

PANCREATIC NEUROENDOCRINE TUMOR (PANNET) PRESENTING WITH A CONCOMITANT AMPULLA OF VATER ABNORMALITY ON ENDOSCOPY

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ABSTRACT

Pancreatic neuroendocrine tumors (PanNETs) are a rare neoplasm, and it is even more uncommon for them to present with lesions in the ampulla of Vater. As a result, case reports detailing this phenomenon are sparse. Here we present a case of a confirmed PanNET along with the corresponding imaging of an ampullary abnormality seen on esophagogastroduodenoscopy, and further discuss the details of the case including approach to ampullary lesions, along with the pathologic characteristics of PanNETs and their management.

KEYWORDS: pancreatic neuroendocrine tumor, ampulla of Vater, ampulla lesion, adenocarcinoma, adenoma.

BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are a rare type of cancer, accounting for only 1 to 2 percent of pancreatic neoplasms.^[1] They can be categorized as non-functioning or functioning, such as in the case of insulinomas, glucagonomas, or VIPomas where there is active secretion of a hormone. A grading system has been developed by the World Health Organization (WHO) which uses the Ki-67 proliferation index and the mitotic index to appropriately classify pancreatic neuroendocrine tumors.^[2] Ki-67 is a marker of tumor proliferation found to have prognostic value in PanNETs.^[3]

The presentation of ampullary lesions (typically reported as ampullary adenocarcinoma) in addition to the presence of a PanNET is extremely rare with few reported cases.^[4,5] These cases are typically associated with biliary obstruction. The following case discusses a patient who presented with acute pancreatitis, was found to have an ampullary abnormality on endoscopy without biliary obstruction and was subsequently diagnosed with a PanNET after undergoing biopsy of the pancreatic head.

CASE REPORT

A 77-year-old Asian male presented to the emergency room with worsening abdominal pain for two weeks. He

described the pain as a fullness sensation in the epigastric region that worsened with movement. He denied nausea or vomiting but noted bloating and constipation. He last had a colonoscopy six years ago which he reported was normal and denied having a prior esophagogastroduodenoscopy (EGD). Additional medical history included two strokes, type 2 diabetes mellitus, hypertension, and hyperlipidemia. The patient denied a history of alcohol use, cholecystectomy, or gallstones. The patient reported taking clopidogrel and aspirin due to his history of stroke and took these medications one day prior to presentation. The patient's initial lipase level was 26962 IU/L. The remainder of the initial labs were normal (Table 1). A computed tomography (CT) scan of the abdomen and pelvis with intravenous (IV) contrast (Figure 1) was performed and showed mild peripancreatic inflammation with associated pancreatic and common bile duct (CBD) dilatation consistent with acute interstitial edematous pancreatitis possibly due to obstruction of the CBD and/or ampulla. This was suspected to be due to a periampullary mass, or CBD stone or stricture. The patient was treated with supportive measures including IV fluids, antiemetics, and opioids for pain control.

Table 1: Initial serum laboratory testing.

Lab	Result	Reference Range
Hemoglobin	9.3 gm/dl	14-18 gm/dl
Platelets	322 x10 ³ uL	15-450
White Blood Cells	7.4 x10 ³ uL	4.8-10.8
Triglycerides	90 mg/dL	≤ 200 mg/dL
Total Bilirubin	0.5 mg/dL	0.1-1.0 mg/dL
Direct Bilirubin	0.4 mg/dL	0-0.7 mg/dL
Indirect Bilirubin	0.1 mg/dL	0.1-0.2 mg/dL
AST	25 IU/L	15-37 IU/L
ALT	27 IU/L	12-78 IU/L
ALP	99 IU/L	45-117 IU/L

