Case Report

A rare case of sporadic mismatch repair deficient pancreatic ductal adenocarcinoma that responded to ipilimumab and nivolumab combination treatment: case report

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Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignant disease with a poor prognosis. Despite high efficacy in multiple cancers, immunotherapy has had very little success in treating PDAC due to unfavorable characteristics such as low tumor mutational burden (TMB), low microsatellite instability (MSI), and non-immunogenic tumor microenvironment. Recently, however, there have been reports of rare PDAC cases with high TMB and DNA mismatch repair deficiency (dMMR) that have demonstrated positive response to immunotherapy. All these cases have also presented with Lynch Syndrome, or germline mutations in MMR genes.

Case Description: Here, we report a 57-year-old male with stage IV PDAC whose tumor profile revealed high TMB, high MSI, and dMMR, but no germline mutations in genes associated with hereditary cancers including those associated with Lynch Syndrome. After a series of ineffective treatments, the patient showed positive response to combined ipilimumab and nivolumab immunotherapy. To our knowledge, this is the first report of an advanced PDAC case with sporadic dMMR, high TMB, and no Lynch Syndrome having a good response to immunotherapy.

Conclusions: This case further supports TMB and high MSI/dMMR being possible biomarkers for immunotherapy of PDAC as well as highlights the importance of both germline and somatic testing of patients with PDAC.

Keywords: Pancreas cancer; tumor mutational burden (TMB); microsatellite instability (MSI); DNA mismatch repair deficiency (dMMR); case report

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an exceptionally malignant disease with a poor prognosis, having an overall 5-year survival rate of below 5% (1). The current standard treatment regimen for advanced and metastatic PDAC is chemotherapy or chemotherapy combined with radiotherapy. There are very few targeted drugs for PDAC listed in the guidelines in the National Comprehensive Cancer Network (NCCN).

In recent years, immunotherapy has proven to be effective in multiple cancers such as melanoma and lung

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Table 1 Patient treatment history

Treatment	Duration (months)	Start CA 19-9 (U/mL)	End CA 19-9 (U/mL)	Treatment outcome
FOLFIRINOX	10	658	128	Progression
Gemcitabine/nab-paclitaxel	4	128	88	Progression
Clinical trial	3	502	11.1	Progression
Ipilimumab/nivolumab	9 (ongoing)	78	32.3	Ongoing

cancer. Immune checkpoint inhibitors (ICIs) targeting programmed death-ligand 1 (PD-L1) have been found to have a high rate of response in patients with microsatellite instability (MSI), high tumor mutation burden (TMB), and/or DNA mismatch repair deficiency (dMMR) (2-4). Patients with higher proportions of genetic mutations tend to express more cancer-associated neoantigens that can be recognized by immune cells. High TMB has been specifically associated with response to anti-PD-1 therapies in other types of cancer, but there remains little evidence showing clear correlation between high TMB and response to checkpoint inhibition in PDAC (5). In addition, only 18.2% (4 out of 22 patients with 1 complete response and 3 partial responses) of pancreatic cancer patients with MSI high and dMMR responded to the anti-PD-1 antibody, pembrolizumab, in the phase II KEYNOTE-158 trial (6).

PDAC characteristics such as immunosuppressive tumor microenvironment, few or no infiltrating immune effector cells, and low antigenicity have limited the effectiveness of immunotherapy in PDAC. A recent systematic review reported that only 1.1% of PDAC patients have high TMB (7). Additionally, in an analysis of 833 PDAC patients, dMMR was found to occur in only 0.8% of patients with all of these cases found to have Lynch Syndrome from germline mutations in MMR genes (8).

Here, we present a PDAC case of no detectable germline mutations in any mismatch repair genes but a somatic profile of a dMMR, high TMB, and a microsatellite instable tumor that has had a positive response to ipilimumab and nivolumab therapy. We present the following article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-587/rc).

Case presentation

A 57-year-old male was initially diagnosed with borderline resectable PDAC in October 2019 by fine needle aspiration of the pancreas head (Figure S1). At diagnosis, his CA19-9 was 658 U/mL. His family history shows only a maternal grandmother with renal cancer.

The patient was first treated with FOLFIRINOX for 10 months (*Table 1*). During this treatment regimen, the patient also received intensity-modulated radiation therapy (IMRT) and capecitabine. After FOLFIRINOX, the patient started gemcitabine and nab-paclitaxel. After 4 months, Whipple procedure was attempted but aborted due to the discovery of metastatic disease and the cancer was restaged to stage IV. In May 2021, he was put on a clinical trial and taken off in August 2021 due to progression. Also in August 2021, the patient was hospitalized due to a cerebrovascular accident.

