CLINICAL VIGNETTE

Pancreatic Neuroendocrine Tumor Diagnosed on a Full Body MRI but Missed on CT Imaging

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Case

A 44-year-old female with meningioma s/p resection, Hashimoto's disease, pernicious anemia and recently diagnosed type-1 diabetes underwent a "preventative" full body MRI and was noted to have a pancreatic mass in the tail of her pancreas.

Ten weeks prior she had a telemedicine visit complaining of acute onset watery diarrhea, bloating, abdominal pain and intermittent loose stools for 9 days. She reported abdominal tenderness and completed an emergent CT scan which noted an unremarkable pancreas without explanation for the abdominal symptoms. Three weeks later the patient reported that her symptoms had resolved but recurred after eating a salad, and resolved with famotidine. She reported feeling well in a telehealth follow-up visit five weeks later. However, she reported feeling a bulging "hernia like" discomfort in her right lower quadrant. Patient had a hernia confirmed on ultrasound 9 years prior. She completed a full body MRI three days later which reported a pancreatic mass.

The patient contacted her primary care physician for follow up. Before receiving an official radiology report the primary care physician expedited a Magnetic Retrograde Cholangiopancreatogram (MRCP) with and without contrast that evening. The MRCP revealed an Ill-defined bulky T1 hypointense T2 hyperintense soft tissue thickening and diffusion restriction in the pancreatic tail, spanning 3.9 cm, predominantly isointense following contrast administration with mild hypovascularity on late venous phase. The radiologist noted the differential included pancreatic adenocarcinoma, confined to pancreas noting that a small percentage of pancreatic adenocarcinoma can be isointense following contrast administration. The radiologist noted once pancreatic adenocarcinoma is excluded, other benign entities including focal autoimmune pancreatitis or sequela of prior pancreatitis could be considered. Ectopic splenic tissue was considered less likely, as the lesions only follow the spleen on certain selected sequences. With the possible diagnosis of pancreatic adenocarcinoma, an endoscopic ultrasound with biopsy was emergently scheduled.

Three days later, the interventional gastroenterologist performed the endoscopic ultrasound (EUS). There was a bilobed well defined isoechoic lesion in the tail of the pancreas about 3 cm in size on cross sectional imaging, without evidence of invasion of any adjacent structures. The fine needle aspiration and biopsy using a 25g Acquire Core biopsy needle was performed. Preliminary cytology was adequate and final pathology confirmed a Pancreatic Neuroendocrine Tumor (PNET). The interventional gastroenterologist reported the remainder of the pancreas was without masses, cysts or parenchymal features of acute or chronic pancreatitis. Upon discovery of the pancreatic mass on the MRI the radiologist reviewed and re-read the prior CT scan. Upon further review in conjunction with the new MRI, there appears to be a subtle hypoenhancing 2.0 cm focus in the tail of the pancreas better appreciated on MRI which corresponded to the EUS findings. To determine staging and management while awaiting the official pathology results, the patient underwent positron emission tomogram (PET) CT imaging including, neck, chest, abdominal pelvis with dotatate contrast. The PET CT noted an intensely DOTATATE avid 3.9 cm mass within the pancreatic tail but without specific DOTATATE or CT evidence of metastatic disease.

Patient met with her endocrinologist to determine if she had a functional neuroendocrine tumor. Her Gastrin hormone level was slightly elevated at 229 pg/mL (0-100). She also had a history of pernicious anemia and the slightly elevated gastrin level was felt to be consistent with atrophic gastritis. Chromogranin A level was normal, as was her pancreatic polypeptide. The patient had a normal Vasoactive intestinal peptide (VIP) at less than 13 pg/mL (13-98.5), C-peptide of 0.8 ng/mL (N 0.3-3.3), and a normal Pancreatic polypeptide, and normal Glucagon level.

