Advanced gallbladder cancer with high tumor mutation burden: a case report and literature review

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Background: Gallbladder cancer (GBC) is a common malignant tumor of the biliary system. It is characterised by insidious onset, rapid progression and poor prognosis. Symptoms often indicate advanced or late-stage disease, with a 5-year survival rate of only 5–15%.

Case Description: We present a case study of a patient with GBC who had a tumor mutation burden (TMB) of 32.5/MB (≥10 muts/MB). The patient received mFOLFIRINOX as first-line chemotherapy, which demonstrated significant efficacy. After stabilizing the disease, a sequential chemotherapy regimen was chosen. This regimen combined the immune checkpoint inhibitor (ICI) toripalimab (JS001), a humanised IgG4 monoclonal antibody targeting programmed cell death protein 1 (PD-1), with S-1 therapy, an oral fluoropyrimidine derivative. However, this treatment did not provide any significant clinical benefit for the patient. Therefore, we hypothesise that combining immunotherapy with chemotherapy may be more effective as a first line treatment for high-TMB advanced GBC. This hypothesis needs to be validated in large-scale clinical studies.

Conclusions: In summary, mFOLFIRINOX is a safe and effective first-line chemotherapy regimen for advanced GBC. The timing of combining immunotherapy with chemotherapy requires careful consideration. Further clinical trials involving immunotherapy in advanced GBC are necessary to identify biomarkers that can guide clinical decisions.

Keywords: Advanced gallbladder cancer (advanced GBC); biliary tract cancer (BTC); immunotherapy; tumor mutation burden (TMB); case report

Received: 25 October 2023; Accepted: 08 February 2024; Published online: 20 March 2024.

doi: 10.21037/acr-23-188

View this article at: https://dx.doi.org/10.21037/acr-23-188

Introduction

Background

Biliary tract cancers (BTCs) are a heterogeneous group of aggressive, rare malignant tumours that originate in the bile ducts, both within and outside the liver (1). BTCs comprise cholangiocarcinoma, gallbladder cancer (GBC), and ampulla of Vater cancer (AVC) (2). GBC is a malignant tumor of the biliary system, accounting for approximately 90% of BTCs (3-6). GBC has an annual incidence rate of 1.5 to 2.7 cases per 100,000 people (7-9), making it the sixth most common gastrointestinal cancer. It is an aggressive malignant tumor with a 5-year survival rate ranging from 4% to 60%, depending on the stage and resectability of the tumor (10-14). For patients with GBC, negative surgical margins are still the only hope for long-term survival. Unfortunately, most GBCs are diagnosed at an advanced stage, and 40–75% of patients diagnosed have metastatic disease (15). Advanced, unresectable and metastatic GBC is associated with a poor prognosis and systemic chemotherapy is the only treatment option for these patients (16). Currently, platinum or fluorouracil are the most commonly used chemotherapeutic agents for advanced GBC. However, an alternative chemotherapy regimen combining gemcitabine and cisplatin (CISGEM) was proposed in the ABC-02 clinical trial for BTCs, including locally advanced or metastatic cholangiocarcinoma, ampullary carcinoma and GBC (17-19). The ABC-02 and BT22 trials have revolutionised first-line treatment and established gemcitabine and cisplatin (CISGEM) as the new standard of care for advanced disease (19,20). The mFOLFIRINOX regimen and the CISGEM regimen have shown favorable activity and tolerability in retrospective and phase II clinical trials in first and/or second line treatment of advanced BTC (21). Results from the phase III TOPAZ-1 trial showed that immunotherapy in combination with CISGEM improved overall survival (OS), suggesting that immunotherapy has significant clinical benefit for cancer patients. However, there are only a few reports of patients with advanced GBC who have received sequential chemotherapy with immunotherapy after first-line chemotherapy. The modest survival benefit of dual agents suggests that there is an urgent need to define new first-line strategies for the treatment of metastatic BTC (22). Here, we report a case of a patient with high cc (TMB) advanced GBC who benefited from first-line treatment with mFOLFIRINOX and underwent sequential chemotherapy with immunotherapy followed by tumor recurrence and metastasis and death, which may provide a reference for clinical optimisation of treatment modalities for patients with advanced GBC. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-188/rc).

Highlight box

Key findings

- A patient with advanced gallbladder cancer (GBC) and high tumor mutation burden (TMB) benefited from first-line treatment with mFOLFIRINOX.
- After undergoing sequential chemotherapy with immunotherapy, the patient experienced tumor recurrence and metastasis.

