

# Tumor-mutation burden as a marker for immunotherapy of pancreatic cancer: the case report and literature review

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**Pancreatic cancer is digestive cancer with limited therapeutic options and a poor outcome. Pancreatic cancer has a high mortality rate, with a 5-year survival rate of less than 5%. The median survival after metastasis of the disease is less than 6 months. Studies have revealed that the standard treatment, including palliative chemotherapy or immunotherapy, is not significantly effective for pancreatic cancer. Herein, we report a case of pancreatic cancer who benefited from a combination of anti-PD-1 immunotherapy and chemotherapy. *Anti-Cancer Drugs* 33: e822–e827 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

*Anti-Cancer Drugs* 2022, 33:e822–e827

**Keywords:** case report, chemotherapy, immunotherapy, pancreatic cancer, PD-1, tumor mutational burden

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Received 26 July 2021 Revised form accepted 26 July 2021

## Introduction

Pancreatic cancer is one of the most malignant tumor diseases in the digestive system. According to global cancer statistics in 2018, pancreatic cancer mortality ranks seventh [1]. Patients diagnosed with pancreatic cancer may present with atypical clinical symptoms, and nearly 50% of patients were diagnosed at an advanced stage [2]. The clinical manifestations of pancreatic cancer are not specific, and there is no more accurate direct examination method. Therefore, early diagnosis is difficult. When symptoms such as abdominal pain, jaundice, anorexia and weight loss appear, it is basically in the advanced stage, and the opportunity for radical surgery is lost. Pancreatic cancer therapy remains a formidable challenge and the limited treatment options lead to a dismal 5-year survival rate ranged only from 3 to 15% [3]. The treatment of pancreatic cancer includes surgery, chemotherapy, radiotherapy and interventional therapy. Radical surgery is the only possible cure for pancreatic cancer so far. However, as mentioned above, most patients lose the opportunity for surgery when they are diagnosed [4]. According to the survey, 90% of patients relapse and die after potentially curative surgery without additional treatment [5]. Of course, radiotherapy and chemotherapy are also essential in pancreatic cancer. According to the 2020 American Society of Clinical Oncology guideline update, the first-line chemotherapy regimens for pancreatic cancer include FOLFIRINOX and Gemcitabine plus nab-paclitaxel [6].

In recent years, immunotherapy has made considerable progress in the treatment of cancer. Most importantly, immune checkpoint inhibitors, such as programmed cell death/programmed cell death ligand 1 (PD-1/PD-L1), have made dramatic breakthroughs in the therapy of multiple solid tumors [7–9]. In terms of survival time, PD-1 combined with chemotherapy has more significant overall survival (OS) and progression-free survival (PFS) than other small-molecule tyrosine kinase inhibitors (TKIs) [10–13]. Due to the particularity of pancreatic cancer tumor microenvironment, immune checkpoint inhibitors do not get satisfactory efficacy [14]. To find the advantageous population of immunotherapy, finding the predictors and biomarkers of immunotherapy has become a clinical hotspot. Potential indicators that can predict response to treatment including PD-L1 expression, tumor-mutation burden (TMB), microsatellite instability (MSI) and mismatch repair deficiency (dMMR) [15,16]. However, it is still not clear how to screen out the advantageous population for immunotherapy of pancreatic cancer. Herein, we reported a patient who was diagnosed with pancreatic cancer with a high TMB and lower expression of PD-L1. Patients with pembrolizumab and chemotherapy had a PFS of 9 months and an OS of more than 2 years.

## Case report

The 61-year-old male patient was diagnosed with a pancreatic malignancy in our hospital in January 2018. When the tumor was first detected in January 2018, laparoscopic radical anterograde modular pancreaticosplenectomy was performed immediately. The patient had a history of type 2 diabetes and was treated with long-term insulin control of blood glucose. The patient had no history of drinking or

