รายงานผู้ป่วย
Case Report

การพบร่วมกันของเนื้องอกตับอ่อนที่สร้างอินซูลินเนื้องอกระบบประสาทต่อมไร้ท่อที่ไม่ทำงานของตับอ่อน และเนื้องอกพาราไทรอยด์ในกลุ่มอาการเนื้องอกต่อมไร้ท่อหลายต่อมชนิดที่ 1: รายงานผู้ป่วย

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บทคัดย่อ

เนื้องอกของตับอ่อนอินซูลิโนมาเป็นเนื้องอกระบบประสาทต่อมไร้ท่อบริเวณตับอ่อนที่หลั่งฮอร์โมนอินซูลินมีอุบัติการณ์ประมาณ 1 ถึง 32 รายต่อประชากรหนึ่งล้านคนต่อปี ผู้ป่วยมักมีอาการแสดงจากภาวะน้ำตาลในเลือดต่ำ ซึ่งสามารถมีอาการทางระบบประสาทหรืออาการทางระบบประสาทอัตโนมัติ โดยอาการจะดีขึ้นหลังจากได้รับประทานอาหาร และจะมีอาการในช่วงอดอาหาร การตรวจทางห้องปฏิบัติการเบื้องต้นพบมีภาวะน้ำตาลต่ำร่วมกับค่าอินซูลินและ c-peptide ที่สูง

รายงานฉบับนี้นำเสนอผู้ป่วยชายอายุ 67 ปี มาด้วยพฤติกรรมเปลี่ยนแปลงและระดับความรู้สึกตัวลดลง การตรวจทางห้องปฏิบัติการพบภาวะน้ำตาลและฟอสเฟตในเลือดต่ำ แคลเซียมในเลือดสูง การสแกนพาราไทรอยด์พบก้อนเนื้องอกที่หลั่งฮอร์โมนผิดปกติ ผลตรวจ Magnetic Resonance Imaging (MRI) และ Computed Tomography (CT) ช่องท้องส่วนบนพบเนื้องอกระบบประสาทต่อมไร้ท่อที่ตับอ่อนจำนวนสองก้อน ได้แก่ เนื้องอกที่บริเวณส่วนปลายของตับอ่อนชนิดที่สร้างอินซูลินและบริเวณส่วนต้นของตับอ่อนชนิดไม่สร้างฮอร์โมน ซึ่งเข้าได้กับกลุ่มอาการเนื้องอกต่อมไร้ท่อหลายต่อมชนิดที่ 1 ผู้ป่วยได้รับการผ่าตัดด้วยวิธีการตัดตับอ่อนส่วนปลาย และการผ่าตัดตับอ่อนส่วนต้นกับลำไส้เล็กส่วนต้นออก ภายหลังการผ่าตัดผู้ป่วยมีภาวะรั่วของตับอ่อนซึ่งได้รับการรักษาแบบประคับประคอง และรายงานฉบับนี้ได้อภิปรายเกี่ยวกับขั้นตอนการวินิจฉัย การผ่าตัด การดูแลและติดตามหลังผ่าตัด และทบทวนวรรณกรรมเกี่ยวกับการเกิดร่วมกันของอินซูลิโนมาและเนื้องอกระบบประสาทต่อมไร้ท่อที่ไม่ทำงานของตับอ่อน

คำสำคัญ: อินซูลิโนมา เนื้องอกระบบประสาทต่อมไร้ท่อ เนื้องอกพาราไทรอยด์ กลุ่มอาการเนื้องอกต่อมไร้ท่อหลายต่อมชนิดที่ 1

รายงานผู้ป่วย
Case Report

Co-existence of insulinoma, non-functional pancreatic neuroendocrine tumor, and parathyroid adenoma in clinically diagnosed MEN1: A case report

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Abstract

Insulinoma is a rare functioning neuroendocrine tumor that typically presents with neuroglycopenic or autonomic symptoms due to hypoglycemia. These tumors are uncommon, with an incidence ranging from approximately 1 to 32 million cases per year, and are the most common cause of hyperinsulinemic hypoglycemia in adults. Symptoms usually resolve after glucose administration or postprandial, with typical manifestations occurring during fasting due to excessive insulin secretion. Laboratory evaluations typically reveal elevated insulin and C-peptide levels.

