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Case Report

Complete Response to Chemotherapy in A Patient with Unresectable Extrahepatic Cholangiocarcinoma

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Abstract

Introduction: Biliary tract cancer (BTC) is an uncommon tumor with bad prognosis. There is no curative treatment for patients with unresectable disease at diagnosis. There is a limited experience with second-line chemotherapy in advanced BTC since clinical trials are difficult to perform due to the rarity and heterogeneity of these tumors. Recent molecular studies have increased our understanding of the pathogenetic mechanism that underly the development of cholangiocarcinoma. These will help us to determine the significance of molecular alterations that occur in this disease and will direct the development of targeted therapy.

Case Report: This case report describes a radiological complete response after three cycles of second-line chemotherapy with the combination of capecitabine and oxaliplatin in a patient with unresectable extrahepatic cholangiocarcinoma, after treatment with the combination of gemcitabine and cisplatin as first-line chemotherapy.

Conclusion: Our case suggests that selected patients may demonstrate very good responses to chemotherapy. There is an urgent need to identify different molecular subtypes that could direct management of these patients.

Keywords: Cholangiocarcinoma; Targeted treatment; Cronic Inflamation

1. Introduction

BTC is a rare malignancy that carries bad prognosis. Complete surgical resection is the only curative treatment. However, even if curative intent surgery is applied to selected patients, 5-year survival rates still remain low (33.1% for bile duct cancer, 52.8% for ampullary cancer, and 41.6% for gallbladder cancer) [1]. BTC patients are often diagnosed with advanced stages and treated with systemic chemotherapy or palliative treatment settings rather than

curative surgery. Gemcitabine has been the cornerstone of the systemic chemotherapy treatment of BTC. Moreover, recent advances in the development of chemotherapy regimens have gained additional survival benefits for patients with advanced BTC. Different combination chemotherapy regimens containing gemcitabine, antracyclines, platinum analogs, S1, etoposide, fluoropyrimidines and mitomycin C reported an ORR of 15–45% with median survival of 6–11 months and 1-year survival ranging from 20% to 40% [2, 3].

Despite the considerable progress that has been made towards molecular profiling of BTC, there remain considerable gaps in our understanding of carcinogenesis of these tumors. It is likely that the complex interactions between various signaling pathways hold the key to deepening our understanding of the basis of cancer heterogeneity and predicting susceptibility of individual tumors to targeted therapy.

2. Case Report

A 56-year-old male with a medical history of dyslipidemia and 10.8 pack-years smoker, presented in October 2016 with colicky right hypochondrium abdominal pain of one-month duration associated with obstructive jaundice. Diagnostic imaging consisted of abdominal ultrasound followed by magnetic resonance cholangiopancreatography (MRCP) demonstrating a 26 mm focal lesion isointense to the hepatic parenchyma in T2 sequence, trapping the cystic duct, the gallbladder infundibulum and the intrahepatic bile duct with retrograde secondary dilation. The lesion showed intense enhancement after intravenous contrast administration. Another 40 mm focal hepatic lesion slightly hyperintense in T2 sequence, adjacent to the gallbladder fundus was shown (Figure 1A-1C).

Endoscopic ultrasound was then performed in November 2016, describing a solid 18 x 25 mm hypoechoic lesion at the level of the common bile duct infiltrating the gallbladder, with probable vascular infiltration of the portal vein. Fine needle aspiration cytology of the common bile duct tumor demonstrated groups of irregular and hyperchromatic nuclei compatible with adenocarcinoma (Figure 2 F). Further staging was performed to determine whether the patient was an appropriate candidate for surgery. Computerized Tomography (CT) scan confirmed severe dilation of the intrahepatic bile duct with stenosis in the common hepatic duct, with no distant lesions.

The patient underwent an exploratory laparotomy, showing the hepatic lesion adjacent to the gallbladder fundus, and another common bile duct tumor infiltrating the right portal branch and hepatic 4b and 5 segments, which was considered unresectable. A biopsy was taken with immunohistochemical (IHC) stains positive for cytokeratin CK7, MOC31, and negative for CK20, with a high mitotic index measured with Ki67, consistent with an extrahepatic cholangiocarcinoma (Figure 2A-2F). Microsatellite instability (MSI) was not detected. Finally, an endobiliary metalic stent was placed resulting in successful biliary decompression.