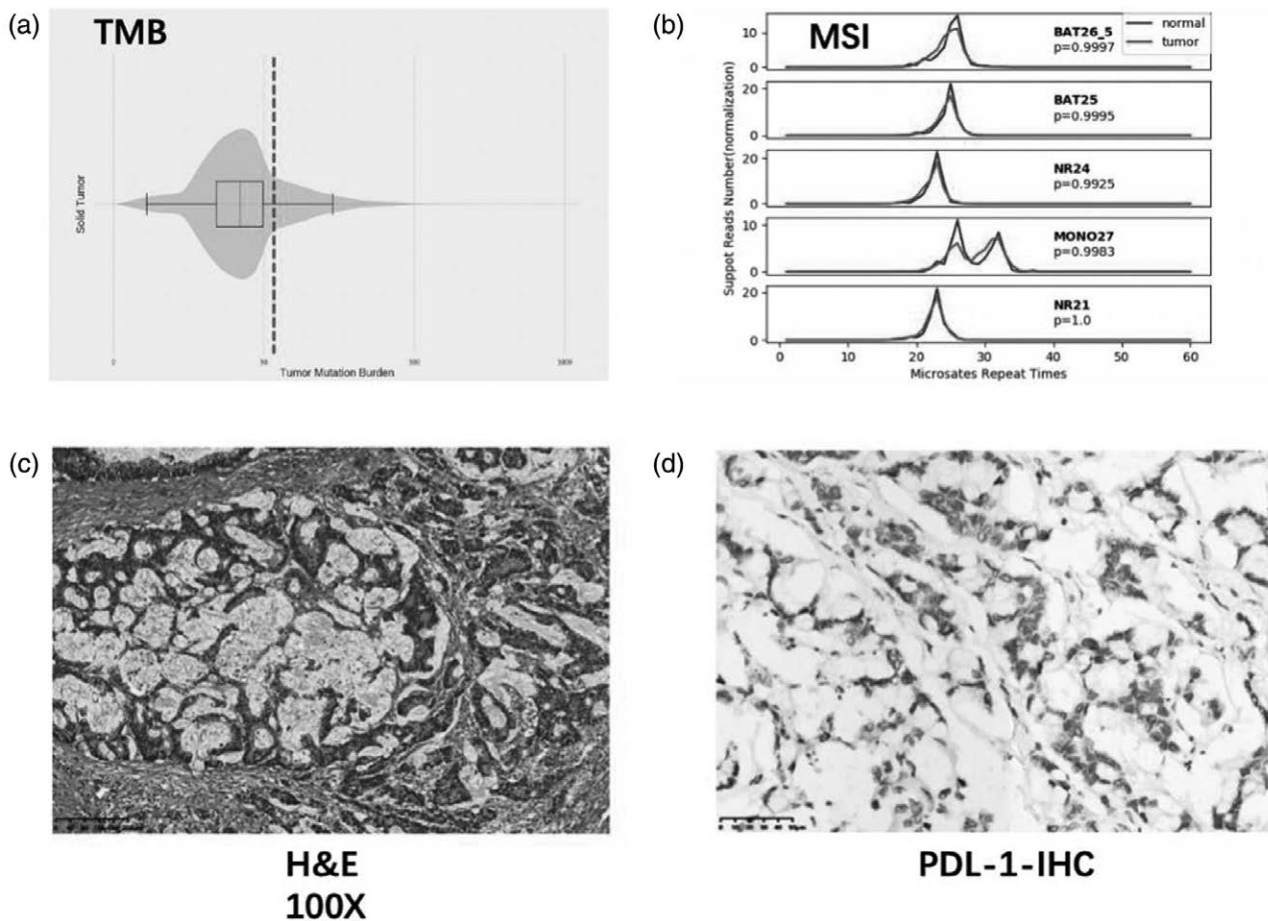
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smoking. He had no family history of cancer. The patient's temperature was 36.9 °C, heart rate was 83 bpm, respiratory rate was 19 breath/min, blood pressure was 130/77 mmHg and oxygen saturation in room air was 98%. There was a palpable hard mass in the left lower abdomen without hepatosplenomegaly. No ascites or edema was observed. Intraoperative pathology revealed cancer cells. It had infiltrated fatty tissue, lymph nodes, and nerves around the pancreas. Pathological genetic tests showed changes in TP53 and KRAS genes. Immune results were PD-L1(-),

TMB-H, MMR (p-MMR), MSI (microsatellite stable) (Fig. 1). Immunohistochemical staining results: tumor cells CK7 (+) and CK20 (-), (-), CDX2 Muc - 1 (-) and Ki67 (about 5%), Muc - 2 (+) oven, Muc - 5 ac (+) oven, CD34 (-), CK19 were (+), CA19-9 (+) and CEA (-), SYN (+), CgA (-), CD56 (-). (Fig. 2). Postoperative paclitaxel plus gemcitabine were selected as the adjuvant chemotherapy regimen. Four courses of chemotherapy were performed from 30 January 2018 to 1 March 2018. Unfortunately, the patient developed disease progression

