QUESTION 23

A 68-Year-Old Man Develops Painless Jaundice. Endoscopic Retrograde Cholangiopancreatography Demonstrates a Large Ampullary Mass. Biopsies Demonstrate Adenocarcinoma. How Should This Patient Be Managed?

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Ampullary and pancreatic cancers originate in close proximity, but they are distinctly different disorders. The ampulla of Vater is a complex junctional structure uniting the common bile duct and ventral pancreatic duct to the duodenal lumen. It is often referred to as the major papilla and encompasses the sphincter of Oddi, the muscle complex encircling the distal portion of these ducts and a shared common channel. Ampullary cancer originates within this complex structure and, as a result, may have an intestinal or pancreatico-biliary histology depending on the site of origin (papillary or intra-ampullary [Figure 23-1]).[1] Ampullary carcinoma should not be confused with peri-ampullary cancers, which may arise from the distal common bile duct, pancreas, or adjacent duodenal mucosa. In advanced stages, peri-ampullary cancers may have overgrown the ampulla, making their site of origin difficult to determine.

The ampulla of Vater is the most common site of cancer originating in the small bowel. Additionally, the risk of ampullary cancer is increased by various polyposis syndromes, including familial adenomatous polyposis syndrome and hereditary non-polyposis colorectal cancer. Despite these facts, ampullary cancer is a relatively rare malignancy, accounting for approximately four to six cases per million population and approximately 0.2% of all

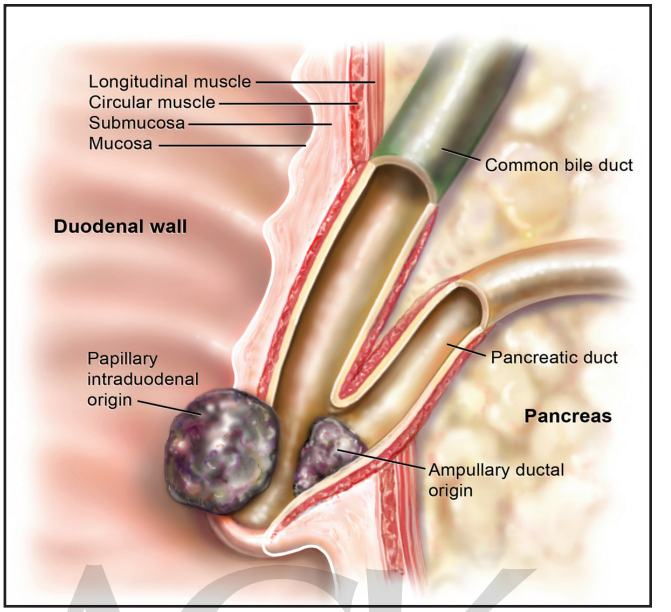

Figure 23-1A. Diagram of sites of origin in ampullary cancer demonstrating papillary cancer arising from duodenal side of ampulla or cancer rising from the intra-ampullary portion of the papilla. (Reprinted with permission from Randal S. McKenzie, AMA, AMCI.)

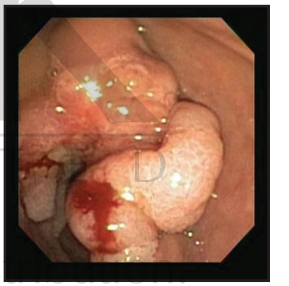

Figure 23-1B. Endoscopic photo of ampullary cancer visible from the duodenum.

gastrointestinal tract malignacies.[2] A review of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program found 5625 cases of ampullary cancer between 1973 and 2005; for unclear reasons, the frequency of the disease has been increasing since 1973.[3] In contrast, pancreas cancer is more common and is the fourth leading cause of cancer death in the United States. In 2009, approximately 42,470 new cases of pancreas cancer were diagnosed, and approximately 35,240 pancreatic cancer-related deaths occurred.[4] Although these disorders are often confused, ampullary and pancreatic cancers differ with regard to presentation, molecular characteristics, prognosis, and therapeutic options.

Clinical Presentation

Patients with ampullary cancer most commonly present with obstructive jaundice due to compression and/or obstruction of the distal bile duct by the tumor. Because of this anatomic origin, jaundice occurs early in ampullary carcinoma and generally when curative interventions are still attainable. Other presenting symptoms of ampullary cancer may include diarrhea due to fat malabsorption (steatorrhea), weight loss, and fatigue.

Up to one-third of patients with ampullary cancer may present with chronic, occult gastrointestinal blood loss with an associated microcytic anemia and/or heme-positive stools. An unusual but pathognomic sign of ampullary cancer is the passage of silver stool known as Thomas's sign (acholic stools mixed with blood will turn a silver color).[5]

Similar to ampullary cancer, pancreatic cancer may present with obstructive jaundice. However, this occurs if the tumor arises from the head of the pancreas and obstructs the intra-pancreatic portion of the common bile duct. Additionally, pancreas cancer may present with epigastric pain, weight loss, digestive problems, enlarged gallbladder (Courvoisier's sign), thrombo-embolic events, and diabetes. Although these symptoms lead to detailed evaluations, their presentation differs from that of ampullary cancer in that they usually occur at points when curative interventions are unattainable.

