A Case of Malignant Ampullary Ulceration

Eskarous, Hany MD [1]; Iskander, Peter MD [1]; Daniel, Mina MD [1]; Sajid, Khadijah MD [1]; Farah, Kanith MD [2]; Aman, Ali MD [3]

1. The Wright Center for GME, Scranton, PA, 18505
2. J.W. Ruby Memorial Hospital, Morgantown, WV 26506
3. Wilkes-Barre General Hospital, Wilkes-Barre, PA, 18764

Abstract:

Ampullary carcinomas, as the name suggests, are rare tumors that are associated with the ampulla of Vater. Due to their location, symptoms may arise relatively faster than other similar malignancies. Because of this, they can typically be identified sooner, yielding better prognosis and survival outcomes. They are diagnosed via pathology; usually from biopsies obtained while performing EUS/ERCP. Management revolves around resection if able to, or chemo/radiation if deemed unresectable or evidence of metastasis is noted. We present a case of a female presenting with abdominal pain associated with jaundice and scleral icterus. The endoscopic evaluation noted ampullary ulceration with biopsies proven to be notable for moderately differentiated adenocarcinoma.

Introduction:

Papillary or ampullary carcinomas (ACs) are malignant tumors in the mucosa of the major duodenal papilla region, also known as the ampulla of Vater. ACs are rare, comprising only about 0.2% of gastrointestinal cancers [1,2]. It's reported that 90% of patient cases diagnosed are predominantly found in Caucasian males [1]. Due to the increasing usage of upper endoscopy for unrelated symptoms and screening of patients with familial adenomatous polyposis, it has been shown that there has been a significant increase in incidence rates of ACs in Western countries over the last few decades [2]. Due to the complexity of the ampulla's anatomy, pancreatic, duodenal, and common bile duct (CBD) tumors are often misdiagnosed as ampullary tumors [3]. Because of the location of ACs, characteristic symptoms such as jaundice and pain usually occur earlier when compared to other conditions, such as pancreatic cancers [4]. ACs generally have a better prognosis due to earlier detection, with a 5-year survival rate of 45% in patients undergoing resection [4]. Two main histological subtypes can be identified in ampullary cancers: intestinal and pancreaticobiliary [5–7]. Intestinal ampullary adenocarcinomas originate in the intestinal epithelium coating the ampulla, while pancreaticobiliary ampullary carcinomas originate in the epithelium of the distal CBD and pancreatic duct [7]. Pancreaticoduodenectomy is the mainstay of management and is usually followed by adjuvant chemo or chemo-radiation therapy [1,7].

Clinical Course:

A 33-year-old female with a past medical history of cesarean section presented to the hospital for episodes of light stool, dark urine, and abdominal pain. On exam, she was noted to have abdominal discomfort to palpation, jaundice, and scleral icterus. She was made NPO, started on IV fluids, and was given medication for pain and nausea. Labs were significant for elevated bilirubin and liver enzymes (Table 1). Gastroenterology (GI) was consulted, and she underwent Endoscopic Ultrasound (EUS) and Endoscopic retrograde cholangiopancreatography (ERCP) to evaluate her further for imaging significant

for dilated gallbladder (GB). She was found to have ampullary ulceration, for which biopsy was notable for adenocarcinoma on pathology (imaging, procedure details, and pathology findings to follow) (Figures 1-3). Her liver function tests were noted to increase post-procedure, but per the GI team, this was to be expected. The patient tolerated the procedure well and was advanced to a low-fat diet. She was discharged later in stable condition with recommendations for stent removal and repeat lab work to follow up on LFTs.

Table 1: Table depicting lab values resulting over hospital stay, with day 1 being the day of admission and day 2 being the day of discharge. The procedure occurred on day 6.

Marker	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
ALP	640	516	551	612			723
ALT	85	64	69	81			114
AST	112	85	96	103			98
Direct bilirubin			2.8				
Total bilirubin	6.7	4.8	4.6	5.1			4.79
WBC	8.1	11.2		10		6.8	7.7
Hgb	13	10.7		11.2		10.6	10.5
Hct	38.6	31.2		33.2		31.7	31.8

Imaging:

US of the abdomen:

GB distension with moderate hypoechoic sludge, an 8mm soft tissue echogenicity consistent with polyp, and mild GB wall thickening (up to 4.7mm) with some pericholecystic edema.

