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Case Report

Multimodality appearance of multiple endocrine neoplasia type 1: A case report

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ABSTRACT

Multiple endocrine neoplasia type 1 is a rare autosomal dominant disorder classically characterized by a predisposition to tumors of the parathyroid glands, anterior pituitary, and enteropancreatic endocrine cells. We present the clinical details of a patient with diarrhea, nephrolithiasis, erectile dysfunction, and new onset abdominal pain, as well as a discussion of the etiology, pathophysiology, and classical imaging findings of this condition.

Introduction

Although Multiple endocrine neoplasia type 1 (MEN 1) can cause a combination of over 20 endocrine and nonendocrine tumors, MEN 1 is clinically defined as the occurrence of 2 or more primary MEN 1 tumor types, or the occurrence of one primary MEN 1 tumor in family members of a patient carrying the MEN 1 diagnosis [1]. The prevalence of MEN 1 is approximately 1 in 200,000 [1]. This disorder has been shown to affect patients of all age groups with a reported age range of 5-81 [14]. The clinical manifestations depend of the site of the tumor and their products of secretion. Parathyroid adenomas, resulting in primary hyperparathyroidism, occur in approximately 95% of patients with MEN 1 [1,2,14,15]. Entero-pancreatic tumors, most commonly gastrinomas, occur in approximately 30%-70% of patients with MEN1 [1]. Anterior pituitary adenomas occur in approximately 30%-40% of patients with prolactinomas occurring most frequently [1].

Other less typical manifestation of MEN1 includes foregut carcinoid tumors, lipomas, facial angiofibromas, and collagenomas [1,14]. Although the clinical diagnosis depends on the patient's clinical manifestations, confirming the diagnosis typically relies on radiological findings via nuclear medicine studies, computed tomography (CT) or magnetic resonance imaging (MRI). In asymptomatic patients with a strong family history of MEN 1, genetic testing can also be used to confirm the diagnosis. This paper reports a case of MEN 1 in a patient who presented with acute onset left flank pain.

Case report

A 35-year-old male presented to an outside hospital for severe left flank pain. A CT of the abdomen and pelvis revealed a 10-mm obstructing calculus in the left ureter. He was symptomatically treated and discharged, but due to worsening pain, he presented to our Emergency Department. On further questioning, he described a 10 year history of renal stones, for which he has received treatment at an outside state. He

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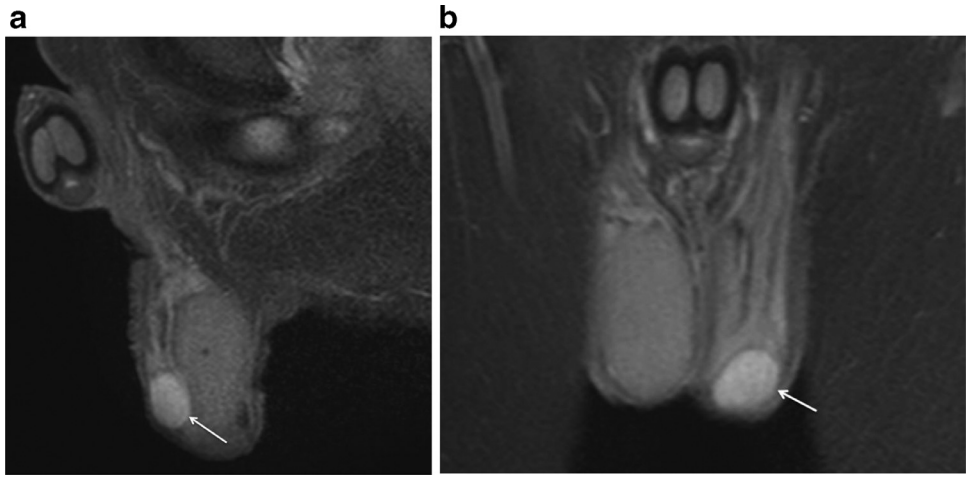

Fig. 1 – Sagittal (a) and coronal (b), fat saturated T1 postcontrast MRI images demonstrating a well-defined, enhancing mass in the tail of the left epididymis, suggestive of an adenomatoid tumor.

underwent a cystoscopy with a left ureteric stent placement without complications. Prior to being discharged, he described a palpable left testicular lump that he has noticed for the past year. An outpatient MRI revealed an 18.6-mm well-circumscribed, enhancing mass within the tail of the left epididymis, suggestive of an adenomatoid tumor (Figs. 1a and b).

