CASE REPORT ◄

Metastatic Gallbladder Cancer with Complete Response after Cisplatinum/ Gemcitabine Chemotherapy; Case Report

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Abstract

Introduction: Gallbladder cancer is the most common and aggressive type of all the biliary tract cancers, with the shortest median survival duration. It is more common in whites than in blacks and its incidence steadily increases with age and women are 2-6 times more likely to be diagnosed with gallbladder cancer than men. Gallbladder cancer is characterized by local invasion, extensive regional lymph node metastases, vascular encasement, and distant metastases.

Case presentation: We report a case of a 64-year-old woman presenting with abdominal pain of one year duration increased in intensity in the last 3 months and was eventually diagnosed to have metastatic gallbladder cancer to liver and anterior abdominal wall with residual disease at the gallbladder bed. This patient was treated with the newly approved Cisplatin/Gemcitabine combination chemotherapy regimen (based on the phase-III ABC-02 trial) and achieved a complete radiological response in the liver as well as the gallbladder bed.

Conclusion: Gemcitabine/Cisplatin combination chemotherapy used in metastatic gallbladder cancer resulted in a complete response in contrast to the accumulating data of poor response of such tumors.

Introduction

The two most common malignancies of the biliary tree are adenocarcinoma of the gallbladder and adenocarcinoma of the bile ducts or cholangiocarcinoma. Cholangiocarcinoma and gallbladder cancer are collectively known as biliary tract cancers. In the United States, an estimated 9,250 cases of biliary tract cancers were diagnosed in 2011 with approximately 3,300 deaths occurring in the same year. **(1)**

Risk factors for gallbladder cancer, of which cholelithiasis is the most prevalent, are associated with the presence of chronic inflammation. Calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been associated with gallbladder cancer. **(2)**

Case Presentation

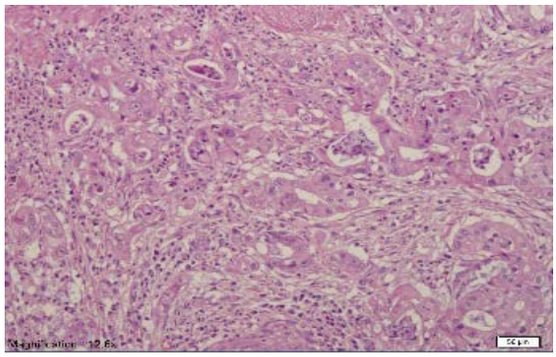
A 64-year-old woman with a diagnosis of adenocarcinoma of the gallbladder metastatic to liver and anterior abdominal wall was referred to the Oncology Centre of King Abdullah Medical City (KAMC) for further management. The main complaint was abdominal pain of one year duration increased in intensity in the last 3 months. This pain was stabbing in nature, radiating to the back, not related to meals and partially relieved by pain killers. Magnetic retrograde cholangiopancreatography (MRCP) done outside revealed a contracted gallbladder with thickened wall and small stones. Laparoscopic cholecystectomy with biopsy from two liver nodules and anterior abdominal wall nodule was performed. Histopathological examination of the cholecystectomy specimen revealed a gallbladder well differentiated adenocarcinoma infiltrating the entire gallbladder wall thickness with peri-neural invasion **(figure 1).** The liver and anterior abdominal wall nodules biopsy revealed a well differentiated adenocarcinoma consistent with the gallbladder primary. Following cholecystectomy, the patient was still complaining of persistent severe right upper quadrant abdominal pain (numerical scale 8- 9/10), with decreased appetite and weight loss.