Eventually the official pathology report confirmed a Grade 1 pancreatic tail neuroendocrine tumor. Subsequently the patient underwent a distal pancreatectomy, splenectomy and resection of seventeen lymph nodes. The official pathology report noted a Grade 2, well-differentiated neuroendocrine tumor, with all margins negative for tumor. The spleen had no histopathologic abnormalities, and seventeen lymph nodes were negative for tumor. The oncologist recommended following the National Comprehensive Cancer Network (NCCN) for functionless PNET without metastasis. The consensus was for the patient to obtain surveillance DOTATATE PET CT at 6 months post-operatively and annually thereafter for 5 years.

Discussion

Neoplasms such as pancreatic neuroendocrine tumor (NETs) are rare tumors arising in the endocrine tissues of the pancreas. NETs can be functional, secreting different hormones but also nonfunctional secreting no hormones. A functional NET can secrete insulin, gastrin, glucagon, and vasoactive intestinal peptide which can lead to a variety of presenting symptoms. Our patient reported a variety of symptoms (diarrhea, bloating and abdominal pain) which could be present with a NET but was fortunate to have functionless NET.

Pancreatic neuroendocrine neoplasms (NENs) nomenclature and grading is based on the proliferative rate to determine histologic grade for pancreatic NENs. The American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) refer to well differentiated tumors as NET regardless of histologic grade. While pancreatic neuroendocrine carcinomas (NEC) are poorly differentiated tumors with a high proliferative rate. The grading of tumors is categorized as idle, well-differentiated tumors and aggressive. Well-differentiated Pancreatic NETs are further divided as being either low-grade (G1; Ki-67 index <3 percent) or intermediate-grade (G2; Ki-67 index 3 to 20 percent) categories according to proliferative rate. Our patient had what appeared to be a Grade-1 NET from the Endoscopic Ultrasound guided biopsy pathology, but surgical resection of the pancreatic tail mass noted a grade 2 well differentiated NET. Poorly differentiated carcinomas are high grade tumors (G3; Ki-67 index >20 percent).

Functionality also impacts how neuroendocrine tumors are classified. Our patient's neuroendocrine tumor was fortunately not functional. Insulinomas are insulin-producing pancreatic NET which often present with hypoglycemic episodes. Hypoglycemic episodes can include unusual behavior, tremors, and sweating. Gastrinomas are gastrin producing neuroendocrine tumors often associated with Zollinger-Ellison Syndrome, which often present with peptic ulcer disease. Other NET may secrete glucagon, somatostatin, and vasoactive intestinal polypeptide (VIP). Glucagonomas present with diabetes mellitus, weight loss, diarrhea and venous thrombosis. The VIPoma syndrome often has watery diarrhea, hypokalemia, and hypochlorhydria. The majority of patients with pancreatic NETs have a non-functioning tumor.[1] In non-functioning tumors we also check chromogranins and pancreatic polypeptide which were negative in our patient. The size of NET at diagnosis has decreased in the last 20 years. More pancreatic NETs are found incidentally, due to increased imaging.

Pancreatic NETs are rare, found in less than 3 percent of all primary pancreatic neoplasms.[2] Pancreatic NETs diagnosis is increasing due to increasing cross sectioning imaging and endoscopy, similar to our patient who underwent full body screening MRI.[3] Pancreatic NETs most often occur in the 4th to 6th decade of life as with our 44-year-old patient. While pancreatic NETs are found randomly they can be associated with genetic and hereditary conditions such multiple endocrine neoplasia I (MEN1), von Hippel-Lindau (VHL) syndrome, neurofibromatosis type I (NF1) and tuberous sclerosis.

The most common presenting symptoms of a nonfunctional NET are abdominal pain, weight loss and nausea which were all present in our patient. With increasing cross sectional abdominal imaging, incidental nonfunctional pancreatic NETs are often found while assessing other symptoms. When NETs are metastatic they often spread to the liver. Patients with biopsy proven Pancreatic NET should have cross-sectional imaging to determine the extent of metastases. Patients also need imaging with radiolabeled somatostatin analogs. Often gallium Ga-68 DOTATATE (68-Ga DOTATATE) positron emission tomography (PET)/CT is completed as in our patient.[4] Detecting primary pancreatic NETs on CT scan remains highly accurate with sensitivity greater than 80 percent.[5] Unfortunately our patient's tumor was not visualized on the CT scan, which can detect tumors as small as 4 mm, but with reduced sensitivity for tumors smaller than 2 cm. Our patient's MRCP detected a pancreatic mass of 3.9 cm which was confirmed to be 3 cm upon surgical resection. Radiology was asked to reread the prior CT imaging 10 weeks prior to MRCP and noted a 2 cm pancreatic mass. NETs are often enhancing vascular lesions but can be hypodense like our patient's isointense mass noted on MRCP.

