

[CASE REPORT]

Microsatellite Instability-high Intrahepatic Cholangiocarcinoma with Portal Vein Tumor Thrombosis Successfully Treated with Pembrolizumab

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Abstract:

A 60-year-old man presented with postoperative recurrence of intrahepatic cholangiocarcinoma with right portal vein tumor thrombosis (PVTT). After failure of standard chemotherapy, a liver biopsy showed that his microsatellite instability (MSI) status was high. Treatment with the immune checkpoint inhibitor (ICI) pembrolizumab was commenced, which resulted in a partial response and resolution of the PVTT. There were no significant immune-related adverse events. According to recently published reports, the frequency of MSI-high biliary tract cancer (BTC) is about 0-2.1%, which is extremely rare. However, ICIs may be effective in patients with MSI-high BTC, such as the present patient.

Key words: microsatellite instability-high, intrahepatic cholangiocarcinoma, portal vein tumor thrombosis, immune checkpoint inhibitor, pembrolizumab

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Introduction

Based on the results of a phase III clinical trial [advanced biliary tract cancer (ABC)-02 trial] (1) and a phase II clinical trial (BT-22 trial) (2), gemcitabine plus cisplatin (CisGem) has become the standard first-line chemotherapeutic regimen for advanced biliary tract cancer (BTC) in Japan and elsewhere. However, the median overall survival (OS) after administration of CisGem for advanced BTC is 11.2-11.7 months, which requires improvement.

The phase II KEYNOTE-158 study revealed that, regardless of their primary site, microsatellite instability (MSI)-high and mismatch repair-deficient (dMMR) tumors have promising responses to immune checkpoint inhibitors

(ICIs) (3). In December 2018, pembrolizumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, was approved in Japan for MSI-high solid cancers that were refractory to standard chemotherapy; this includes BTC.

We herein report a patient with MSI-high intrahepatic cholangiocarcinoma (ICC) with portal vein tumor thrombus (PVTT) in whom pembrolizumab was effective.

Case Report

A 60-year-old man with hepatitis C virus (HCV)-related cirrhosis developed ICC (Fig. 1A, B), for which hepatic S6 partial resection and cholecystectomy were performed (Fig. 1C-G). After the surgery, he was treated twice for