Baseline computed tomography (CT) of the abdomen done at KAMC revealed multiple hypodense non-enhancing liver metastases scattered in both lobes with an ill-defined hypodense soft tissue lesion at the region of gallbladder bed and porta hepatis abutting the adjacent pancreatic and hepatic tissues measuring 4.4 x 2.4 cm. There was mild intrahepatic biliary radicals' dilatation (IHBRD) with no abdominal wall masses or nodules detected **(figure 2).**

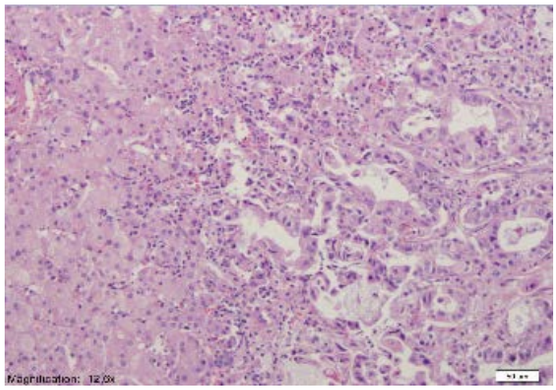
The patient was started on the combination chemotherapy regimen composed of cisplatin 25 mg/m^2 day 1, day 8 and gemcitabine 1000 mg/m^2 day 1, day 8, repeated every 3 weeks. Initial cycles of chemotherapy was not well tolerated (prolonged neutropenia and thrombocytopenia). Non-hematological side effects included grade I-II fatigability, Grade I-II nausea and loss of appetite. After 3 cycles of chemotherapy, CT scan showed minimally persistent IHBRD and no hepatic focal lesions with reduction in the soft tissue lesion at the surgical bed to 2.4 x 2 cm **(figure 3).** Magnetic resonance imaging (MRI) of the liver confirmed the complete resolution of the previously described hepatic metastases. With the subsequent 3 cycles of chemotherapy the dose was reduced by 20% and given on days 1 and 15 every 28 days due to avoid the prolonged neutropenia

and thrombocytopenia experienced before. There were no episodes of serious infections or neutropenic fever.

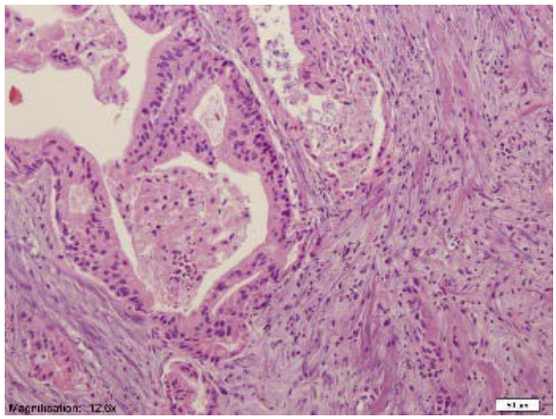
Re-evaluation after 6 cycles of chemotherapy revealed complete resolution of the previously described soft tissue mass at the surgical bed with persistent minimal IHBRD with no focal hepatic lesions **(figure 4).** Additional two cycles of the modified protocol were given and the patient was put on regular follow up.