Newer techniques of MRI sequencing have increased accuracy in detecting pancreatic NETs. MRI T1-weighted images display a low signal intensity and T-2 weighted images display a high signal intensity.[6] Our patient's MRI noted T1 hypointense T2 hyperintense soft tissue thickening and diffusion restriction in the pancreatic tail, spanning 3.9 cm. This was predominantly isointense following contrast administration with mild hypovascularity on late venous phase. Endoscopic ultrasound provides the best visualization of the pancreas, detecting lesions as small as 2-3 mm.

Post-surgical resection for nonfunctional NETs can be monitored checking peptides like chromogranin A (CgA) and pancreatic polypeptide (PP). These peptides are nonspecific and lack adequate sensitivity for routine monitoring nonfunctional pancreatic NETs. In patients with functional pancreatic NETs, checking insulin, glucagon, gastrin, and vasoactive intestinal polypeptide can correlate with tumor burden.[6]

Tumor staging is based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system using stages from the European Neuroendocrine Tumor Society (ENETS). The AJCC/UICC staging uses tumor, node, metastasis (TNM) classification.[7] Our patient had a 3 cm pancreatic NET with TNM staging of T2N0M0 as the 2 to 4 cm pancreatic NET was limited to the pancreas without lymph nodes involvement or distant metastasis.

Surgical resection of pancreatic NETs is recommended for both functional and nonfunctional cases, as resection is the only cure.[8] Resection of functional Pancreatic NET will eliminate hormone overproduction. For patients with nonfunctional

Pancreatic NET tumor removal will avoid compressive symptoms. The hope is that resection of the pancreatic NET will decrease risk of malignancy or metastases. North American Neuroendocrine Tumor Society (NANETS) advises nonfunctional Pancreatic NETs smaller than 1 cm can be observed. Tumors between 1 and 2 cm can undergo surgery based on patient preference.[9] Both 2016 European Neuroendocrine Tumor Society (ENETS) guidelines and consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) recommend very close observation for nonfunctional pancreatic NETs smaller than 2 cm.[10] Individual patients with a nonfunctional tumor smaller than 2 cm may not want to undergo surgery based on the risk involved with a major pancreatic resection. Most patients with a functional or nonfunctional pancreatic NET undergo surgical resection of the mass with the appropriate lymphadenectomy. Pancreaticoduodenectomy is recommended for patients with pancreatic NETs in the head, uncinate or neck of pancreas. Distal pancreatectomy is recommended for patients with masses in the body or tail of pancreas. Distal pancreatectomy will often require a splenectomy.

Surveillance guidelines post pancreatic NET resection vary by organization. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend cross sectional imaging with a somatostatin receptor-based imaging like Dotatate scanning 4 to 12 months after initial resection to assess if a new lesion is present and checking functional hormone levels. Repeat assessments are advised every 6 to 12 months for a maximum of 10 years.[11] Our patient was advised to obtain surveillance DOTATATE PET CT at 6 months postoperatively and annually thereafter for 5 years.

Conclusion

Pancreatic neuroendocrine tumors are a rare subset of all primary pancreatic neoplasms. Advancements in imaging including higher fidelity techniques of MRI and CT studies and introduction of radiolabeling have improved our ability to detect these rare tumors at an early stage. While NETs are largely nonfunctional, they still represent a heterogeneous group of tumors with risks of malignancy. Treatment should be carefully considered with a multidisciplinary team. We hope this patient helps to clarify management of neuroendocrine tumors.

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