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Multiple Endocrine Neoplasia Type 1: A Case Report

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Abstract

Background: Multiple endocrine neoplasia type 1 (MEN1) is a rare genetic syndrome inherited in an autosomal dominant pattern, resulting from mutations in the MEN1 tumor suppressor gene. Diagnosis is typically established based on clinical criteria, characterized by the presence of two or more primary MEN1-associated tumors (including parathyroid, anterior pituitary, and pancreatic islet tumors). Here, we present the case of a patient who exhibited classic clinical features and imaging findings consistent with MEN1.

Case Report: A man in his early thirties, known for hyperparathyroidism presented with abdominal symptoms suggestive of Zollinger-Ellison syndrome: worsening epigastric pain, nausea, vomiting, and diarrhea. Abdominal contrast-enhanced computed tomography (CT) revealed hyperenhancing lesions in the pancreas indicative of a pancreatic neuroendocrine tumor (gastrinoma). Thyroid ultrasound and sestamibi scintigraphy demonstrated a parathyroid adenoma.

MRI brain revealed pituitary micro adenoma. Based on the comprehensive clinical history, imaging findings, and confirmed tumors, the patient was diagnosed clinically with MEN1 syndrome and underwent appropriate surgical and medical interventions.

Conclusion: This case underscores the classic clinical presentation and imaging characteristics of MEN1 syndrome, encompassing pancreatic neuroendocrine tumors, parathyroid adenomas, and adrenal adenomas. Physicians should maintain a high index of suspicion for MEN1 when encountering patients with suggestive symptoms, prompting thorough endocrinologic evaluation, laboratory assessments, and targeted imaging studies of pertinent endocrine organs, as illustrated in this case.

Keywords: Clinical Criteria, Pituitary Micro Adenoma, Imaging Findings, Thyroid

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an uncommon autosomal dominant syndrome resulting from mutations in the MEN1 tumor suppressor gene. Diagnosis typically requires the presence of at least two primary MEN1-associated tumors, such as those originating from the parathyroid glands, anterior

pituitary, and pancreatic islet cells. Herein, we present a case report of a patient exhibiting all three primary MEN1 tumors with characteristic imaging findings.

Case Report: A man in his early thirties sought care at the emergency department (ED) following three weeks of escalating burning epigastric abdominal pain, accompanied by nausea, vomiting, and diarrhea. Additionally, he had experienced two episodes of calcium-rich kidney stones in his late twenties and was subsequently diagnosed with hypercalcemia and hyperparathyroidism during an outpatient endocrinology evaluation. Family history revealed a paternal grandmother with a pituitary tumor and a paternal aunt with a thymic tumor, while his father's cause of death remained unknown. Prior to presentation, the patient had discontinued a proton pump inhibitor (PPI) approximately three weeks earlier to accurately assess serum gastrin levels due to suspicion of gastrinoma in the context of potential MEN1 syndrome. His abdominal symptoms intensified, prompting his ED visit before scheduled follow-up with endocrinology. Upon admission to the ED, contrast-enhanced computed tomography (CT) of the abdomen and pelvis, a well defined focal lesion in the body/tail of the pancreas measures approximately 1.5 cm. It exhibits intense and uniform enhancement during the arterial phase with mild sustained enhancement during later phases. Additionally, a small, well-defined soft tissue mass lesion is observed in the left adrenal gland. (Figure 1A, 1B).

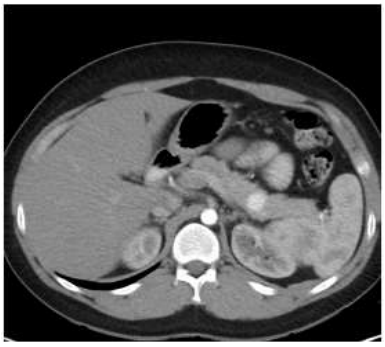

Figure 1 A:

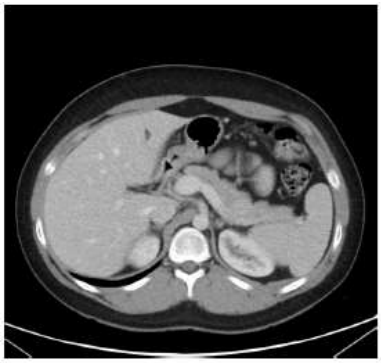

Figure 1 B:

The patient was admitted for further evaluation. A markedly elevated serum gastrin level of 758 pg/mL (reference range, 0.0-110.0 pg/mL) was obtained prior to reintroducing proton pump inhibitor (PPI) therapy. Esophagogastroduodenoscopy revealed esophagitis, gastritis, and multiple non-bleeding duodenal ulcers. Biopsy of which indicated a well-differentiated neuroendocrine tumor consistent with a gastrinoma. Symptoms improved upon restarting PPI therapy, and the patient was discharged on twice daily PPI treatment. Somatostatin scintigraphy was inconclusive for metastatic disease in the known pancreatic neuroendocrine tumors. Subsequently, the patient underwent distal pancreatectomy with lymph node dissection. Pathological analysis confirmed two well-differentiated neuroendocrine tumors, including a 6.6 cm intermediate-grade (World Health Organization grade 2) tumor with one metastatic inferior pancreaticoduodenal lymph node identified. Cortisol testing yielded normal

results, indicating nonfunctional adenomas. Plasma metanephrine and normetanephrine levels were within normal limits, ruling out pheochromocytoma before surgery.

Further MRI of the brain was conducted, revealing a round enlargement of the pituitary gland to the right of the midline, causing slight displacement of the stalk to the left. On post-contrast images, it shows less enhancement compared to the surrounding pituitary gland. Figure 2A, 2B).

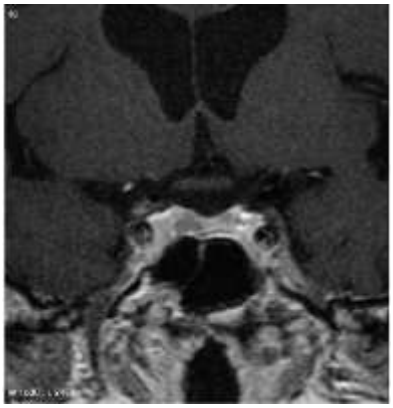

Figure 2 A:

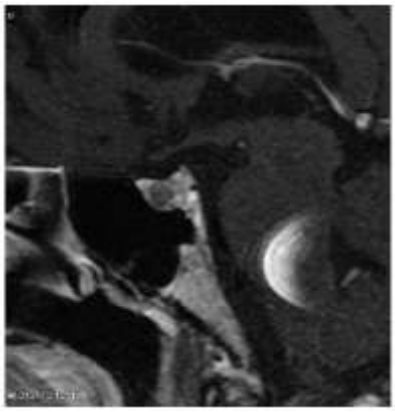

Figure 2 B:

An ultrasound of the neck was subsequently performed, revealing a well-defined, homogeneous lesion located posterior-inferior to the right lobe of the thyroid gland. The lesion appears hypoechoic compared to the thyroid gland and does not exhibit any calcifications or cystic spaces. It causes elevation of the echogenic posterior capsule of the thyroid gland. Additionally, there are a few detectable flow signals within the lesion(Figure 3A, 3B).

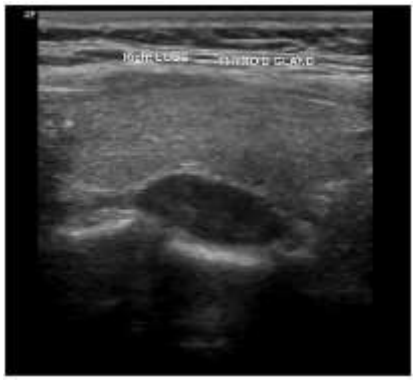

Figure 3 A:

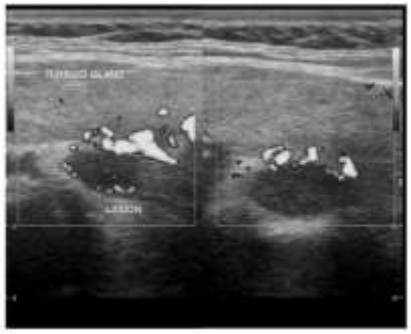

Figure 3 B:

Technetium Tc-99m sestamibi parathyroid scintigraphy confirmed delayed radiotracer washout near the lower pole of the right thyroid lobe corresponding to the ultrasound findings, indicative of a parathyroid adenoma (Figures 4).