We report a case of a 67-year-old male who presented with behavioral changes and altered consciousness. Initial laboratory investigations revealed hypoglycemia, hypophosphatemia, and hypercalcemia. A parathyroid scan identified a hyperfunctioning parathyroid adenoma. MRI and CT imaging of the upper abdomen revealed Pancreatic Neuroendocrine Tumors (PNETs) in both the distal pancreas (insulinoma) and the pancreatic head (non-functional NET). With two major endocrine tumors, the patient can be clinically diagnosed with MEN1. The patient underwent surgical resection, including distal pancreatectomy and pancreaticoduodenectomy. Postoperatively, the patient developed feeding intolerance and a pancreatic fistula, both of which were managed conservatively. We discuss the diagnostic workup, surgical management, postoperative management, surveillance and review the current literature on the co-existence of insulinomas and non-functional pancreatic neuroendocrine tumors.

Keywords: insulinoma, neuroendocrine tumor, parathyroid adenoma, MEN1

Introduction

Pancreatic Neuroendocrine Tumors (PNETs) are neoplasms originating from the endocrine cells of the pancreas.[1,2] These tumors are categorized into functioning and non-functioning types based on their hormone secretion. Functioning PNETs, such as insulinomas, typically present with symptoms related to hormone overproduction, like hypoglycemia in the case of insulinomas.[2,3] In contrast, non-functioning PNETs usually present with nonspecific symptoms caused by tumor growth or metastasis. Many non-functioning PNETs still secrete substances such as pancreatic polypeptide, ghrelin, neurotensin, neuron-specific enolase, and chromogranin, although these do not usually result in clinical symptoms. The co-occurrence of insulinomas and Non-Functional Pancreatic Neuroendocrine Tumors (NF-PNETs) in a single patient is extremely rare. PNETs are often associated with genetic syndromes such as Multiple Endocrine Neoplasia type 1 (MEN1), von Hippel-Lindau disease, neurofibromatosis type 1, and tuberous sclerosis. The presence of parathyroid or pituitary tumors frequently suggests a genetic mutation, particularly in MEN1, with insulinomas being found in approximately 6% to 7% of MEN1 cases.[2,4] While parathyroid adenomas, benign tumors of the parathyroid glands, are the leading cause of primary hyperparathyroidism and are relatively common, their co-occurrence with pancreatic neuroendocrine tumors-especially in patients with both insulinoma and non-functional PNETs-has been rarely reported. Imaging such as parathyroid scan is crucial for identification of hyperfunctioning glands and vital to identifying treatment options.

This case report aims to present a patient with co-existing insulinoma, NF-PNET, and parathyroid adenoma, highlighting the diagnostic workup, management challenges, and a review of the current literature. Through this case, we aim to underscore the importance of a multidisciplinary approach to clinical evaluation and the potential implications for treatment in patients with multiple neuroendocrine and endocrine tumors.

Case presentation

A 67-year-old male presented to Taksin Hospital with a two-month history of early morning behavioral changes, transient loss of consciousness, and visual and auditory hallucinations, which typically resolved after breakfast. Upon arrival at the emergency department, his random plasma glucose level was 32 mg/dL (65-110 mg/dL). He was immediately treated with 50% dextrose, followed by a continuous infusion of 10% dextrose. Vital signs were stable, and the physical examination was unremarkable.

Further evaluation during a spontaneous hypoglycemic episode confirmed Whipple's triad. Laboratory investigations revealed plasma glucose of 32 mg/dL (normal range: 80-180mg/dL), serum insulin of 4.7 μU/mL (normal range during hypoglycemia:< 3 μU/mL), C-peptide of 1.4 ng/mL (normal range during hypoglycemia: <0.2 ng/mL), serum ketones at 0.4 mmol/L (normal range: <0.6 mmol/L), and a morning cortisol level of 13.3 μg/dL (2.68-10.5 μg/dL), consistent with endogenous hyperinsulinemic hypoglycemia. Neurological causes were initially considered, but brain imaging and cerebrospinal fluid analysis were unremarkable. CT imaging of the upper abdomen pancreatic protocol revealed a 2.7 cm arterial-enhancing nodule in the pancreatic tail, suggesting an insulinoma/PNET (Figure 1).