Based on these findings, he was diagnosed with unresectable extrahepatic cholangiocarcinoma and started first-line chemotherapy with the combination of gemcitabine and cisplatin. CT evaluation after 3 cycles of treatment revealed a partial response to treatment (PR), with the disappearance of the gallbladder fundus lesion and stability of the infundibulum lesion (Figure 1D, 1E).

The patient presented grade 4 afebrile neutropenia, grade 1 anemia and grade 3 renal failure as main treatment toxicities. For this reason, after 6 cycles of chemotherapy with maintained PR, we decided to continue with gemcitabine monotherapy. After 3 cycles of treatment in September 2017, the CT scan revealed disease progression, with an increase of the infundibulum tumor volume (Figure 1F).

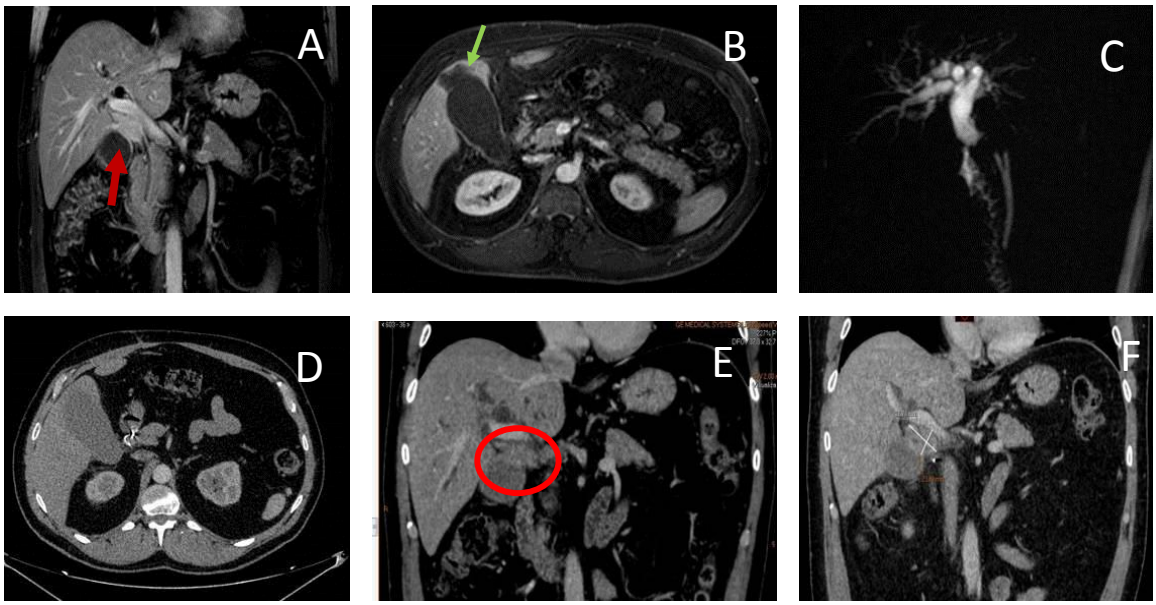

Figure 1: A. MRI Imaging showing focal hepatic lesion trapping the bile duct (red arrow). B. focal hepatic lesion adjacent to the gallblader fundus (green arrow). C. MRCP shows Bile duct dilation with stenosis of the common bile duct. D.E. CT scan shows disappearance of the gallbladder fundus lesion and stability of the infundibulum lesion after treatment (red circle). F. Disease progression, with an increase of the infundibulum tumor volume.

At this point, the patient had recovered from the previous treatment toxicities and maintained an excellent general status, so we started second-line chemotherapy treatment with capecitabine and oxaliplatin combination. A new CT scan was performed in December 2017 after receiving 3 cycles of treatment, which showed disappearance of the tumor lesion. The CR was also confirmed with Hepatic magnetic resonance imaging (MRI) (Figure 3). As an incidental finding, a mold of biliary mud with retrograde secondary dilation of the hepatic common duct was seen.