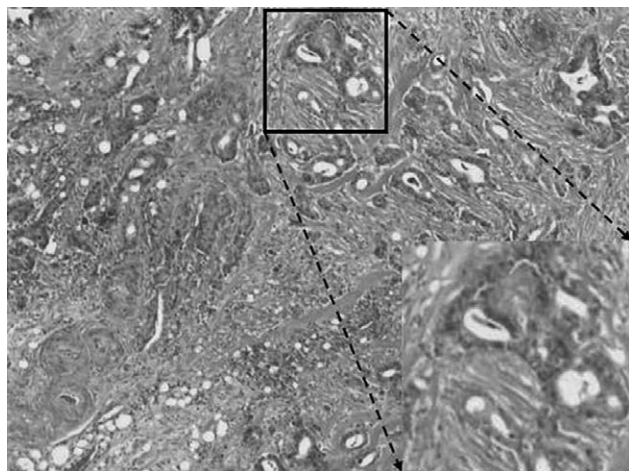
in June 2018 (Fig. 3). As a result, clinicians had to switch patients to FOLFIRINOX (oxaliplatin, irinotecan, leucovorin and fluorouracil) combined with nivolumab. Fortunately, after eight cycles of chemotherapy combined with immunotherapy, the patient did not progress and the PFS reached 9 months (Fig. 4). However, the patient eventually developed chemotherapeutic resistance and the immune-related adverse effects occurred. The rash and mucositis were rated to grade 3 adverse effects and we had to stop the immunotherapy regimen. In addition, we subsequently tried again intermittent use of PD-1 in combination with albutipacaxel, and to our surprise, the patient continued to benefit from the treatment. But, before long, the patient experienced severe immune side effects again. We had to give up this treatment because the patient could not tolerate it. Finally, we changed different treatment regimens, including other chemotherapy regimens and immunotherapy, and also tried the peptide vaccine, but the treatment effect was not very good. And the patient died in January 2020.

**Fig. 1**



Analysis of immunotherapy results.

**Fig. 2**

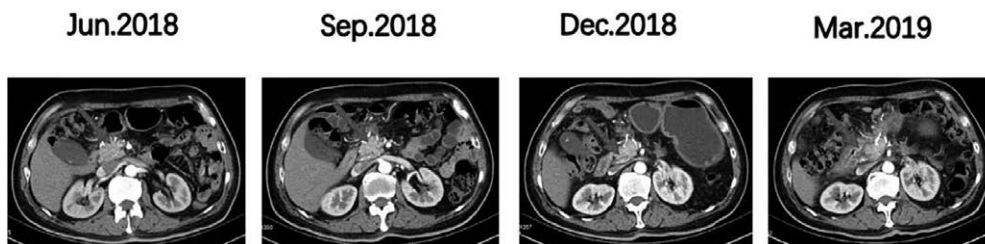


Histology of the tumor tissue.

of the clinical hotspots. TMB has been widely studied as a marker for predicting the efficacy of immune checkpoint inhibitors. We report a case of a pancreatic cancer patient with TMB-H who has benefited from immunotherapy. These results suggest that TMB can be used as a prognostic indicator for immunotherapy of pancreatic cancer, which needs to be further studied and translated into clinical practice.

At present, palliative chemotherapy is the first choice for advanced pancreatic cancer. The most commonly used first-line chemotherapy regimens are FOLFIRINOX and Gemcitabine plus nab-paclitaxel [6]. A clinical trial involving 342 patients with pancreatic cancer showed a median PFS of 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37–0.59;  $P < 0.001$ ) [17]. Although various chemotherapies have some effect, it is NS in extending the survival time and improving the quality of life of patients [18,19]. In recent years,