Genetic testing through Invitae (San Francisco, CA, USA) using the Multi-Cancer Panel (91 genes) revealed the patient to be negative for germline mutations. Further testing of tumor biopsies using genomic sequencing through both Caris Life Sciences (Phoenix, AZ, USA) and Ashion Analytics (Phoenix, AZ, USA) reported high TMB and high MSI status. The results of the patient tumor molecular/genomic workup are summarized in *Table 2*.

Based on the genetic testing results of high TMB and unstable microsatellite tumor, the patient began receiving the combination of ipilimumab and nivolumab in September 2021. The dosing was as follows: ipilimumab 1 mg/kg with nivolumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 480 mg (all intravenously) every 4 weeks. His CA 19-9 upon starting the treatment was at 78 U/mL. The patient was hospitalized a week after his first treatment with nausea/vomiting. He only complains of loose stools (not diarrhea) which he claims to be the same as before starting this treatment and have since resolved. His CA 19-9 has improved to 32.3 U/mL as of June, 2022. His computed tomography (CT) scan taken in April 2022 showed normalization of the liver metastasis compared to the baseline scan taken in September 2022 (*Figure 1A*,*1B*). His fluorodeoxyglucose-positron emission tomography (FDG-PET) scan in May 2022 showed minimal activity. At the time of writing this report,

Table 2 Genomic testing results

Test	Provider	Results
Multi-Cancer Panel (germline DNA)	Invitae (San Francisco, CA)	Negative
GEM ExTra Test (tumor DNA and RNA)	Ashion Analytics (Phoenix, AZ)	Genomic alterations in *ARID1A*, *BRCA2*, *CHEK2*, *KDM6A*, *MEN1*, *POLD1*, *RASA1*, *BAX*, *KMT2B*, *KMT2D*, high TMB (30 mut/Mb), high MSI
Comprehensive Molecular Profiling (tumor tissue and tumor DNA)	Caris Life Sciences (Phoenix, AZ)	Pathogenic or likely pathogenic alterations were found in *ARID1A*, *BRCA2*, *CHEK2*, *EPHA2*, *FLCN*, *KDMA6A*, and *KMT2D*, variants of uncertain significance were also found in *ATM* and *BRCA2*, no mutations were found in *KRAS*, *BRAF*, *BRCA1*, *NRG1*, *PALB2*, *SMAD4*, and *NTRK1/2/3*, mismatch repair deficient, high MSI, high TMB (28 mut/Mb)

TMB, tumor mutational burden; MSI, microsatellite instability.

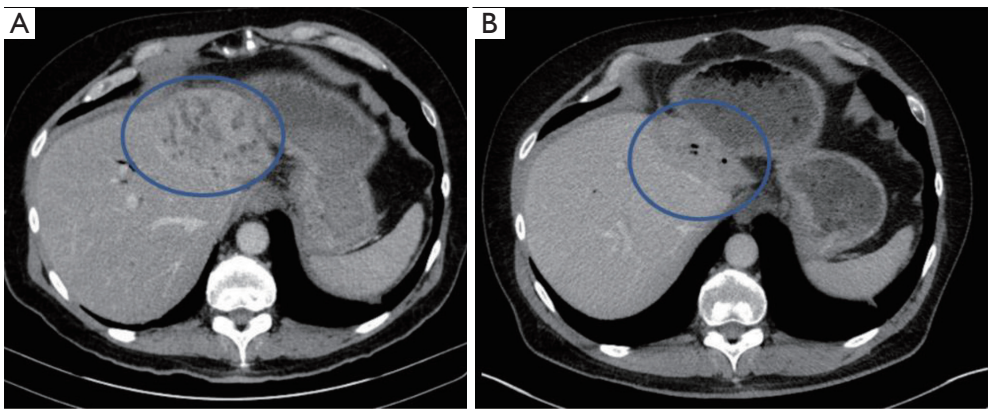

Figure 1 Patient's liver metastatic lesions were normalized after treatment with the combination of ipilimumab and nivolumab. (A) Baseline CT scan image taken in September 2021 prior to initiation of ipilimumab and nivolumab. (B) CT scan image taken in April 2022, 6 months after initiation of treatment. Blue circles in (A,B) indicate the liver metastatic lesions before and after treatment, respectively. After 4 cycles of therapy, the patient remains on nivolumab alone as a monthly maintenance. CT, computed tomography.

the patient is continuing to respond well with no additional complaints with an Eastern Cooperative Oncology Group (ECOG) performance status of 0.