**Figure 1: CT of the abdomen and pelvis with IV contrast.**

Magnetic resonance cholangiopancreatography (MRCP) of the abdomen (Figure 2) was obtained and confirmed pancreatitis with a CBD measuring 11 mm proximally and 6 mm in the midportion with tapering towards the ampulla. There was mild to moderate intra and extrahepatic biliary ductal dilatation and a mildly enlarged peripancreatic lymph node measuring 1.3 by 1.6 cm. An ultrasound of the abdomen was also obtained to evaluate for cholelithiasis and negative. The patient underwent EGD after a five-day washout period for clopidogrel, and it was notable for an ulcerated lesion adjacent to the ampulla (Figures 3-4). The lesion was not biopsied due to its friable appearance and concern for bleeding given recent clopidogrel use. Portal hypertensive gastropathy was also noted, however the remainder of the procedure yielded normal endoscopic findings. The patient then underwent endoscopic ultrasound (EUS) with fine needle aspiration (FNA) which was significant for dilated intrahepatic ducts, a severely inflamed ampulla, a diffusely heterogeneous pancreas, CBD measuring 6 mm, pancreatic duct measuring 5 mm, an enlarged peripancreatic lymph node measuring 12 x 15 mm, and an anechoic lesion consistent with a pseudocyst measuring 40 x 37 mm in

the pancreatic tail. FNA of the pancreatic head was performed and biopsy returned positive for pancreatic neuroendocrine tumor. Biopsy staining was positive for synaptophysin (Syn), chromogranin A (CgA), pancytokeratin, and CD56. The Ki-67 index was greater than 20%, indicating a high-grade neuroendocrine tumor.

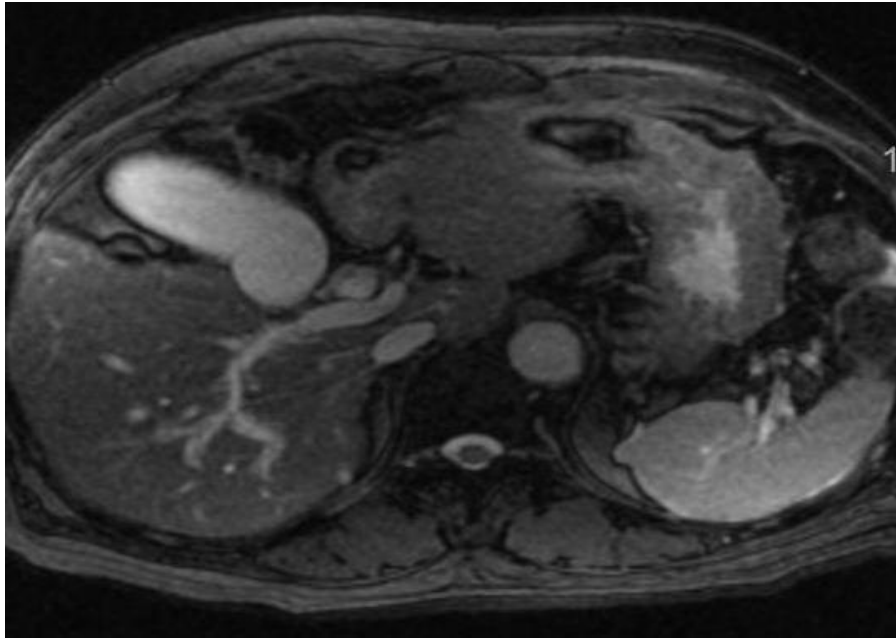


Figure 2: MRCP of the abdomen.



a



b

Figure 3: a and 3b. Different vantage points of the ampullary lesion seen on EGD.

DISCUSSION

The majority of ampulla lesions are either adenomas or adenocarcinomas.^[6] The American Gastroenterological Association (AGA) has specific recommendations regarding ampullary lesions and advises performing biopsy of ampullary lesions if malignancy is suspected, or endoscopic papillectomy if the lesion is less than 2 centimeters in size. Imaging with EUS, MRCP, or CT is recommended in situations where these criteria are not met.^[7] It is suspected the lesion in our case was either ampullary adenocarcinoma, or possibly residual inflammation of the ampulla itself. The absence of biliary obstruction as indicated by normal LFTs and bilirubin levels points to the latter, however without biopsy this cannot be definitively confirmed. As previously mentioned, the lesion was not biopsied due to its friable appearance, concern for bleeding, and the patient having active pancreatitis. The ampulla also

appeared severely inflamed on EUS, therefore it was recommended that the patient return in six to eight weeks for a repeat EUS and biopsy.