Prognosis and Molecular Characteristics

According to the American Cancer Society, the 1-year relative survival rate for all pancreatic cancer stages combined is 20%, and the 5-year relative survival rate is 4%.[4] These low rates are mainly due to the fact that, at the time of diagnosis, less than 10% of tumors are confined to the pancreas. The cancer has already spread, and in the majority of cases, it has progressed to the point where surgery is no longer a viable treatment option. In contrast, data show that patients with ampullary cancer have consistently better survival rates.[1,3,6-8] The obvious explanation for this difference is that ampullary cancers are detected relatively early due to the appearance of jaundice and thus have a more favorable prognosis. There is also evidence to suggest that ampullary cancers are less aggressive than pancreatic cancers, which may be due to molecular differences between these cancers that favor better survival rates for ampullary cancer.[1,8] Data show that ampullary cancers, particularly intestinal type, have a lower incidence of epidermal growth factor receptor (EGFR) and mutant p53 over-expression and fewer activating K-ras mutations. This may contribute to the relatively favorable prognosis of ampullary cancer compared to pancreatic cancer, even in node-positive disease. Additionally, studies have shown that while p53 over-expression does occur in ampullary carcinomas, its presence is rare in precursor ampullary adenomas supporting a genetic alteration model of adenoma to carcinoma sequence similar to colorectal cancer as opposed to pancreatic cancer.[1,8]

Therapeutic Options

The surgical intervention for resectable ampullary cancers and certain pancreas cancers (those arising from the head of the pancreas) is a pancreaticoduodenectomy (Whipple's procedure). For premalignant ampullary adenomas, endoscopic or transduodenal resection should be considered, and a Whipple's procedure should be avoided if possible. The staging of ampullary cancers is performed by the combination of computerized tomography (CT), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). These imaging modalities are also important in determining the endoscopic resectability of a premalignant ampullary adenoma. Ampullary carcinomas and advanced adenomas with ductal extension are better served with a Whipple's procedure due to higher rates of incomplete resection and recurrence (Figures 23-2 and 23-3).[9] Endoscopic removal, in general, should not be attempted in patients with ampullary cancer.

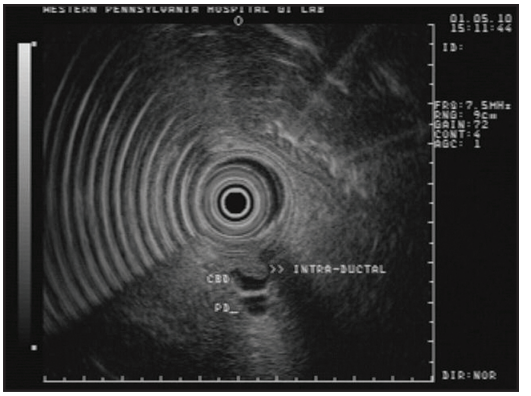

Figure 23-2. EUS of an ampullary cancer with extension into the common bile duct. (Reprinted with permission from Manish Dhawan, MD, Western Pennsylvania Hospital.)

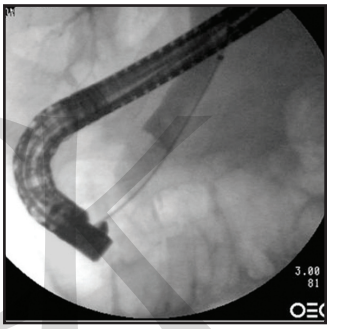

Figure 23-3. Cholangiogram showing intraductal extension of ampullary cancer manifesting as a distal filling defect in the common bile duct.

As with ampullary cancers, CT, EUS, and ERCP also play important roles in pancreas cancer. ERCP with metal biliary stenting can be therapeutic in patients with obstructive jaundice requiring neoadjuvant therapy or palliation. ERCP may also be diagnostic in cases where CT scan fails to reveal a pancreas mass and EUS is not available. Stenting of the injected duct should be performed at the time of ERCP in such circumstance. CT scan and EUS are complimentary technologies that allow for improved diagnostic accuracy and staging of pancreatic cancer. Such accuracy is essential in determining which patient would be best suited for surgical intervention with or without neoadjuvant therapy and those that should be treated palliatively.

In the current vignette of the 68-year-old man with painless jaundice, duodenoscopy with biopsy at the time of ERCP was diagnostic in determining the etiology of jaundice. Both a CT scan and EUS should be performed to accurately stage the ampullary cancer. If deemed resectable, curative resection in the form of a Whipple's procedure should be attempted provided the patient is medically clear for the surgery. Depending on the stage, adjuvant chemotherapy may be necessary.

With regards to drainage, permanent, self expanding metal stents should be placed in unresectable disease provided the biliary orifice can be identified and accessed. The role of preoperative biliary stenting in resectable ampullary cancer has not been widely studied. As such, pre-operative endoscopically-placed biliary stents may be dependent on several factors including surgical preference, whether patients are symptomatic with cholangitis or pruritis, or if a cholangiogram is performed at the time of ERCP.

Clinical Significance

While ampullary and pancreatic cancers are often associated and confused, there distinction as described is critically important as treatment is dependent on appropriate diagnosis and staging. Behavioral characteristics highlight the differences with improved outcomes in patients with ampullary cancer. However, with the introduction of neoadjuvant therapy coupled with surgery in high-volume centers, survival in pancreas cancer is being optimized.

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