:

Nephrolithiasis

Gastroesophageal reflux disease

Medications:

Omeprazole as needed for epigastric pain

Allergies or Adverse Reactions:

None

Social History:

He lives with his wife. He drinks alcohol very rarely. He has never smoked cigarettes or used other drugs.

Box 2: Vital Signs

Temperature: 36.9°C (oral); heart rate: 75 beats per minute; blood pressure: 112/79 mm Hg; respiratory rate: 16 breaths per minute; and O₂ saturation: 98% breathing ambient air.

without murmurs or extra heart sounds. The abdomen was neither distended nor tender to superficial or deep palpation, and bowel sounds were normal. There was normal strength in the bilateral upper and lower extremities. The skin was clear, with no rashes or petechiae.

Part 2: Formulating the Problem Representation and Building the Differential Diagnosis

The problem representation can be formulated as follows: a 59-year-old man with nephrolithiasis and GERD presents with persistent fatigue, impaired concentration, epigastric pain, and constipation for the past 2 years, with no abnormal findings on physical examination.

The differential diagnosis for this constellation of symptoms spans a wide range of potential etiologies, including infectious, metabolic, inflammatory, and vascular

conditions, as well as other systemic disorders. An initial workup focusing on serum electrolytes, renal function, blood counts, and liver biochemical tests will help refine the problem representation and guide further evaluation.

INITIAL RESULTS

The initial investigations, summarized in [Figure 1](#), demonstrate elevated serum calcium and low serum phosphorus levels. Hypercalcemia can cause a wide range of symptoms, including fatigue, kidney stones, excessive urination, increased thirst, constipation, and gastrointestinal discomfort, such as peptic ulcer disease. Some of these symptoms align with the patient's clinical presentation. Calcium homeostasis is regulated by a complex system involving parathyroid hormone (PTH), activated vitamin D (calcitriol, or 1,25-dihydroxy vitamin D), renal calcium handling, and bone turnover ([Fig. 2](#)).¹ PTH elevation increases serum calcium by promoting renal calcium reabsorption, stimulating osteoclastic bone resorption, and enhancing intestinal calcium absorption through increased synthesis of 1,25-dihydroxy vitamin D. Elevated PTH levels are associated with decreased serum phosphorus due to increased renal phosphate excretion, reflecting the inverse regulatory relationship between calcium and phosphorus. Activated vitamin D is produced in the kidneys through hydroxylation of 25-hydroxy vitamin D by the enzyme 1-alpha-hydroxylase. Ectopic production of 1-alpha-hydroxylase, as occurs in granulomatous diseases like sarcoidosis or tuberculosis, can lead to uncontrolled synthesis of 1,25-dihydroxy vitamin D, resulting in hypercalcemia independent of PTH regulation. Hypercalcemia may also arise from vitamin D toxicity or excessive calcium consumption, historically known as milk-alkali syndrome.² Some medications, such as thiazide diuretics, lithium, omeprazole, aromatase inhibitors, and vitamin A, can contribute to hypercalcemia. Prolonged immobility can lead to hypercalcemia through increased osteoclastic bone resorption. Reduced mechanical stress on bones disrupts the balance of bone turnover, favoring resorption over formation and resulting in elevated calcium levels. Endocrine conditions, such as thyrotoxicosis, adrenal insufficiency, acromegaly, and pheochromocytoma, can also contribute to hypercalcemia through distinct mechanisms. In thyrotoxicosis, excess thyroid hormone stimulates osteoclast activity, increasing bone resorption and calcium release. Adrenal insufficiency leads to decreased glucocorticoid levels, enhancing intestinal calcium absorption and reducing renal calcium excretion. Acromegaly promotes calcium release through increased bone turnover driven by elevated levels of growth hormone and insulin-like growth factor 1 (IGF-1). Pheochromocytoma, though rare, may

