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A RARE CASE OF PRIMARY WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR (NET) GRADE 1 OF THE PANCREAS: DIAGNOSTIC AND THERAPEUTIC INSIGHTS

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Abstract: Neuroendocrine Tumors (NETs), are a group of rare neoplasms that arise from specialized cells in the neuroendocrine system, affecting approximately 6 in 100,000 people worldwide. Their most frequent locations are the gastrointestinal tract (GI), pancreas and lungs[1]. Those originating from the pancreas are known as Glucagonomas, which arise from the alpha cells of the pancreas and are in their majority malignant [2]. **Goal:** To report an atypical case of a patient with a stage 1 well-differentiated neuroendocrine tumor (NET) in the pancreas. **Case report:** We report the case of a 49-year-old female diagnosed with a well-differentiated neuroendocrine tumor (NET) Grade 1 (Ki-67 < 3%) of the pancreas. The patient presented with clinical features consistent with glucagonoma, erythema necrolyticum migrans, and a history of bariatric surgery. She underwent multimodal imaging, including PET-CT with 18F-NOTA-Octreotide and PET-CT with Gallium-68 DOTATATE. The patient received Lutetium-177 therapy with four cycles between 28/11/2023 and 09/07/2024, followed by surgical resection of the tumors and subsequent follow-up imaging. This report highlights the importance of precise imaging and histopathological evaluation for accurate diagnosis and effective management. **Discussion / Final Considerations:** This case highlights the diagnostic complexity of well-differentiated NETs, where clinical symptoms overlap with metabolic syndromes. This case underscores the importance of multidisciplinary management for optimal outcomes.

Keywords: case report, glucagonoma, neuroendocrine tumors, necrolytic migratory erythema (NME), hepatectomy.

INTRODUCTION

Neuroendocrine tumors (NETs), are a group of uncommon neoplasms that develop from neural crest cells in the gastrointestinal tract, pancreas, lungs and genitourinary tract affecting about 6 in 100,000 people worldwide [1]. Approximately 90% of NETs originate in the gastrointestinal tract, while 7% develop in the pancreas[2]. Although they can also develop in any area containing neuroendocrine cells such as the thyroid, parathyroids, pituitary, adrenals or thymus[1].

Furthermore, NETs can be classified endocrinologically as inert or active. When classified as an endocrinologically active NET, they produce hormones and when classified as inert, they do not. Endocrinologically active NETs are named after the hormone they secrete. For instance, pancreatic NETs such as Gastrinomas hypersecrete gastrin causing ulcers due to gastric acid secretion. Vipomas, hypersecrete vasoactive intestinal peptide, therefore causing diarrhea. Insulinomas result in hypoglycemia because they hypersecrete insulin. Lastly and more pertinent to this case, Glucagonomas lead to hyperglycemia due to the hypersecretion of glucagon. On the other hand, endocrinologically active gastrointestinal NETs secrete histamine, serotonin and other hormones that when hypersecreted can result in carcinoid syndrome. Other rare NETs may secrete somatostatin, growth-releasing factor (GRF) or adrenocorticotropic hormone (ACTH)[2].

Pancreatic neuroendocrine tumors (PNETs) arise from hormone-producing islet cells of the pancreas and are classified by functionality and grade of differentiation. The most common types of PETs are glucagonomas and insulinomas. They can occur sporadically or as a part of an inherited condition such as: Von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 1 (MEN1) and tuberous sclerosis

(TSC). The majority of PNETs are metastatic, most commonly to the liver.