A-Gallbladder wall with invasive well-differentiated adenocarcinoma

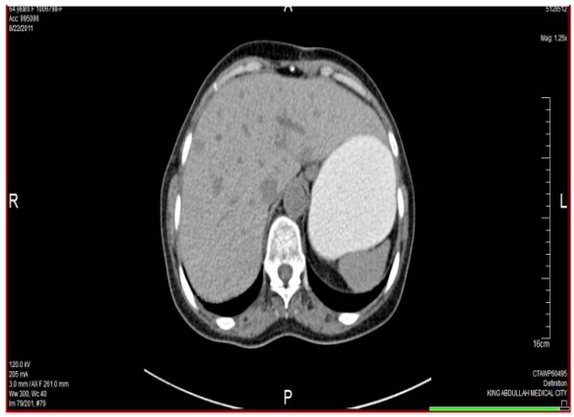


B-Liver nodule biopsy showing deposit of well-differentiated adenocarcinoma

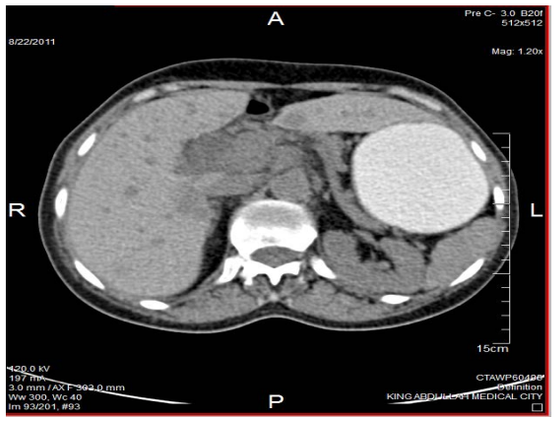


C-Abdominal wall biopsy showing deposit of well-differentiated adenocarcinoma

Fig 1: Histopathology



A -Multiple liver deposits



B -Soft tissue lesion at the gall bladder bed

Fig 2: Baseline CT abdomen

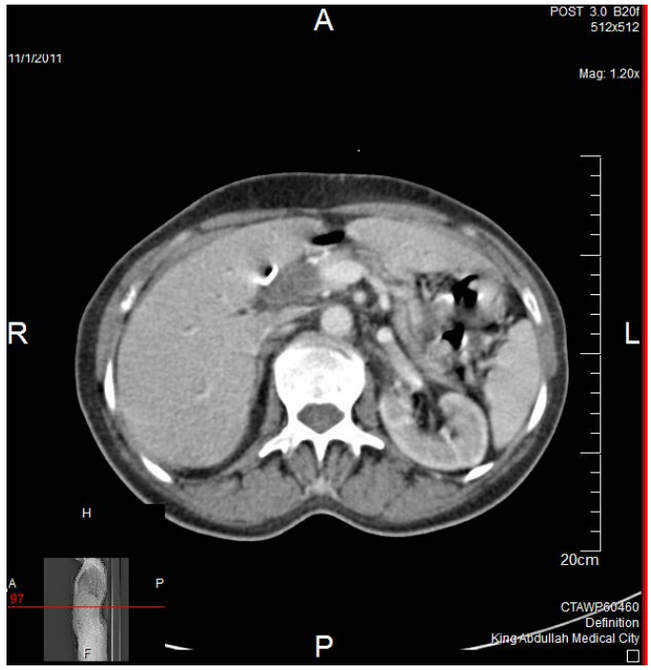


Fig 3: CT abdomen showing no hepatic focal lesions with reduction in the soft tissue mass at the surgical bed

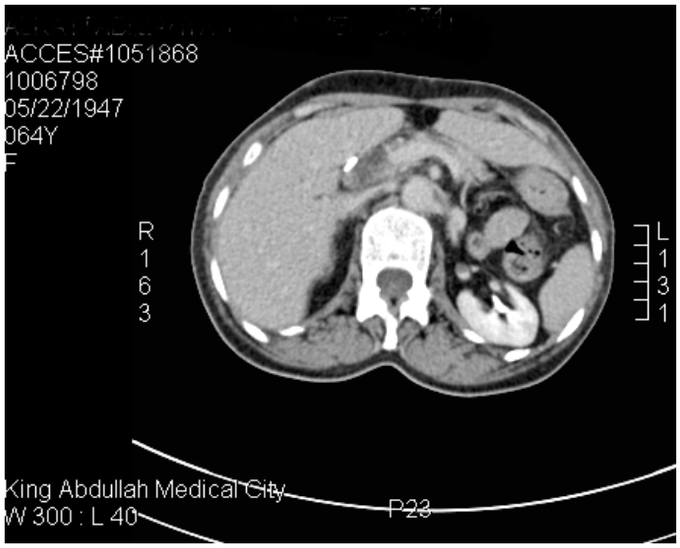


Fig 4: CT abdomen showing complete resolution of the previously described soft tissue mass at the surgical bed