Two months following this initial encounter, he presented to an outpatient clinic for acute onset abdominal pain. Upper endoscopy revealed multiple ulcers in the first and second parts of the duodenum, a 1.5-cm distal esophageal ulcer, antral and prepyloric chronic gastritis. Further history revealed that in his early 20s, he began to have diarrhea consisting of 2-6 loose, watery bowel movements per day. By his mid 20s, he began having nephrolithiasis as described above. Three years ago, during a workup for erectile dysfunction at an outside state, he was found to have a pituitary adenoma.

Given this history and endoscopic findings, a presumed diagnosis and workup for MEN1 was initiated. At that time, gastrin, chromogranin A, and prolactin levels were 550, 1829, and 523 ng/mL respectively. Nuclear medicine indium-111 pentetreotide scan revealed a 2.5-cm pentetreotide avid neoplasm along the fourth portion of the duodenum (Fig. 2). Nuclear medicine sestamibi scan of the neck demonstrated a single focus of persistent increased radiotracer activity in the inferior right thyroid gland, consisting of a parathyroid adenoma (Fig. 3). MRI of the brain with and without intravenous contrast revealed a hypoenhancing sellar and suprasellar mass with apparent invasion into the left cavernous sinus, consistent with a pituitary macroadenoma (Figs. 4a and b). Finally, multiphase CT scan of the pancreas with intravenous contrast demonstrated the aforementioned enhancing mass in the fourth portion of the duodenum, along with an additional 1.2-cm enhancing mass in the second portion of the duodenum and three adjacent 1.5 cm and smaller enhancing masses in the pancreatic body and tail. These were consistent with neuroendocrine tumors (Figs. 5a-c). At the time of writing, the patient's symptoms have resolved with conservative therapy. Genetic testing and surgical planning are underway, with a tentative plan to remove the larger duodenal lesion given its metastatic potential based on size. However, management of the other lesions remains controversial and discussions between the patient, surgeons, and endocrinologists are ongoing.

Discussion

MEN 1, also known as Wermer's syndrome, is defined by a mutation of the MEN1 gene and results in an increased predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islets cells [14]. While these diseases frequently occur sporadically and individually, there are multiple factors that are unique to MEN1 that are imperative to understand, as they carry important clinical and radiographical implications. The remainder of this discussion will focus on several differences between MEN1-associated tumors and their sporadic counterparts, as well as their imaging characteristics across different modalities.

As described previously, primary hyperparathyroidism is the commonest presentation, though there are several differences between primary hyperparathyroidism in the setting of familial MEN1 and the more common, sporadic form of the disease. Sporadic primary hyperparathyroidism typically presents in the fourth to sixth decades of life, while hyperparathyroidism in MEN1 most frequently presents in the second to fourth decade of life [8,11]. In approximately 80%-85% of patients with sporadic disease, a single parathyroid adenoma is affected, whereas multiple glandular disease is typical of MEN1 [5]. Finally, the rate of recurrence following parathyroidectomy for patients with MEN1 has been described as high as 50%, strongly suggesting an increase proliferative drive of parathyroid cells in these patients [11]. This has resulted in much debate with respect to surgical management of the disorder.

As previously eluded, the most common type of pituitary adenoma in MEN1 is a prolactinoma, though other types such as secretory adenomas are also possible. Similar to our