What is known and what is new?

- Combining chemotherapy with immunization enhances the first-line treatment of advanced GBC.
- The timing of combination therapy needs to be carefully selected as the immunotherapy may be best employed at an early stage.

What is the implication, and what should change now?

- The use of immunotherapy in combination with chemotherapy may not be appropriate in advanced stages with high TMB.
- More clinical trials involving immunotherapy in GBC are appealed to identify biomarkers that can guide clinical decisions for a new era of individualized therapy.

Case presentation

Here, we report the case of a 57-year-old woman with a 9-year history of diabetes. A timeline summarizing the main events of this case report is shown in *Figure 1*. On 11 June 2019, she developed yellow skin and sclera, dark-colored urine, loss of appetite, fatigue, and abdominal distension, which worsened after meals. These symptoms were accompanied by tolerable back and right upper abdominal pain and nausea without vomiting. An upper abdominal computed tomography (CT) scan was performed in the outpatient clinic and showed an obstruction in the area of the hepatic portal vein. Liver function tests showed elevated levels of glutamic-pyruvic transaminase: 152 U/L (normal: 7–40 U/L), glutamic-oxaloacetic transaminase: 90 U/L (normal: 13–35 U/L), total bilirubin: 244.5 μmol/L (normal: 5–21 μmol/L), direct bilirubin: 219.8 μmol/L (normal 0–6 μmol/L), and indirect bilirubin: 24.7 μmol/L (normal: 2–15 μmol/L). Following an enhanced abdominal CT scan, she was diagnosed with “hilar metastasis of gallbladder tumor, pulmonary metastasis and intrahepatic bile duct dilatation”. On 19 June 2019, the patient underwent