PETs are classified by grades using the marker of proliferation known as Ki-67, to determine whether they are well-differentiated (grades 1-3) or poorly differentiated tumors. They are also classified by functionality, 75%-90% being nonfunctional. Among the functional variety, insulinomas en glucagonomas are the most common as well. The diagnosis and staging of PETs is based on pancreatic protocol computed tomography (CT), MRI with Evoist (gadoxetate disodium) which is a superior extracellular contrast for detection of liver metastases, somatostatin-receptor-based PET (DOTATATE PET) and endoscopic ultrasound (EUS) with subsequent biopsy. For functioning PNETs the testing of hormone levels is fundamental, along with checking tumor markers such as chromogranin (CgA) and pancreastatin. The treatment for PETs may include surveillance, surgical resection of the primary lesion, and in metastatic cases microwave ablation with liver debulking. Other multiple systemic treatment options used are everolimus, sunitinib, temozolomide, capecitabine and radioligand therapy in SSTR2 positive tumors. It is important to emphasize that surgery is recommended as first-line treatment for well-differentiated PNETs less than 2cm in size and for any tumor characterized by being functional or presenting symptoms [4].

Glucagonomas are rare, slow-growing, average age of symptom onset is 50 years, typical survival rate is 15 years and 80% of patients are female. Most are malignant, and some cases are associated with multiple endocrine neoplasia type 1 (MEN-1). This tumor produces the hormone glucagon, which is secreted by the pancreas when blood glucose levels are low. Furthermore, it supports glycogenolysis in the liver, and as a result increases glucose levels in the blood. The signs and symptoms of glucagonoma are those seen in diabetes since it elevates blood glucose levels. On occasion, normochromic anemia, hypolipidemia and hypoaminoacidemia are correlated to these cases. However, the most prominent clinical feature of this tumor is a chronic cutaneous eruption with superficial necrosis and a centrifugal spread in the extremities, known as necrolytic migratory erythema (NME). Though most commonly linked to glucagonoma, NME may also occur in other conditions such as liver disease or intestinal malabsorption, known as pseudoglucagonoma syndrome. However, due to its rarity and nonspecific features, it is often misdiagnosed[5] (**Figure 1)**.

In order to diagnose a tumor like a Glucagonoma, serum glucagon levels are measured, most patients with the tumor have glucagon levels above 1000 pg/ml while normal levels are considered to be below 200 pg/ml. Correlation with symptoms is required in order to rule out other diagnoses, since moderate elevations in glucagon are seen in acute pancreatitis, severe stress, fasting and renal insufficiency. The imaging studies of choice for diagnosis and staging of glucagonomas is that of PNETs: pancreatic protocol computed tomography (CT), MRI with Evoist, somatostatin-receptor-based PET (DOTATATE PET) and endoscopic ultrasound (EUS) with subsequent biopsy[4].

Treatment for the localized disease is surgical resection of the glucagonoma, which eliminates all symptoms. On the other hand, metastatic cases are treated with chemotherapy. And lastly, to suppress the production of glucagon and alleviate the erythema, the medication of choice is a somatostatin analog such as Ocreotide. Unresectable, recurrent or metastatic glucagonomas are treated with a combination of doxorubicin and streptozocin, which are known to decrease the levels of immunoreactive glucagon, improve response rate and diminish symptoms. However, they are unlikely to improve survival rate[3].

CASE REPORT

A 49-year-old female underwent bariatric surgery in July 2022. Following the procedure, she developed significant anemia, progressive weight loss, and general health decline. On April 2, 2023, she was diagnosed with a pancreatic neuroendocrine tumor (NET). Histopathology confirmed a well-differentiated Grade 1 NET with a Ki-67 index of less than 3%. During the course of her illness, she developed deep vein thrombosis (DVT) in the left lower limb, which progressed to DVT in the right lower limb and pulmonary embolism despite oral anticoagulation therapy, indicating therapeutic failure. As a result, a vena cava filter was placed for pulmonary protection, and her treatment was switched to unfractionated heparin. Clinically, she presented with symptoms consistent with glucagonoma, including necrolytic migratory erythema (**Figure 1**) and difficulty maintaining glycemic control.