Na⁺ 137 (135–145 mEq/l)	Cl⁻ 100 (98–108 mEq/l)	BUN 17 (8–25 mg/dl)	Glu 117 (70–110 mg/dl)	Hgb 13.2 (14–18 g/dl)	PLT 420 (150–450×10 ³ /μl)
K⁺ 4.3 (3.4–5 mEq/l)	HCO₃⁻ 19 (23–32 mEq/l)	Cr 1.06 (0.6–1.5 mg/dl)		WBC 6.7 (4.4–11×10 ³ /μl)	
T. Prot. 7.4 (6.4–8.2 g/dl)	Alb 4.5 (3.4–5.0 g/dl)	Other Tests Calcium: 11.5 (8.6–10.4 mg/dl) Phosphate: 1.2 (2.5–4.5 mg/dl)		Differential <i>Neutrophils:</i> 3.4 (1.80–6.90×10 ³ /u) <i>Lymphocytes:</i> 2.1 (1.30–3.40×10 ³ /ul) <i>Monocytes:</i> 583 (0.20–0.80×10 ³ /u)	
Tb 1.0 (0.0–1 mg/dl)	Db 0.2 (0.0–0.4 mg/dl)				
AST 17 (10–40 units/l)	ALT 22 (10–55 units/l)				
ALK 61 (45–115 units/l)					

Figure 1. The Patient's Laboratory Results.

Reference ranges are given in parentheses. Alb denotes albumin; ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cl⁻, chloride; Cr, creatinine; Db, direct bilirubin; Glu, glucose; HCO₃⁻, bicarbonate; HCT, hematocrit; Hgb, hemoglobin; K⁺, potassium; Na⁺, sodium; PLT, platelet; ALK, alkaline phosphatase; T. Prot., total protein; Tb, total bilirubin; and WBC, white blood cell.

cause hypercalcemia through the production of parathyroid hormone-related protein or catecholamine-mediated bone resorption. To evaluate hypercalcemia effectively, distinguishing between PTH-mediated and PTH-independent mechanisms is key, as outlined in [Box 3](#).

WHAT ADDITIONAL QUESTIONS WOULD HELP REFINE THE PROBLEM REPRESENTATION AND DIFFERENTIAL DIAGNOSIS?

Q1: Has the patient noticed visual problems, headaches, or weight loss?

Rationale for question: Visual problems, headaches, and weight loss may indicate increased intracranial pressure, which could be associated with conditions such as parathyroid carcinoma or malignancies with central nervous system metastases.

Answer: The patient did not report any visual problems, headaches, or weight loss.

Q2: Does the patient have any specific dietary habits, particularly involving calcium-rich products or supplements?

Rationale for question: Patients may consume calcium-containing tablets to alleviate symptoms like epigastric discomfort, leading to hypercalcemia. Excessive vitamin D intake from high-dose supplementation or unregulated dietary products can also result in hypercalcemia.

Answer: The patient did not report consuming calcium-rich products or supplements.

Q3: Has he had any prolonged periods of immobility?

Rationale for question: Prolonged immobility, as occurs in conditions such as spinal cord injury, prolonged bed rest, or paralysis, accelerates bone resorption through increased osteoclastic activity, leading to hypercalcemia.

Answer: The patient maintains a consistent daily exercise routine and has not had any prolonged immobility.