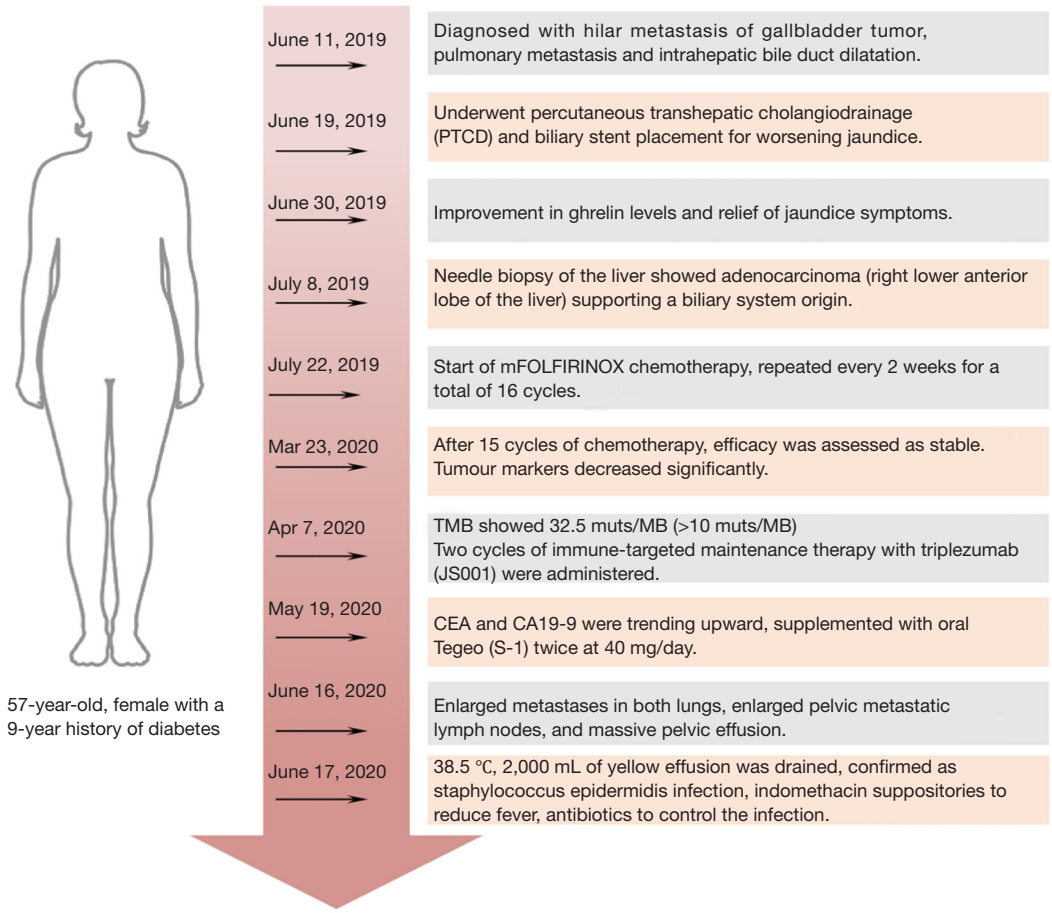

Figure 1 A timeline summarizing the main events of this case report. TMB, tumor mutation burden; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

percutaneous transhepatic cholangiodrainage (PTCD) and biliary stent placement for worsening jaundice. Post-operative catheter drainage was uneventful. Eleven days later, liver function tests showed improved glutamic-pyruvic transaminase levels: 43 U/L, glutamic-oxaloacetic transaminase: 35 U/L, total bilirubin: 80.2 μmol/L, direct bilirubin: 75.3 μmol/L, and indirect bilirubin: 4.9 μmol/L. Jaundice symptoms were also relieved.

On 8 July 2019, an ultrasound-guided needle biopsy of the liver was performed. The results confirmed an adenocarcinoma (of the right lower anterior lobe of the liver), which supported the origin of the bile duct system. Immunohistochemistry results were: carbohydrate antigen 19-9 (CA19-9) (+), CD34 (–), CK19 (+), CK7 (+), Heppar-1 (–), KI-67 (20%), β-catenin (–), CK8/18 (+), CK20 (–), and Villin (+). Imaging and pathology are shown in *Figures 2,3*, respectively. The results of gene detection by puncture pathology showed that the TMB was 32.5 muts/MB, including three mutations were in critical genes (*Table 1*).

On 22 July 2019, she was prescribed mFOLFIRINOX, a 4-drug combination regimen. On the first day of each cycle, oxaliplatin 85 mg/m^2 [intravenous (IV), 120 min], irinotecan 150 mg/m^2 (IV, 90 min), leucovorin 400 mg/m^2 (IV, 2 h, at the same time as irinotecan), and 5-fluorouracil (5-FU) 2,400 mg/m^2 (IV for 46 h), were administered and repeated every two weeks. A total of 16 cycles of the chemotherapy regimen were administered. Imaging evaluation after six cycles of chemotherapy showed a partial response (PR) and a significant reduction in lung metastases and bilateral iliac fossa nodules (*Figure 4*). After 10 cycles and 15 cycles of chemotherapy, the patients were re-evaluated with enhanced CT of the chest and abdomen, and were found to be in stable condition (*Figure 5*), with tumor markers such as CA19-9 and carcinoembryonic antigen (CEA) decreasing