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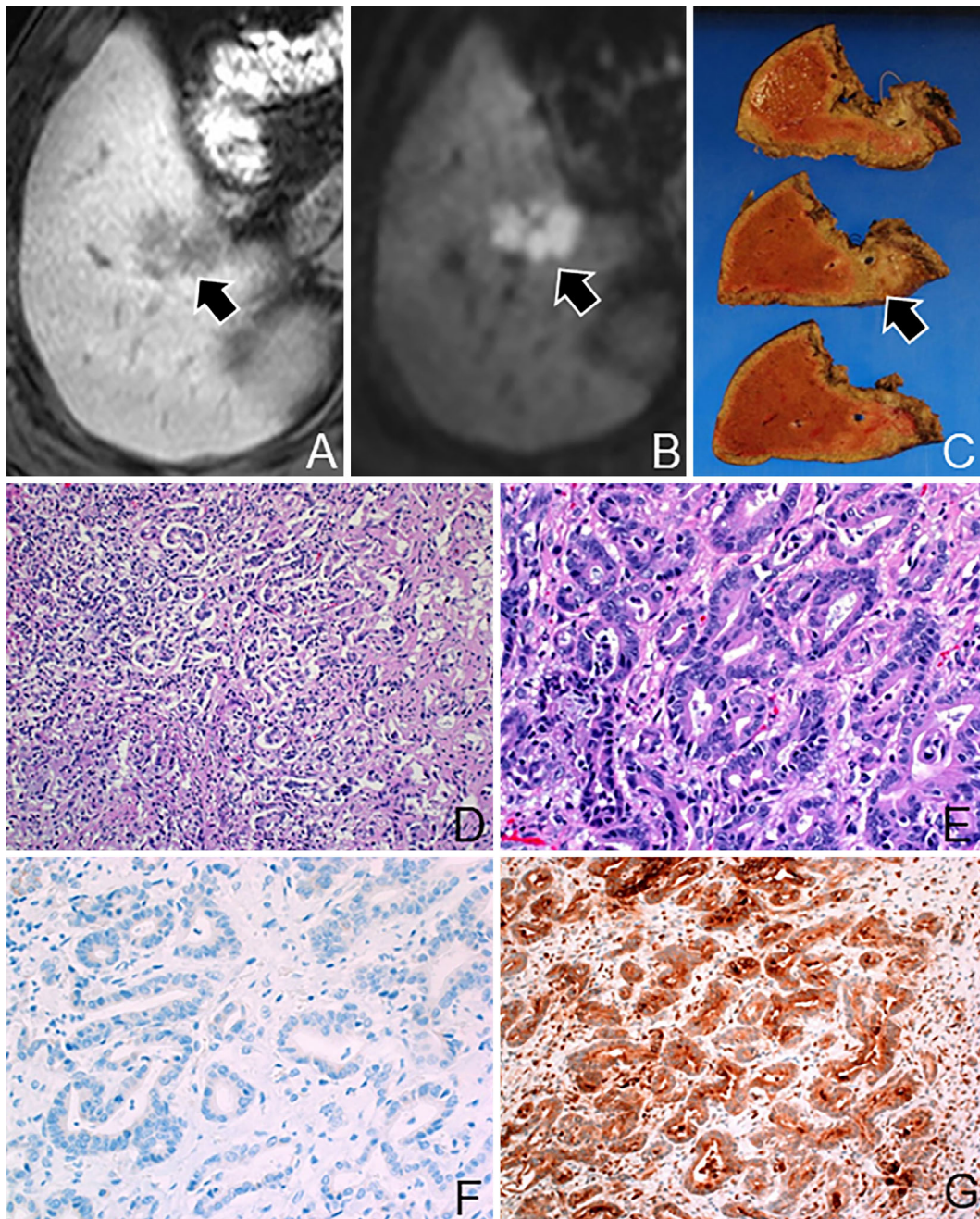


Figure 1. Gadolinium ethoxybenzyl diethylenetriamine magnetic resonance imaging (Gd-EOB-DTPA-MRI) (A, B). Gd-EOB-DTPA-MRI showing strong contrast between the liver parenchyma and a focus of intrahepatic cholangiocarcinoma that has obvious hypointensity (black arrow) (A). Diffusion-weighted imaging showing the high signal intensity of the lesion (black arrow) (B). Gross slices of a fixed specimen from hepatic S6 partial resection: The parenchymal lesion (black arrow) was diagnosed as the primary tumor (C). Photomicrographs showing moderately differentiated adenocarcinoma (D-G). Hematoxylin and Eosin (H&E) staining ($\times 100$) (D). H&E staining ($\times 400$) (E). Immunohistochemical staining revealed the tumor cells to be negative for alpha-fetoprotein (F) and positive for carcinoembryonic antigen (G).

HCV infection with direct-acting antivirals (sofosbuvir/ledipasvir and daclatasvir/asunaprevir/beclabuvir). His HCV relapsed after both treatments, although HCV RNA became negative during treatment with both direct-acting antiviral combinations. He had been using insulin for type 2 diabetes. There was nothing of note in his family history.