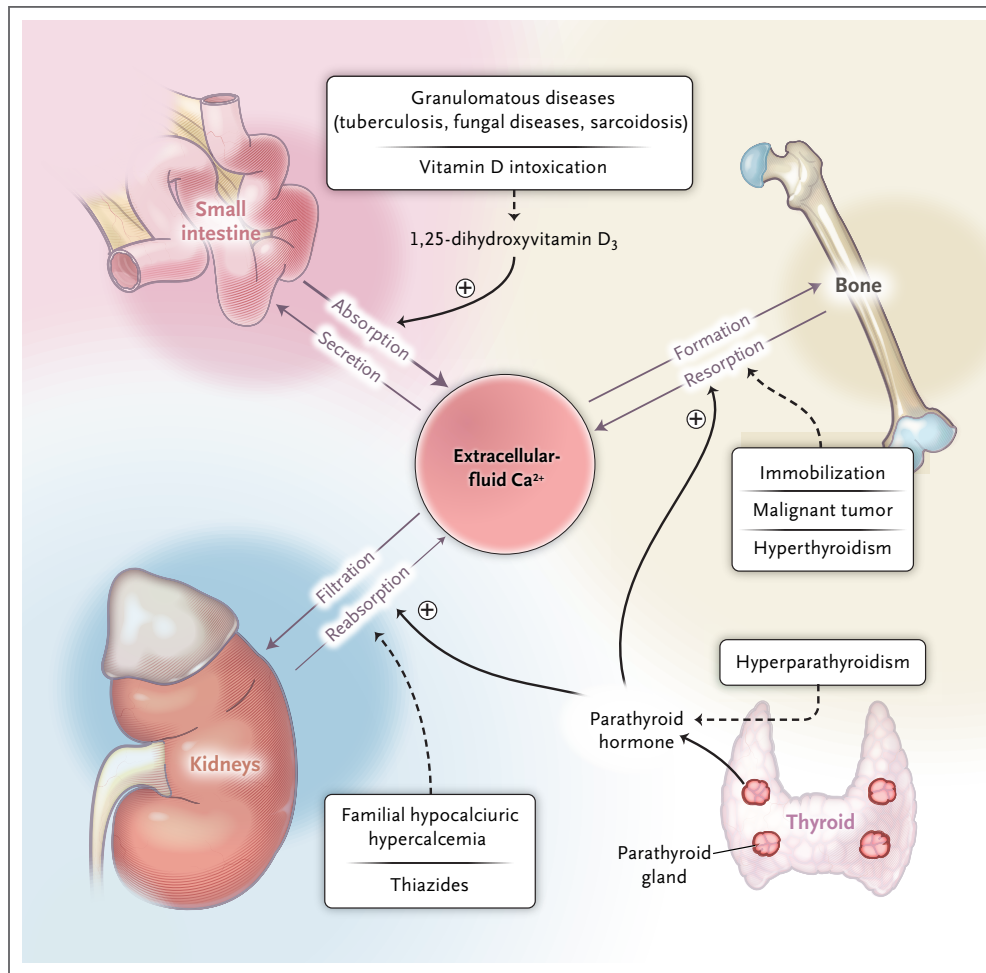


Figure 2. Regulation of Calcium Homeostasis and Common Causes of Hypercalcemia.

Reprinted, with permission, from El Saleeby, et al.¹

WHAT ADDITIONAL INVESTIGATIONS WOULD BE HELPFUL?

Serum PTH levels are essential for distinguishing PTH-dependent causes from PTH-independent causes of hypercalcemia. Assessment of renal function and vitamin D metabolites, including 25-hydroxyvitamin D and 1,25-dihydroxy vitamin D, can help identify vitamin D intoxication or signal conditions such as granulomatous diseases. Parathyroid ultrasonography and sestamibi scans are valuable tools for identifying parathyroid adenomas or hyperplasia. Parathyroid adenomas in ultrasound images typically appear as homogeneously hypoechoic nodules compared with the overlying thyroid gland. Sestamibi scans detect increased radiotracer uptake in metabolically active parathyroid lesions, with persistent activity on delayed imaging

providing additional precision for localization. Contrast-enhanced computed tomography (CT) of the chest and abdomen can help detect malignancies, granulomatous diseases, or sarcoidosis as potential contributors to hypercalcemia.

RESULTS

The results of laboratory evaluation demonstrated a markedly elevated PTH level of 778 pg/ml (reference range: 14 to 64 pg/ml), consistent with parathyroid overactivity. The 25-hydroxy vitamin D level was 18 ng/ml (reference range: 30 to 100 ng/ml). Ultrasonography of the neck demonstrated bilateral hypoechoic nodules inferior to the thyroid gland (Fig. 3A). A sestamibi parathyroid scan identified multiple nodules within the parathyroid glands (Figs. 3B and 3C).