An Endoscopic retrograde cholangiopancreatography *(*ERCP*)* with direct cholangioscopy was then performed, confirming the absence of the tumor and the existence of the lithiasic mold which was partially removed. The biliary stent was changed and another ERCP was programed for complete stone removal. Given the accumulative hematological toxicity and the absence of disease in the imaging tests, we decided to stop chemotherapy treatment in February 2018. Another ERCP with direct cholangioscopy was done in January 2019, in which a fibrinoid ulcer was seen and biopsied with no signs suggestive of malignancy in the histopathological examination. At the present time, the patient remains without evidence of tumor recurrence, more than 30 months from the time of his initial diagnoses.

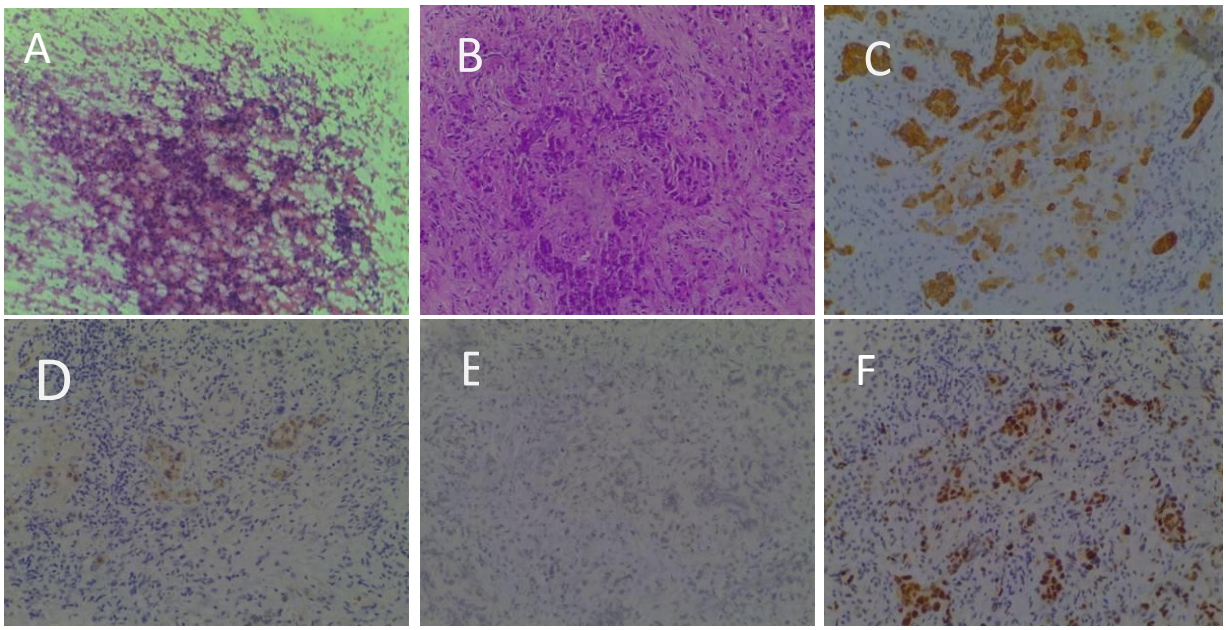

Figure 2: A. Citology: groups of irregular and hyperchromatic nuclei compatible with adenocarcinoma. A B C D E : H&E (B): Stromal infiltration of poorly differenciated adenocarcinoma; Immunohistochemical stains positive for cytokeratin CK7, MOC31 (C, D), negative for CK20 (E), and a high mitotic index measured with ki67 (F), consistent with an extrahepatic colangiocarcinoma.

