

A Rare Case of a Non- Functioning Pancreatic Neuroendocrine Tumor in a Young Female

Yaser Khalid¹, DO; Neethi Dasu¹, DO; Herman Suga¹, DO; Debashis Reja², MD; Kirti Dasu³, BA; Richard Gordon⁴, DO; Donald McMahon⁵, DO

1 Division of Internal Medicine, Rowan University School of Medicine at Jefferson Health System, Stratford, New Jersey, United States;

2 Division of Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, United States;

3 Division of Biology, Syracuse University, Syracuse, New York, United States;

4 Division of Hematology/Oncology, Comprehensive Cancer and Hematology Specialists, Voorhees, New Jersey, United States;

5 Division of Gastroenterology, Rowan University School of Medicine at Jefferson Health System, Stratford, New Jersey, United States.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Neethi Dasu, Division of Internal Medicine, Rowan University School of Medicine at Jefferson Health System, Stratford, New Jersey, United States.

Email: dasu@rowan.edu

Telephone: +1-347-782-2136

Received: April 7, 2020

Revised: April 20, 2020

Accepted: April 22, 2020

Published online: June 21, 2020

ABSTRACT

Pancreatic neuroendocrine tumors (PNETs) are extremely rare and represent about 1-2% of all pancreatic tumors. Non-functional PNETs (NF-PNETs) represent approximately 85% of all PNETs. Most are

found incidentally at an advanced stage because patients are asymptomatic, and the tumors do not secrete hormones that would manifest with symptoms. We report a case of 32-yr-old female who initially presented with increasing abdominal girth and lower extremity swelling up to the hip and she was incidentally found to have a widely metastatic intermediate grade NF-PNET stage IV T2N0M1 with metastasis to the liver, peritoneum, bones, and gallbladder. Computed tomography (CT) is the imaging modality of choice, but other diagnostic imaging tools need to be investigated for earlier detection of this insidious and fatal disease. Surgical treatment is preferred, but only palliative chemotherapy and radiation is currently available for advanced disease.

Key words: Pancreatic NET; Pancreas; Neuroendocrine tumor; Surveillance; Female mortality; Tumor markers

© 2020 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Khalid Y, Dasu N, Suga H, Reja D, Dasu K, Gordon R, McMahon D. A Rare Case of a Non- Functioning Pancreatic Neuroendocrine Tumor in a Young Female. *Journal of Gastroenterology and Hepatology Research* 2020; **9(3)**: 3231-3233 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2883>

INTRODUCTION

More than 95% of the pancreatic neoplasms arise from the exocrine component of the pancreas. The remaining 5% of pancreatic neoplasms arising from the endocrine pancreas are neuroendocrine tumors (NETs). NETs are a family of neoplasms that include carcinoid tumors, PNETs, medullary thyroid cancers, and pheochromocytomas. PNETs comprise approximately 7% of all NETs^[6]. PNETs are rare neoplasms of the pancreas, with an incidence 1/100,000/year and account for about 1-2% of all pancreatic neoplasms^[2]. Nonfunctional PNETs (NF-PNETs) account for about 85% of pancreatic neuroendocrine tumors^[6].

Although PNETs may manifest at any age, they most frequently occur in the fourth to sixth decades of life^[4]. More than 10% are associated with genetic syndromes such as MEN-1^[3]. A slight male predominance, 55% male vs. 45% female, is reported and the median

age at presentation is around 50 years^[8]. PNETs can express neuroendocrine markers such as synaptophysin, neuron-specific enolase and chromogranin A, which is present in 88-100% of patients with a PNET^[3]. The detection rate of PNETs has increased by five-fold in the last two decades, due to improved radiological diagnostic techniques that have developed^[2]. For patients with pancreatic neuroendocrine tumors that have metastasized, prognosis is poor, with a survival of only 1-3 years^[6].

Historically, the 9 commonly recognized functional P-NETs (F-PNETs) include insulinoma (40-50% with 10% malignant), gastrinoma (20-50% with 60-90% malignant), glucagonoma (with 50-80% malignant), VIPoma (40-70% malignant), somatostatinoma (>70% malignant), GRFoma, ACTHoma, PTHrp-oma, and PNET causing carcinoid syndrome^[6]. They can secrete a variety of peptide hormones, including gastrin, insulin, glucagon, and vasoactive intestinal peptide (VIP). Insulinoma is the most common functioning pNET characterized by hypoglycemia and hyperinsulinemia^[8]. Calcitonin (Ct) is mainly secreted by medullary thyroid carcinoma (MTC) but it is also rarely secreted by pNETs, occasionally leading to diagnostic confusion^[5].

NF-PNETs are often found incidentally because patients are asymptomatic and non-functioning tumors do not secrete hormones that would manifest with symptoms. When they are discovered, 70% are greater than 5 cm^[6]. They usually present with advanced disease due to late discovery and >60% of patients have liver metastases^[6]. Symptoms can be caused by tumor growth. These symptoms may be abdominal pain (40-60%), weight loss (25-50%) and jaundice (30-40%)^[3]. NF-PNETs may occur in association with the multiple endocrine neoplasia type 1 syndrome, von Hippel-Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis^[7].