Discussion

Gallbladder cancer is often diagnosed at an advanced stage due to the aggressive nature of the tumor which can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation which mimics that of biliary colic or chronic cholecystitis. Hence, it is not uncommon for a diagnosis of gallbladder cancer to be an incidental finding at surgery or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis, other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound or in patients presenting with jaundice. Surgery remains the only curative modality for gallbladder cancer. Factors determining gallbladder tumor resectability include the stage of the tumor as well as tumor location. Nodal disease outside of this area (most commonly celiac, retropancreatic or in the interaortocaval groove) should be considered unresectable. **(3)**

For patients with unresectable or metastatic disease (includes distant metastases, nodal metastases beyond the porta hepatis and extensive involvement of the porta hepatis causing jaundice or vascular encasement) after preoperative evaluation, a biopsy should be performed to confirm the diagnosis. Treatment options for these patients include fluoropyrimidine-based or gemcitabine-based chemotherapy fluoropyrimidine chemoradiation, participation in a clinical trial or best supportive care. In patients with unresectable or metastatic gallbladder cancer and jaundice, biliary drainage is an appropriate palliative procedure and should be done before instituting chemotherapy if technically feasible. CA 19-9 testing can be considered after biliary decompression. Biliary drainage followed by chemotherapy can result in improved quality of life. **(4)**

The prognosis of patients with advanced biliary tract cancers is poor and the median survival time for those undergoing supportive care alone is short. **(5)** The survival benefit of chemotherapy in patients with advanced biliary tract cancer was suggested in a trial comparing the regimen of 5-FU, leucovorin and etoposide versus best supportive care. **(6)** A subsequent phase III trial evaluating patients with advanced biliary tract cancer randomly assigned to receive either 5-FU,leucovorin and etoposide or 5-FU, cisplatin and epirubicin did not show one regimen to be significantly superior with respect to the overall survival (12 months vs. 9 months, respectively) although the trial was underpowered to detect such a difference. **(7)** A number of other chemotherapy combinations as well as single agents have been evaluated in clinical studies for the treatment of advanced biliary tract cancers as reviewed by Hezel and Zhu. **(8)**

Examples of chemotherapy combinations demonstrated in phase II trials to have activity in the treatment of advanced biliary tract cancers include: gemcitabine and cisplatin,(9) gemcitabine and capecitabine, (10) gemcitabine and oxaliplatin, capecitabine and oxaliplatin, capecitabine and cisplatin and 5-FU and cisplatin. **(9-14)** Results of a recent pooled analysis of 104 trials of patients with advanced biliary tract cancers showed that the subgroup of patients receiving a combination of gemcitabine and platinum-based agents had the greatest benefit. **(15)**

Additional support for gemcitabine as an anchor drug for the treatment of advanced biliary tract cancers comes from a retrospective review of 304 patients with advanced biliary tract cancer who received gemcitabine, a cisplatin-based regimen, or a fluoropyrimidine-based regimen. **(16)** In that study, patients receiving a gemcitabine-based regimen were shown to have a lower risk of death.

Most importantly, the recently published randomized controlled phase III ABC-02 study which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer demonstrated that the combination of gemcitabine and cisplatin improved overall survival and progression-free survival by 30% over gemcitabine alone. Median overall survival was 11.7 months and 8.1 months (hazard ratio=0.64; 95% CI, 0.52-0.80; P<0.001), and median progression-free survival was 8.0 months vs. 5.0 months (hazard ratio=0.63; 95% CI, 0.51-0.77; P<0.001), both in favor of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the 2 arms. Based on the results of this study, the combination of gemcitabine and cisplatin is considered to be the standard of care as first-line chemotherapy for patients with advanced or metastatic biliary tract cancers. **(17)**

Our patient was treated initially with the protocol based on the ABC-02 Trial for the first 3 cycles. The protocol had to be modified due to hematologic toxicities. Fortunately, the patient achieved a complete radiologic remission which was maintained despite this modification.

As observed in our patient's case, Gemcitabine/Cisplatin combination chemotherapy used in metastatic gallbladder cancer resulted in a complete response in contrast to the accumulating data of poor response of such tumors.

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