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Exceptional Response to A Single Cycle of Immunotherapy in a Lynch Syndrome Patient with Metastatic Pancreatic Adenocarcinoma

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 65-year-old
Final Diagnosis: Lynch syndrome • pancreatic cancer
Symptoms: Abdominal pain • liver masses
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual or unexpected effect of treatment

Background: Pancreatic adenocarcinoma (PDA) is associated with an 8.6-fold increased risk in Lynch syndrome patients. Here, we report the case of a Lynch syndrome PDA patient with an exceptional response to a single cycle of pembrolizumab immunotherapy.

Case Report: A 65-year-old male patient with Lynch syndrome mismatch repair (MMR) deficient PDA with metastatic liver disease, received 1 cycle of pembrolizumab (200 mg) after progressing on 2 standard lines of treatment. His initial computed tomography (CT) showed 3×2.5 cm PDA. At that time, the disease was considered borderline resectable, and the patient received 6 cycles of FOLFIRINOX followed by chemoradiotherapy with capecitabine. A follow-up CT scan showed multiple new liver lesions. The biopsy showed metastatic PDA and tumor tissue demonstrated high microsatellite instability with abnormal/lost expression of MLH1 and PMS2 proteins. The patient was started on pembrolizumab. Only 1 cycle was given due to the development of thromboembolic complications: pulmonary embolism and myocardial infarction. His thrombophilia workup was negative. Restaging CT scans at 3, 6, and 9 months after 1 cycle of pembrolizumab revealed an excellent response with shrinkage of liver lesions. Restaging at 11 months showed the eventual resolution of most liver lesions. No new metastatic disease developed. A repeat biopsy of the dominant liver lesion showed no morphological evidence of PDA.

Conclusions: Only 1 cycle of pembrolizumab resulted in clinical complete response and pathologic response in metastatic PDA. We emphasize the importance of testing for MMR status and treating with immunotherapy in metastatic PDA patients with MMR deficiency.

MeSH Keywords: DNA Mismatch Repair • Immunotherapy • Lynch Syndrome II • Pancreatic Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/923803

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Background

Lynch syndrome is caused by mutations of DNA mismatch repair (MMR) genes. Inherited colorectal cancer and endometrial cancer are frequently seen in Lynch syndrome patients [1]. Pancreatic adenocarcinoma (PDA) has been associated with Lynch syndrome with an 8.6-fold increase risk compared with the general population [2]. Previously reported studies showed a cumulative risk of developing pancreatic adenocarcinoma of 3.68% by age 70 years, with cases among families with a history of Lynch syndrome occurring at an earlier age than sporadic cases [3].

DNA deficiency MMR (dMMR) causes microsatellite instability (MSI). This MMR deficiency causes failure to repair errors that normally occur during the replication of repetitive DNA sequences [4]. Inactivation of MMR genes can result in MSI. These genes include *MLH1, MSH2*, and *MSH6*. Originally, MSI was shown to correlate with germline/inherited defects in DNA MMR genes in families with hereditary non-polyposis colorectal cancer Lynch syndrome. However, it is now recognized that in about 37% of sporadic colorectal cancer and 45% of non-colorectal cancer, MSI occurs in the absence of germline MMR mutations [5–7]. Inactivation of the *hMLH1* gene by DNA methylation is shown as the principal mechanism for MSI in sporadic colorectal cancer [8].

dMMR in rare in PDA. Hu et al. showed dMMR occurred in 0.8% of pancreatic ductal adenocarcinoma cases (7 out of 833 cases) and it was associated with high mutational load [9]. A study looking at MSI in PDA reported by Lupinacci et al. performed immunohistochemical analyses of 445 pancreatic cancer samples. It showed dMMR occurred in 1.6% of cases overall; of these, 6.9% were in intraductal papillary type and 1.3% in other types of PDA [10]. A study by Yamamoto et al. [11] evaluated the genetic features of 13 sporadic PDA patients with MSI and showed epigenetic and genetic inactivation of the *hMLH1* gene. Frameshift mutations of multiple genes were also detected; 6 sporadic cases (46%) showed hypermethylation of the *hMLH1* promoter [11].

