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LATE RECURRENCE OF CHOLANGIOCARCINOMA

Stella Pak[1], Nataly Torrejon[2], Alejandro Calvo[3]

[1]Kettering Medical Center, Graduate Medical Education Department, Dayton, Ohio.
[2]Universidad Privada del Valle School of Medicine, Cochabamba, Bolivia
[3]Kettering Cancer Center, Kettering, Ohio.

ABSTRACT: *Cholangiocarcinoma is associated with a poor prognosis usually due to advanced stage at the time of diagnosis and limited treatment options. In patients with localized disease, surgical resection of the malignant lesion remains the only potentially curative treatment. Duration of surveillance after tumor resection and adjuvant therapy remains controversial. Most oncologists will see patients periodically for up to 5 years. We present a case of a 71-year-old woman with recurrence of cholangiocarcinoma in the lung 11-years after curative resection. This case report suggests that prolonged surveillance beyond 5 years may be indicated for cholangiocarcinoma patients at high risk for recurrence after curative resection.*

KEYWORDS: Cholangiocarcinoma, Late Recurrence, Surgical Resection, Surveillance

INTRODUCTION

Cholangiocarcinoma (CCA) is a solid tumor arising from the epithelial cells of the biliary tract, widely known for its nonspecific and late-stage symptomatology.[1] Considering its typically late-stage diagnosis and refractoriness to chemotherapy, CCA has a notoriously poor prognosis, with a five-year survival rate of only 5 to 10% [2]. Unfortunately, chemotherapy with gemcitabine and cisplatin is usually given with palliative rather than curative intent, due to advanced stage at diagnosis and resistant nature of cholangiocarcinoma. [1] Surgical resection, if feasible, is the only curative option for localized CCA. The five-year survival rate in patients who underwent surgical resection of the malignant lesion is 11 to 44%. [3] Among patients who undergo surgical resection, recurrence rates fluctuate between 49 to 64 %. The vast majority of recurrences present within the initial 5 years from surgical resection. Despite dismal prognosis, the length of survival in patients who undergo resection is on the rise due to advancements in medical technology, specifically for management of postsurgical complications. [4] Herein, we present the case of a 71-year-old woman who presented with biopsy-proven cholangiocarcinoma lesions in the right lung and pleural surface 11 years after extensive extrinsic bile duct tumor resection that included a partial hepatectomy and right adrenalectomy followed by adjuvant chemotherapy.

Case Presentation

A 71-year-old woman presented with intermittent pain in the right side of the abdomen, occasional night sweats, and nausea, with no other associated symptoms. Physical examination was remarkable for an epigastric mass and tenderness to deep palpation in the right mid and upper abdominal quadrants. Computed tomography (CT) of the abdomen and pelvis revealed a 5.7 X 4.3-cm mass with an irregular contour in the right hepatic lobe, contiguous with the gallbladder (Figure 1). CT-guided biopsy showed a poorly differentiated adenocarcinoma.

Positron emission tomography (PET) with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose visualized a 6.5-cm focus of increased uptake in the right lobe of the liver with a maximal standardized uptake value (SUV) of 10.8. Carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 were not elevated. Extensive surgical resection was performed including right liver lobe resection, cholecystectomy, and partial right adrenalectomy. In the liver, a white, firm, irregularly lobulated tumor mass approximately 5.5 x 3.5 x 4.0 cm was found in irregular trabecula associated with focal perineural invasion. Centrally, the tumor was densely sclerotic with fibrous tissue predominating. Surgical margins were negative, with tumor extending to within 2 mm of the margin. A panel of immunohistochemistry stains showed positivity for cytokeratin (CK) -7, CK -19 and negative for CK -20. Polyclonal CEA cytoplasmic positivity was also present. A block was sent to Genzyme laboratories for HepPar-1 testing, which returned negative. The immunohistochemical features were consistent with the diagnosis of cholangiocarcinoma. Examination of the gallbladder revealed a normal appearing mucosal surface and three 1 to 1.5 cm in diameter stones, consistent with chronic cholecystitis and cholelithiasis. Analysis of the resected right adrenal gland was found to be benign, only with a central area of red gelatinous appearing thrombus (3.7 x 2.0 x 5.0 cm), diagnosed as an organizing hematoma. The patient was then treated with four cycles of adjuvant chemotherapy with a combination of gemcitabine and capecitabine. She was followed periodically with physical exams, laboratory work and imaging studies over a five-year period. After that, she was considered cured and was released to continue regular visits with her primary care provider.