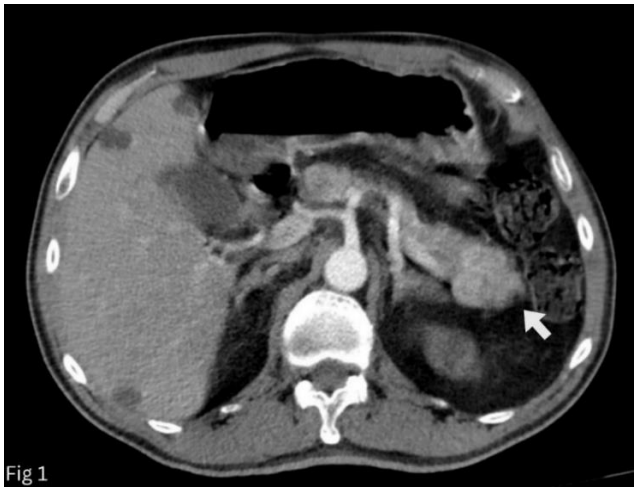

Figure 1: 2.7-cm enhancing nodule at tail of pancreas on arterial phase, suggesting insulinoma

While investigating the etiology of hypoglycemia, routine metabolic panels revealed hypercalcemia of 12 mg/dL (normal range: 8.5-10.2mg/dL) and hypophosphatemia of 1.2 mg/dL (normal range: 2.4-4.5mg/dL), with an elevated Parathyroid Hormone (PTH) level of 441 pg/mL (normal range: 10-65pg/mL), suggesting primary hyperparathyroidism. Hypercalcemia was managed with intravenous hydration and bisphosphonates. A parathyroid scan (Figure 2) identified hyperfunctioning tissue inferior to the right thyroid lobe. Further evaluation for MEN1 included pituitary MRI and hormonal studies, which excluded pituitary involvement. Pituitary MRI and hormonal assays, including IGF-1: 200ng/mL (normal range: 115-337ng/mL), prolactin: 15.99ng/mL (normal range:<20ng/mL) and TSH, were within normal limits, ruling out pituitary adenoma. The patient underwent subtotal parathyroidectomy four months later. Histopathology, which consisted of right superior and inferior parathyroid gland, revealed a hypercellular parathyroid gland without malignant features, and serum calcium levels normalized postoperatively.

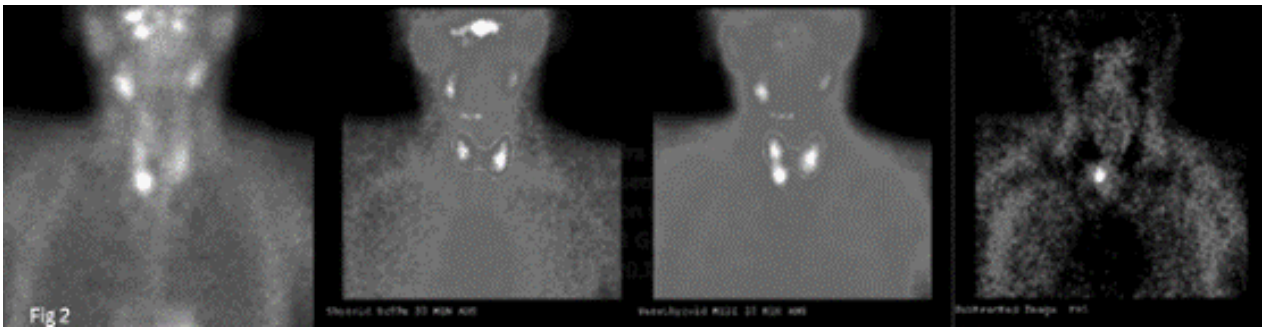

Figure 2: 99mTc-sestamibi SPECT images of parathyroid scan, showing hyperfunctioning tissue inferior to the right thyroid lobe

In the meantime, localization studies for insulinoma were performed. MRI of the upper abdomen identified the same arterial enhancing lesion at the tail of the pancreas on CT and another 2.8 cm hypointense lesion at the uncinate process of the pancreas, suggestive of a neuroendocrine tumor (Figure 3).