Four years after his surgery, a nodule that appeared in the

right posterior segment of the liver was biopsied and found to be a recurrence of ICC (Fig. 2A, B). Retroperitoneal lymph node metastasis was also found near the right renal vein (Fig. 2D), and oral oxycodone was started to control the right hypochondrial pain caused by it. CisGem was commenced as first-line chemotherapy, which achieved stable disease (SD). Thrombocytopenia necessitated progressive re-

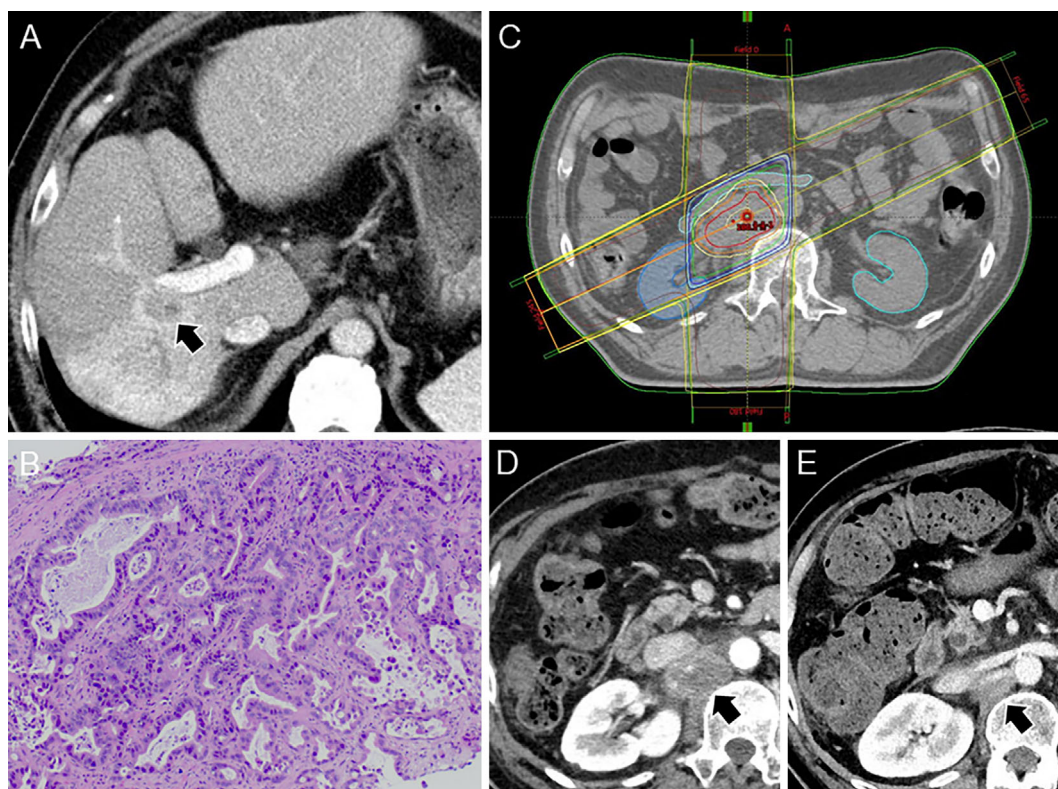


Figure 2. Contrast-enhanced computed tomography showing the recurrent tumor (black arrow) (A). Photomicrograph of a specimen of the recurrent tumor obtained by a percutaneous liver tumor biopsy. As in the primary lesion, a histopathological examination revealed poorly differentiated adenocarcinoma (Hematoxylin and Eosin staining, $\times 100$) (B). Plain computed tomography for radiation therapy planning (C). Contrast-enhanced computed tomography showing retroperitoneal lymph node metastasis (black arrow) (D). After radiation therapy (total 46 Gy/23 fraction), the metastatic lesion had shrunk significantly (E).

duction of his CisGem to a 60% dose. Finally, despite this dose reduction, he developed grade 3 thrombocytopenia after three courses and CisGem therapy was discontinued (Fig. 3).