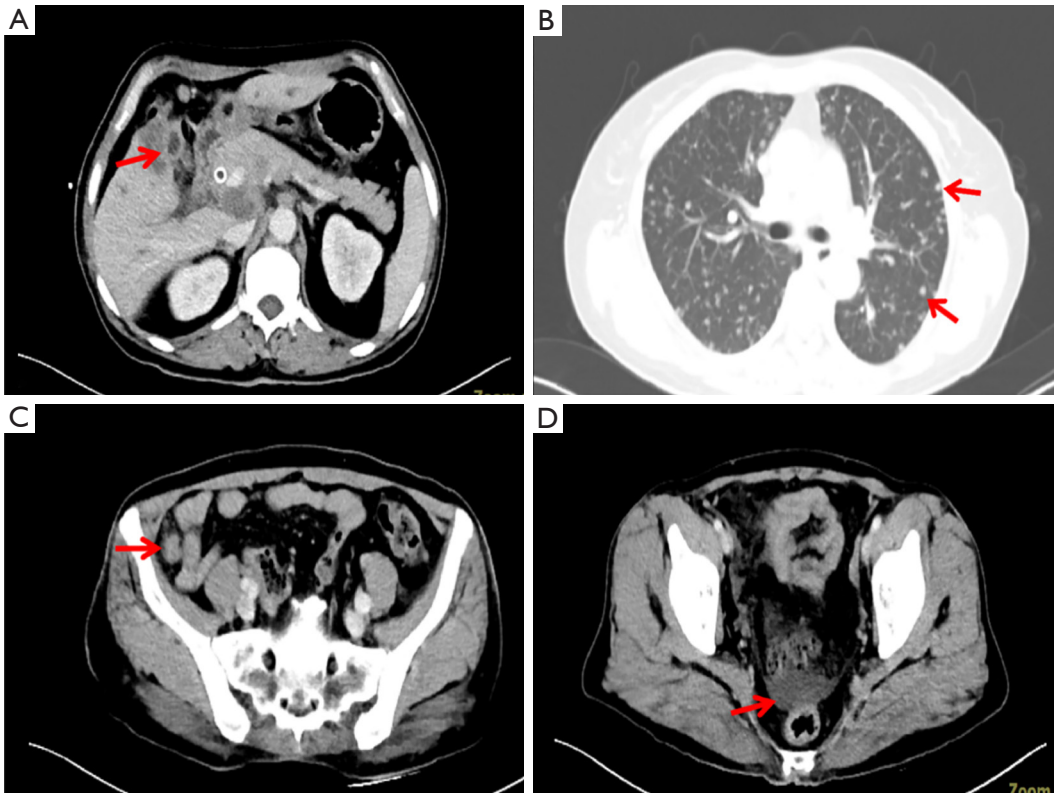

Figure 2 Major lesions prior to chemotherapy (red arrows). (A) Abdominal enhanced CT: around the liver, gallbladder and pancreatic portal vein head frequent malignant tumors and lymph node metastasis, PTCD and bile duct stenting after change; (B) chest enhancement CT: the multiple metastases; (C) pelvic enhancement CT: iliac fossa metastasis nodule; (D) pelvic enhanced CT: pelvic effusion in small quantities. CT, computed tomography; PTCD, percutaneous transhepatic cholangiodrainage.

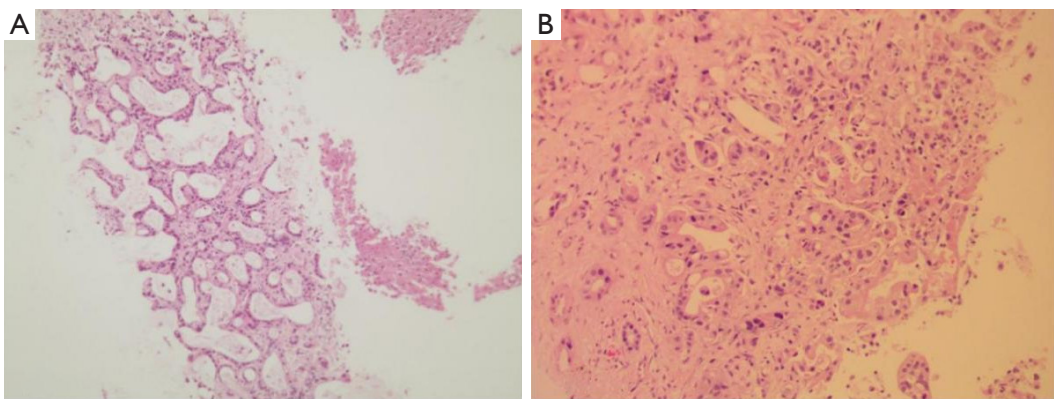

Figure 3 Light microscope pathology. The results of hematoxylin-eosin staining (HE): (A) 100×; (B) 400×.

significantly. Patient's cough and sputum also showed significant improvement, and her weight increased by 10 kg.

Notably, the patient experienced some significant side effects during chemotherapy and related treatments. The patient developed mild tongue numbness and sporadic abdominal discomfort on the first day after the first cycle of chemotherapy, which may be due to the neurotoxicity of oxaliplatin. The patient also developed delayed

diarrhoea with watery stools, which was treated with oral Imodium. A blood test on admission prior to the ninth cycle of chemotherapy showed grade II post-chemotherapy myelosuppression, and pegylated recombinant human granulocyte stimulating factor (rhG-CSF) was administered.

However, after the last cycle of mFOLFIRINOX chemotherapy (cycle 16), the patient felt weak and was unable to tolerate systemic intravenous chemotherapy. The gene puncture test showed that the patient had a TMB of 32.5 muts/MB (≥10 muts/MB). Two cycles of immune-targeted maintenance therapy with triplezumab (JS001) were administered from 7 to 28 April 2020. During the second cycle of immunotherapy, the tumor blood markers CEA and CA19-9 showed an increasing trend, so the second cycle was supplemented with two oral treatments of 40 mg of S-1 per day.

