A Rare Case of Functional Pancreatic Neuroendocrine Tumor with Multi-organ Involvement in a 25-year Old Female*

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Abstract

Significance: Pancreatic neuroendocrine tumors (pNET) account for 1-10% of tumors arising in the pancreas, with functional pNETs reported less commonly than their non-functional counterpart. Glucagonoma is an even rarer form of functional pNET which has a reported annual incidence of 0.01-0.1 per 100,000.

Clinical Presentation: This is a case of a 25-year old female presenting with a two-year history of palpable epigastric mass, abdominal pain and weight loss. She came in at our institution with worsened signs and symptoms in which she already had chronic diarrhea, anemia, glossitis, and dermatitis eventually leading to development of early onset diabetes, stroke and cardiomyopathy.

Management: Initial contrast-enhanced CT scan revealed a pancreatic mass and was confirmed by endoscopic sonography as a large solid encapsulated mass at the head to the body of the pancreas measuring 7.7x5.5cm. Histopathologic and immunohistochemical tests to tissue specimen obtained by fine needle aspiration biopsy of the mass revealed a well-differentiated pancreatic neuroendocrine tumor confirmed as glucagonoma by a remarkably elevated plasma glucagon level. The mass was deemed non-resectable at the time of diagnosis, hence the patient was started on octreotide LAR depot injection. Multi-systemic complications caused by the functional tumor were also managed through multidisciplinary approach. Medical management resulted to marked improvement of the signs and symptoms and lead to a better quality of life.

Recommendation: In rare cases such as this, diagnosis is often a dilemma and causes delay in treatment. Prompt diagnosis will lead to early intervention preventing life-altering complications, disease progression, and mortality.

INTRODUCTION

Pancreatic neuroendocrine tumors (pNET) account for 1-10% of tumors arising in the pancreas, with functional pNETs reported less commonly than their non-functional counterpart (1, 2). Glucagonoma is an even rarer form of functional pNET which has a reported annual incidence of 0.01-0.1 per 100,000 [(3)].

Glucagonoma secretes excessive amounts of glucagon and the syndrome, characterized by dermatitis, glossitis, cheilitis, glucose intolerance, anemia, venous thrombosis, diarrhea, abdominal pain, and neuropsychiatric disturbance, has an estimated incidence of 1 in 20 million (4). Early recognition allows prompt diagnosis of the tumor and subsequent intervention. All patients with localized tumor should be planned for resection (5) but initial medical treatment is directed at symptomatic management, improvement of nutritional status, and control of hyperglycemia, since patients generally are poor operative candidates markedly affected by their nutritional status and greater risk of venous thrombosis [(6)].

CASE PRESENTATION

We present a case of a 25-year old female with a 2-year history of palpable epigastric mass associated with progressive unintentional weight loss. No consult was done until further progression in the size of the

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mass after a year, which prompted consult with a surgeon. Initial complete blood count showed anemia and whole abdominal ultrasound revealed a pancreatic mass. She was then advised further workup. In the interim, there was onset of generalized weakness, poor appetite, glossitis, nausea, bilious vomiting and watery diarrhea, 6-12 bouts per day, hence consult to our institution. She was initially seen by Surgery service and requested for a Dynamic CT scan of the pancreas revealing a large lobulated heterogeneously enhancing mass with mixed cystic and predominantly soft tissue components at the region of the pancreatic head-body measuring 7.7 x 8.4 x 12.0 cm, with intralesional vascularity, dilated

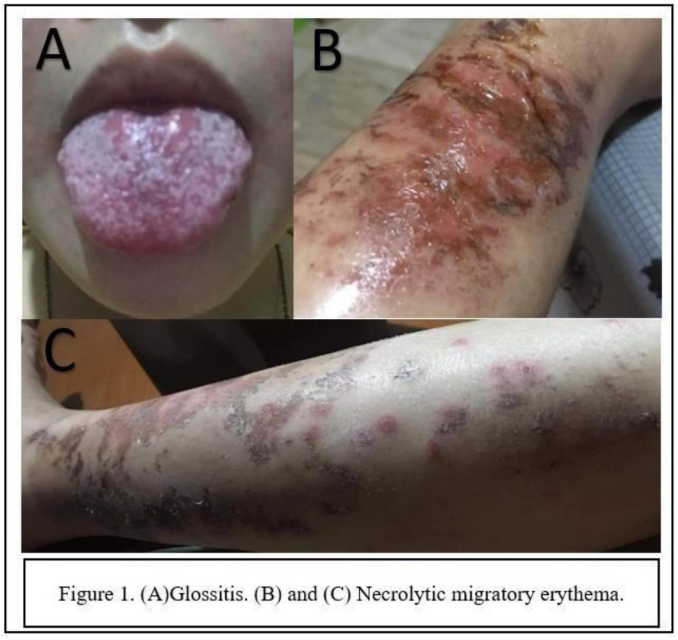

Figure 1. (A)Glossitis. (B) and (C) Necrolytic migratory erythema.