He then commenced oral S-1 as second-line chemotherapy. This initially maintained SD; however, he was found to have progressive disease (PD) one year later. His performance status deteriorated, and the decision was made to concentrate on palliative care. He was given radiation therapy (total 46 Gy/23 fractions) to the retroperitoneal lymph node metastasis to control his cancer pain, which was alleviated along with significant shrinkage of the metastatic lesion (Fig. 2C-E). Fifteen months after the initial chemotherapy, his intrahepatic lesions had grown, accompanied by right PVTT (Vp3; portal invasion at the first branch; Fig. 4A, B). His MSI status was determined by an examination of liver biopsy specimens from the site of recurrence. Because the MSI status was high, he was started on an ICI (intravenous pembrolizumab 200 mg, every three weeks). This achieved a partial response (PR) and disappearance of the Vp3 PVTT (Fig. 4C, D). During the subsequent year, the PR was maintained. Nine months after the start of ICI, the level of carcinoembryonic antigen (CEA) increased again; however, whole-body computed tomography showed no apparent new

lesions, and PR was maintained. Ten months after the start of ICI, the CEA level showed a downward trend (Fig. 3).

Thus far, he has shown no significant adverse events, such as immune-related adverse events (irAEs).

Discussion

ICIs have revolutionized the treatment of patients with various advanced-stage cancers. Several studies have shown that MSI-high/dMMR is a positive predictor of the response to ICIs (4). In May 2017, the Food and Drug Administration granted accelerated approval to the anti-PD-1 monoclonal antibody pembrolizumab for treatment of patients with unresectable or metastatic MSI-high or dMMR solid tumors that continued to progress after standard chemotherapy based on the data from 233 patients with MSI-high or dMMR cancers who had been enrolled in the phase II KEYNOTE-158 study. This was the first time that the Food and Drug Administration had approved a cancer treatment based on that tumor's specific genetic features, regardless of its primary site.

In December 2018, pembrolizumab was also approved in Japan for the treatment of advanced or recurrent MSI-high solid tumors that continue to progress after standard chemo-

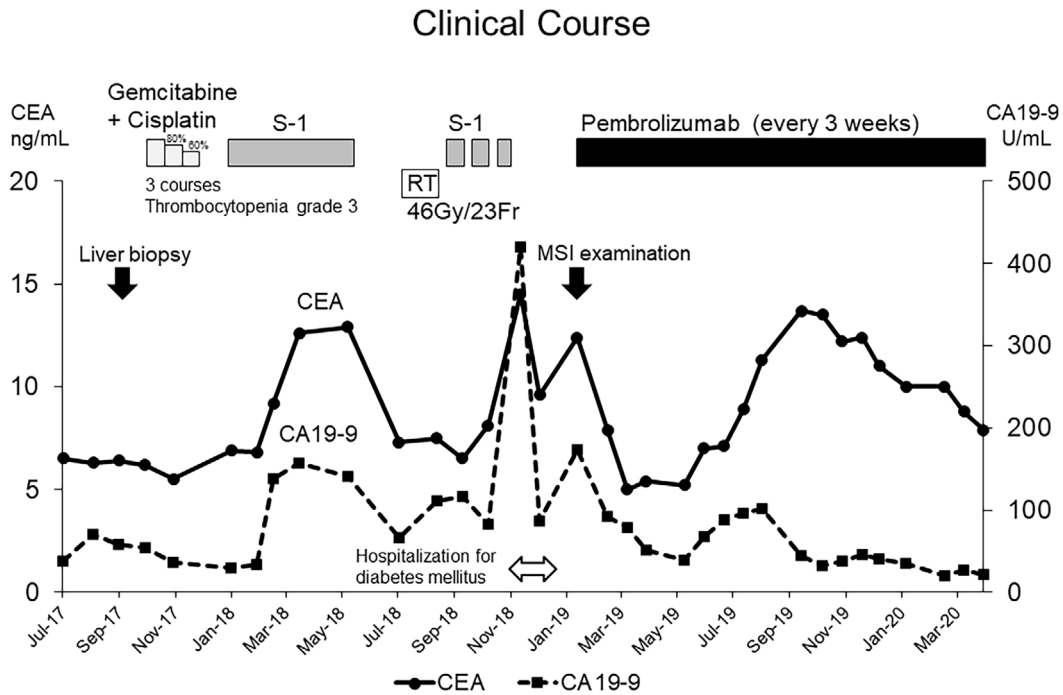


Figure 3. Clinical course showing changes in the concentrations of tumor markers and a summary of the main treatment.

