CLINICAL VIGNETTE

Ampullary Adenocarcinoma: A Case of Mistaken Identity

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Case

A 75-year-old man presented to the Emergency Department with two months of hematuria, melena and jaundice. PMHx included diabetes, hypertension, hypercholesterolemia, and fatty liver. He also reported a 20 pound weight loss. Laboratory studies raised concerns for obstructive jaundice with elevated AST of 109 U/L, ALT of 139 U/L, total bilirubin of 11.3 mg/dL with direct bilirubin of 6.7 mg/dL and alkaline phosphatase of 365 U/L. He also had mild anemia, without leukocytosis. Despite the history, urinalysis was negative for hematuria and stool guaiac was also negative.

Abdominal ultrasonography revealed choledocholithiasis. Computed Tomography of the abdomen showed gallstones as well as dilation of the intrahepatic bile ducts and common bile duct concerning for choledocholithiasis (Figure 1) and he was admitted for endoscopic retrograde cholangiopancreatography (ERCP) and further evaluation of weight loss, melena, and jaundice. ERCP showed a 1.6 x 1.5-centimeter hypoechoic, heterogenous ampullary mass with invasion into the pancreas (see Figure 2).

Biopsy of the mass revealed mucinous adenocarcinoma stage 2A, with the tumor location being both intra-ampullary and peri-ampullary (mixed type) (Figure 3). Histology type was intestinal with signet ring differentiation with lymphovascular invasion, but no perineural invasion. Staging was PT3N0M0 and he underwent pancreaticoduodenectomy with antrectomy and cholecystectomy. He was originally planned to start gemcitabine plus capecitabine, given the histological type of his mucinous adenocarcinoma was intestinal. However, after additional consultation, the treatment was changed to six cycles of capecitabine monotherapy for colon adenocarcinoma with microsatellite stability.

Discussion

Ampullary cancers are rare, accounting for 0.2% of all gastrointestinal cancers and 7% of all peri-ampullary cancers. They arise from the ampullary complex, distal to the convergence of the common bile duct and pancreatic duct.[1] Ampullary cancers usually present at an earlier stage with obstructive jaundice, weight loss, and can often be confused with choledocholithiasis. Ampullary cancers are typically diagnosed at early stage while evaluating for other intra-abdominal pathologies. They usually have excellent prognosis with early resection, unlike periampullary adenocarcinomas that usually present later, with more extensive disease and increased mortality.[2] Therefore, it is important to maintain a broad approach when evaluating patients with potential biliary obstruction, especially with concerning symptoms like our patient.

Given the chronicity of the patient's symptoms, elevated direct bilirubin, and weight loss, there was a higher suspicion for malignancy than choledocholithiasis. The melena, was likely due to the friable ampullary malignancy which can cause intermittent bleeding.

Determining optimal treatment for ampullary adenocarcinoma was difficult due to lack of clinical studies and consensus on the regimen of adjuvant chemotherapy with localized disease.[3] The published studies have conflicting results. A randomized controlled trial investigating the use of adjuvant chemotherapy in periampullary cancers from Japan evaluated the role of 5-FU and mitomycin C following resection versus surgery alone. In the ampullary cancer subgroup (n = 56), no significant survival benefit was observed with the addition of adjuvant chemotherapy.[4] ESPAC-3, the largest phase III randomized study to evaluate the role of adjuvant chemotherapy in periampullary carcinomas, included three study groups: observation, 5-FU/leucovorin, or gemcitabine. The initial primary analysis did not find significant benefit with adjuvant chemotherapy. However subsequent multivariate analysis, adjusting for additional prognostic variables found a statistically significant survival benefit with adjuvant gemcitabine. However, the study included bile duct and pancreatic duct malignancies with periampullary tumors. Because of the low incidence of the different tumor types, the study design required combining tumor types for adequate power to detect survival advantage.[4] At this time, there is no clear standard for specific adjuvant chemotherapeutic agent. However based on this study, gemcitabine is commonly used.

Other clinical trials examined other factors affecting outcomes and/or treatment and have been largely inconclusive. Some studies examined influence of histological subtype of origin.[2] Our patient's histologic subtype was intestinal influencing the decision to treat as colonic adenocarcinoma. The ESPAC-3 study included post-hoc analysis and did not identify survival

differences associated with histological subtypes. Genomic sequences in ampullary cancers have also been studied and genetic abnormalities in KRAS, SMAD4, and PTEN may provide future targets for therapy.[5]

Conclusion

Ampullary carcinoma is a rare malignancy that is difficult to diagnose with little clinical data on targeted treatment or prognostic factors. It can it be easily missed due to signs and symptoms mimicking other intra-abdominal pathologies. Due to rarity there are few clinical trials to support evidence-based standard of care treatment protocols. Additionally, variability in ampullary carcinomas presentation, natural history and response to treatment complicate choice of therapy. Currently, for localized disease, surgical resection followed by adjuvant chemotherapy with gemcitabine and/or capecitabine is favored, while more advanced disease is treated with chemotherapy alone.[6] Given the rarity of the disease, it will continue to be difficult to perform well-powered randomized controlled clinical trials to guide new therapies or better assess prognosis based on histologic characteristics.