Noteworthily, on 16 June 2020, an imaging study showed an increase in metastatic tumors in both lungs, enlarged metastatic lymph nodes in the pelvic cavity and a large amount of fluid in the pelvic cavity (*Figure 6*). The patient received a percutaneous peritoneal fluid puncture for drainage and approximately 2,000 mL of yellow fluid

Table 1 TMB and genetic mutations in the tumor

Important mutations variation	Mutation rate of abundance/copy
TP53: NM_000546: exon8: c.886delC: p.H296fs, %	25.20
ERBB2: NM_004448: copy number, %	2.83
IDH1: NM_005896: exon4: c.C395T: p.R132H	1.00
TMB, muts/MB	32.50
Objective response rate, %	36.90

TMB, tumor mutation burden.

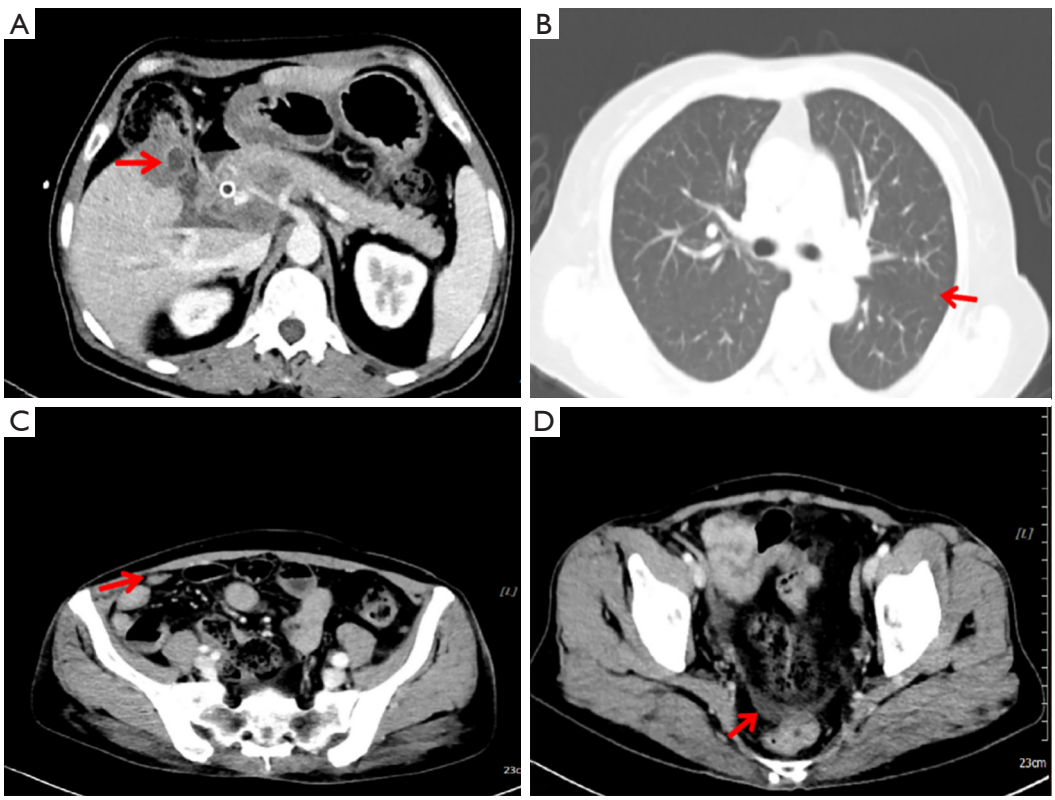

Figure 4 Major lesions after six cycles of chemotherapy. Significant changes indicated by red arrows. (A) The abdominal enhanced CT image; the gallbladder and the surrounding intrahepatic metastasis basically stable, reduced bile duct expansion; (B) the chest-enhanced CT image: double lung multiple metastases significantly reduced, close to all but disappear; (C) the pelvis enhanced CT image; Iliac fossa metastasis nodules are smaller and be insufflated and pushed to the abdominal wall; (D) the pelvic enhanced CT; the pelvic effusion decreased significantly. CT, computed tomography.