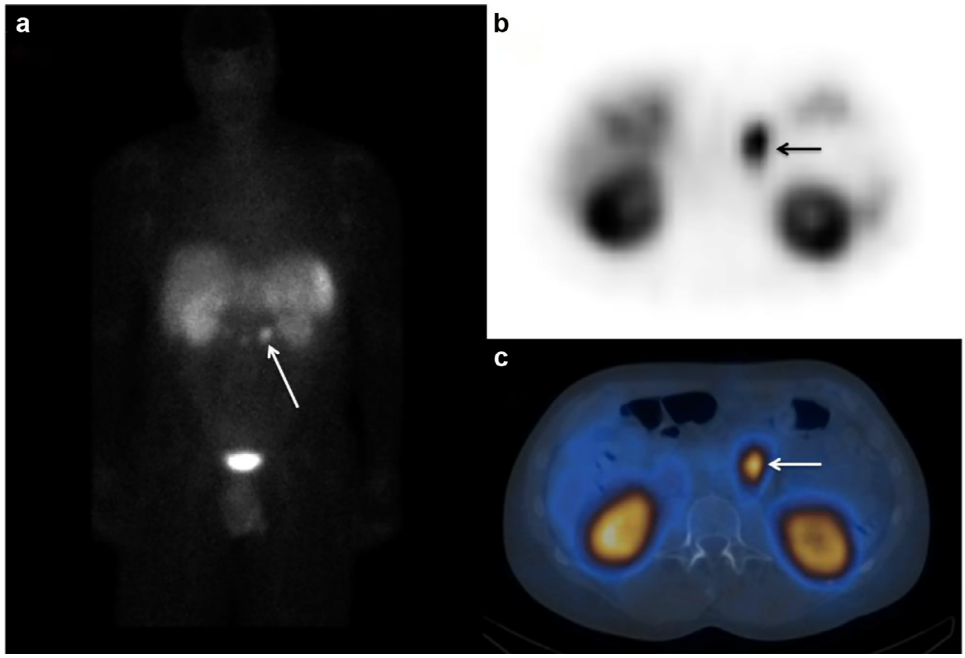

Fig. 2 – Whole body (a), axial (b), and SPECT/CT (c) images of an Indium-111 pentetriotide scan emphasizing a 2.5-cm pentetriotide avid neoplasm in the fourth portion of the duodenum.

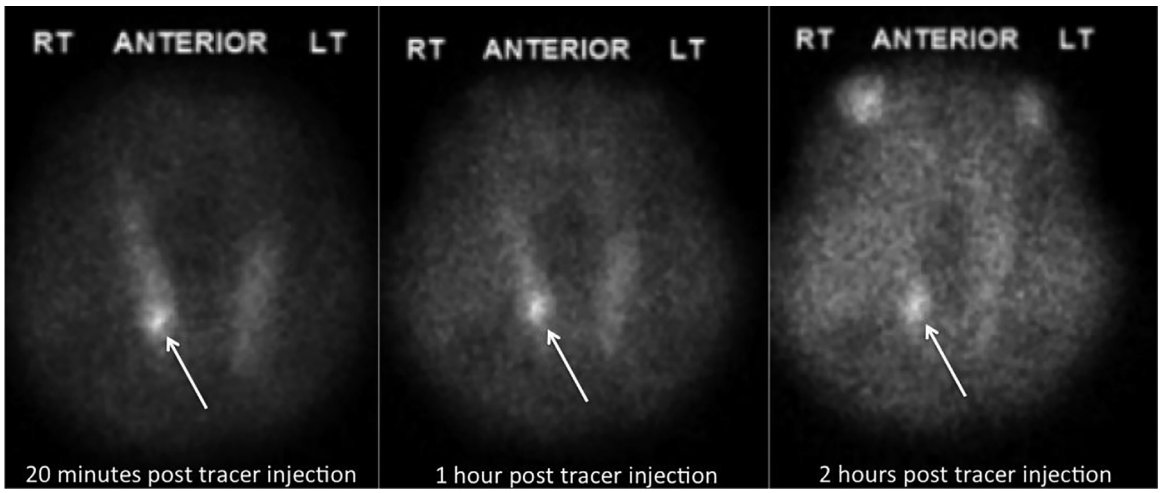

Fig. 3 – Sequential pinhole images from a sestamibi scan show an abnormal focus of tracer uptake along the inferior right thyroid lobe, which retains uptake on delayed images. These findings are compatible with a parathyroid adenoma.

previous discussion, several differences have been observed between sporadic pituitary adenomas and MEN1 patients with pituitary adenomas. A multicenter study consisting of 246 patients with pituitary adenomas, 136 of which had a diagnosis of MEN1, demonstrated that 85% of MEN1 patients with pituitary adenomas had macroadenomas, vs 42% of non-MEN1 patients [16]. This same study also noted that adenomas in MEN1 patients were larger and more aggressive, as evidenced by normalization in hormonal hypersecretion in 42% of MEN1 patients after treatment, compared to 90% in non-MEN1 patients [16]. Despite this observation, the diagnostic approach and treatment of sporadic and MEN1-related pituitary adenomas is similar.

Aside for a few differences in sporadic and MEN1-related parathyroid and pituitary adenomas, the clinical outcome for both sets of patients remains similar and generally effective. However, given the malignant potential of pancreatic islet cell and/or gastrointestinal tumors, these have become the primary life-threatening manifestation of MEN1 [6,7]. This is due to several key differences in the biological nature of these