11-years after surgical resection, the patient returned with a 10-pound unintentional weight loss over a 3-month period and with progressive shortness of breath associated with a later identified right pleural effusion. Diagnostic thoracentesis yielded cytology negative for malignancy. Her fluid reaccumulated quickly after each thoracentesis. PET scan showed increased uptake along the pleural surface of the right lung, SUV values ranging up to 11.9 (Figure 2). Magnetic resonance imaging (MRI) of the brain was negative for any metastatic lesion. In the setting of persistent dyspnea associated with recurrent effusion, the patient underwent video-assisted thoracoscopic surgery (VATS) with talc pleurodesis and biopsy of parietal pleural tissue. The biopsy revealed metastatic adenocarcinoma extensively involving fibrous tissue (Figure 3). Tumor cells were positive for CK-7, CK-19, anti-human epithelial antigen (BerEP4) and negative for CK-20, p-63, calretinin, Napsin A, thyroid transcription factor (TTF)-1, estrogen receptor (ER), progesterone receptor (PR), caudal type homeobox protein (CDX)-2, WT (Wilms tumor)-1, P-40, S-100, GATA-3, and D2-40. These immunohistochemical features suggested the diagnosis of metastatic cholangiocarcinoma. Considering this late presentation of cholangiocarcinoma, samples were sent to Johns Hopkins Medical Center for a second opinion. Additional stains performed at Johns Hopkins included Cell D2-40, WT-1, P-40, S100 and GATA 3 which returned negative and BerEp4, which was strongly positive. This pattern supported the diagnosis of a metastatic poorly differentiated cholangiocarcinoma.

CEA was normal, CA 19-9 was elevated to 573 U/ml. Molecular profiling of the right lung tumor showed positivity for isocitrate dehydrogenases (IDH)-1, polybromo (PRBM)-1 and low tumor mutation burden with programmed death ligand (PDL)-1 expression of 0 %, microsatellite status was reported as stable. The patient was treated with a combination of infusional 5-fluorouracil, leucovorin, irinotecan and Avastin achieving a solid partial response.

DISCUSSION

In the case presented above, recurrence of cholangiocarcinoma occurred 11 years after initial diagnosis, several years after concluding a standard five-year surveillance period. The finding of a solitary mass diagnosed as cholangiocarcinoma in the lung suggests metastatic dissemination of the primary tumor prior to surgical resection. This patient was at an increased risk for recurrence as she had an extensive primary lesion involving the right lobe of liver and adrenal gland with poorly differentiated malignancy. For patients at high risk for recurrence, extended surveillance beyond 5-years may be beneficial. Extended follow-up, along with early detection and management of metastatic disease could lead to improved survival and quality of life in these patients.