CASE REPORT

This is a case of a 32-yr-old female with no significant past medical history who initially presented with abdominal bloating and constipation. She also had increasing abdominal girth, decreased mobility, and lower extremity swelling up to the hip. She underwent a computed tomography of the abdomen and pelvis (CT) initially that revealed a massively enlarged liver with diffuse metastases. Her largest liver lesion measured 5.8 × 4.9 cm. She also had a 3.5 × 3.6 cm pancreatic tail mass as well as a 10.3 × 11 cm mass in her pelvic area extending to the vaginal wall. She underwent a core biopsy of her liver and pathology showed a metastatic neuroendocrine tumor with Ki 67 of 40% and a mitotic rate of 10 per 10 HPF.

She was started on capecitabine and temozolomide and then had a repeat CT of the abdomen and pelvis which showed significant decrease in her pancreatic mass and liver metastases. Her chromogranin A level had decreased from 5800 to 35 ng/dL. The patient then completed 6 cycles of chemotherapy and then underwent an exploratory laparotomy, lysis of adhesions, and bilateral oophorectomy with the gynecology service. Unfortunately, she was found to have metastatic disease with peritoneal deposits to her sigmoid colon and her peritoneum. Her treatment regimen was changed to octreotide and everolimus postoperatively until an magnetic resonance imaging (MRI) of her abdomen showed progression of her liver metastases. She was then subsequently changed to doxorubicin, 5-fluorouracil (5-FU), and streptozocin. Repeat imaging showed improvement of liver lesions. She received four cycles of treatment and she then received Y90 radioembolization to her liver. She then underwent a repeat MRI of the abdomen that showed stable disease in her liver. After having significant bone pain, she underwent a bone scan which revealed multiple bone lesions. She received one cycle of platinum and etoposide with



Figure 1 CT abdomen pelvis with and without contrast showing diffuse metastasis of PNET to the liver.



Figure 2 CT abdomen pelvis with and without contrast showing PNET as well as kidney metastases.

improvement in her bone pain.

A gallium 68 positron emission tomography (PET) CT was recommended to clarify if the patient had an overexpression of somatostatin receptors and this would be more consistent with a slower growing NET. The patient would then receive treatment with Peptide Receptor Radionuclide Therapy (PRRT).

She was diagnosed with widely metastatic intermediate grade NF-PNET stage IV T2N0M1 to the liver, peritoneum, bones, and gallbladder.

DISCUSSION

According to the World Health Organization (WHO) classification, three classes of NETs can be identified based on histology and pathology: well-differentiated NETs can be classified as G1 tumors, when they express < 2 mitoses/10 HPF and ≤ 2% Ki-67 index; as G2 tumors, when they express 2-20 mitoses/10 HPF and 3-20% Ki-67, whereas, neuroendocrine carcinomas (NECs) usually belong to G3 category, with > 20 mitoses/10 HPF and > 20% Ki-67 index^[2]. Our patient had Ki 67 of 40%.

Potential risk factors for PNETs include diabetes, smoking, a previous history of chronic pancreatitis, and genetic factors (hereditary endocrinopathies, including multiple endocrine neoplasia

types I)^[4]. However, our patient had no risk factors for this disease.

Appropriate imaging for NF-PNETs would include the following: octreoscan, (a scintigraphic study in which radiolabeled octreotide is used to detect somatostatin-receptor expressing tumors), and CT scans should preferably be obtained in 3 phases (arterial, venous, and noncontrast) in order to maximize sensitivity^[1]. Our patient had a negative octreoscan and underwent multiple CT scans and MRIs of her abdomen and pelvis for surveillance and staging. Endoscopic ultrasonography (EUS) is highly sensitive to detect occult smaller (sub-centimeter) pancreatic NETs, and it plays an important role in the evaluation of patients with functional NETs undetectable using conventional imaging techniques^[4]. Our patient may have benefited from evaluation with EUS.

Patients with newly diagnosed NETs should be evaluated for presence of concurrent hormonal syndromes. For example, in patients with diarrhea and gastroesophageal reflux, a serum gastrin level should be measured; for flushing and/or diarrhea a measurement of 24-hour urine 5-HIAA levels; for chronic hyperglycemia and weight loss, serum glucagon should be measured^[1]. Our patient tested negative for increased levels of all these hormones and biomarkers. Serum levels of CgA, a neuroendocrine secretory protein, are elevated in the majority of patients with advanced NETs so levels of CgA can be used to monitor disease progression^[1]. Circulating CgA is expressed in 80-90% of all patients with pancreatic neuroendocrine tumors^[2]. Our patient had elevated levels of CgA, and the levels were monitored for both progression and treatment of disease.