The Food and Drug Administration gave accelerated approval to pembrolizumab immunotherapy for solid cancers with dMMR and MSI-H on May 23, 2017 [12]. The approval was based on findings of durable responses among 149 patients with MSI-H or dMMR cancers. This was bases on 5 single-arm multicohort multicenter KEYNOTE trials number 012, 16, 028, 158, and 164. Patients received pembrolizumab immunotherapy 200 mg given every 3 weeks or 10 mg/kg given every 2 weeks. The treatment was continued up to 24 months or unacceptable toxicity or progression of the disease [12].

Of these 5 trials, an updated analysis of KEYNOTE-158 included a total of 22 PDA patients. It showed the median duration of response of 13.4 months (95% confidence interval [CI]: 8.1–16+ months). Response was seen in 18.2% (95% CI: 5.2–40%), including complete response in 1 patient. Median overall survival was 4.0 months (95% CI: 2.1–9.8 months) [13]. Similarly, Le et al. conducted a phase 2 study which included 8 PDA patients with dMMR who received pembrolizumab. The objective response rate was 62% with a 75% disease control rate [14].

All these studies have strongly shown that dMMR PDA patients respond to immunotherapy. MSI is found in 4% of all advanced solid tumor patients and in 1–3% of patients with pancreatic cancer, which makes them candidates for this type of immunotherapy.

Here, we report the case of exceptional response to a single cycle of pembrolizumab immunotherapy in a metastatic pancreatic adenocarcinoma patient with Lynch syndrome.

Case Report

The patient was a 65-year-old African American male with a previous history of colon cancer diagnosed at age 45, stage III status previously treated with right hemicolectomy, chemotherapy, and radiation in 1997 after which he was free of disease. He had negative colonoscopies in 2002, 2005, and 2010, with a 4-mm tubular adenoma observed in 2010. He had a history of acoustic neuroma diagnosed at age 62. He never smoked and never used smokeless tobacco. He did not drink alcohol or use illicit drugs.

His family history was remarkable for a son and a daughter with colon polyps diagnosed in their early 20s. His sister, who was a smoker, was diagnosed with breast cancer and lung cancer in her 60s. His maternal uncle in his 50s had colon cancer. The patient's son was diagnosed with brain cancer in his 40s. A maternal uncle was diagnosed with a benign brain tumor. A maternal cousin was diagnosed with colon cancer in his 20s. A maternal cousin was diagnosed with a brain tumor, which was reportedly benign.

Our patient presented to the hospital with abdominal pain in March 2018. Severe biliary and pancreatic ductal dilatation was seen on computed tomography (CT) scan of the abdomen and pelvis. CT revealed a 3×3×2.5 cm hypodense lobulated mass-like lesion in the right anterolateral aspect of the pancreatic head, sub-centimeter right liver lobe hypo densities, a cluster of enlarged lymph nodes measuring 3.3×1.5 cm superior to the pancreatic head. Endoscopic ultrasound with endoscopic retrograde cholangiopancreatography was performed. Pathology of a fine-needle aspiration showed adenocarcinoma.

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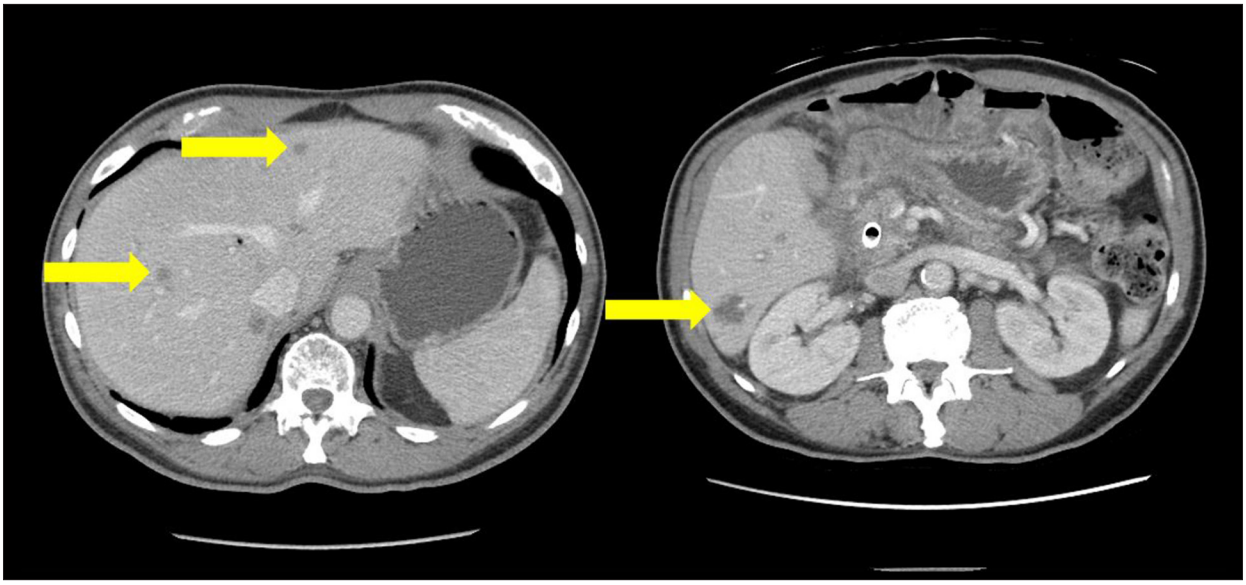