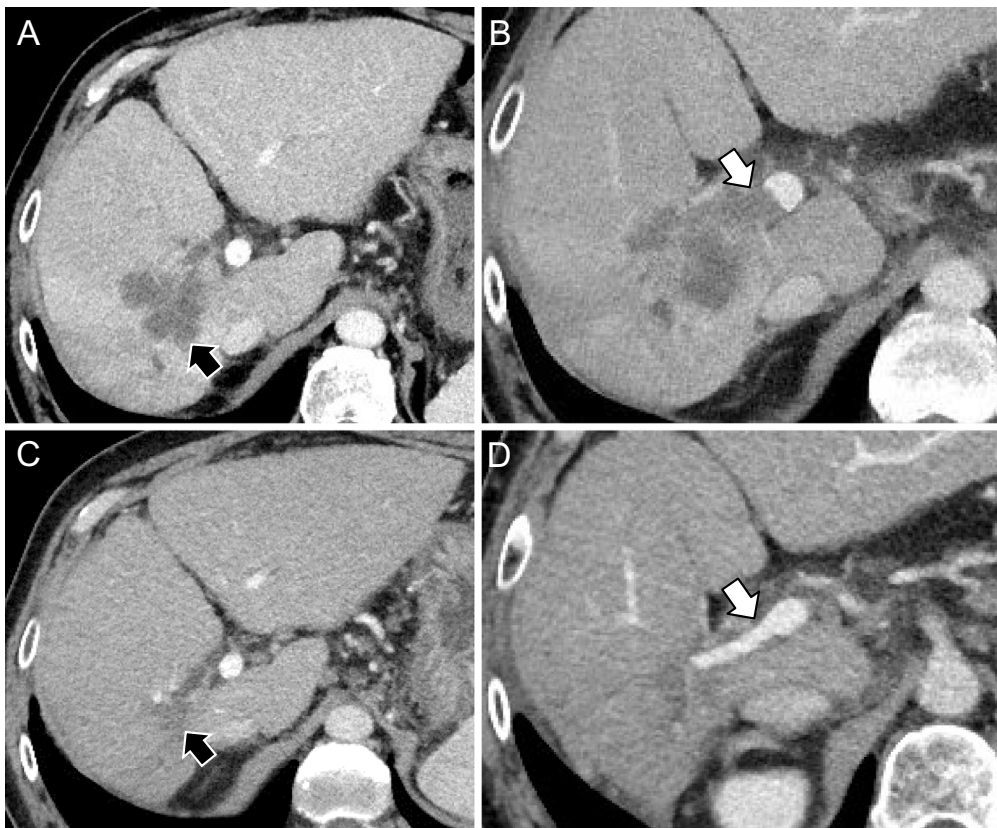


Figure 4. Contrast-enhanced computed tomography images. Recurrent intrahepatic cholangiocarcinoma (ICC) that had been refractory to chemotherapy (black arrow) (A). Portal vein tumor thrombosis (PVTT) (white arrow) (B). One year after commencing pembrolizumab, the recurrent ICC lesion (black arrow) showed a sustained partial response (C), and the PVTT (white arrow) had almost completely resolved (D).

Table 1. Reported Biliary Tract Cancers (BTCs) with Frequency of Microsatellite Instability-high/mismatch Repair Deficient Characteristics.

| Type of BTC | Frequency, % (n) | Study | Year of report |
|---------------------------------|------------------|-------|----------------|
| Intrahepatic cholangiocarcinoma | 18.2% (4/22) | (6) | 2001 |
| Intrahepatic cholangiocarcinoma | 4.7% (1/23) | (7) | 2002 |
| Ampullary carcinoma | 5.6% (3/54) | (8) | 2010 |
| Gallbladder carcinoma | 7.8% (6/77) | (9) | 2015 |
| Cholangiocarcinoma | 1.4% (1/74) | (10) | 2017 |
| Biliary tract cancer | 2.1% (8/375) | (11) | 2018 |
| Biliary tract cancer | 0% (0/99) | (12) | 2018 |