Box 3: Framework for Building the Differential Diagnosis of Hypercalcemia

- Parathyroid hormone–dependent conditions
 - Primary hyperparathyroidism
 - Genetic/inherited disorders
 - Multiple endocrine neoplasia type 1 or type 2A
 - Familial hypocalciuric hypercalcemia
 - Tertiary hyperparathyroidism
- Parathyroid hormone–independent conditions
 - Hypercalcemia of malignancy
 - Secretion of parathyroid hormone–related peptide
 - Increased calcitriol production via ectopic 1- α -hydroxylase activity (e.g., lymphoma, multiple myeloma)
 - Osteolytic bone metastases
 - Vitamin D intoxication
 - Chronic granulomatous disorders
 - Increased calcitriol via ectopic 1- α -hydroxylase activity (e.g., sarcoidosis)
- Drugs
 - Vitamin A intoxication, milk-alkali syndrome, thiazide diuretics, theophylline, lithium
- Immobilization
- Other endocrine conditions
 - Thyrotoxicosis
 - Adrenal insufficiency
 - Acromegaly
 - Pheochromocytoma

hypercalcemia or granulomatous diseases. Furthermore, the patient has no history of receiving treatment with medications known to cause hypercalcemia, such as thiazide diuretics, lithium, or excessive vitamin D supplementation. He maintains an active lifestyle and has no history of prolonged immobility, eliminating immobilization-induced hypercalcemia as a possibility. In addition, he exhibits no clinical features suggestive of thyrotoxicosis (e.g., tremors, weight loss, or tachycardia), adrenal insufficiency (e.g., hypotension, hyperpigmentation, or hyponatremia), acromegaly (e.g., coarsening of facial features, enlarged hands or feet), or pheochromocytoma (e.g., paroxysmal hypertension, sweating, or palpitations). Normal kidney function excludes chronic kidney disease and tertiary hyperparathyroidism as contributors to his hypercalcemia. The refined differential diagnosis focuses on PTH-mediated causes and is summarized in [Box 4](#).

WHAT ARE THE NEXT STEPS IN THE EVALUATION?

Imaging studies identified multiple parathyroid adenomas as the likely cause of primary hyperparathyroidism and hypercalcemia. However, inherited disorders that cause hypercalcemia, such as familial hypocalciuric hypercalcemia and multiple endocrine neoplasia type 1 (MEN1) or type 2A (MEN2A), should also be considered. MEN1 is an autosomal dominant disorder characterized by the development of tumors in multiple endocrine glands, most commonly involving the parathyroid glands, pancreas, and pituitary gland. MEN2A is an autosomal dominant syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, and primary hyperparathyroidism. Familial hypocalciuric hypercalcemia is inherited in an autosomal dominant manner and is caused by inactivating mutations in the calcium-sensing receptor gene, leading to altered calcium homeostasis. A detailed family history may provide clues about heritable patterns of disease and is helpful in assessing the risk of these genetic conditions. In addition, measurement of 24-hour urinary calcium excretion can be helpful, as familial hypocalciuric hypercalcemia is characterized by low urinary calcium levels, whereas primary hyperparathyroidism typically leads to normal or elevated urinary calcium excretion.