All procedures performed in the 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). Signed informed consent was not obtained due to policies by the IRB. Patient was verbally informed of the case report and provides verbal consent.

Discussion

PDAC has a poor prognosis and its diagnosis and treatment remain challenging. The only curative option for PDAC patients is surgical resection which is only applicable in 10–15% of patients (9). While combination therapies, such as FOLFIRINOX and gemcitabine plus nab-paclitaxel, have improved overall survival compared to monotherapies, overall survival remains very poor in addition to significant side effects that occur (10,11).

Despite the recent development of cancer immunotherapy having a massive impact on other tumor types, immune checkpoint blockade has had minimal effect in most individuals with PDAC. One possible reason for this is how poorly immunogenic PDAC tumors are with ten times less somatic mutations compared to highly immunogenic tumors such as melanoma and lung cancer (12). dMMR is mainly a result of germline mutations in the MMR genes, but somatic

mutations in MMR genes have also been correlated with higher TMB and higher overall survival time (13).

Recently, it was reported that ipilimumab/nivolumab therapy was associated with a positive response in PDAC patients with pathogenic germline variants (PGVs) and homologous recombination deficiency (HRD) associated genes (*BRCA1*, *BRCA2*, *RAD51*, and *ATM*) (14). Out of the 10 PDAC patients who had PGVs in HRD genes, 2 had complete response, 1 had partial response, and 2 had stable disease (14). However, until now there have been few reports of successful immunotherapy in patients with dMMR, high TMB, high MSI, but no detectable germline mutations in cancer associated genes. In a retrospective study, Botta *et al.* reported patients with alterations in the switch/sucrose nonfermentable (SWI/SNF) chromatin genes including *ARID1A* could have favorable responses to ICIs (15). Here we report to our knowledge the first case of a stage IV PDAC patient with no germline mutations manifesting as Lynch Syndrome, with high TMB and MSI demonstrating a positive response to ipilimumab/nivolumab treatment.

The success of immunotherapies relies on the recognition of cancer specific antigens by immune cells. Neoantigens from somatic mutations that are only expressed in tumor cells can also result in immune cell response (16). While somatic variations are rare in PDAC, neoantigen recognition has been demonstrated in PDAC patients, indicating possible success of immunotherapies (17). Indeed, a patient was reported to have responded to neoantigen T cell receptor gene therapy further confirming that new promising treatment is on the horizon to overcome the challenges of PDAC resistance to immunotherapies (18). Additionally, Cox *et al.* recently described a case in which neoadjuvant immunotherapy with pembrolizumab given to a patient that initially presented with unresectable locally advanced dMMR PDAC significantly reduced tumor size, rendering the tumor resectable (19). This highlights the importance of testing the MMR status of all PDAC patients regardless of initial diagnosis stage especially since chemotherapy is not very effective for dMMR tumors. While tissue may not be available from every patient, liquid biopsy has been found to be a viable alternative to detect high MSI and predict response to immunotherapy in patients with PDAC (20). With stage IV PDAC having an overall 5-year survival rate of <1% (1), finding new effective treatments is imperative. Thus, both germline and somatic testing to profile tumors are essential to uncover possible genomic targets and open the door to more effective treatment options for patients with advanced PDAC.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-587/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-587/coif). EB assumes an advisory role at Imaging Endpoints, BioNTech AG, Vivacitas Oncology, NanOlogy, Boehler Life Science Advice, and TD2. EB reports institutional research funding from Bristol-Myers Squibb, Pharmacyclics, Idera, Daiichi Sankyo, Minneamrita Therapeutics, Lilly, Samumed, Merck, Helix, BioNTech AG, and Corcept Therapeutics. MYH has 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 the 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). Signed informed consent was not obtained due to policies by the IRB. Patient was verbally informed of the case report and provides verbal consent.

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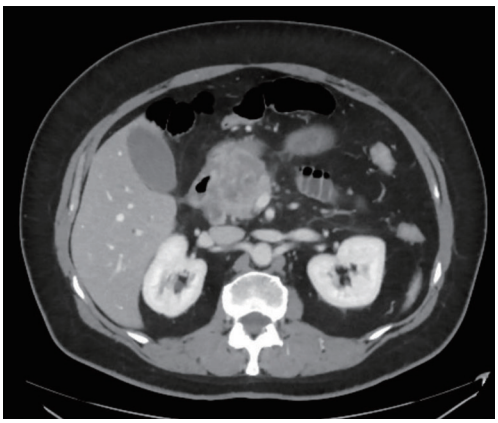

Figure S1 Patient's initial diagnostic CT scan on November 19, 2019 demonstrating his primary pancreas head lesion.

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