BTC: biliary tract cancer

Table 2. Case Reports of Biliary Tract Cancers Treated with Pembrolizumab.

| Type of BTC | Age, sex | MSI status | Duration of survival after starting pembrolizumab | BOR | Author | Year of report |
|---------------------------------|--------------|------------|---|-----|----------|----------------|
| Cholangiocarcinoma | 67 y, female | Unknown | 12 months (alive) | PR | (14)* | 2017 |
| Extrahepatic cholangiocarcinoma | 24 y, female | MSI-high | 13 months (alive) | PR | (15) | 2017 |
| Gallbladder cancer | 70 y, female | Unknown | 30 months (alive) | CR | (16) | 2019 |
| Distal cholangiocarcinoma | 51 y, female | Unknown | 30 months (alive) | CR | (16) | 2019 |
| Intrahepatic cholangiocarcinoma | 38 y, female | Unknown | PFS, 2 months | PD | (17) | 2019 |
| Intrahepatic cholangiocarcinoma | 60 y, male | MSI-high | 13 months (alive) | PR | Our case | 2020 |

BTC: biliary tract cancer, BOR: best response, MSI: microsatellite instability

PFS: progression free survival, CR: complete response, PR: partial response, PD: progressive disease

*This patient was enrolled in a clinical study and received folinic acid, fluorouracil and oxaliplatin (FOLFOX) plus pembrolizumab.

therapy. This new indication marks a paradigm shift in the strategies for treating cancers; however, MSI-high/dMMR solid tumors are very rare (5). According to published reports, they account for only 0-18.2% of BTCs (6-12) (Table 1). In studies published in the last 3 years, the frequency of MSI-high BTCs was only 0-2.1%. Silva et al. reported that MSI-high tumors accounted for 5% of gallbladder cancer and extrahepatic cholangiocarcinomas; however, they account for 10% of ICC and papillary carcinomas (13). Interestingly, the frequency of MSI-high BTCs may vary by tumor location.

Since 2017, six cases of BTCs treated with pembrolizumab have been reported (Table 2) (14-17). Among these cases, the responses achieved with ICI treatment were durable. Thus, other patients with MSI-high BTC besides our own have also reportedly achieved good therapeutic effects with ICIs. Table 3 shows the results of clinical trials concerning the treatment of BTCs with pembrolizumab (3, 12, 18, 19). In the trials where patients were treated with pembrolizumab, irrespective of their MSI status, the objective response rate (ORR) was 5.8-17%, and the OS was 6.4-9.1 months. By comparison, in the KEYNOTE-158 study (6), which enrolled only patients with MSI-high tumors, the results of the treatment of 22 patients with advanced BTC with pembrolizumab were as follows: complete response (CR), 2 patients; PR, 7 patients; ORR 40.9%, median progression-free survival (PFS) 4.2 months [95% confidence interval (CI) 2.1 to not reached (NR)]; and median OS 24.3 months (95% CI 6.5 to NR) (3). Thus, the out-

comes were significantly better than in trials that did not take the MSI status into consideration. In the ABC-02 study, the results of treating advanced BTC with CisGem were as follows: ORR 26.1%, median PFS 8.0 months (95% CI, 6.6-8.6) and median OS 11.7 months (95% CI 9.5-14.3) (1). Therefore, the outcomes of treating patients with MSI-high BTC with pembrolizumab are excellent compared with the results of CisGem, which has been the standard chemotherapy for patients with BTC. Because a long-term survival has been reported in patients with various carcinomas that have responded to ICIs (20), worsening of the performance status because of the failure of second-line treatment with CisGem should be avoided whenever possible. It would instead be preferable to determine the MSI status as early as possible after starting CisGem therapy. In the future, ICIs may become the first-line chemotherapy for MSI-high ICC.