Figure 1. Computed tomography scan of the abdomen performed before starting immunotherapy showing multiple hepatic lesions consistent with pancreatic cancer metastases as shown using the arrows.

Placement of a biliary stent was unsuccessful. The patient had a percutaneous tube placement with a left biliary drain. The patient's total bilirubin level subsequently declined from 15.3 mg/dL to 2.7 mg/dL.

His case was discussed by the multidisciplinary pancreatic tumor board and recommendations were that the patient's condition appeared to be resectable. However, the plan was to proceed with neoadjuvant chemotherapy for 4 cycles followed by restaging and an attempt at surgical resection. Cycle 1 of FOLFIRINOX consisted of oxaliplatin (85 mg/m^2 over 2 hours), leucovorin (400 mg/m^2 over 2 hours), irinotecan reduced dose at 75% (135 mg/m^2 over 90 minutes), and 5-FU (400 mg/m^2 bolus then 2400 mg/m^2 over 46 hours), all on day 1, and then repeated every 2 weeks. He received a total of 4 cycles of chemotherapy with the same dose aforementioned starting in April until June 2018.

Unfortunately, a CT scan performed in June showed progressive disease with evidence of 2 new and enlarging lesions in the liver. Liver needle biopsy on July 3, 2018 was negative for carcinoma. It showed minimal to mild portal inflammation with foci of sinusoidal dilatation/congestion, negative for carcinoma.

The tumor board reviewed imaging and concluded the liver lesions were less concerning for metastatic disease. He received 2 additional cycles of FOLFIRINOX chemotherapy with the same dose aforementioned starting in July until August. It was also noted that MSI testing was requested on the tumor but was not done due to a lack of cells. A magnetic resonance imaging study of the abdomen did not show any liver metastasis.

His case was again discussed at the multidisciplinary pancreatic tumor board. Recommendations were to proceed with chemoradiation and then evaluate candidacy for surgical resection. In August, he started chemoradiotherapy with capecitabine, which was completed on October 2, 2018.

Given his personal history of colon cancer and now pancreatic cancer and the history of family members with colon cancer, the patient proceeded with genetic testing, which came back positive for *MLH1* mutation. The 17-gene panel from Ambry Genetics (Aliso Viejo, CA, USA) identified an *MLH1* mutation, c.350C>T (p.T117M). This Lynch syndrome result essentially explanted his history of colon and pancreatic cancer. We suspected that this likely came from his mother's side given his 3 relatives with colon cancer.

Unfortunately, a CT scan showed numerous (>15) new hypoattenuating hepatic lesions measuring up to 2.0 x 1.6 cm in size with the development of pulmonary nodules highly suspicious for metastasis with the relatively stable appearance of the pancreas (Figure 1). At that time, palliative chemotherapy was recommended. It was also recommended that he have a repeat biopsy of the liver, which was sent for MSI analysis. The right lobe lesion's needle biopsy revealed metastatic adenocarcinoma, consistent with the patient's known history of pancreaticobiliary primary.