MRCP:

Marked intra/extrahepatic biliary ductal dilation. CBD measuring up to 3.2cm, tapering to 1.2 cm distally, proximal to the ampulla of Vater. GB distension, mild wall thickening/edema, sludge, and edema.

Procedures:

EGD:

Hill Class III hiatal hernia.

EUS:
Moderate intra-hepatic biliary dilation, a massively dilated CBD measuring 35.5 mm proximally and 21.5 mm distally, and a small amount of sludge noted in the bile duct. No stones were seen.

ERCP:
The ampulla was noted to be ulcerated with a significantly dilated intraduodenal portion of the CBD, which is massively dilated. A careful biliary sphincterotomy was carried out with no complications. No obvious stones were seen; balloon sweeps yielded only sludge. The ampullary orifice appeared to be ulcerated. It was unclear whether this was secondary to an impacted stone causing ulceration (due to obstruction) or a small ampullary carcinoma. Aggressive biopsies of the ulcerated ampullary area were taken to rule out cancer, mainly focusing on the biliary orifice. This was followed by placing 10 French 12 cm plastic stents in the bile duct.

Pathology:
Markedly atypical glands associated with inflammation and fibrosis. Immunohistochemical stains for pan-cytokeratin, CK7, and CEA were positive with a high Ki-67. Negative for CDX2, P53, CK20, and CA 19-9. Reports verified a superficially invasive and moderately differentiated adenocarcinoma with marked ulceration. Background adenoma with high-grade dysplasia was noted.

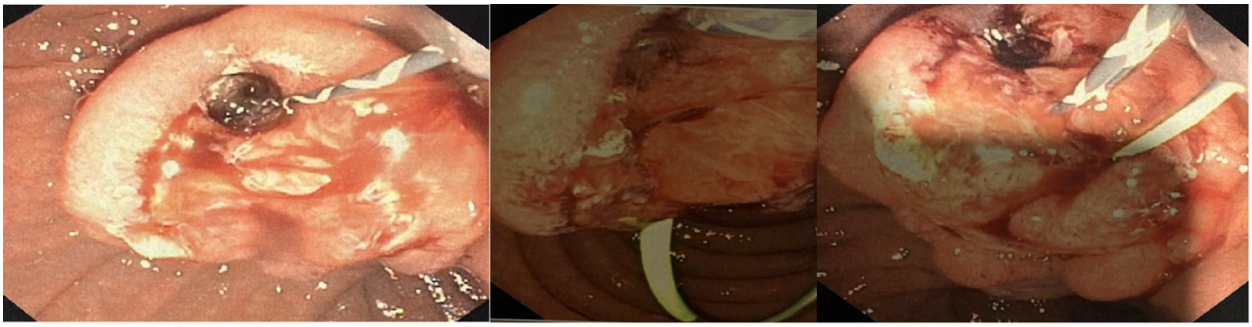

Figure 1: Endoscopic imaging revealing ulceration noted within the ampulla of Vater.

Discussion:

Several cancers exist in and around the ampulla, such as pancreatic ductal adenocarcinomas (PDACs), cancers of the duodenum, and ACs [1]. Ampullary or papillary carcinomas are tumors originating from the mucosa (epithelium) located in the major duodenal papilla, a complex area of bile and pancreatic ducts. This rare cancer comprises only 0.6-0.8% of digestive cancers, while it accounts for about 6-17% of periampullary carcinomas (PACs). Literature supports a slightly higher occurrence of ACs among men than women. The incidence rate of adenocarcinoma increases with age, and the highest rate is seen among people above 50 years of age. More specifically, based on the Surveillance, Epidemiology, and End Results (SEER) database, in the USA, the median age at diagnosis is 65 years, with a slight preference for males [8–11].

The majority of ACs consist of adenocarcinomas, with two main histologic subtypes described according to their epithelium of origin: intestinal- and pancreaticobiliary-associated ACs [12]. The occurrence of the intestinal subtype is often associated with the growth pattern of duodenal adenoma. It appears

suspicious for colon cancer, unlike the pancreaticobiliary subtype, which is prevalent in pancreatic tumors and cholangiocarcinoma.