Our patient's ICC was associated with right PVTT. PVTT occurs more frequently in association with hepatocellular carcinoma than with ICC; thus, there is little clinical information concerning the latter. Lu et al. reported that patients with ICC PVTT have a poorer post-hepatic resection prognosis than those without PVTT (21). In general, ICC with PVTT is characterized by an aggressive disease course, poor hepatic function, high incidence of complications related to portal hypertension and poor tolerance to treatment. However, our case shows that pembrolizumab may be an effective treatment for ICC with PVTT. The good response to pembrolizumab may have been related to our patient undergoing radiotherapy (RT) for retroperitoneal lymph node me-

Table 3. Clinical Trials of Treatment of Biliary Tract Cancers with Pembrolizumab.

| Tumor type of BTC | Number of patients | Characteristics of patients | MSI status | Duration of survival after pembrolizumab | ORR | Author | Year of report |
|----------------------|--------------------|---|------------------------------------|---|------------------------------|--------|----------------|
| Biliary tract cancer | 89 | 58% male; median age, 64 y; One prior therapy, 100% | Unknown | Not available | ORR 17% | (18) | 2015 |
| Biliary tract cancer | 26 | 31% male; median age, 63 y; One prior therapy, 100% | Unknown | Median OS, 6.4 months (95% CI, 4.2–13.3) | ORR 4% | (19)* | 2018 |
| Biliary tract cancer | 104 | 49% male; median age, 63 y; Two prior therapies, 52% | 99 pts, negative 5 pts, unknown | Median OS, 9.1 months (95% CI, 5.6–10.4) | ORR 5.8% | (12) | 2018 |
| Cholangiocarcinoma | 22 | Not available | All MSI-high | Median OS, 24.3 months (95% CI, 6.5–NR) | ORR 40.9% (CR 9%, PR 32%) | (3) | 2019 |

BTC: biliary tract cancer, MSI: microsatellite instability, ORR: objective response rate, OS: overall survival, NR: not reached, pts: patient, CR: complete response, PR: partial response

*Ramcirumab combination therapy

tastasis. A phenomenon whereby RT to one site is associated with regression of metastatic cancer at distant, non-irradiated sites has been described and called the abscopal effect (22). Of interest, the enhancement of antitumor effects of ICIs through the concomitant use of local RT has been reported for various advanced cancers, including melanoma (22, 23). When a tumor is irradiated, the cellular stress or injury within the tumor, manifesting as necrotic and apoptotic tumor cells, may lead to the release of neo-antigens, here referred to as tumor-associated antigens (TAAs). A substantial increase in the number and diversity of TAAs can stimulate a tumor-specific immune response. Thus, this is a possible mechanism underlying the enhancement of the therapeutic effect of ICIs by RT.

While there have been many reports of the simultaneous initiation of RT and ICIs, a PubMed search did not yield any reports of the effective treatment with an ICI after a time lag of nearly six months following RT, as in our patient. However, Yaguchi et al. reported a case of postoperative recurrence of lung adenocarcinoma (pleural seeding, cancerous lymphangitis, brain metastases, and multiple bone metastases) in which the patient received palliative RT (30 Gy) at the site of right hip joint bone metastases followed by nivolumab 1 month later (24). In this patient, nivolumab was effective and achieved a close to complete response. Thus, this patient appeared to respond to an ICI in a similar fashion to our own patient, which suggests a possible abscopal effect. The potential utility of a combination of RT and an ICI for various cancers is currently being investigated in a number of clinical trials (25). Further research is needed to determine whether or not this combination can improve the prognosis of patients with BTC.

The toxicity profile of ICIs differs substantially from that

of classic cytotoxic agents. Although our patient developed no irAEs, the possibility of irAEs should always be kept in mind during such treatment.

To our knowledge, this is the first report of pembrolizumab being effective in a patient with ICC and PVTT. More cases need to be accumulated to confirm the effectiveness of pembrolizumab in advanced BTC with MSI-high status.

The patient gave his written informed consent for the publication of the details of his case.

The authors state that they have no Conflict of Interest (COI).

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