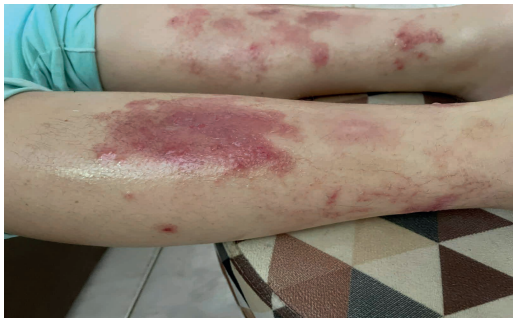

Figure 1: necrolytic migratory erythema (NME) is a hallmark skin manifestation of glucagonoma.

Diagnostic evaluation included laboratory tests showing persistent hyperglycemia and elevated glucagon levels. Imaging studies provided further insights. Abdominal MRI revealed multiple hepatic nodules, the largest in segment IV measuring 72 x 50 mm with extensive solid-cystic septations, along with para-aortic and mesenteric lymphadenopathy. A PET-CT with 18F-NOTA-Octreotide (March 20, 2023) confirmed somatostatin receptor–positive pancreatic lesions and mesenteric lymph node involvement, with gradual SUVmax reduction over time. A specialized PET-CT using somatostatin analogues was conducted to investigate the primary site and tumor staging. Imaging highlighted hyperexpressive nodular lesions in the body and tail of the pancreas, the largest measuring 26 x 17 mm (SUVmax: 86.4), with signs of cystic-necrotic degeneration. Additional findings included hypercaptation in paraesophageal, mesenteric, and para-aortic lymph nodes (SUVmax up to 68.1), as well as at least five hypercaptating hepatic nodules, the largest 49 x 43 mm (SUVmax: 41.3). Other incidental findings included calcified subgaleal nodules, bilateral maxillary sinus thickening, pulmonary mosaic perfusion, a small pericardial effusion, and diverticular disease. A follow-up PET-CT (October 14, 2024) showed a reduction in the size of pancreatic and lymph node lesions, along with signs of response to Lutetium-177 therapy.

Therapeutic interventions included peptide receptor radionuclide therapy (PRRT) with four cycles of Lutetium-177 administered between November 28, 2023, and July 9, 2024. The patient also underwent extensive surgical resection, including segmental hepatectomy of segments VI and VII, pancreatectomy, lymphatic resection, vena cava surgery, cholecystectomy, and enteropexy. Histopathology confirmed a well-differentiated Grade 1 pancreatic NET with chromogranin positivity and Ki-67 < 3%, along with hepatic metastases. Somatostatin analogue therapy with Octreotide LAR had been attempted prior to PRRT but yielded no objective response. Supportive management included nutritional supplementation, glycemic control, anticoagulation with unfractionated heparin (60 mg every 12 hours), and vena cava filter placement after failure of oral anticoagulation.

The patient demonstrated favorable outcomes, including significant reduction in lesion size and SUVmax values, resolution of skin lesions within three months post-treatment, and stabilization of thrombotic events under heparin therapy. Glycemic control remained challenging but manageable with medication adjustments. Post-surgical follow-up over six months revealed no signs of recurrence. Overall, the patient experienced an improved quality of life and continues under periodic PET-CT monitoring.

DISCUSSION

This case highlights the diagnostic complexity of well-differentiated NETs, where clinical symptoms overlap with metabolic syndromes. MRI and PET-CT with 18F-NOTA-Octreotide and Gallium-68 DOTATATE proved valuable for lesion detection and treatment monitoring. Lutetium-177 therapy demonstrated efficacy in reducing lesion dimensions and metabolic activity. Personalized treatment, including targeted radionuclide therapy and surgical resection, plays a crucial role in managing such rare cases. The presence of necrolytic migratory erythema and a history of bariatric surgery adds further complexity to the clinical picture. The development of venous thrombosis and pulmonary embolism required additional intervention with anticoagulation and vena cava filter placement.

FINAL CONSIDERATIONS

Primary well-differentiated NET Grade 1 of the pancreas is a rare but manageable condition with appropriate imaging, targeted therapy, and surgical intervention. This case underscores the importance of multidisciplinary management for optimal outcomes.

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