If histomorphology is used exclusively, it may not be able to differentiate tumor entities, so further immunohistochemical markers can be stained. This is where the intestinal form, in most cases, has CDX2 and CK20 markers for colon cancers. In contrast, the pancreaticobiliary form tends to have markers typical for cholangiocarcinoma and pancreatic cancer, such as CK7, as seen with our patient [9]. Pancreaticobiliary abnormalities were primarily observed in the KRAS and TP53 genes [9,11,13], and the most apparent mutations in the APC gene were observed in the intestinal type.
Several histological classifications of ACs have evolved based on their microscopic appearance and growth pattern from the intestinal side or tumor extension.

Three distinct categories of carcinomas are recognized after the correlation of gross and microscopic features: (1) intra-ampullary neoplasms, wherein the growth preinvasive neoplasms are mainly intraluminal, commonly including the neoplasm that protrudes into the duodenal lumen from patulous orifices of the papilla of Vater; (2) peri-ampullary, which often manifest as vegetating, ulcerous components originating on the Identification: ulcerating part correlates with the invasive phase, meanwhile vegetating part corresponds with the preinvasive phase; and (3) mixed exophytic and mixed ulcerated lesions. The fact is that ulcerating tumors are usually found on tumors that have associated poor survival rates [14].

ACs usually present symptoms and signs frequently observed in extrahepatic cholangiocarcinoma and pancreatic adenocarcinoma: jaundice, diarrhea, steatorrhea, and gastrointestinal bleeding with melena appear to be frequent. This malignancy can be diagnosed early due to these symptoms, as they can appear earlier than other similar cancers. EUS, ERCP, and FNAC are the preferred techniques for AC diagnosis, while CT of the chest, abdomen, and pelvis stand out as essential staging tests. Endoscopic pulpectomy is the primary diagnostic tool and may be curative in some exceptional cases—for instance, early AC, in situ carcinoma, or low-grade dysplasia [10,13].

Typically, noninvasive ACs are asymptomatic and are discovered incidentally during EGD for some other indications. Some patients present with different symptoms, such as jaundice, abdominal pain, diarrhea, pancreatitis, cholangitis, steatorrhea, and melaena, which add up to the differential diagnosis with choledocholithiasis, extrahepatic cholangiocarcinoma, and pancreatic adenocarcinoma [13].

Ampullary cancer manifests mainly as obstructive jaundice, a symptom that accounts for about 85% of the cases because the tumor compresses the biliary duct of the distal portion of the organ. However, in carcinomas, jaundice would rather be persistent though not intermittent, making it very possible for the abdomen to become palpably engorged (Courvoisier's sign), although it is an uncommon event (it accounts for only 15% of the cases. A gallstone case is a constituent in a third of patients, making the diagnosis problematic [14].

Many patients also experience symptoms such as significant weight loss, fatigue, and abdominal discomfort. Acute pancreatitis, as compared to ampullary cancer, is less common; however, the two should not be ranked compared to this case. The rate of bleeding may lie between mild to severe, with

as many as one-third of the patients being unable to emit any gastrointestinal blood until the time they bleed heavily. Sometimes, large lesions can impede the outlet of the belly, which may lead to gastric outlet obstruction [14].

In terms of differential diagnosis, the most crucial consideration is the distinction between primary ACs, pancreatic cancers, distal cholangiocarcinoma, and small bowel cancers. However, FNAC also faces issues distinguishing ACs from other PACs; therefore, a surgical biopsy is often necessary to make realistic conclusions [12]. Unlike other periampullary cancers, true ampullary cancers start presenting earlier with biliary obstruction symptoms [10,13].

Although patients with an oncological ampullary adenoma can be managed conservatively with endoscopic therapy, the oncological presence of a localized carcinoma requires oncologic pancreatoduodenectomy resection. Nevertheless, the significant recurrence rate has prompted multimodal therapy to be the first choice in many patients [9].

Extensive surgical resection with lymphadenectomy forms the basis of treatment for AC, and pancreaticoduodenectomy (PD) equals the current modality for operations against cancer, with 50% of cases believed to be possible at wider resection [9].

One of the main issues in the procedure is the nodes' high rate (not less than 30–40%) involvement, especially those located in the vicinity of the superior mesenteric artery and the pancreaticoduodenal area. This significantly indicates the pivotal role of proper and adequate lymphadenectomy for both lymph node dissection and the reckoning of at least 12. First-line therapy in AC is surgery followed by extended oncological resection of the head of the pancreas with lymphadenectomy taken systematically [9].