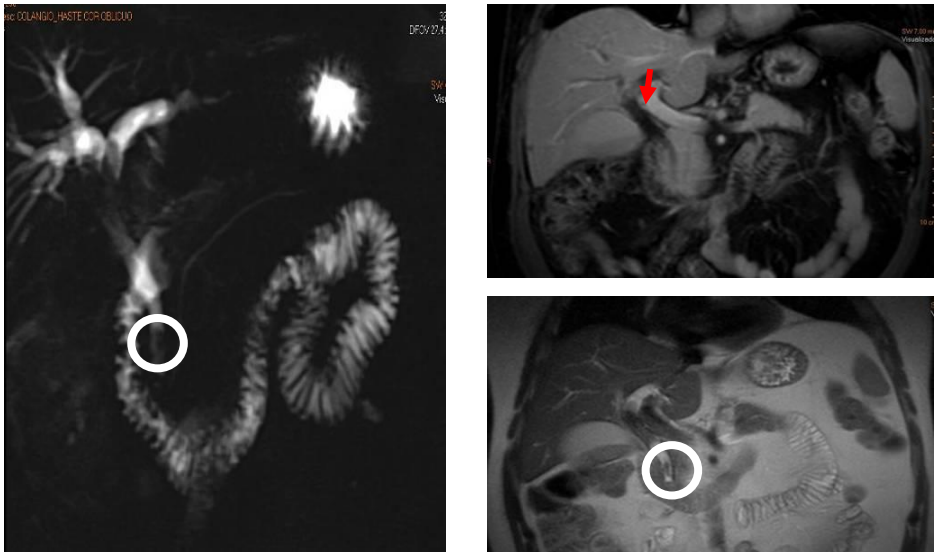

Figure 3: MRI imaging shows complete response to treatment (red arrow). Marked dilation of the bile duct by a biliary mud mold (white circle).

3. Discussion

BTC is an uncommon disease with bad prognosis. More than 75% of the patients are considered unresectable at the time of diagnosis and, even in the subset of patients with resectable disease, relapse rate remains high [4]. Chemotherapy has been commonly used to improve the outcome of these patients and to delay tumor progression. Few prospective trials have been performed in the first-line setting in advanced BTC. In the multicenter ABC-02 trial, cisplatin plus gemcitabine was associated with a significant overall survival (OS) advantage without the addition of substantial toxicity, as compared with gemcitabine alone (11.7 vs 8.1 months) [5]. A similar study was performed in a Japanese population, demonstrating a greater OS with the combination regimen (11.2 vs 7.7 months) [6].

However, gemcitabine plus cisplatin chemotherapy has not been directly compared in phase III trials with other gemcitabine-containing regimens (capecitabine, irinotecan or oxaliplatin), with the exception of gemcitabine plus S-1 in the Japanese phase III FUGA-BT trial. In a preliminary report of this trial presented at the 2018 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, Gemcitabine plus S-1 was not inferior in terms of median OS, median progression-free survival (PFS) and overall response rate (ORR) [7]. Despite the outcome improvement with first-line chemotherapy, almost all of the patients will experience disease progression. Approximately a half of them maintain a good performance status and are willing to undergo further treatment. No standard salvage chemotherapy regimen has been identified in this setting. Limited experience with second-line chemotherapy in advanced BTC is reported in the literature since clinical trials are difficult to perform due to the rarity and heterogeneity of these tumors.

For patients progressing on gemcitabine plus cisplatin regimen, options for chemotherapy include a fluoropyrimide, alone or in combination with oxaliplatin. The addition of oxaliplatin to capecitabine in patients progressing after first-line treatment with gemcitabine-based chemotherapy yielded an ORR of 3–8.5% and a median PFS and median OS of 15–17 and 17–24.7 weeks respectively which, probably, may be in the range of the results observed with a single agent therapy [8, 9].

In other study, 56 patients diagnosed with BTC (36 cholangiocarcinoma and 20 gallbladder cancer) received the combination of capecitabine and oxaliplatin. In a preliminary report, two complete and seven partial responses were observed, and a great proportion of patients experienced prolonged periods of stable disease [10]. The unusual good response to chemotherapy of our case is worth reporting, especially because systemic chemotherapy is considered little effective in disseminated or unresectable cholangiocarcinoma and there is still no established protocol in the second-line setting. Previous studies have reported isolated cases of pathological complete response (pCR) to chemotherapy in advanced BTC. In a single center phase II study that evaluated the combination chemotherapy of (GEMOX) for advanced Gallbladder cancer patients, Sharma et al. reported one case of pCR [11]. Another case report also showed a pCR in a patient with BTC after five courses of the GEMOX regimen [12]. Walker et al. reported a case of pCR in a locally advanced common bile duct cancer with the gemcitabine-cisplatin combination

regimen [13]. Other authors have also described cases of pCR in advanced disease with the combination chemotherapy of gemcitabine and S-1 [14, 15] and gemcitabine-cisplatin-S1 [16] (Table 1).