(2 cm) pancreatic duct, splenomegaly, encasement of the superior mesenteric vein, inferior portion of the portal vein, left gastric artery and non-delineation of the splenic vein. Also seen is a 2.7 x 3.6 cm hypoenhancing nodule with a central fluid density in the segment IVB of the liver. Patient was then referred to our service, underwent endoscopic ultrasound revealing mixed echogenic and anechoic areas at the head to the body of the pancreas measuring 7.7 x 5.5 cm abutting the bifurcation of the celiac trunk going to the common hepatic artery. There were no lymphadenopathies noted. Histopathologic and immunohistochemical tests to tissue specimen obtained by fine needle aspiration biopsy of the mass revealed a well-differentiated, pancreatic neuroendocrine tumor, grade 3 (Chromogranin A and synaptophysin positive, CA19-9 negative, mitotic rate 22 per 10 hpf, Ki-67 index 33.6%).

Patient was then referred to Endocrine and Medical Oncology services with orders for further testing to confirm the type of pNET and rule out MEN-1 syndrome. Initial tests available were all within the reference range (Gastrin, prolactin, iPTH, ACTH, Vitamin D). Plasma glucagon and VIP were not available and were sent out to Mayo Clinic Laboratory for testing. Multidisciplinary supportive management were provided while waiting for the confirmatory results.

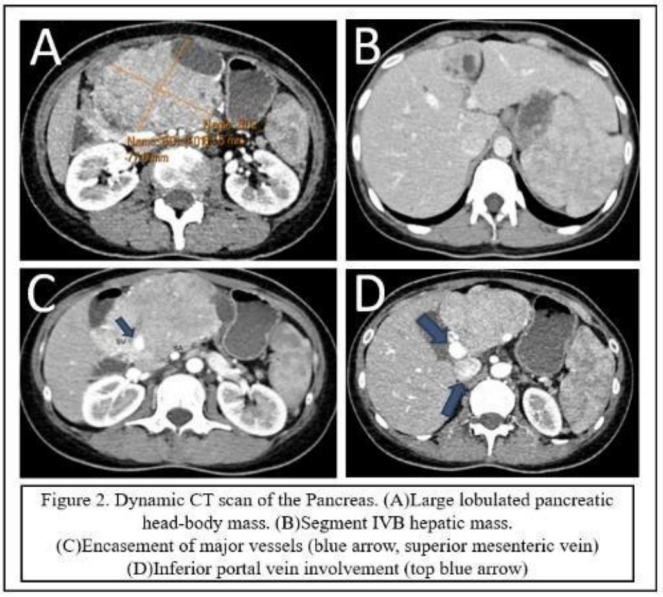

Figure 2. Dynamic CT scan of the Pancreas. (A)Large lobulated pancreatic head-body mass. (B)Segment IVB hepatic mass. (C)Encasement of major vessels (blue arrow, superior mesenteric vein) (D)Inferior portal vein involvement (top blue arrow)

During her course, patient eventually had sudden onset of right sided body weakness, slurring of speech and dysphagia confirmed by cranial MRI as Acute lacunar infarct of the right precentral gyrus. She also developed heart failure symptoms (NYHA class III-IV) confirmed by echocardiogram as dilated left ventricle, global hypokinesia, and an ejection fraction of 20.9%. Patient's functional status declined (ECOG 4), enteral feeding was started.

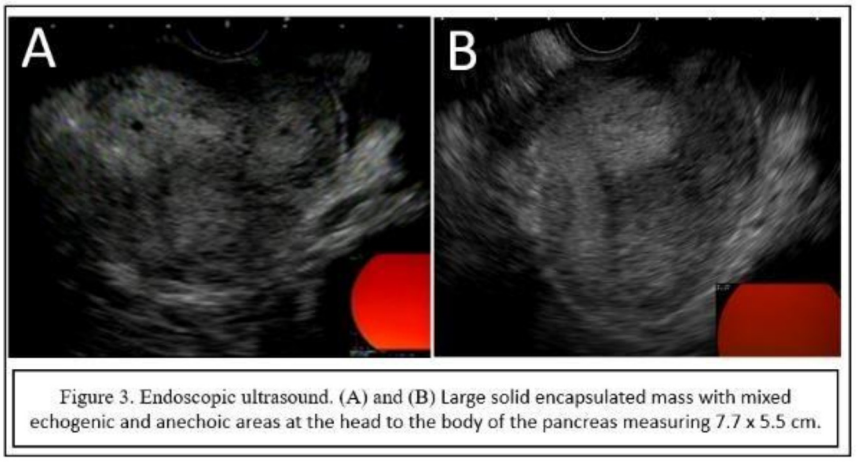

Figure 3. Endoscopic ultrasound. (A) and (B) Large solid encapsulated mass with mixed echogenic and anechoic areas at the head to the body of the pancreas measuring 7.7 x 5.5 cm.