Immunostains were performed with appropriate controls on separate slides to determine the presence or absence of protein expression for MLH1, MSH2, MSH6, and PMS2. Lymphocytes and normal epithelium exhibit strong nuclear staining and served as positive internal controls for staining of

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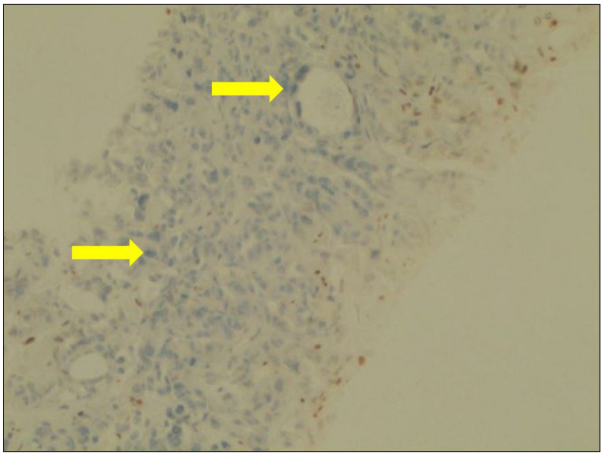

Figure 2. Immunohistochemistry of a liver biopsy specimen (hematoxylin and eosin stain, 100×) showing abnormal/lost expression of MLH1 protein as shown using arrows. Lymphocytes and normal epithelium exhibit strong nuclear staining and serve as positive internal controls for staining of this protein.

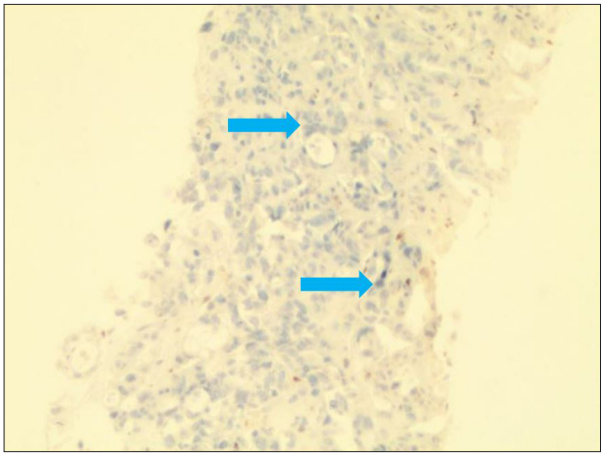

Figure 3. Immunohistochemistry of a liver biopsy specimen (hematoxylin and eosin stain, 100×) showing abnormal/lost expression of PMS2 protein as shown using arrows. Lymphocytes and normal epithelium exhibit strong nuclear staining and serve as positive internal controls for staining of this protein.

these proteins. MSI testing was performed using polymerase chain reaction (PCR) based assay with microsatellite markers. Immunohistochemistry showed abnormal/lost expression of MLH1 (Figure 2) and PMS2 proteins (Figure 3). Thus, tumor tissue demonstrated MSI-H genotype.

He was started on pembrolizumab immunotherapy and received cycle 1. Unfortunately, a week after cycle 1 of immunotherapy infusion, he developed a gastrointestinal bleed. During hospital admission, he was diagnosed with pulmonary embolism and deep venous thrombosis and he suffered an acute embolic stroke as well as ST-elevation myocardial infarction. He had an inferior vena cava filter placed as he was unable to be placed on anticoagulation due to the gastrointestinal bleed. He was then discharged to a rehabilitation facility with residual left-sided weakness.

He continued to improve from a neurologic standpoint. He was readmitted for a syncopal episode. His hemoglobin was down to 6.7 g/dL. The stool hemoccult was positive. Esophagogastroduodenoscopy (EGD) showed friable gastric mucosa in the antrum. There was evidence of active oozing and erythematous duodenopathy. He was treated with argon photocoagulation laser. This controlled the bleeding. Since then, he has not had any further episodes of syncope or gastrointestinal bleeding. During this time, he underwent 3 EGDs. All showed similar findings. Although there was no visual invasion of the stomach from pancreatic cancer, it was still a possibility. The bleeding occurred 1 week after the initiation of anticoagulation. The presence of tumor in the surgical bed in conjunction with the immune response and anticoagulants could have resulted in the endoscopic findings of increased friability and subsequent bleed.

He presented for a follow-up appointment at which point we were concerned about the re-initiation of pembrolizumab given his significant thromboembolic complications, which happened right after the pembrolizumab and also the relative contraindication to anticoagulation given his gastrointestinal bleed. He was considered at an increased risk for gastrointestinal bleed.

Given his significant issues with thromboembolic complications, an extensive hypercoagulation workup was done, which included beta-2 glycoprotein antibodies, anticardiolipin antibodies, lupus anticoagulant, protein C, and protein S, all of which were negative. Prothrombin G20210A, Factor V Leiden were ordered, but not performed due to insurance issues.