Part 3: Refining the Differential Diagnosis

Hyperparathyroidism with hypercalcemia strongly supports PTH-dependent conditions, effectively ruling out PTH-independent causes such as malignancy-associated

Clinical Course 1

A 24-hour urine calcium excretion test showed that calcium levels were not reduced, effectively ruling out familial hypocalciuric hypercalcemia. The patient reported a family history of pancreatic tumors in his father and brother,

Box 4: Refining the Differential Diagnosis

- Parathyroid hormone–dependent conditions
 - Primary hyperparathyroidism
 - Genetic/inherited disorders
 - Multiple endocrine neoplasia type 1 or type 2A
 - Familial hypocalciuric hypercalcemia
 - Tertiary hyperparathyroidism
- Parathyroid hormone–independent conditions
- Drugs
- Immobilization
- Other endocrine conditions

both of whom had passed away, raising suspicion for a syndromic etiology of hypercalcemia. Further evaluation with contrast-enhanced CT imaging of the abdomen was performed to identify potential pancreatic tumors, revealing multiple lesions, including a bilobed hypervascular lesion in the pancreatic tail (Fig. 4).

HOW DOES THIS INFORMATION AFFECT YOUR APPROACH TO THE CASE?

MEN1 is diagnosed when a patient has at least two of the three primary tumors associated with the syndrome: parathyroid adenomas, pancreatic neuroendocrine tumors (NETs), and pituitary adenomas.³ Additional evaluation should include a detailed assessment for pituitary tumors and pancreatic neuroendocrine tumors. Magnetic resonance imaging (MRI) of the pituitary can identify pituitary adenomas, and should be complemented by hormonal testing for prolactin, IGF-1, adrenocorticotrophic hormone

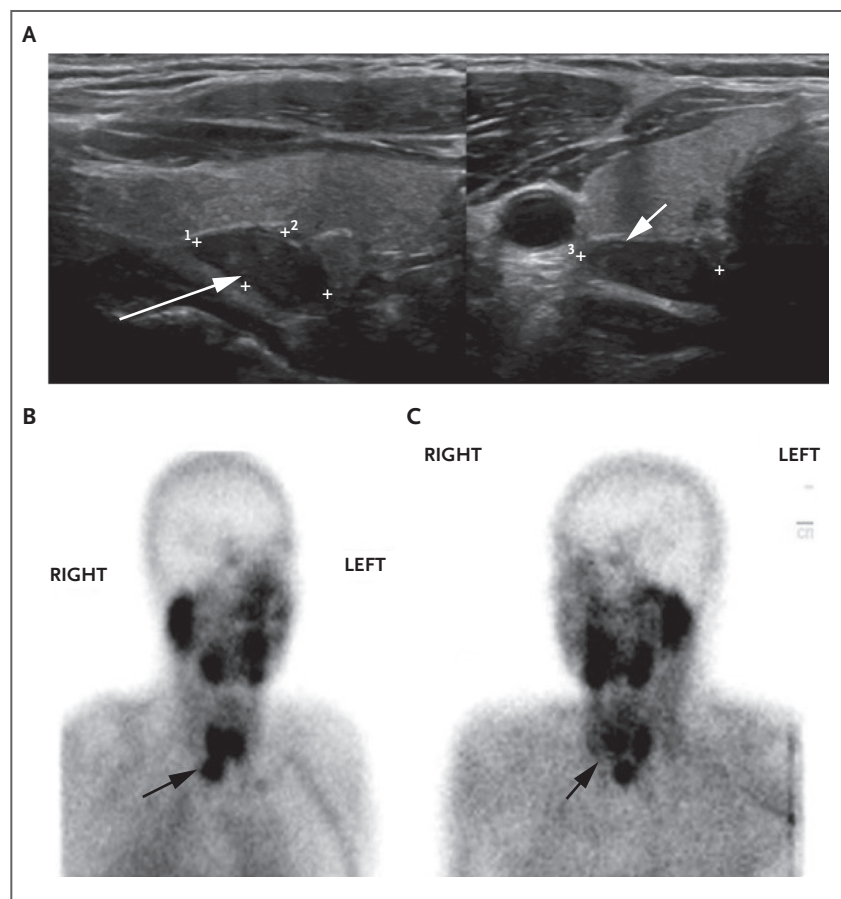


Figure 3. Ultrasound and Sestamibi Imaging of Parathyroid Adenomas.