Clinical management involves a multidisciplinary approach, but surgery remains the only curative therapy for early-stage disease. Radical surgery for PNETs offer a 5-year survival rate of 45-92%, highlighting the importance of accurate diagnosis and appropriate referral of a patient for surgery^[9]. Numerous retrospective studies have demonstrated prolonged survival durations among patients with limited liver metastases who undergo complete or near-complete resection of metastases^[1]. Our patient had debulking of tumors and resection which did lead to prolonged survival. Radiofrequency ablation, which has proved successful in patients with hormonally active tumors as well as tumors >5cm in size, is an option for liver metastases that are considered unresectable^[1]. Our patient could have benefited from radiofrequency ablation. Hepatic artery embolization or chemoembolization is another option for patients with liver metastases who are not candidates for surgical resection^[9]. Medical treatment with drugs such as somatostatin analogs (octreotide or lanreotide) is used in patients who do not benefit with surgery alone. A chemotherapy regimen with doxorubicin, 5-FU and streptozocin has significant activity in patients with locally advanced and metastatic pancreatic endocrine carcinomas^[3]. Our patient benefited from treatment with octreotide, doxorubicin, 5-FU, and streptozocin. Molecular targeted therapy, including anti-epidermal growth factor receptor or anti-vascular endothelial growth factor receptor therapy such as sunitinib, are currently being investigated for future treatment options^[7].

CONCLUSION

Due to the rarity of PNETs, there aren't many randomized controlled

studies and current treatment recommendations are based primarily on case series and individual treatment approaches^[7]. Our patient's medical course illustrates the recent evolution of systemic treatments for patients with NETs, particularly those originating in the pancreas. PNETs demonstrate an increased somatostatin receptor expression both in primary and metastatic lesions^[2]. Further research is under way on newer, investigational drugs. For example, an ongoing phase 2 study examining the effect of the tyrosine kinase inhibitor pazopanib among patients resistant to sunitinib or everolimus was discussed at ASCO 2011^[1].

REFERENCES

1. Strosberg, J. (n.d.). *A 53-Year-Old Woman With a Neuroendocrine Tumor: A Case Discussion* (Medscape Education Oncology). Retrieved April 30, 2019, from <https://www.medscape.org/viewarticle/744319>.
2. Tankova L, Gerova V, Getsov P, Nakov R, Churchev S, Terziev I, Kostadinova I, Vitkova M, Nakov V, Damyranov D, Topuzanska N, "Metastatic Nonfunctional Pancreatic Neuroendocrine Tumor - Case Report and Review of the Literature." *American Journal of Medical Case Reports* 2015; **3(7)**: 205-208. [DOI: 10.12691/ajmcr-3-7-6]
3. Amador Cano A, Garcia F, Espinoza A, Bezies N, Herrera E, De Leija Portilla J. Nonfunctional neuroendocrine tumor of the pancreas: Case report and review of the literature. *Int J Surg Case Rep.* 2012; **4(2)**: 225-228. [DOI: 10.1016/j.ijscr.2012.10.018]
4. Radu EC, Saizu AI, Grigorescu RR, Croitoru AE, Gheorghe C. Metastatic neuroendocrine pancreatic tumor - Case report. *J Med Life.* 2018 Jan-Mar; **11(1)**: 57-61. [PMID: 29696066]; [PMCID: PMC5909947.5]
5. Alexandra Chrisoulidou, Gregory Kaltsas, Stylianos Mandanas, Eleftherios Chatzellis, Georgios Boutzios, and Kalliopi Pazaitou-Panayiotou (2015) Pancreatic Neuroendocrine Tumors Presenting with Hypercalcitonemia. *AACE Clinical Case Reports: Autumn* 2015; **1(4)**: e269-e272. [DOI: 10.4158/EP14495.CR]
6. Xu B, Wang Y, Li X, Lin J. Nonfunctional pancreatic neuroendocrine tumor masked as anemia: A case report. *Medicine (Baltimore).* 2017; **96(27)**: e7441. [DOI: 10.1097/MD.0000000000007441]
7. Tremmel T, Holland-Cunz S, Günther P. Metastasized pancreatic neuroendocrine tumor in a teenage girl: a case report. *J Med Case Rep.* 2015; **9**: 230. Published 2015 Oct 5. [DOI: 10.1186/s13256-015-0708-3]
8. Modica R, Sarno AD, Colao A, Faggiano A. Pancreatic neuroendocrine tumor with hypoglycemia and elevated insulin-like growth factor II: a case report. *J Cancer Metastasis Treat* 2016; **2**: 345-347. [DOI: 10.20517/2394-4722.2016.44]
9. Masaya Muneke, Hiromichi Maeda, Tsutomu Namikawa, Takuhiro Kosaki, Atsushi Kigi, Makoto Hiroi, Michiya Kobayashi, Kazuhiro Ha nazaki, Neuroendocrine tumor within main pancreatic duct: a case report, *Annals of Cancer Research and Therapy*, 2017, Volume 25, Issue 2, Pages 63-66, Released September 26, 2017, Online ISSN 1880-5469, Print ISSN 1344-6835. [DOI: 10.4993/acrt.25.63]
10. Lybaert W, Van Hul E, Woestenborghs H: Long-Term Disease Control of a Pancreatic Neuroendocrine Tumor with Lanreotide Autogel®: A Case Report. *Case Rep Oncol* 2014; **7**: 673-680. [DOI: 10.1159/000368207]