**Fig. 3**



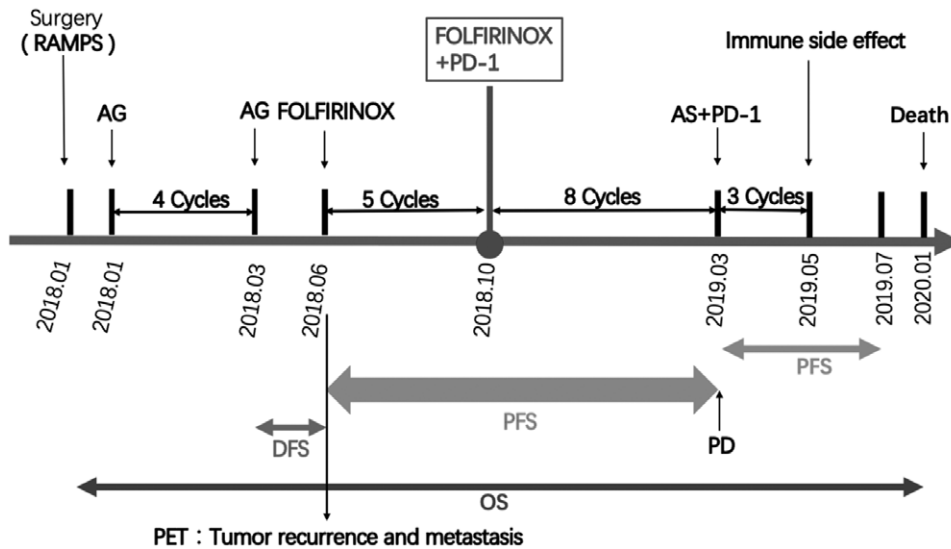
Different stages of the metastatic lesions over time (red arrows).

**Discussion**

As far as we know, this is the first case report of successful treatment of PD-1-negative and TMB-H advanced pancreatic cancer by combining immunotherapy and chemotherapy. This means that TMB has important guiding significance in the immunotherapy of pancreatic cancer. Immunotherapy combined with chemotherapy may become a new option for the treatment of advanced pancreatic cancer. Tumor immunotherapy is a hot topic at present. In recent years, as an important drug in tumor immunotherapy, PD-1/PD-L1 mAb has made great progress in the treatment of solid tumors. However, its application in the treatment of pancreatic cancer has not made much progress. The tumor microenvironment of pancreatic cancer is rich in mesenchymal cells, whose fibrous connective tissue plays an immune barrier role, thus hiding immune targets, which makes it difficult for PD-1/PD-L1 mAb to activate the body’s own immune function and exert its antitumor effect. How to screen the superior population of pancreatic cancer immunotherapy and explore the target of therapeutic effect prediction is one

immunotherapy has made great progress in the treatment of cancer. The current immunotherapy options for pancreatic cancer include PD-1, CTLA-4 inhibitors, oncolytic viruses and so on [6]. New evidence suggests that anti-PD-1 immunotherapy has therapeutic effects on various types of cancer. Especially in glioblastoma, melanoma, anal cancer have obvious antitumor activity [20–22]. In a clinical trial of patients with metastatic nodal cancer, pembrolizumab resulted in significantly longer PFS than chemotherapy [23]. Unfortunately, when PD-1 is used as a single drug, its clinical efficacy in the treatment of PC is limited, which may be partly due to the unique immunosuppressive tumor microenvironment (TME) [24,25]. Studies have shown that the induction of PD-L1/PD-1 blockade by inflammatory factors in the tumor microenvironment may be one of the most important factors affecting the efficacy of PD-L1/PD-1 blockade, including immunoreactive fibronectin- $\gamma$ , tumor necrosis factor-A, cell growth factors, hypoxia and exosomes [26]. PD-L1 is a transmembrane protein that is considered to be a predictive biomarker for tumor

Fig. 4



Treatment timeline of patient.

Fig. 5

Num	Item	Result
1	Tumor mutation Burden, TMB	11.7 Muts/Mb
2	Micro Satellite Instability, MSI	MSS
3	MLH1	-
4	MSH2	-
5	MSH6	-
6	PMS2	-
7	PDL1 score	0
8	Tumor Neoantigens	19

Analysis of immunotherapy results.

treatment. In this case, we comprehensively analyzed the immunohistochemical in the tumor tissue and found that the PD-L1 expression level was low, but the TMB expression level was high. There is considerable evidence that TMB may be a predictive biomarker of tumor response to immune checkpoint inhibitors (ICIS) in several cancer types [27–29]. TMB is defined as the total number of somatic gene coding errors, base substitutions and gene insertion or deletion errors detected per million bases [29]. TMB can reflect the amounts of mutations in tumor cells. TMB has been proved to be a predictive biomarker of ICIS in MSI-H and MSS tumors. Patients based on TMB-H may better select ICIS patients or potentially expand the candidate pool of immunotherapy. The bridge between TMB and the benefits of immunotherapy may be that new tumor-mutation-specific antigens can be exhibited on the major histocompatibility

complex (MHC) on the surface of tumor cells and then identified by tumor-infiltrating T cells. Therefore, higher TMB will generate more new antigens, which can trigger T cells in the tumor, and ICIS enables them to attack and destroy tumor cells [28,30,31]. Since neoantigens are produced by mutations, the higher the TMB, the more likely some of the neoantigens presented by MHC proteins to produce immunogenicity, thereby increasing the chance of T cells to recognize and remove cancer cells [32]. It had been demonstrated by investigators that TMB-H was considered to be associated with a better prognosis after ICI treatment [33].