This operation involves the removal of the GB together with the transverse section of the CBD immediately cranially off the bifurcating cystic duct originating from the duodenum, the first jejunal loop after the ligament of the Treitz, and the pancreatic head. This is performed as an en bloc resection [9]. Regional lymph nodes of the hepatoduodenal ligament, superior margin of pancreaticoduodenal part, to the celiac trunk, and in the triangle between the portal vein and splenic/lienal artery and splenic/lienal vein make up the resectate [9]. It is not easy to differentiate between primary ampullary and other periampullary cancers by anatomic site by preoperative imaging. In the beginning, ampullary cancers are surgically treated, just like pancreatic cancers. They are usually eliminated using a Whipple procedure, which involves removing the duodenum and pancreas.

The management of unresectable and metastatic disease is mainly chemotherapy comprising fluoropyrimidine, gemcitabine, and a platinum compound (usually cisplatin or oxaliplatin) [13]. Even if performing radical surgery is extremely challenging for early-stage AC, the recurrence rate is still about 50%. On this basis, i.e., a class of cancer treatment techniques like chemotherapy, radiation therapy, or chemoradiation has been compared over time in certain studies.

In addition, the histological subtype is considered when imparting an adjuvant and first-line treatment. Hence, ACs that are pancreaticobiliary-like are treated as pancreatic adenocarcinoma and occasionally biliary tract cancer [12]. The historical approach indicates a poor prognosis, even at the resectable stage,

and raises questions about possible further improvement in the metabolic course by chemotherapy administration, 5-FU, or gemcitabine [9].

The current evidence points out that subtypes of resectional parts affect the biological behavior and, thus, the patient's response. Accordingly, jaundice is a harbinger of the advanced stages of the disease and the accumulation of the disease in the tissues, interfering with their function [8]. Hence, it is very instrumental in avoiding and improving the effectiveness of this condition.

Recurrence can be regionally adjacent to the excision site (involves the tumor bed, para-aortic lymphatics, or any distant site). Often enough, the lymph nodes perivisceral are involved. In these cases, the disease progression tends to remain localized in the region. The spreading of AC generally follows a halsteadian progression: it usually originates in the nodes, which undergo the first changes, and the liver becomes affected. Metastases proceed to other organs [14].

The general survival rate at 5 years is randomly indicated from one source to another, slightly from 32% to 67.7%. A favorable result or not is associated with the allocation of lymph nodes, the degradation of cellular elements, and the invasion of the pancreas into resectable patients [14]. From all those, AC offers a better prognosis in comparison to pancreatic and bile duct adenocarcinoma, because of their early presentation, the resection rate is high as compared to other periampullary carcinomas [8,13]. When it comes to surgical treatment (e.g., pancreatoduodenectomy), there is a uniform approach irrespective of whether it is ampullary adenocarcinoma or pancreatic cancer adenocarcinoma. However, the long-term outcomes among periampullary adenocarcinomas can be markedly different [13].
More than 80% of ampullary cancers, with also good 5-year survival, ranging from 30% to as high as 50%, are being resected, which is far better than the rates of resection and survival seen in bile duct cancers and pancreatic cancer. Nevertheless, though pancreatic tumors are more resectable compared to ampullary adenocarcinomas, only a few patients with AC that have been resected live longer [13]. After curative resection, nodal status is one of the strongest predictors of survival: on the other hand, in one series performed, pancreaticoduodenectomy with the negative paternosc's zone showed a survival rate of 80% of patients after 5 years, whereas with positive nodes, only 25% of patients were alive for 5 years [14].

Conclusion:

AC presents as a rare but significant malignancy of periampullary cancers. Despite advancements in diagnostic modalities, including endoscopic and radiological techniques, definitive diagnosis often necessitates histopathological examination. Surgical resection, particularly pancreatoduodenectomy, remains the cornerstone of treatment, offering the best chance of cure. However, the high recurrence rate underscores the importance of multimodal therapeutic approaches. Prognosis varies based on histological subtype, nodal involvement, and resection margins. ACs generally have a better prognosis than pancreatic and bile duct adenocarcinomas.
While challenges persist in managing AC, advancements in understanding its biology and refining therapeutic strategies offer hope for improved outcomes, underscoring the need for multidisciplinary approaches tailored to individual patients.

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