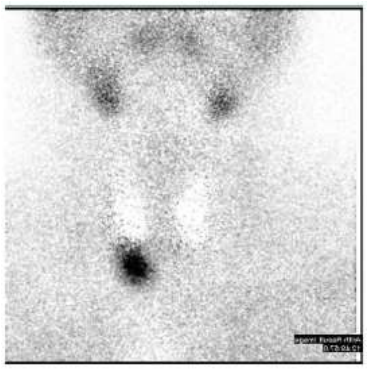

Figure 4:

Subtotal parathyroidectomy removed 3.5 of 4 glands, confirming adenoma in the right lower gland and hyperplasia in the rest. Postoperatively, parathyroid

hormone levels normalized to 24 pg/mL. Due to regional nodal metastasis from the gastrinoma, the patient receives monthly lanreotide infusions and undergoes periodic imaging. He continues daily cabergoline therapy for residual prolactinoma, monitored with periodic MRI and prolactin levels.

Discussion

MEN1 syndrome is predominantly inherited in an autosomal dominant pattern (90%), although sporadic cases have been reported, with a postmortem incidence of 0.25%. The diagnosis of MEN1 can be established clinically based on family history or confirmed through genetic testing for MEN1 mutations. Clinical diagnosis of MEN1 requires the presence of two or more primary endocrine tumors associated with the syndrome, such as parathyroid adenomas, entero-pancreatic tumors, and pituitary adenomas. Alternatively, diagnosis can be made based on family history if a first-degree relative has been diagnosed with MEN1 and has at least one of the associated tumors. In our case, the patient had a history of pituitary prolactinoma and newly identified pancreatic and parathyroid tumors, fulfilling the clinical criteria for diagnosis. Although his young age at presentation and family history of neuroendocrine tumors on his father's side suggest familial MEN1, diagnostic criteria strictly require affected first-degree relatives. Parathyroid adenomas are the most common tumors seen in MEN1 patients, affecting 90% by the age of 40. These adenomas often lead to primary hyperparathyroidism, presenting with hypercalcemia, renal stones and osteitis fibrosa cystica are commonly associated complications in patients with MEN1 syndrome. The onset of symptoms from parathyroid adenomas typically occurs earlier in MEN1 patients compared to those without the syndrome, typically manifesting around 20-25 years of age versus 55 years of age, respectively. Our patient presented in his early thirties, having previously experienced two episodes of nephrolithiasis in his late twenties with calcium-rich stones. During his evaluation in the emergency department, elevated serum calcium and parathyroid hormone levels were noted. Evaluation of hyperparathyroidism in patients usually begins with ultrasound as a primary screening tool to identify underlying parathyroid adenomas, followed by nuclear technetium Tc-99m sestamibi scintigraphy for confirmation. Sestamibi scintigraphy demonstrates high sensitivity and specificity (>90%) in lesions that retain the sestamibi radiotracer on delayed imaging. Surgical removal of overactive parathyroid glands, typically through subtotal or total parathyroidectomy, is the mainstay of management for parathyroid adenomas. However, it's crucial to note that patients with MEN1 have a higher risk of persistent or recurrent hypercalcemia following subtotal surgery, often due to their predisposition to multiglandular disease. In our case, initial ultrasound screening identified one parathyroid adenoma, confirmed by sestamibi scintigraphy. Subsequently, the patient underwent subtotal parathyroidectomy, with pathology confirming the diagnosis. Annual biochemical screening for primary hyperparathyroidism, including monitoring serum calcium and parathyroid hormone levels, is recommended for patients with MEN1.

Although less common than other tumors associated with MEN1, malignant entero-pancreatic neuroendocrine tumors represent a significant cause of mortality in patients with MEN1 syndrome are influenced significantly by associated tumors of the pancreatic islet cells, which can either secrete hormones (functioning tumors) or not (non-functioning tumors). Hormone-secreting tumors include gastrinomas (40% incidence), insulinomas (10% incidence), and rarer types such as