Ultrasound images of the right thyroid lobe (Panel A) demonstrate a hypoechoic nodule inferior to the right lobe (long and short arrows). Immediate (Panel B) and delayed (Panel C) sestamibi scans show focal increased radiotracer uptake with delayed washout along the right thyroid lobe (black arrows), consistent with a parathyroid adenoma.

(ACTH), and morning serum cortisol. For pancreatic neuroendocrine tumors, chromogranin A is a sensitive marker for neuroendocrine tumor activity, and 5-hydroxyindoleacetic acid (5-HIAA) levels can help identify serotonin-secreting tumors. Testing for serum levels of insulin, gastrin, glucagon, and vasoactive intestinal polypeptide is also helpful for detecting functional pancreatic NETs. Positron emission tomography (PET)-CT imaging using copper-64 dotatate, a radiotracer that binds to somatostatin receptors, is highly sensitive for detecting neuroendocrine tumors.

RESULTS OF ADDITIONAL EVALUATION

The patient was admitted to the hospital for further investigations. MRI of the pituitary, performed with and without contrast, demonstrated a 10-mm macroadenoma. Hormonal testing showed mild hyperprolactinemia with a prolactin level of 32 ng/ml (reference range: 2.0 to 18.0 ng/ml), while levels of IGF-1, at 165 ng/ml (reference range: 50 to 317 ng/ml); morning cortisol, at 12.6 µg/dl (reference range: 5 to 25 µg/dl); and ACTH, at 23 pg/ml (reference range: 6 to 50 pg/ml), were within normal limits. Further testing revealed an elevated morning serum chromogranin A level of 198 ng/ml (reference range: 0 to 103 ng/ml) and a urine 5-HIAA level of 14.7 mg/24 hours (reference range: ≤6.0 mg/24 hours), findings consistent with a neuroendocrine tumor. Other hormonal assays, including serum levels of gastrin, insulin, glucagon, and vasoactive intestinal peptide, were within normal limits. Copper-64 dotatate PET/CT imaging highlighted multiple pancreatic lesions, supporting the diagnosis of a pancreatic neuroendocrine tumor.

Part 4: Making the Diagnosis

Fine-needle aspiration of an accessible pancreatic lesion was performed, and cytopathology confirmed a low-grade, well-differentiated neuroendocrine tumor consistent with a carcinoid tumor. This finding, in conjunction with the presence of multiple parathyroid adenomas and a pituitary macroadenoma, establishes the diagnosis of MEN1 syndrome. MEN1 syndrome is caused by mutations in the *MEN1* gene, which encodes the tumor suppressor protein menin.⁴ This protein is involved in regulating cell proliferation, and mutations result in tumor development in multiple endocrine organs. Genetic testing confirms the diagnosis by identifying pathogenic variants in the *MEN1* gene. Beyond guiding clinical management for the patient, this testing has implications for family members, who may benefit from genetic screening and early surveillance for MEN1-associated tumors. For this patient, the genetic analysis identified a rare mutation, c.445 + 10,445 + 11delinsA>G, a likely pathogenic variant linked to MEN1 syndrome.⁵

Clinical Course 2

The patient underwent total parathyroidectomy to manage hyperparathyroidism. Histopathologic evaluation confirmed the presence of three parathyroid adenomas. The left inferior parathyroid gland was histologically normal and was autotransplanted to the right arm to preserve parathyroid function. To manage the pancreatic neuroendocrine tumors, the patient underwent distal pancreatectomy and splenectomy. Histopathologic analysis of the resected pancreatic lesions was consistent with well-differentiated