Pancreatic cancer has a very poor prognosis, with a 1-year survival rate of only 24% and a 5-year survival rate of about 4%. Even for resectable pancreatic cancer patients, the 5-year survival rate is only 17% [34]. Most patients are in the advanced stage at the time of treatment and the median survival is only about 6–10 months [35]. Surgery is the only cure for pancreatic cancer, but early diagnosis of pancreatic cancer is difficult. Adjuvant chemotherapy after surgical resection is typically the preferred option to treat early pancreatic cancer. Although FOLFIRINOX and gemcitabine/nab-paclitaxel can improve the prognosis of advanced pancreatic cancer, the development of chemoresistance still leads to poor clinical outcomes. Chemotherapy as adjuvant therapy for pancreatic cancer has also been gradually improved, whereas modified FOLFIRINOX only marginally improved survival [36]. Pancreatic cancer is one of the most chemoresistant cancers [37]. More detailed, TME plays an important role in chemotherapy resistance. In pancreatic cancer, the stroma in the TME constitutes a physical barrier to chemotherapeutic drugs, and an anoxic microenvironment contributes



to chemotherapeutic resistance. In the TME, pancreatic stellate cells cluster with other immune cells and promote chemotherapeutic resistance through different cytokines and signaling pathways [38]. Nevertheless, more pancreatic cancer patients will benefit from precision treatment and targeted drugs [19]. Combination therapy is more effective than immunotherapy alone and can increase the effective response rate [39]. Immunotherapy combined with chemotherapy in the treatment of many cancers has been proved to be very effective and has achieved satisfactory therapeutic effect [40]. According to a clinical trial: the addition of pembrolizumab to chemotherapy resulted in significantly higher rates of response and longer PFS than chemotherapy alone [41]. Among patients receiving taxanes plus ramucirumab, an obvious higher objective response rate was noticed in the anti-PD-1-exposed group compared with the anti-PD-1-naïve group (60.6 vs. 20.0%) [42]. The PD-1 blockade approach has unique advantages compared to standard therapies. Conventional chemotherapies usually target a specific molecule in the tumor cells. The tumor cells can escape the treatment with mutations of the target molecules, leading to rapid regression. The PD-1 blockade is suitable for a wide range of cancers and provides a long-term response because it triggers an anti-tumor immune system that can target mutated proteins [43]. In the present case, immunohistochemical analysis in the tumor tissue revealed low expression of PD-L1 and high expression of TMB-H, with 11.7 Muts/MB (Fig. 5). The patient's immunohistochemical results were negative for PD-L1 and positive for tumor load. Furthermore, we found that although the patients had PD-1 side effects in the early stage, the patients could not tolerate PD-1 and the treatment of PD-1 was terminated. However, after our series of antisense effects treatments, when we tried again to use PD-1 in combination with chemotherapy, the patients again benefited from the treatment. It is reasonable to speculate that patients sensitive to immune side effects seem to respond better to PD-1. So, we use chemotherapy combined with immunotherapy to treat pancreatic cancer, obtaining a satisfactory therapeutic effect.

### Conclusion

Here, we reported a Chinese patient with pancreatic cancer, a high TMB and low expression of PD-L1 who responded well to the combined therapy of pembrolizumab and chemotherapy. In our case, the combination of PD-1 inhibitors and chemotherapy to control pancreatic cancer is a promising treatment approach. The link between TMB and immunotherapy is well demonstrated in this case. And it may lead to a promising combination treatment option for advanced pancreatic cancer with a high TMB.

### Acknowledgements

The study received informed written consent from all participants. These case studies were based on the principles outlined in the Declaration of Helsinki. The

protocol was approved by the ethics committee of the Zhejiang Provincial People's Hospital. Informed written consent was obtained from the patients for publication of this report and any accompanying images.

P-F.Z. and Y-W.C. contributed equally to this work; Z-L.C. and L.Y. diagnosed the patient; P-F.Z., Y-W.C., M-X.W., Y-Y.D. and S-Y.P. analyzed the literature data; All authors wrote and revised the manuscript and issued the final approval for the version to be submitted.

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

### Conflicts of interest

There are no conflicts of interest.

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