Journal Name	**Year of publication**	**First Author**	**Treatment**	**Tumor Type**
Surgical Case Report	2017	Takeshi Watanabe	Gemcitabine-TS-1	Cholangiocarcinoma
Gastrointestinal Cancer Research	2015	Moussata D	Oxaliplatin-Gemcitabine	Gallblader
Journal Gastrointestinal Oncology	2014	Walker EJ	Gemcitabine-Cisplatin	Cholangiocarcinoma
Gut and Liver	2013	Lim JH	Gemcitabine-TS-1	Cholangiocarcinoma
Molecular Clinical Oncology	2016	Tokuhiro Matsubara	Gemcitabine/cisplatin/S-1	Cholangiocarcinoma

Table 1: Published case reports of Biliary Tract Cancer with Complete Response.

Recent molecular studies have increased our understanding of pathogenetic mechanism that underly the development of cholangiocarcinoma. These have helped us to determine the significance of molecular alterations that occur in this disease and will direct the development of targeted therapy. Different studies have revealed that BTC develops in the context of chronic inflammation and cholestasis [17]. In these studies cholangiocarcinogenesis is associated with proinflammatory cytokines such as interleukin-6 (IL-6) [18]. BTC cells synthesize and secrete IL-6, with subsequent auto-and paracrine stimulation of the IL-6 receptor. Negative feedback mechanisms regulating IL-6 signaling are frequently inactivated in these tumor cells. Activation of the IL-6 receptor results in activation of JAK/STAT3, MAPK, ERK1/2 and PI3K/Akt pathways and carcinogenesis [18].

Inducible nitric oxide synthase (iNOS) has also been implicated in cholangiocarcinogenesis [18]. iNOS over-expression could be induced in BTC cell lines by proinflammatory cytokines [19]. iNOS causes oxidative damage to DNA and limits the cellular ability to repair such damage. Once malignant transformation has occurred; cells gain the ability of uncontrolled proliferation, invasion across the basement membrane, and escape apoptotic pathways [20]. Among others, erb-2, cyclooxygenase-2 and epidermal growth factor receptors (EGFR) have been identified as key molecular contributors in cholangiocarcinogenesis [21].

Erlotinib is a tyrosine kinase inhibitor (TKI) that prevents activation of EGFR through reversible blockade of the receptor's ATP binding site. It has been studied in combination to either gemcitabine and oxaliplatin (GEMOX) [21] or the VEGF inhibitor bevacizumab [22].The addition of erlotinib in these studies failed to prolong survival beyond that which would be expected from GEMOX or bevacizumab alone in patients with BTC. Cetuximab and panitumumab are monoclonal antibodies that selectively block the extracellular ligand-binding domain of EGFR

Receptor. In combination with GEMOX, cetuximab failed to demonstrate a benefit of PFS or OS in the final analysis of the study [23].

Panitumumab, on the other hand, has consistently improved survival in patients with BTC. A single arm study of 35 patients with cholangiocarcinoma that received treatment with gemcitabine, irinotecan, and panitumumab had a median PFS and OS of 9.7 mo and 12.9 mo respectively [24]. The results of this trial, while promising, were demonstrated in relatively small patient population that lacked a control group for comparison. In addition, future studies should identify biomarkers to predict response to cetuximab and panitumab, such as EGFR, KRAS, and BRAF mutations.