The biopsy of the pancreatic head was notable for scattered discohesive cells with a high nucleus to cytoplasm ratio, which is characteristic of an aggressive PanNET.^[8] Immunohistochemical analysis returned positive for the following markers: synaptophysin (Syn), chromogranin A (CgA), pan-cytokeratin, and CD56. Synaptophysin is a marker found in the synaptic vesicles of neuroendocrine cells, while chromogranin A is associated with neuroendocrine secretory granules for multiple pancreatic hormones.^[9] PanNETs are associated with high positivity rates for both Syn and CgA on immunohistochemical staining.^[10] It is important to note that CgA levels in the serum are also used as a diagnostic marker for PanNETs, although this topic remains somewhat controversial due to concerns for its accuracy

particularly with insulinomas. The serum CgA level was not obtained in our case, therefore we will not expand on this discussion. Positive staining for pan-cytokeratin is also associated with neuroendocrine tumors, with a recent study finding an 83% positivity rate.^[11] CD56, a neural cell adhesion molecule, is a marker of severe pancreatic inflammation and can be associated with degeneration of pancreatic tissue, and a recent study has found it to be useful in predicting organ invasion and grading of PanNETs.^[12,13]

The Ki-67 index from the biopsy of the pancreatic head in our case was found to be greater than 20%. Ki-67 is a protein maker of cell proliferation and is present throughout all active phases of the cell cycle. Its primary utility is through the calculation of an “index” whereby the percentage of positive cells is calculated and its significance is determined by a certain threshold. In the case of PanNETs, the WHO has developed a grading system which utilizes the Ki-67 index with an index of 2% or less corresponding to grade 1, an index between 3% and 20% corresponding to grade 2, and an index greater than 20% corresponding to grade 3.^[2] A potential pitfall of using Ki-67 is there are various methods for pathologists to calculate the index, and this can lead to inaccuracies or inconsistencies which may impact treatment decisions.^[14,15]

The patient presented with severe pancreatitis, although the exact etiology is not confirmed, it is possible the pancreatitis may have been caused by the PanNET. The patient denied history of alcoholism or current alcohol use, and there was no evidence on imaging consistent with gallstones. Several cases of acute pancreatitis secondary to a PanNET have been reported, and this must be considered in our case given the absence of other identifiable causes.^[16,17]

PanNETs are classified into functional or non-functional. A functional PanNET must include a clinical syndrome (i.e., hypoglycemia with an insulinoma), and our patient did not demonstrate any discernible clinical symptoms consistent with a functional PanNET. The proper treatment approach can be established once the functional status of the PanNET is determined and if metastatic disease (typically to the liver) is present, however surgery; distal pancreatectomy for distal pancreatic involvement or pancreatoduodenectomy with regional lymph node dissection for pancreatic head involvement is recommended in nearly all situations.^[18-20] The treatment for non-functional PanNETs is contingent upon size as surgery is recommended if it is greater than 2 centimeters. If it is less than 2 centimeters, observation can be considered depending on location and if the PanNET was an incidental finding, however surgery or enucleation are still usually recommended.^[20] Treatment for functional PanNETs without metastases involve a dual approach with surgery and medical management with somatostatin analogues, and/or the appropriate supportive measures such as proton-pump

inhibitor for gastromas or hyperglycemic management for glucagonomas. In cases where metastatic disease is present, management largely depends on the extent of disease burden. Surgery can be considered if resection of the metastatic lesions are in an anatomically viable location, however it is not an option when there is a high disease burden. In this situation, chemotherapy and/or molecular-targeted therapy with drugs such as everolimus (an mTOR inhibitor) or sunitinib (a VEGF inhibitor) can be considered.^[18]

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