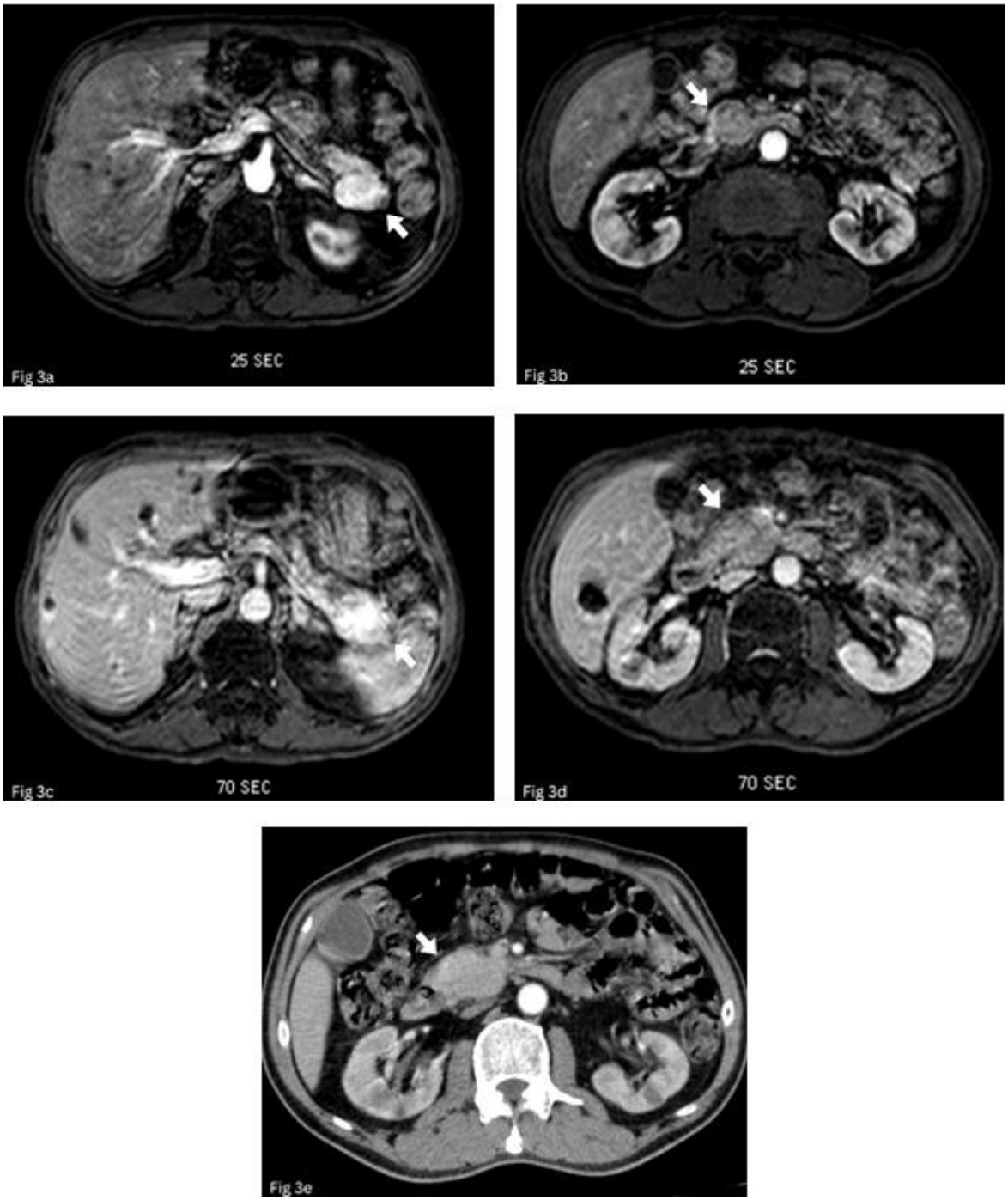

Figure 3: (a) MRI A-phase showing enhanced nodule at tail of pancreas, the hyposignaling lesions in liver are liver cysts (b) MRI A-phase showing another 2.8 cm hypointense lesion at uncinate process of pancreas (c) MRI V-phase lesion at tail of pancreas (d) MRI V-phase lesion at uncinate (e) reviewing first CT scan shows mildly enhancing mass like lesion at uncinated

Endoscopic Ultrasound (EUS) with Fine-Needle Aspiration (FNA) of both lesions confirmed the presence of two distinct well-differentiated neuroendocrine tumors. One was located at the uncinate process and classified as a grade 1 neuroendocrine tumor, while the second, at the pancreatic tail, was identified as a small round cell tumor consistent with a neuroendocrine tumor.