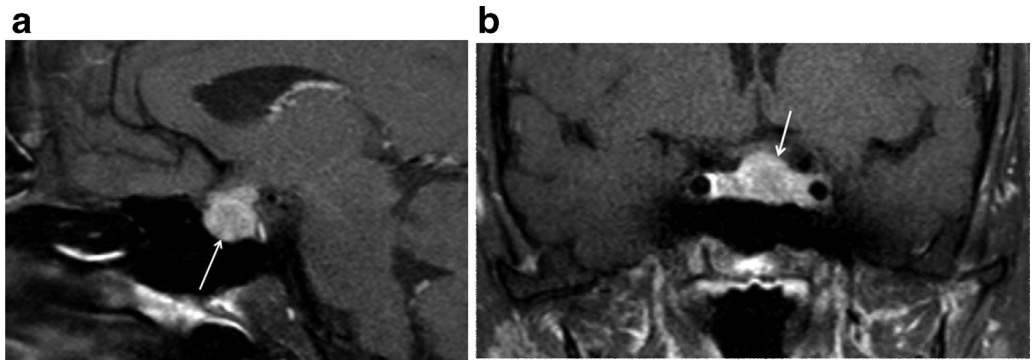

Fig. 4 – Sagittal (a) and coronal (b), T1-weighted postcontrast MRI images through the pituitary gland demonstrating an enhancing sellar/suprasellar mass with apparent extension into the medial aspect of the left cavernous sinus, consistent with a pituitary adenoma.

Fig. 5 – Contrast-enhanced CT images through the abdomen highlighting several well-circumscribed enhancing lesions. (a) Arterial phase image with lesion in the descending duodenum. (b) Portal venous phase image with lesion in the distal transverse duodenum. (c) Arterial phase image with pancreatic tail lesions.

tumors. Gastrinomas, for example, occurring in approximately 30% of patients with MEN1, have been shown to be unsuccessfully treated by surgical excision in these patients, despite being a successful treatment approach for non-MEN1 patients. The basis for this failure is that in contrast to non-MEN1 patients, gastrinomas in MEN1 patients are multifocal, and often too small to be detected surgically or radiographically [3]. Other endocrine cell tumors such as insulinomas, glucagonomas, and VIPomas have similar biological profiles as just described. Additionally, approximately two-thirds of patients with endocrine cell tumors do not have clinical symptoms, probably due to defective hormone processing or secretory mechanism [10]. As a result, asymptomatic patients tend to present later, at which point they are more likely to have malignant disease. This, in combination with the biological nature of these tumors, further complicates the treatment options that can be offered to MEN1 patients with entero-pancreatic tumors.

Imaging and diagnosis

Although the diagnosis of MEN1 requires thorough medical and family history, as well as physical and biochemical testing to assess for signs and symptoms of hormone excess, imaging plays a central role in accurate detection and/or confirmation, staging, presurgical planning, and surveillance. Given the wide clinical spectrum of MEN1, the following discussion will focus on imaging highlights for the more classical manifestations of the disease.

Parathyroid adenomas typically appear with ultrasonography as well-defined, hypoechoic masses posterior to the thyroid gland [17]. However, given the propensity of MEN1 to present as multiple tumors, there are a sizeable number of adenomas that will be ectopic, and thus inaccessible to ultrasound. While contrast-enhanced CT and MR imaging have higher sensitivity for the localization of ectopic parathyroid masses, nuclear medicine sestamibi scan of the neck and mediastinum are preferentially obtained for presurgical planning and surveillance given their higher sensitivity for the localization of metabolically active parathyroid adenomas [13].

The imaging modality of choice for pituitary adenomas is gadolinium-enhanced MR. However, in patients who cannot undergo MR imaging, contrast-enhanced CT with thin section and planar reformats may be used. On CT, pituitary adenomas typically present as isointense to the gray matter, which demonstrate moderate, heterogeneous enhancement on postcontrast sequences. They have similar features on MRI as they follow the intensity of gray matter on T1- and T2-weighted sequences and have heterogeneous enhancement postcontrast [4,13]. When large enough, compression of adjacent structure or erosion of the sellar floor can also be seen [13].

As for enteropancreatic tumors, ultrasound remains the first-line investigative modality [12]. Although endoscopic ultrasound is more sensitive than transabdominal ultrasound, lesions in the distal pancreatic body or tail are often missed. As a result, contrast-enhanced CT remains the most widely used modality for detection of these tumors [12,13]. Tumors are typically indistinguishable from normal surrounding tissues on unenhanced sequences. However, both primary and metastatic tumors enhance avidly on arterial phase given their high vascularity [9,12]. Despite the increase in sensitivity of CT over ultrasound, gadolinium-enhanced MR has greater sensitivity over CT for identifying smaller lesions. On MR, tumors tend to be hypointense relative to normal pancreas on T1-weighted images, hyperintense on T2-weighted images, and enhance similarly to contrast-enhanced Ct on postcontrast MR sequences [9]. Note that given the slow growing, low metabolic rate of these tumors, FDG PET is typically not localized within the tumor cells [13]. Although there may be increased use of PET in the future, at the time of writing, there is insufficient evidence to validate its use.

Conclusion

This case highlights the typical presentation and classical imaging features of multiple endocrine neoplasia type 1. Early recognition and knowledge of this disease, particularly how its associated tumors behave, is essential for optimal surgical planning and satisfactory treatment.

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