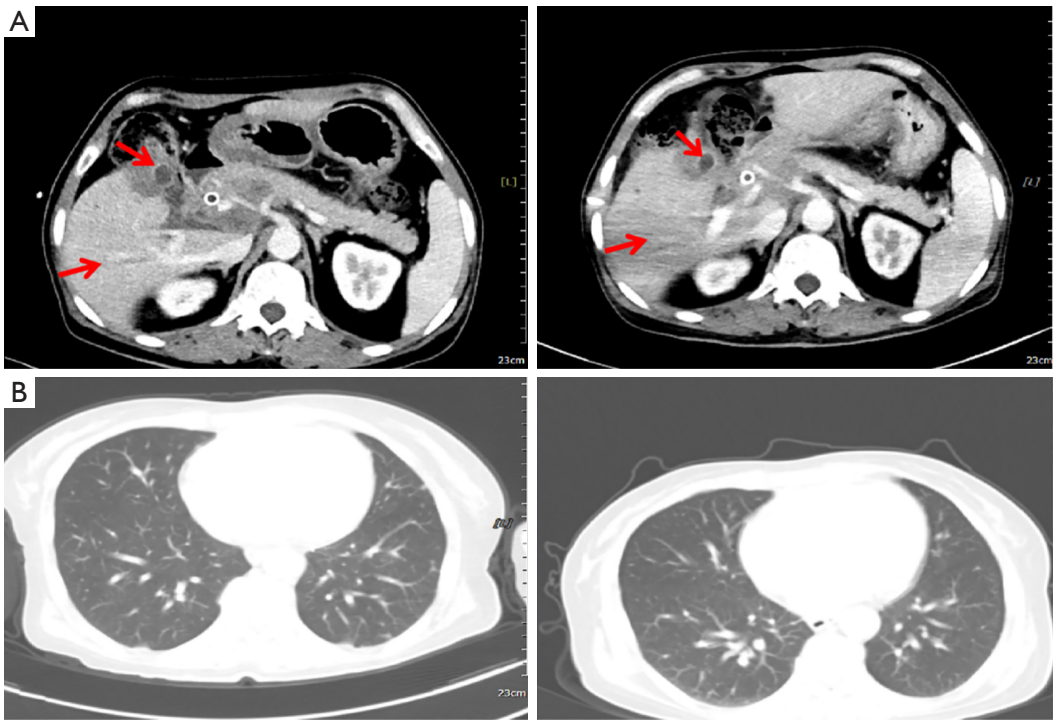

Figure 5 The patient's condition has improved. Significant changes indicated by red arrows. (A,B) Thoracic and abdominal enhanced CT was repeated after 10 (December 15, 2019) and 15 (March 23, 2020) cycles of chemotherapy, and lung lesions, gallbladder and liver lesions was stable. CT, computed tomography.

was drained. During the drainage procedure she developed a fever with a body temperature of 38.5 ℃. The fever was reduced with an indomethacin suppository. Microbiological cultures confirmed the presence of staphylococcus aureus in the ascites. Antibiotics (levofloxacin) were given according to the sensitivity of the bacterial culture. In addition, given the progression of the tumor, discontinuation of immunotherapy was recommended. The patient chose to be discharged from hospital and eventually died at home.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family member for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

GBC is the most common type of BTC. It is usually diagnosed at an advanced stage, which leads to a poor prognosis and limited treatment options. The CISGEM regimen is the reference first-line chemotherapy for patients with advanced BTC (17). It is also recommended as first-line treatment for unresectable and metastatic BTCs, including unresectable GBC. Meanwhile, FOLFIRINOX is currently applied in the post-operative adjuvant treatment of pancreatic ductal adenocarcinoma (PDAC) and advanced metastatic pancreatic cancer. The FOLFIRINOX regimen was opted, because of the similarities in histology, treatment, and prognosis between BTCs and pancreatic adenocarcinoma (PA). Then, the patient experienced higher grade III/IV toxicity, particularly neutropenia, diarrhoea and peripheral neuropathy, similar to a landmark study by Conroy *et al.* (23). To reduce toxicity, mFOLFIRINOX protocols with reduced irinotecan or 5-FU doses are commonly used (24).