A final preoperative CT scan was performed 9 months after the initial imaging to assess resectability and to exclude metastasis. Intraoperative ultrasound was performed, confirming the presence of only two separated lesions at the uncinate and tail of the pancreas. Both of which are larger than 2 cm. Therefore, we aim to preserve pancreatic function in this patient by performing both distal pancreatectomy and pancreaticoduodenectomy, leaving a total pancreatic remnant of approximately 4 cm. Herein a concomitant en-bloc splenectomy was done due to a technical preference. We dissected some grossly seen peripancreatic lymph nodes together with the pancreaticoduodenectomy specimen without extensive nodal Dissected specimen of PNET and gallbladder (Figure 4)

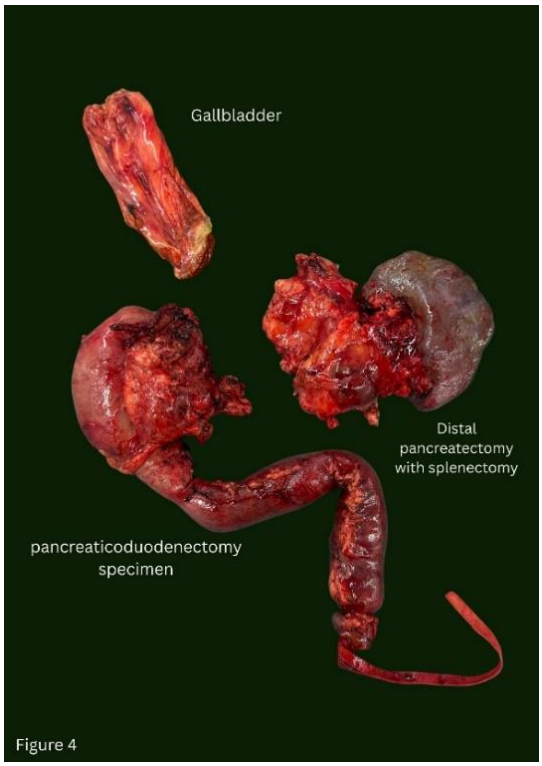

Figure 4: the specimen removed from the patient, included 1-pancreticoduodenectomy specimen 2-distal pancreatectomy with splenectomy specimen 3-gallbladder

Postoperatively, the patient experienced feeding intolerance and a low-output pancreatic fistula, both of which were managed conservatively. He was eventually discharged in good condition with preserved pancreatic function.

Final histopathological analysis revealed that the uncinate lesion was a well-differentiated non-functioning neuroendocrine tumor with a low mitotic index, no necrosis, and metastasis to four of five resected lymph nodes. The distal pancreatic

lesion showed positive insulin staining, confirming it as an insulinoma. Although it exhibited tumor necrosis, it remained well-differentiated, and showed no lymphovascular or perineural invasion. Both tumors stained positively for synaptophysin and chromogranin A, with a Ki-67 index of less than 3%. The spleen and gallbladder were free of tumor involvement.

Surprisingly, the final diagnosis revealed a malignant Pancreatic Neuroendocrine Tumor (PNET) due to nodal metastasis at the uncinate process and a functioning insulinoma at the pancreatic tail. These findings are compatible with clinical diagnosis of MEN1, despite the absence of clinically apparent pituitary involvement or history of first degree relative of MEN1. Due to certain limitations, genetic testing for germline mutation of MEN1 was not evaluated.

Discussion

This patient is an unusual case of co-existing functional and non-functional neuroendocrine tumor of the same organ. While insulinomas have an incidence rate of 1 in 32 million per year,[1] data on the incidence of coexisting pancreatic neuroendocrine tumors is limited, and there are no reports documenting their coexistence with parathyroid adenomas. Some case reports describe the co-occurrence of gastrinomas and insulinomas or pancreatic adenocarcinoma with PNET.[5] There is a report of co-existing two different types of pancreatic neuroendocrine tumor in a 23 years old male with MEN1.[6]

Although the coexistence of insulinoma, non-functioning pancreatic neuroendocrine tumor, and parathyroid adenoma in this patient strongly suggests MEN1, a definitive diagnosis could not be established in this case. The patient did not exhibit clinical or radiographic evidence of pituitary involvement, presented at a later age than typically observed in MEN1, and reported no family history of the syndrome. Genetic testing for MEN1 mutations was not performed due to financial constraints. Therefore, while the clinical presentation raises strong suspicion for MEN1, the diagnosis remains probable but unconfirmed in the absence of genetic confirmation, which is indicative in this situation. In this instance, de novo mutation of pathogenic MEN1 may be a more plausible explanation due to lack of first degree relative of family history and elderly onset of the disease.