Figures

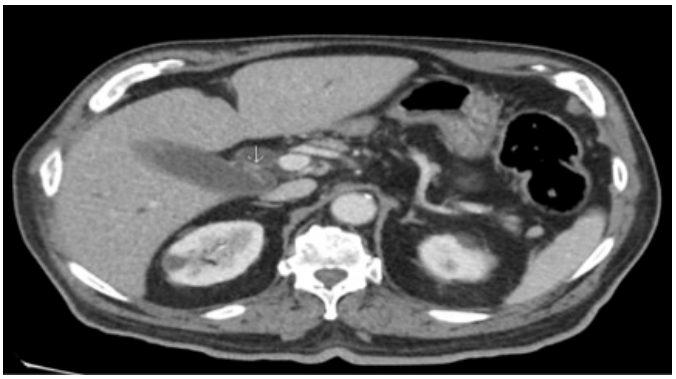

Figure 1. Transverse view of CT abdomen revealing dilation of the intrahepatic and common bile duct.

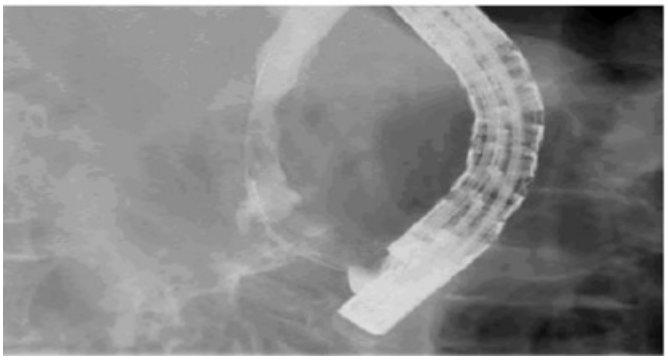

Figure 2. ERCP confirming the presence of an infiltrative mass involving the major papilla.

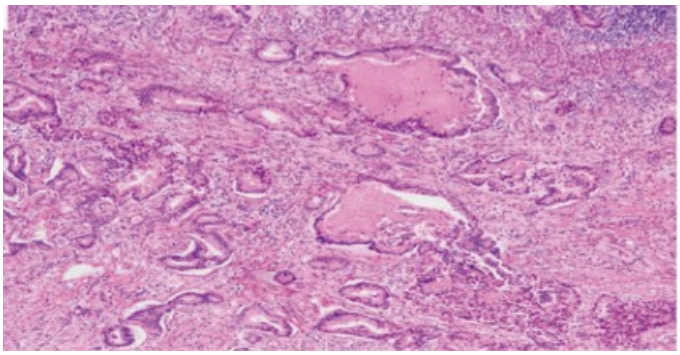

Figure 3. Histology of ampullary adenocarcinoma, intestinal type. Note the presence of large tubules lined by tall columnar cells with elongated, pseudostratified, hyperchromatic nuclei resembling colonic-type adenocarcinoma.

REFERENCES

1. **Ahn DH, Bekaii-Saab T**. Ampullary cancer: an overview. *Am Soc Clin Oncol Educ Book*. 2014:112-5. doi: 10.14694/EdBook_AM.2014.34.112. Review. PubMed PMID: 24857067; PubMed Central PMCID: PMC4966534.
2. **Westgaard A, Pomianowska E, Clausen OP, Gladhaug IP**. Intestinal-type and pancreatobiliary-type adenocarcinomas: how does ampullary carcinoma differ from other periampullary malignancies? *Ann Surg Oncol*. 2013 Feb;20(2):430-9. doi: 10.1245/s10434-012-2603-0. Epub 2012 Sep 7. PubMed PMID: 22956064.
3. **Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M**. Predictors of survival in periampullary cancers following pancreaticoduodenectomy. *Ann Surg Oncol*. 2010 Apr;17(4):991-7. doi: 10.1245/s10434-009-0883-9. Epub 2010 Jan 28. PubMed PMID: 20108122; PubMed Central PMCID: PMC2861840.
4. **Bhatia S, Miller RC, Haddock MG, Donohue JH, Krishnan S**. Adjuvant therapy for ampullary carcinomas: the Mayo Clinic experience. *Int J Radiat Oncol Biol Phys*. 2006 Oct 1;66(2):514-9. Epub 2006 Jul 25. PubMed PMID: 16863684.
5. **Schultz NA, Werner J, Willenbrock H, Roslind A, Giese N, Horn T, Wøjdemann M, Johansen JS**. MicroRNA expression profiles associated with pancreatic adenocarcinoma and ampullary adenocarcinoma. *Mod Pathol*. 2012 Dec;25(12):1609-22. doi: 10.1038/modpathol.2012.122. Epub 2012 Aug 10. PubMed PMID: 22878649.
6. **Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators**. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010 Apr 8;362(14):1273-81. doi: 10.1056/NEJMoa0908721. PubMed PMID: 20375404.