Over the past decade, immunotherapy has changed the treatment paradigm for a wide range of solid tumors, improving clinical outcomes and achieving unprecedented response rates (25,26). The OS benefit was more pronounced in the intrahepatic cholangiocarcinoma (iCCA) subgroup of the KEYNOTE-966 study, which may be due

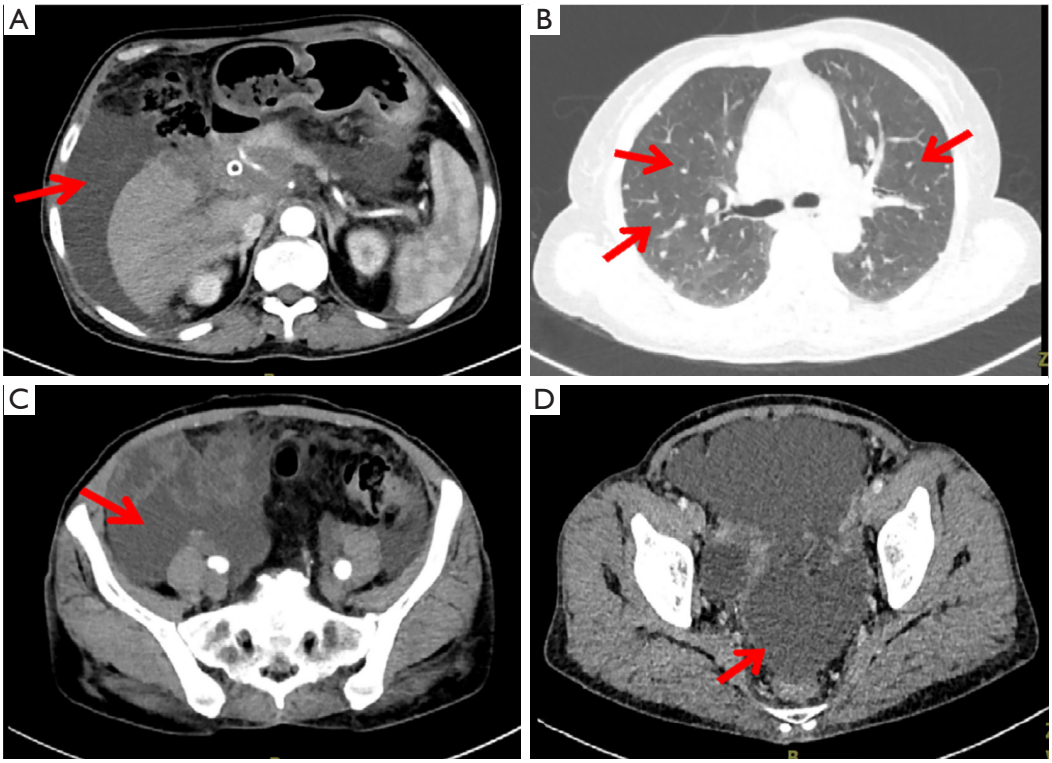

Figure 6 Patient with poor outcome after sequential chemotherapy with immunotherapy and multiple metastases of the tumor. Significant changes indicated by red arrows. (A) Abdomen with large amount of ascites; (B) lungs suggestive of multiple metastases; (C) increased abdominal mass; (D) pelvic metastatic lymph nodes were enlarged; and fluid accumulation was increased.

to the fact that these patients were not inherently sensitive to CISGEM and were more sensitive to immunotherapy. MOUSEION-01 study shows that women who receive single-agent immunotherapy benefit less than men who receive placebo (27). The recent MOUSEION-06 study showed that checkpoint inhibitor monotherapy or immune-based combination therapy was associated with improved survival regardless of whether the ECOG PS was 0 or 1. We need real-world clinical trials with more patients (28). In current clinical practice, there are a number of cases where patients with GBC have achieved a survival benefit after receiving immunotherapy, which means that there must be patients with GBC who can benefit from the survival benefit of immunotherapy. More immunotherapy trials for bile duct cancer are underway.

Genetic testing showed that the patient had a TMB of up to 32.5 muts/MB (TMB ≥10 muts/MB). Samstein *et al.* showed that TMB and OS are positively correlated, suggesting that TMB can predict the clinical response to immune checkpoint inhibitors (ICIs) (29). A meta-analysis found a significant correlation between TMB and objective response rate (ORR) in 27 different tumors, including GBC (30). In the KEYNOTE-158 study, patients with TMB-H (≥10 muts/MB) had a higher ORR with pembrolizumab than patients with TMB <10 muts/MB (29% *vs.* 6%) across 10 tumors, including anal canal and BTC (31). The TOPAZ-1 trial (NCT03875235) represents a breakthrough in the first-line treatment of advanced BTC with a combination approach of immunotherapy and chemotherapy. In addition, a phase I clinical trial conducted in Japan found that the ICI (nivolumab), either alone or in combination with cisplatin + gemcitabine chemotherapy, had a manageable safety and efficacy profile and that first-line immunotherapy in combination with chemotherapy was more effective (32). Patients with advanced tumors who cannot receive standard treatment may benefit from immunotherapy if they have a high TMB. However, TMB is not unanimously accepted (33,34). The CheckMate 227 study updates OS data and finds that TMB does not predict OS gain. In the KEYNOTE-021/189/407 study, there was no correlation between TMB and the efficacy of pembrolizumab + chemotherapy. In conclusion, TMB