Bevacizumab is a humanized monoclonal antibody that blocks VEGF receptor. This agent has been studied in combination to chemotherapy with promising results. A single arm phase II study of bevacizumab with GEMOX demonstrated good efficacy against BTC, with median PFS of 7 mo and OS of 12.7 mo [25]. These results, while encouraging, should be approached with precaution as the known efficacy of GEMOX and absence of an internal control group makes it difficult to estimate the true benefit conferred by bevacizumab. The MEK inhibitor Selumetinib is a newer targeted treatment that has demonstrated activity against BTC with a favorable toxicity profile [26]. Studies of melanoma and colorectal cancer have suggested that tumors with activating mutations of BRAF are sensitive to MEK inhibition [27]. This association has not yet been investigated in BTC.

Genetic heterogeneity of cholangiocarcinomas was detected in the whole genome and epigenomic analysis of 489 tumors, performed by the International Cancer Genome Consortium. In this analysis four distinct genetic clusters were identified, defined by mutation and copy number profiles, gene expression, and epigenetics [28]. Cluster 1 was enriched in *TP53, ARID1A, BRCA1/2* mutations, and HER2 amplification. Cluster 2 was enriched with *TP53* mutations. Both clusters occurred equally as extrahepatic and intrahepatic tumors and were liver fluke-positive or fluke-negative. Cluster 4 was enriched in *BAP1* and *IDH1/2* mutations as well as fibroblast growth factor receptor (FGFR) alterations and was predominantly intrahepatic and fluke-negative, as was cluster 3. In this study, approximately 60% of patients in cluster 4 were alive at 7 years, compared with 0% to 40% of patients in the other clusters ($P < 0.0001$).

The better prognosis for cluster 4 may be partly due to its enriched presence of *FGFR2* fusion, as they have been associated with improved outcomes. *FGFR* fusions are driver events that result in ligand-independent activation of the FGFR pathway. BGJ398 is an orally, selective, ATP-competitive pan-FGFR inhibitor that showed activity in tumor models with FGFR alterations. In the phase II trial of BGJ398 in 61 heavily pretreated patients with *FGFR* alterations (79% had *FGFR* fusions), ORR was 14.8% (18.8% FGFR2 fusions only), disease control rate was 75.4% (83.3% FGFR2 fusions only), and estimated median PFS was 5.8 months (95% CI, 4.3 to 7.6 months) [29]. Other agents have shown activity against *FGFR2* resistance mutations. In a phase I/II basket trial of TAS-120 that included 23 patients with *FGFR2* fusion and other *FGFR*-altered cholangiocarcinomas, 4 of 9 patients achieved

a partial response, and 8 patients had tumor regression. TAS-120 is currently being evaluated in a large basket trial with planned enrollment of over 800 patients [30].

Another new target is the isocitrate dehydrogenase-1 *(IDH1)* mutation, which occurs in about 20% of intrahepatic tumors. Ivosidenib (AG-120), is an oral, selective, reversible inhibitor of mutant *IDH1* currently been evaluated in phase III trials of cholangiocarcinoma and acute myelogenous leukemia [31]. About 2.5% of cholangiocarcinomas have mismatch repair (MMR) deficiency, which makes them a target for programmed cell death protein 1 (PD-1) inhibitors. In a series of five uncontrolled, single-arm, multi-center clinical trials, pembrolizumab was assesed in MMR-deficient (dMMR)/MSI-high (MSI-H) advanced solid tumors ($N = 149$) [32]. Eleven of the 149 patients enrolled in these studies had BTCs. This small subset of BTCs showed an ORR of 27%, with a duration of response ranging from 11.6 to 19.6 months [26]. dMMR/MSI occurred across all BTC subtypes, most frequently in intrahepatic cholangiocarcinoma [33].

Finally, by integrating targeted therapy with the molecular profiles of tumor, we hope to accomplish the goal of precision treatment of patients with malignant diseases of the biliary tract.

4. Conclusion

In conclusion, we experienced a patient with unresectable BTC who was treated with capecitabine and oxaliplatin combination and achieved complete response after progression to first-line treatment with gemcitabine-cisplatin. Our case also suggests that selected patients may demonstrate robust or even complete responses to chemotherapy. There is a need to further characterize the molecular networks driving its progression and identify different molecular subtypes that could direct management of these patients.

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