The most frequently utilized imaging modality for postsurgical surveillance of cholangiocarcinoma is CT scan of the abdomen and pelvis. [5]Although extended follow-up surveillance for high-risk patients would be reasonable, the risk of radiation exposure with repeat CT imaging in a low-risk patient population may outweigh the potential benefits of surveillance. Alternative imaging modalities include MRI and FDG-PET but are less available and are more expensive and time-consuming. However, several studies support higher sensitivity of FDG-PET for cholangiocarcinoma.[5] Future development of evidence-based guidelines, which incorporate imaging modality and interval recommendations for post-resection patients based on individual risk factors would greatly benefit this patient population. Currently known risk factors for recurrence include the presence of lymph node metastasis, advanced grade or stage, positive surgical resection margins, vascular or perineural invasion, advanced age, and size of tumor resected. [6] A study by Hyder and colleagues, investigated rates and patterns of recurrence in 301 patients after operative intervention for intrahepatic cholangiocarcinoma. This study designed a clinical scoring system to stratify patients according to prognosis using the following 3 independent variables: tumor size of 5 cm or greater, major vascular invasion, and lymph node status. Patients lacking all 3 risk factors were given a clinical score of 0, patients with only 1 risk factors had a score of 1, patients with 2 risk factors were assigned a score of 2, and patients with 3 risk factors were assigned a score of 3. The 5-year recurrence-free survival (RFS) for patients with scores of 0, 1, 2, and 3 was 61.8%, 36.2%, 19.5%, and 9.6%, respectively. [7] Although this scoring system analyzed RFS for up to 5 years, it could be helpful in deciding the duration of patient surveillance times.

To the best of our knowledge, there is only one other case illustrating late recurrence of cholangiocarcinoma more than 10 years from surgical resection with curative intention. That case was reported by Dr. Machimoto and colleagues in Japan. Unlike the present case, in that report the metastatic mass was found as a locoregional recurrence in the rectus abdominis muscle.[8] Our case is unique in that the recurrence of cholangiocarcinoma occurred as a distant recurrence in the lung, outside the abdominal compartment, 11-years after complete surgical resection of primary cancer.

CONCLUSION

The case detailed above suggests that prolonged surveillance beyond 5 years may be needed for patients at high risk for recurrence of cholangiocarcinoma. A comprehensive risk stratification system for recurrence of cholangiocarcinoma is necessary to evaluate these patients, but unfortunately not available. Development of evidence-based guidelines, which

incorporate imaging modality and interval recommendations for post-resection patients based on individual risk factors would greatly benefit this patient population. In the era of precision oncology, the molecular characteristics of this tumor type may need to be evaluated as another potential prognostic factor during risk stratification.