may predict response to ICI therapy in some cases, but conclusions are inconsistent, and caution should be exercised, especially when TMB predicts long-term outcomes and the efficacy of combination immunotherapy. Combining multiple biomarkers, such as programmed cell death-ligand 1 (PD-L1) and TMB, may be a better way to screen for immunotherapy benefit. Other immunotherapy trials for GBC are underway.

Toripalimab is approved for the second-line treatment of unresectable or metastatic malignant melanoma following failure of prior systemic therapy, recurrent or metastatic nasopharyngeal carcinoma and metastatic urothelial carcinoma following failure of prior systemic therapy. Given the patient's financial situation, we administered toripalimab (JS001) for 1 cycle. In addition, the oral fluorouracil derivative S-1, with or without gemcitabine, is considered a promising treatment for advanced GBC. In the Japanese randomized phase II study JCOG 0805 (35), the median progression-free survival (PFS) with S-1 monotherapy was 4.2 months. Due to the increased trend of CEA and CA19-9 prior to immunotherapy in the second cycle and the frail physical condition of the patients, S-1 was included in the therapeutic regimen. Unfortunately, after two months of immunotherapy, the patient had massive fluid accumulation in the abdominal cavity and abnormal levels of tumor markers. Percutaneous peritoneal effusion puncture drainage was performed to drain the ascites. During the drainage, antibiotics were given to reduce the abdominal infection.

Based on the findings of Ueno *et al.* (32) and our case, we speculate that immunotherapy combined with chemotherapy may be more effective for first-line use in advanced GBC with high TMB. Maybe we should try to use immunotherapy as early as possible. In addition, our patient was weak and susceptible to infection after receiving chemotherapy, which was exacerbated by the combination of antibiotics and immunotherapy, which may have contributed to the failure of our treatment. The duration of antibiotic exposure is an important influence on the relationship between antibiotics and ICB response. Whether patients' OS and PFS would be affected after the combination of antibiotics and immunotherapy was an open question that needs to be validated in a large sample of clinical trials to further assess the efficacy of these combination regimens. A 2019 meta-analysis reported longer OS and PFS in patients who were not exposed to antibiotics during immune checkpoint lockdown blockade (ICB) (36). It has been reported that the use of antibiotics 42 days before starting ICB appears to be harmful (36). Of note, the heterogeneity in terms of mutational burden and poor prognosis in patients with GBC should be taken into account, as the use of immunotherapies such as ICB can cause hyper-progressive disease (HPD) (37). Therefore, further studies are needed to determine the curative effect of immunotherapy in GBC and the molecular mechanisms involved in transformation to HPD.

Conclusions

In conclusion, we report the case of an advanced GBC patient treated with an mFOLFIRINOX chemotherapy whose PFS and OS were significantly prolonged with tolerable side effects. Further sequential immunotherapy in the patient had a poor effect, suggesting that the use of immunotherapy in combination with chemotherapy at a later stage may be inappropriate and that the timing of combination therapy needs to be carefully chosen. Therefore, more clinical trials of immunotherapy in GBC are needed to identify biomarkers to guide clinical decisions and open a new chapter in individualized therapy.

Acknowledgments

We thank the Departments of Pathology, Invasive Technology, and Hepatology, Qilu Hospital (Qingdao) for their support in the collection of pathological and clinical data.

Funding: The study was supported by the Graduate Student Research Grant from Weifang Medical University (2022YJSCX019).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-188/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-23-188/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-188/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's family member for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/acr-23-188
Cite this article as: Wang J, Liu J, Yan C, Wang K, Li Q, Yu J. Advanced gallbladder cancer with high tumor mutation burden: a case report and literature review. AME Case Rep 2024;8:53.