

AEROMEDICAL CONSIDERATIONS OF CHOLANGIOCARCINOMA

CASE REPORT, BY BILLY D. PRUETT, MD, MPH

Cholangiocarcinomas are rare malignancies arising from the epithelial cells of the intrahepatic and extrahepatic bile ducts. These cancers have an extremely poor prognosis, with an average five-year survival rate of 5 to 10 percent, with a median survival of less than 24 months following diagnosis. Surgery provides the only possibility for a cure. Both the devastating nature of the disease and the likely significant impact of the therapies are causes for aeromedical concern.

History

In March 2010, a 65-year-old male third-class pilot began experiencing abdominal pain and jaundice. A work-up subsequently revealed an apparent non-functioning gallbladder, and a cholecystectomy was scheduled. Unfortunately, the planned laparoscopic procedure was aborted due to a combination of the technical difficulty of the procedure, as well as the gallbladder's appearance. An open cholecystectomy was performed, and the resultant pathology demonstrated a poorly differentiated, infiltrating adenocarcinoma. The patient underwent endoscopic retrograde cholangiopancreatography with stent placement, and his jaundice subsequently resolved.

The airman was eventually diagnosed as having pT3N1MX stage IIB distal extrahepatic cholangiocarcinoma. He underwent three cycles of cisplatin plus gemcitabine, followed by bile duct excision, hepaticojejunostomy, and portal lymph node dissection. Pathology from this procedure revealed a positive distal margin in the common bile duct. He was then treated with intensity modulated radiation therapy to the hepatic ileum and pancreatic head, but brachytherapy was not recommended. His treatment was concluded with capecitabine.

The airman underwent all phases of therapy without difficulty. His recovery was good, and he then began a period of intense post-therapy surveillance. His physician stated in a letter that the patient's incisions were completely healed, that he suffered no pain or obvious sequelae, and that he had returned to his pre-surgical performance status.

Aeromedical Concerns

As with most cancer diagnosis, the primary aeromedical concern with cholangiocarcinoma revolves around the potential effects of the primary or recurrent tumor on the airman's ability to safely operate in the aviation environment. And as was pointed out in the sidebar, not only is the mortality rate from this diagnosis extremely high, but the clinical symptoms associated with both the cancer and its associated therapies are significant. Cholangiocarcinoma renders an airman ineligible for civilian medical certification under Title 14, Code of Federal Regulations 67.113(b), 67.213(b), and 67.313(b).

Outcome

The airman in this case was denied a Special Issuance. His advanced age, the lymph node involvement, his IIB staging, and the presence of poorly differentiated adenocarcinoma and positive surgical margins are all poor prognostic indicators. Given that his surgery was not curative, his biliary tree stenting and subsequent neoadjuvant therapy would all have to be considered palliative. The case was referred to an FAA consultant. After reviewing the information, the consultant recommended that the airman's case not be reconsidered for at least one year.

Etiology

Cholangiocarcinoma, the most common bile duct tumor, arises from the biliary epithelium in the intra- and extrahepatic biliary tree. The classification of extrahepatic can be further divided into hilar or distal bile duct cancers, and accounts for 80% to 90% of cholangiocarcinomas.¹ Distal bile duct tumors represent approximately 20% to 30% of all cholangiocarcinomas, while cholangiocarcinomas as a whole represent less than 2% of all malignancies.²

The most common clinical manifestations of intrahepatic cholangiocarcinoma are abdominal pain accompanied by systemic symptoms such as cachexia, malaise, and fatigue. Extrahepatic disease most often presents as painless jaundice secondary to malignant biliary obstruction. In 10% of patients, bacterial cholangitis is the initial presenting symptom.³ Of those patients with distal extrahepatic disease, 75% to 90% will experience progressive jaundice, and less than one-third will have abdominal pain, weight loss, fever, or pruritus.