vipomas and glucagonomas (2% incidence). Gastrinomas, the most prevalent enteropancreatic tumors in MEN1 patients, frequently manifest as multiple tumors, with approximately 50% of patients showing metastases at diagnosis. Malignant gastrinomas are responsible for the majority of MEN1-related deaths from neuroendocrine tumors. Clinically, gastrinomas lead to excessive gastric acid secretion and recurrent peptic ulcers with diarrhea, a syndrome known as Zollinger Ellison syndrome (ZES). Symptomatic ZES can typically be managed effectively with proton pump inhibitors (PPIs), and abrupt cessation of PPI therapy for serum gastrin assessment can exacerbate symptoms, as observed in our patient. Death due to complications of gastric acid hypersecretion has become rare with the widespread use of PPIs. Pancreatic neuroendocrine tumors appear as well-defined hyperenhancing masses in arterial phase contrast-enhanced CT scans, contrasting with the hypoenhancing appearance of pancreatic ductal carcinomas in the venous phase. Our patient had two hyperenhancing pancreatic masses confirmed pathologically as well-differentiated neuroendocrine tumors, accompanied by clinical signs of excessive gastrin secretion. Somatostatin receptor scintigraphy is valuable for detecting smaller lesions or metastases, offering superior sensitivity and specificity compared to CT or MRI, particularly for extrahepatic gastrinomas. The somatostatin analog octreotide, which selectively binds to somatostatin receptors types 2 and 5, is commonly used in this imaging modality. Since 80% of enteropancreatic neuroendocrine tumors commonly express somatostatin receptor subtype 2, somatostatin scintigraphy typically demonstrates good sensitivity in detecting these tumors, ranging from 60% to 90%. Our patient's gastrinoma did not exhibit uptake on initial somatostatin receptor scintigraphy, likely because his specific tumor did not express either of these two somatostatin receptor subtypes, limiting the usefulness of this test for assessing metastases and ongoing monitoring. While symptoms of hypergastrinemia can be managed medically, definitive treatment of these tumors involves surgical resection and regional lymphadenectomy due to their potential for metastasis. Additionally, recent data from 2014 suggest that treatment with lanreotide, a somatostatin analog, can extend progression-free survival in patients with metastatic grade 1 and grade 2 enteropancreatic neuroendocrine tumors. Given the identification of a metastatic lymph node during surgery, our patient is receiving monthly lanreotide infusions. In patients known to have MEN1 syndrome, annual biochemical screening for enteropancreatic neuroendocrine tumors should include fasting gastrointestinal hormone profiles (including gastrin, glucagon, and vasointestinal polypeptide). Radiologic screening of the pancreas and duodenum using CT, MRI, or endoscopic ultrasound should occur at least annually, though consensus on the optimal screening interval remains undecided.

Pituitary tumors may occur in up to 60% of MEN1 patients, with variability in reported frequencies. Prolactinomas are the most prevalent pituitary tumors in MEN1, affecting 20% by age 40. Less common pituitary tumors include somatotropin-producing adenomas, corticotropin adenomas, and nonfunctioning tumors. Symptoms of pituitary tumors can include headaches and visual field deficits due to tumor size and growth. Prolactinomas specifically can lead to erectile dysfunction and decreased libido in men or amenorrhea and galactorrhea in women due to elevated prolactin levels. Management typically involves transsphenoidal tumor resection or medical treatment with bromocriptine or cabergoline. However, MEN1-associated pituitary

tumors often exhibit greater aggression and resistance to treatment compared to sporadic pituitary tumors, necessitating vigilant follow-up for symptom onset.

In patients with MEN1, annual biochemical screening for pituitary tumors is recommended (including serum prolactin and insulin-like growth factor 1 levels), along with MRI surveillance of the pituitary gland every 3-5 years. Although not a defining characteristic of MEN1, adrenal tumors have been observed in 20%-40% of affected individuals, typically presenting as benign and nonfunctional adenomas. However, pheochromocytomas and adrenocortical carcinomas have been reported. Screening for adrenal lesions in MEN1 patients should include abdominal imaging (MRI or CT) every three years. If a lesion is found, ongoing imaging surveillance is necessary to assess for malignancy, although specific intervals for follow-up have not been established. Biochemical assessment with aldosterone and cortisol levels should be considered only if clinical symptoms are present or if the lesion measures greater than 1 cm. The life expectancy of patients with MEN1 is generally lower than that of the general population, with an average age of death around 55 years. Management should involve a multidisciplinary team experienced in neuroendocrine tumors, providing appropriate biochemical and radiologic surveillance.

Conclusion

Our patient presents a characteristic manifestation of MEN1 syndrome, featuring tumors in all three primary endocrine organs: pituitary prolactinoma, parathyroid adenoma, and pancreatic neuroendocrine tumors (gastrinomas). When there is a strong clinical suspicion of MEN1, it is recommended to pursue thorough evaluation by endocrinologists, including appropriate laboratory investigations and targeted imaging of the typical endocrine organs detailed in this case. This comprehensive approach should be complemented by careful multidisciplinary management and ongoing follow-up.

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