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APPENDIX

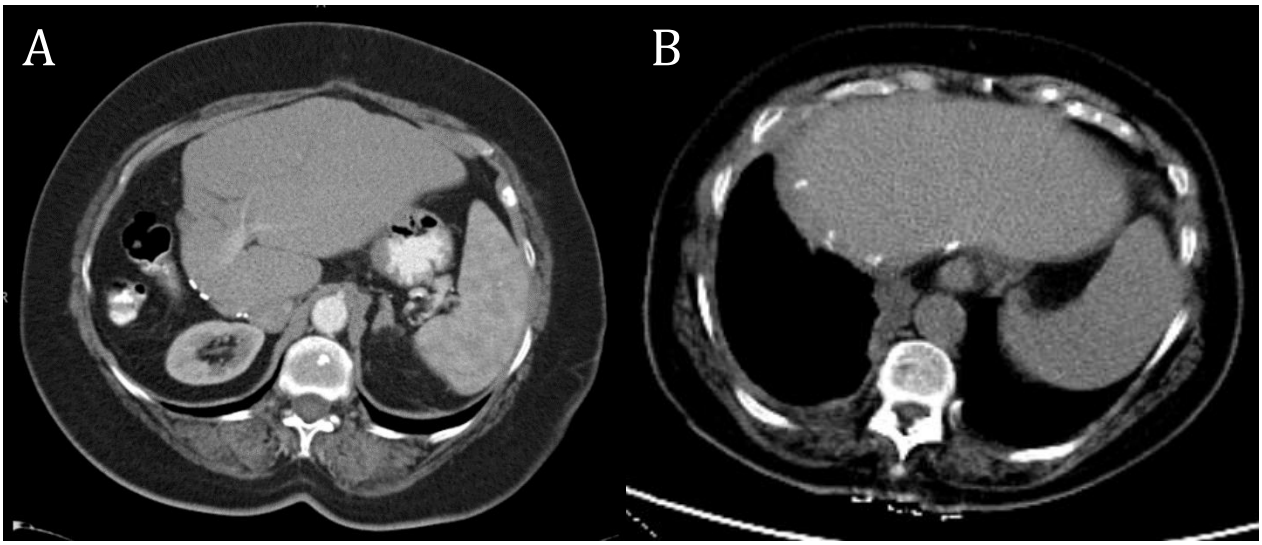

Figure 1: Computed tomography (CT) of the abdomen on presentation (A) and with malignancy recurrence (B), year 2006 and 2016 respectively.

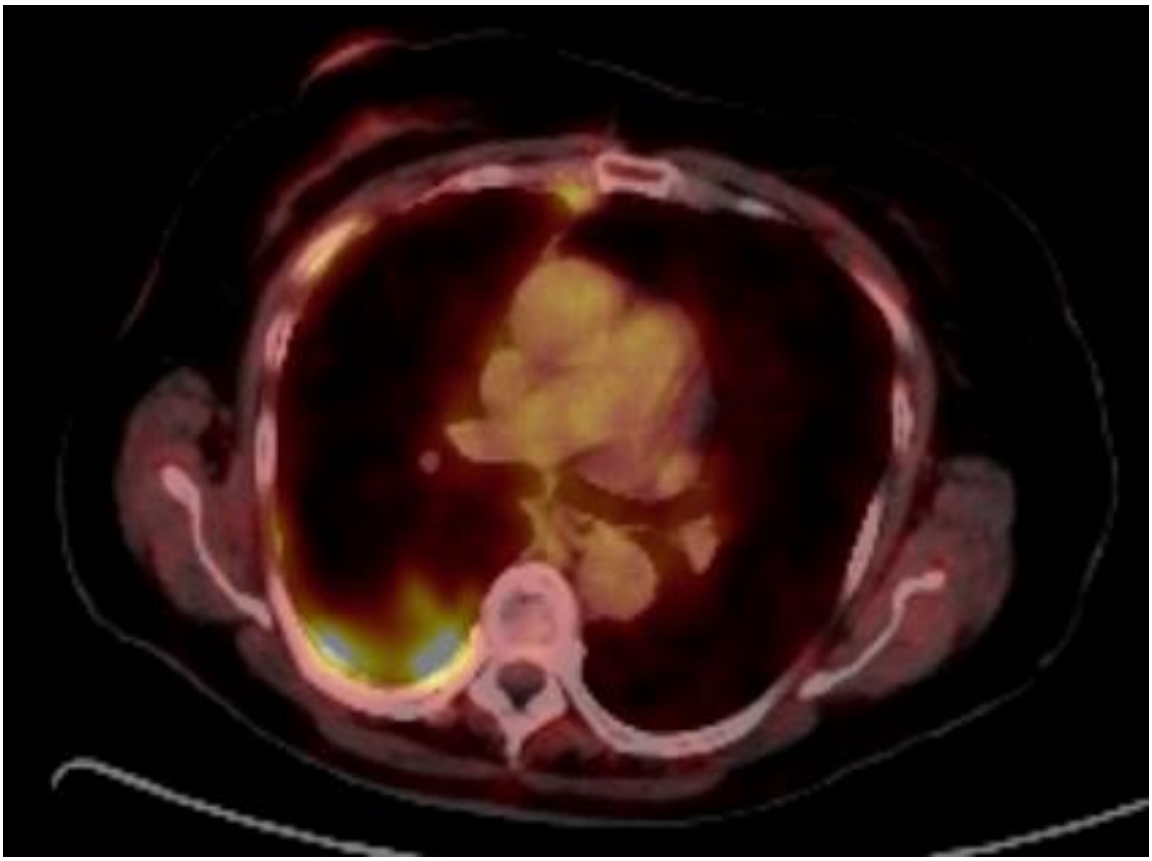

Figure 2: Positron emission tomography (PET) showing increased uptake along the pleural surface of the right lung, SUV values ranging up to 11.9.