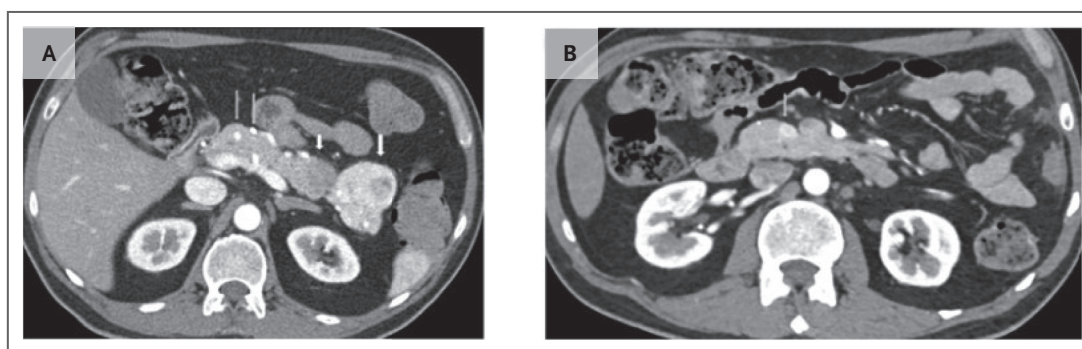


Figure 4. Contrast-Enhanced Computed Tomography Images of the Abdomen Demonstrating Pancreatic Lesions.

Axial images from multiphase contrast-enhanced computed tomography reveal hyperenhancing nodules in the pancreatic uncinate process and neck (tall thin arrows; Panels A and B) and a bilobed hypervascular lesion in the pancreatic tail (thick arrows; Panel A).

pancreatic neuroendocrine tumors. On the first day following parathyroidectomy, the patient's serum calcium level was 7.8 mg/dl (reference range: 8.7 to 10.5) and PTH was 7 pg/ml (reference range: 14 to 64 pg/ml). He received treatment with calcitriol and calcium carbonate, which increased the calcium levels. By 1 week post parathyroidectomy, both the serum PTH and serum calcium levels had normalized, confirming the resolution of primary hyperparathyroidism. At the time of discharge, the chromogranin A level had also decreased to within the normal range.

FINAL DIAGNOSIS/WRAP-UP

The final diagnosis was MEN1 syndrome, presenting as primary hyperparathyroidism caused by multiple parathyroid adenomas, pancreatic neuroendocrine tumors, and a pituitary macroadenoma. The diagnosis was confirmed through biochemical evaluation, imaging studies, and genetic testing, which identified a rare, likely pathogenic mutation in the *MEN1* gene.

Parathyroid adenomas occur in nearly all individuals with MEN1 and are often the first presenting feature.³ MEN1-associated neuroendocrine tumors most frequently involve the pancreas, but can also affect other sites, including the lungs, stomach, thymus, or bronchopulmonary tract.⁶ Management of MEN1 syndrome involves regular biochemical and imaging evaluations to detect tumor development and progression. Patients typically undergo periodic monitoring of serum calcium, PTH, prolactin, chromogranin A, and gastrin levels, along with imaging studies such as MRI or PET/CT to identify developing neuroendocrine tumors.

Genetic testing can identify at-risk family members, allowing for early detection and management of MEN1-associated tumors. The family history of pancreatic tumors in this patient's father and brother is consistent with the autosomal dominant inheritance pattern of *MEN1*. He was counseled on the importance of genetic testing for relatives and the necessity of ongoing surveillance to detect and manage potential complications of MEN1 syndrome.

Take-Home Points

- MEN1 is a rare genetic syndrome characterized by the presence of multiple endocrine tumors, including

pituitary adenomas, pancreatic neuroendocrine tumors, and parathyroid adenomas.

- Patients with MEN1 syndrome can present with a wide range of symptoms, such as confusion, abdominal discomfort, nephrolithiasis, and hormonal imbalances, reflecting the diverse effects of the associated endocrine tumors.
- Long-term management of MEN1 syndrome includes routine surveillance for the early detection of tumors in at-risk organs, as well as genetic counseling and testing for family members to identify carriers of *MEN1* mutations who may benefit from early intervention and monitoring.

Disclosures

Author disclosures are available at evidence.nejm.org.

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