Eventually, with an extensive patient and family discussion, it was decided that we would continue to follow him with routine CT scans and re-initiate pembrolizumab cautiously with anticoagulation if and when there was evidence of disease progression.

Three months after pembrolizumab treatment, his CT chest-abdomen-pelvis (CAP) showed a decrease in the metastatic disease, with a decrease in the size of most of the liver lesions. There was no evidence of new metastatic disease elsewhere in the CAP. Seven months after pembrolizumab, CT CAP showed interval improvement with diminished hepatic metastases (Figure 4). No new liver, chest, or pelvic lesions were seen.

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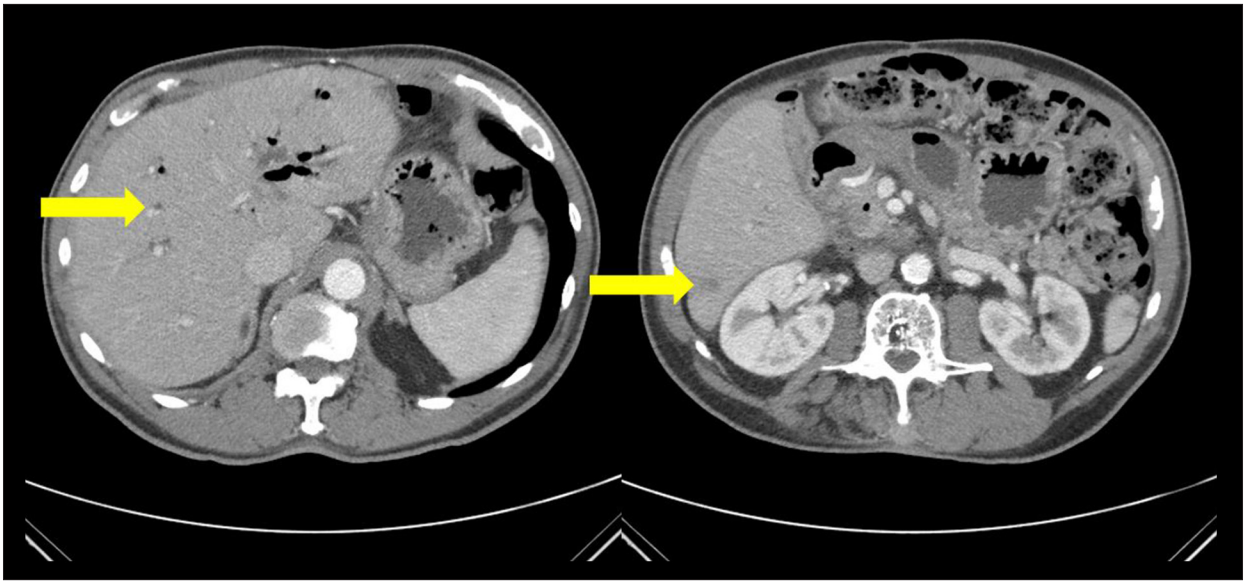

Figure 4. Computed tomography scan of the abdomen performed 7 months after 1 cycle of immunotherapy showing decreasing size of multiple hepatic lesions consistent with treatment response as shown using arrows.