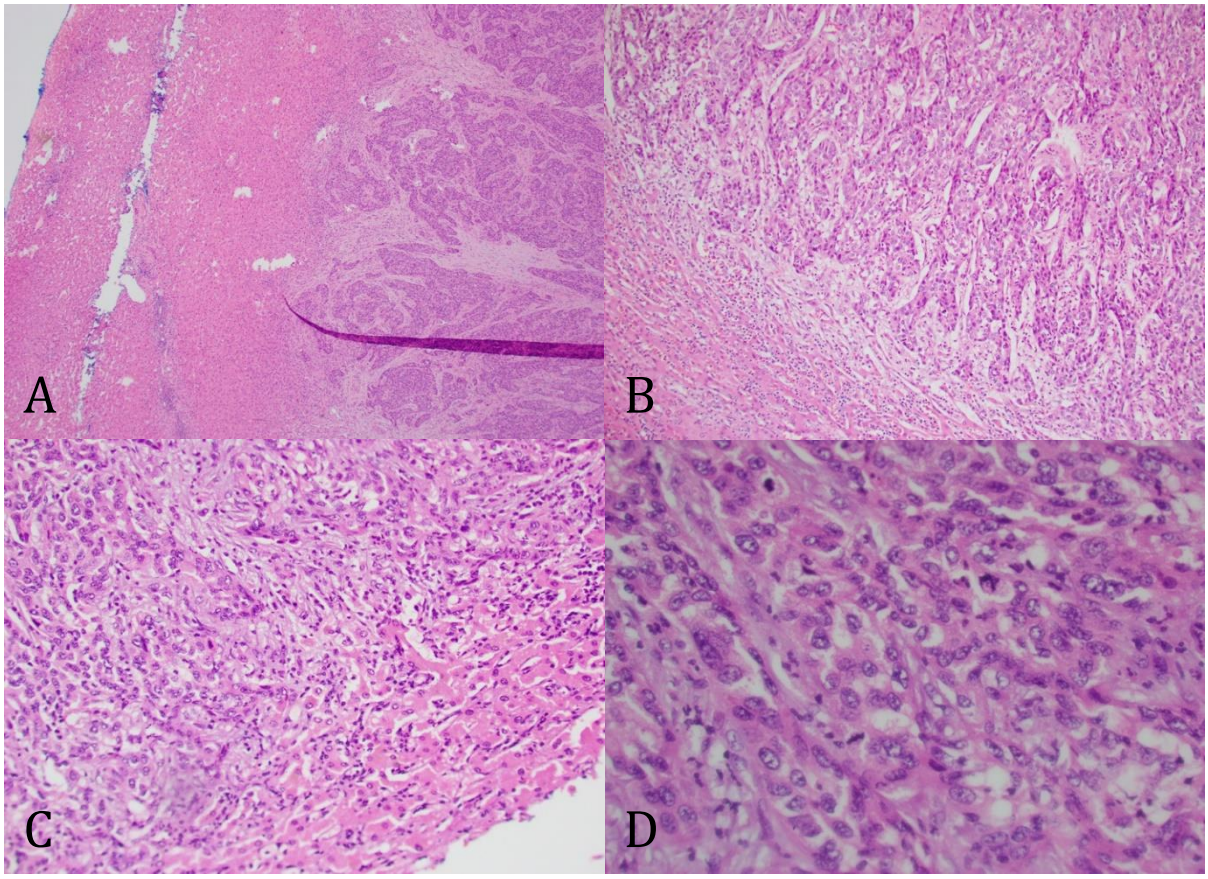

Figure 3: Lung biopsy revealing metastatic adenocarcinoma extensively involving fibrous tissue. (A) Tumor margins at x4 magnification, (B) x10 magnification, (C) x20 magnification and (D) x40 magnification.