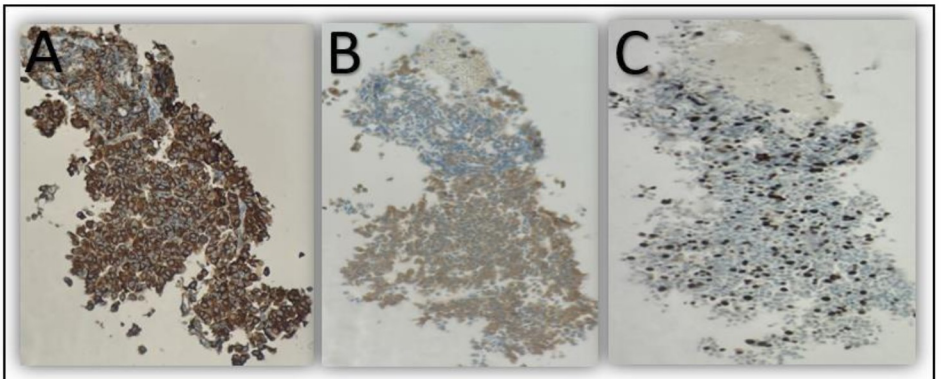

Figure 4. Immunohistochemical Testing. (A)Chromogranin stain (+). (B) Synaptophysin stain (+). (C)Ki-67 index 33.6%

Referral to Neurology, Cardiology, Clinical Nutrition and Rehabilitation services for optimal management was done.

After confirmation of Glucagonoma (plasma glucagon >25,000 pg/mL, ref.<80 pg/mL, VIP within normal range), treatment with Octreotide LAR depot injection every 28 days ensued, with subsequent significant improvement of all parameters including control of abdominal pain, resolution of watery diarrhea, improvement of skin rash and glossitis, improvement in the functional status (ECOG 4→2, MRS 4-5→2) and functional class (NYHA class III-IV→II). Although tumor was assessed to be advanced and non-resectable, optimal medical management resulted to marked improvement of the signs and symptoms and lead to a better quality of life.

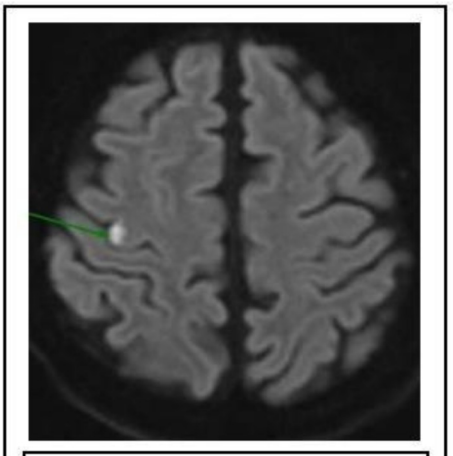

Figure 5. Cranial MRI. Acute lacunar infarct, right precentral gyrus

DISCUSSION

Pancreatic neuroendocrine tumors produce multiple GI hormones, which can be localized by immunohistochemical methods. Functional pNET syndrome should be diagnosed only if the appropriate clinical symptoms are present, and not only based on immunohistochemistry alone. Poorly differentiated neuroendocrine carcinomas are highly aggressive with high proliferative activity and virtually all poorly differentiated tumors are high grade.

Glucagonoma can be confirmed by demonstrating an increase in fasting plasma glucagon concentration with marked elevation in plasma glucagon level seen at presentation in most patients (7). The high level of glucagon secreted by the tumor promotes glycogenolysis and gluconeogenesis which causes hyperglycemia. Weight loss is secondary to the catabolic effect of glucagon (8). Prolonged elevation of glucagon levels causes the typical rash and the presence of hypoaminoacidemia may also cause the dermatitis. Decreased erythropoiesis due to hyperglucagonemia is said to contribute to anemia. The role of glucagon in causing venous thromboembolism and neuropsychiatric problems is still unclear (9).

Somatic mutations of MEN-1 were observed in 44% of cases in a whole-exome study of 68 sporadic pNETs by Jiao et al. and glucagonoma could be part of the MEN-1 syndrome (10). Testing is prudent to allow adequate intervention.

While tumor confirmation and localization studies are ongoing, initial medical management of glucagonomas is directed at symptomatic treatment, improving nutritional status, and controlling hyperglycemia.

Surgical resection is the recommended treatment for localized tumors. For advanced, metastatic, non-resectable tumors, somatostatin analogs have been useful in controlling symptoms. A small randomized, controlled trial demonstrated an improvement in time to tumor progression with octreotide LAR injection compared with placebo for metastatic midgut tumors with extrapolation of data occasionally considered for pNET tumor stabilization [11].

CONCLUSION / RECOMMENDATION

A multidisciplinary, collaborative, and proficient team augments the management of patients with pNETs. Different options may be significant and of considerable importance at different times in the disease process.

In rare cases such as this, diagnosis is often a dilemma and causes delay in treatment. Lack of accessible tests also cause this delay. Prompt diagnosis will lead to early intervention preventing life-altering complications, disease progression, and mortality.

Author's Statement

The manuscript is original material and is not being considered for publication or has not been published or accepted for publication elsewhere, in full or in part, in print or in electronic media.

The manuscript has been read and approved by all the authors and all four criteria for authorship have been met by each author.

Conflict of Interest

The authors declare no conflict of interest.

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