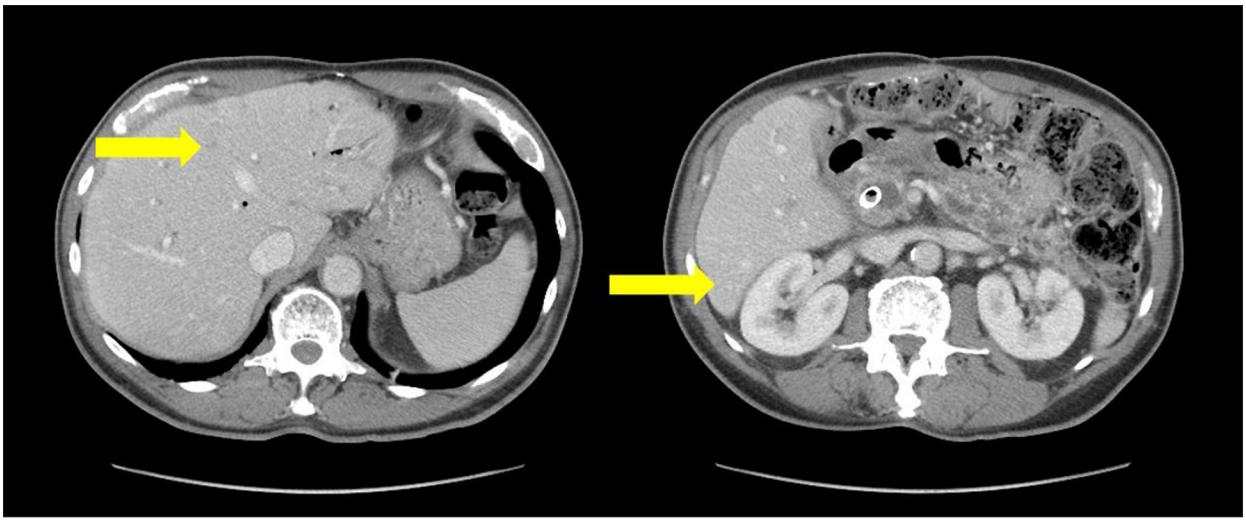

Figure 5. Computed tomography scan of the abdomen performed 11 months after 1 cycle of immunotherapy showing continued decrease and resolution of multiple hepatic lesions consistent with persistent treatment response as shown using arrows.

Eleven months after 1 cycle of pembrolizumab, CT CAP showed less conspicuous liver metastases. No new liver lesions were evident (Figure 5). There was no evidence of new metastatic disease in the CAP.

Discussion

Despite recent advances in chemotherapy and immunotherapy regimens, metastatic pancreatic cancer has dismal outcomes. There are ongoing studies combining immunotherapy with vaccines, chemotherapy, and radiation therapy.

Immunotherapy has changed the management of various cancers especially non-small cell lung cancer, melanoma, bladder cancer, and dMMR/MSI-H solid cancers. Compared to systemic chemotherapy, single-agent immunotherapy generally has better safety and toxicity profile and is better tolerated by most patients. Studies have shown that a single-agent or combination immunotherapy has high response rates, prolonged progression-free as well as overall survival.

Metastatic PDA is very aggressive and has a worse prognosis. Traditionally PDA has been considered nonimmunogenic with the immunosuppressive microenvironment. This was due to limited effector T cells in the tumor [4]. Studies have also

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reported regulatory T cells to increase in the tumor. In our patient, we are unable to obtain MSI results on initial cytology material due to inadequate tumor tissue for DNA extraction and thus the patient had a liver biopsy. MSI/dMMR testing is considered complex for PDA patients due to the lack of tumor material, poor cellularity, and often requires new tissue biopsy [10]. However, it should be incorporated in standard genomic testing in PDA at all stages. Several studies point to the potential role of MSI in the prognostication of resectable PDA. Nakata et al. studied the role of MSI in resected PDA. Patients with MSI have a better prognosis in terms of median overall survival likely given the intense immunoreactivity seen in these tumors [15]. In a study by Eatrides et al., the incidence of MSI in resected PDA samples was 22%, however, the response to immunotherapy in this subset was unknown [16].

In the metastatic setting, the incidence of PDA is considerably lower (0.8–1.5%) [9,10]. Despite this decreased prevalence, the National Comprehensive Cancer Network (NCCN) guidelines recommend routine testing for MSI/dMMR in metastatic PDA and the use of pembrolizumab in the second-line setting for MSI/dMMR tumors.

Checkpoint inhibitors immunotherapy is a second-line treatment option for MSI solid cancers, however, only a small number of patients with PDA are treated with pembrolizumab. As of now, this is the first report of sporadic Lynch syndrome PDA with an exceptional response to single-cycle pembrolizumab after progression with FOLFIRINOX and capecitabine-radiotherapy, leading to a persistent and ongoing response for at least 11 months.

Our results support this observation as after 1 cycle with pembrolizumab, our patient's liver metastases were significantly decreased or resolved. This also confirms that immunotherapy can give an excellent response in MSI-H PDA. This is especially helpful for patients who cannot tolerate systemic chemotherapy. This highlights the importance of MMR testing in metastatic PDA patients.

Conclusion

Our case showed an excellent and persistent response to a single cycle of immunotherapy treatment in a Lynch syndrome patient with PDA. We emphasize the importance of MMR testing in PDA cancer patients with metastatic disease.

Acknowledgments

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Conflicts of interest

None.

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