Parathyroid adenoma is the most common cause of hyperparathyroidism, accounting for about 80% of all cases.[7,8] In most cases, parathyroid adenoma is sporadic with unknown etiology. The most common genetic mutation associated with sporadic adenomas is the cyclin D1/PRAD1 gene and 12% to 22% of cases are associated with MEN1. Clinically relevant neoplasia occurs in 90% of MEN1 individuals between 20 and 25 years of age.[8] The treatment of choice is surgical resection with localization using nuclear imaging, with a curative rate of 97.8%.[7,8] In a diagnosed MEN-1 patient, surgical resection of parathyroid adenoma as subtotal to total parathyroidectomy is the option with highest curative rate and lowest recurrence.[9]

Pancreatic neuroendocrine tumors are rare neoplasms that can be either functional or non-functional. Functional PNETs, such as insulinomas, typically present earlier than non-functional ones due to the symptoms they cause, such as hypoglycemia, flushing, or abdominal pain. As a result, functioning PNETs are usually smaller in size at the time of diagnosis. In contrast, non-functional PNETs are often discovered incidentally or due to symptoms related to mass effects, such as abdominal pain or weight loss.[2] Once discovered, the tumor tends to be larger than functioning PNETs and have nodal metastasis at the diagnosis, hence causing higher morbidity and mortality.[2,10] Insulinoma is one of the most common functioning PNET.[2,4] In most cases, insulinoma is sporadic, but up to 30% are associated with YY1 and Kras genes. Generally, insulinomas are benign and treated with surgical resection.[4] Parenchymal sparing enucleation is one of the options, indicated in insulinoma smaller than 2 cm in size and the lesion not involving the main pancreatic duct. Likewise, enucleation is also indicated in functioning PNETs smaller than 2 cm.[2,4] On the contrary, NF-PNETs can be approached in a 'wait and see' manner; however, most experts agree on an aggressive approach in early removal of primary and metastatic tumor as much as possible.[2]

For PNETs, surgical resection remains the mainstay of treatment. Tumors larger than 2 cm are generally treated with standard pancreatectomy.[4,9] In cases of multifocal non-functioning PNETs, surgical management is the preferred choice.[11] Currently, there are no systematic review of treatment in multifocal functioning and non-functioning PNET to determine the outcome of each surgical resection option.[9] Total pancreatectomy may be considered in this case.[11] However, total pancreatectomy leads to the loss of both exocrine and endocrine functions, necessitating lifelong replacement therapy. While exocrine replacement therapy can improve survival after pancreaticoduodenectomy for periampullary malignancy, the quality of life following total pancreatectomy remains lower than that of the general population.[12]

Due to its limited data on timing of surgery, standard treatment protocols, and treatment outcomes, each patient treatment should be tailored on the basis of organ preservation if feasible. When approaching multiple abnormal functioning endocrine tumors, physicians should evaluate the possibility of MEN and genetic testing. In the hindsight of our situation, we didn't evaluate the possibility of MEN1 during the process of diagnosis, but after the diagnosis was firmly established on 2 major organs of MEN1. Surgical evaluations and management of both PNET and parathyroid adenoma were not done under the premise of MEN1, since there were no genetic evaluations for confirmation. Overall, our clinical evaluation and practice were congruous under each tumor's guidelines, regardless of whether or not the patient is diagnosed with MEN1.

Surveillance in MEN1 can be mentioned to patients prior to treatment, which usually consists of biochemical testing of calcium, parathyroid phosphate level, prolactin, IGF-1, chromogranin-A, etc., depending on the conditions screening for. The usual

age to initiate the screening is 5 years old.[13,14] Interval imaging is another modality included for testing with a starting age of 5 for brain MRI and age of 20 for abdominal CT scan at the interval of 3-5 years.[13] There are no current guidelines in post-operative surveillance specifically made for MEN1, due to lack of evidence. We made post operative surveillance regarding each endocrine's organs. The patient was evaluated for calcium and parathyroid hormone levels the next morning post-parathyroidectomy, and had been followed up every month for parathyroid adenoma. For PNET, the patient underwent interval abdominal CT scan at 6 months interval, which revealed no recurrence nor progression of the disease.

Conclusion

This case highlights a rare coexistence of functional and non-functional pancreatic neuroendocrine tumors, along with parathyroid adenoma, suggesting a clinically possible but atypical presentation of MEN1. Once considered as a differential diagnosis, comprehensive diagnostic work-up, including biochemical testing and multimodal imaging, is crucial for identifying multifocal lesions and alerting multidisciplinary teams for planning surgical interventions. Organ-preserving surgery may be a feasible option in selected patients to maintain long-term pancreatic function and quality of life. Given the rarity of such presentations, this case adds valuable insight into the complexity of diagnosing and managing multifocal neuroendocrine tumors and underscores the need for individualized, multidisciplinary care.

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