Diagnosing cholangiocarcinoma typically requires a multidisciplinary approach, which includes clinical evaluation combined with laboratory, endoscopic, and radiologic studies. Laboratory analysis often reveals evidence of obstructive cholestasis with serum alkaline phosphatase and bilirubin levels being elevated. Levels of several serum tumor markers (CA 19-9, carcinoembryonic antigen [CEA], and Ca-125) may also be elevated; however, none of these serum markers is specific, and can be elevated in other gastroenterologic or gynecologic malignancies and in the setting of biliary inflammation or infection. The most commonly used marker is CA 19-9.⁴

Cholangiography is an essential part of the work up, providing both anatomic information and tissue for diagnosis. Both endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography (THC) provides information on intrabiliary tumor extension and allows cytologic sampling and therapeutic intervention. And while no such interventions are possible with magnetic resonance cholangiopancreatography, the technique has the benefit of being noninvasive and provides information on the extent of extrabiliary tumor, metastases, vascular encasement, and the relation of the primary tumor to surrounding structures.

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Note that, in the setting of distal bile duct stricture and a clinical presentation consistent with cholangiocarcinoma, histologic confirmation is generally unnecessary when operative therapy is planned. Benign strictures of the lower bile duct are difficult to differentiate from the malignant variety without resection. Percutaneous needle biopsy often ranges from difficult to impossible, and endoscopic brushings of the bile duct have an unacceptably low sensitivity.⁵

Cholangiocarcinoma is a naturally aggressive cancer. The median survival following diagnosis is less than 24 months. Surgery is the only potentially curative treatment but is often precluded by the advanced stage of the disease at the time of diagnosis. Resection of intrahepatic tumors has a five-year survival rate, ranging from 22% to 42%. Survival positively correlates with early tumor stage, younger age, and better performance status.

When resection of extrahepatic cholangiocarcinomas produces clear surgical margins, five-year survival rates are 11% to 41% for hilar and 27% to 37% for distal. Unfortunately, the rates of such clear margins are less than 50%.³ In a 2007 study, Murakami conducted a retrospective chart review of 43 patients with distal cholangiocarcinoma that underwent surgical resection. Of these, 35 underwent pancreatoduodenectomy, and eight had segmental bile duct resections. Overall survival rates were 72%, 53%, and 44% for 1, 3, and 5 years, respectively; with a median survival time of 26.0 months. Poor prognostic indicators were older age, pathological pancreatic invasion, lymph node metastasis, perineural invasion, positive surgical margin, and TNM stages II and III ($P < 0.05$). Lymph node metastasis and positive surgical margin were found to be significant, independent predictors of poor prognosis.⁶

Gemcitabine remains the only FDA-approved chemotherapeutic drug. No randomized, controlled, phase III trials have shown a significant survival benefit derived from chemotherapy for patients with cholangiocarcinoma. Therefore, chemotherapy's only benefit is in either the palliative or neoadjuvant settings. Similarly, the use of radiation therapy remains controversial.¹

As was previously noted, there is substantial morbidity associated with cholangiocarcinoma. Patients' quality of life is typically limited by cholestasis, abdominal pain, and cachexia. Subsequently, palliative care plays an essential role in the management of these patients. Palliative care options include chemo- and radiation therapies; restoration of biliary drainage through endoscopic, percutaneous, and surgical techniques; and more recently, photodynamic therapy (PDT).⁷ The first two of these options have been shown to be relatively ineffective.

Conversely, early intervention with biliary stenting has been shown to not only improve palliation, but also to normalize bilirubin levels. And recently, PDT has demonstrated an ability to reduce cholestasis, improve quality of life, and possibly even provide a survival benefit. In PDT, the patient receives a photosensitizing agent (e.g., hematoporphyrin) prior to localized illumination of the tumor using a specific wavelength of light. Cytotoxicity then occurs as a result of reactive oxygen species-mediated cell death, tumor-vessel thrombosis, and tumor-specific immune reactions. The procedure is well tolerated with a low complication rate.³

References

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