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CASE REPORT

Case report: a case of R0 resection in a patient with PD-L1-negative, microsatellite-stabilized advanced pancreatic cancer after down-stage treatment with a PD-1 inhibitor in combination with chemotherapy

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Abstract

Background Pancreatic ductal adenocarcinoma (PDAC) is a gastrointestinal tumor with high morbidity and mortality. Despite advances in diagnostic and therapeutic modalities, the outcome and prognosis of PDAC remain poor. Most patients have locally advanced disease (30%–35%) or distant metastases (50%–55%) at the time of diagnosis. The treatment of unresectable pancreatic ductal adenocarcinoma (UR-PDAC) remains an urgent problem. In this study, we report that a patient with UR-PDAC underwent significant tumor shrinkage after PD-1 inhibitor combination chemotherapy, and obtained R0 (pathologically negative margin) resection and long-term survival.

Case presentation A 51-year-old woman was diagnosed with pancreatic cancer (stage III). She underwent 3 cycles of preoperative neoadjuvant therapy (NAT) with programmed cell death protein 1 (PD-1) antibody in combination with chemotherapy and the tumor shrank from 4.0 × 3.3 cm to 0.9 cm without significant adverse effects. The patient underwent conversion surgery (CS) and achieved R0 resection, and no tumor cells remained as confirmed by pathology.

Conclusion PD-1 antibody combination chemotherapy regimens have significant efficacy and do not add additional side effects in UR-PDAC patients, heralding advances in UR-PDAC treatment. We may have a way to give UR-PDAC patients access to curative treatment and long-term survival. This case of UR-PDAC patient with PD-L1-negative and microsatellite stability (MSS) gives us a more comprehensive understanding of the treatment options of immune-combination chemotherapy.

Keywords Unresectable pancreatic ductal adenocarcinoma · Conversion surgery · Chemotherapy · Immune checkpoint inhibitors · Neoadjuvant therapy · PD-1 antibody

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor of the digestive system with high incidence and very poor prognosis, with a 5-year survival rate of approximately 10%. PDAC is projected to be the second leading cause of

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cancer-related deaths in the United States by 2030 (Rahib et al. 2014). Based on the extent of vascular involvement, particularly venous (portal or superior mesenteric vein) and arterial (superior mesenteric artery or celiac trunk and its branches), patients with pancreatic cancer are categorized as having resectable, junctional resectable, and unresectable (locally advanced, metastatic) pancreatic cancer (Mizrahi et al. 2020). Poor prognosis is a distinguishing feature of patients with pancreatic cancer, with approximately 35% of patients having unresectable pancreatic ductal adenocarcinoma (UR-PDAC) at the time of first diagnosis (Heestand et al. 2015). Neoadjuvant therapy (NAT) can improve and control systemic disease in patients with UR-PDAC, especially when the tumor size is large or there is major vascular invasion, and can reduce the complexity of surgery and increase the R0 resection rate of UR-PDAC patients (Versteijne et al. 2020). In recent years, significant advances have been made in the treatment of UR-PDAC with NAT, and commonly used regimens include chemotherapy (Mataki et al. 2021), radiotherapy (RT) (Parikh et al. 2023), and chemoradiotherapy (CRT) (Roselló et al. 2020). These regimens have been used in the treatment of UR-PDAC, and some patients have achieved radical surgery after NAT, which is called "conversion surgery (CS)". However, these therapeutic options have limited responsiveness and durability, and are associated with strong toxic side effects. Therefore, there is an urgent need for new therapeutic strategies for this disease.

Here, we report a case of UR-PDAC with successful CS after PD-1 (programmed cell death protein 1) antibody in combination with chemotherapy, achieving R0 resection. Our results suggest that this NAT is an effective regimen for the treatment of UR-PDAC.

Case presentation

A 51-year-old female patient was admitted to the hospital on August 12, 2022, with the primary cause of "epigastric distension and discomfort for more than 2 months". She had no previous medical history and no abnormalities on physical examination. Her body mass index (BMI) was 29.6 kg/m^2 and her ECOG (Eastern Cooperative Oncology Group) physical status score was 1. Laboratory results showed a glycan antigen 199 (CA-199) level of 579 IU/ml (normal range 0–37) and a glycan antigen 50 (CA-50) level of 366 IU/ml (normal range 0–25) (Fig. 1). Enhanced CT showed a hypodense round-like mass in the head-neck junction area of the pancreas measuring 4.1 × 3.2 × 3.3 cm, which was poorly demarcated from the distal part of the main portal vein trunk (more than 180 degrees). The mass encircled the splenic artery and the proximal segment of the gastric omental artery, resulting in localized narrowing of these arteries.

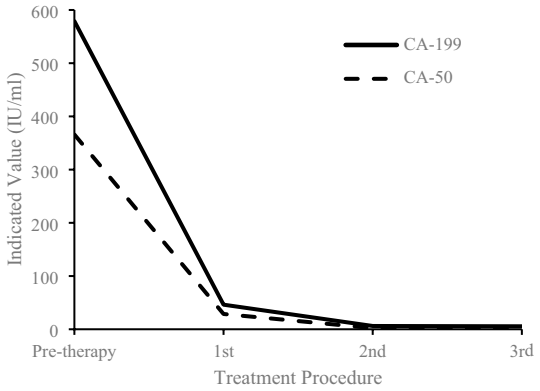

Fig. 1 CA-199 and CA-50 levels during treatment. 1st: receipt of the first PD-1 antibody and AG treatment. 2nd: receipt of the second treatment. 3rd: receipt of the third treatment

The mass invaded the left gastric artery and the lesser curvature of the stomach, and multiple enlarged lymph nodes in the retroperitoneum and the abdominal cavity, the larger of which was 1.6 × 0.7 cm, were considered pancreatic cancer (Fig. 2A). Finally, the patient was diagnosed with pancreatic ductal adenocarcinoma (pT3NxM0) after biopsy (Fig. 2B).

According to the resectable classification of PDAC proposed by the National Comprehensive Cancer Network (NCCN) (Park et al. 2024), this patient's tumor encircled the distal portal vein (more than 180 degrees) and was an unresectable tumor (UR-PDAC). After multidisciplinary discussion, this patient was first treated with downstaging before surgery. On August 18, 2022, the patient was started to receive the PD-1 inhibitor: Tislelizumab (Bacitracin®) 200 mg (day 1, 21-day cycle) in combination with gemcitabine 1000 mg/m^2 (day 1 and day 8) and albumin paclitaxel 125 mg/m^2 (day 1 and day 8) (AG) as the first-line chemotherapy regimen for every 21-day cycle. Enhanced CT at the end of 3 courses of treatment showed: pancreatic cervicobody junction area occupying 0.9 cm in diameter, the lesion was significantly reduced in size compared with the previous one, and the surrounding pancreatic parenchyma was atrophic; no abnormality of the splenic artery and proximal segment of the gastro-epiploic artery was seen; and there were multiple intra-abdominal and retroperitoneal lymph nodes of slightly enlarged lymph nodes, which were reduced in size compared with the previous one (Fig. 2A). The Multidisciplinary Team (MDT) recommended surgical treatment. On December 16, 2022, pancreatic body-caudal resection and splenectomy were performed. Histopathological examination showed localized intrapancreatic cystic lumen formation, large amount of necrotic tissue was detected in the lumen, and peripheral fibrous tissue hyperplasia, which was consistent with pathological changes after complete regression of chemotherapy, no cancerous tissue was seen at the margins, and there was

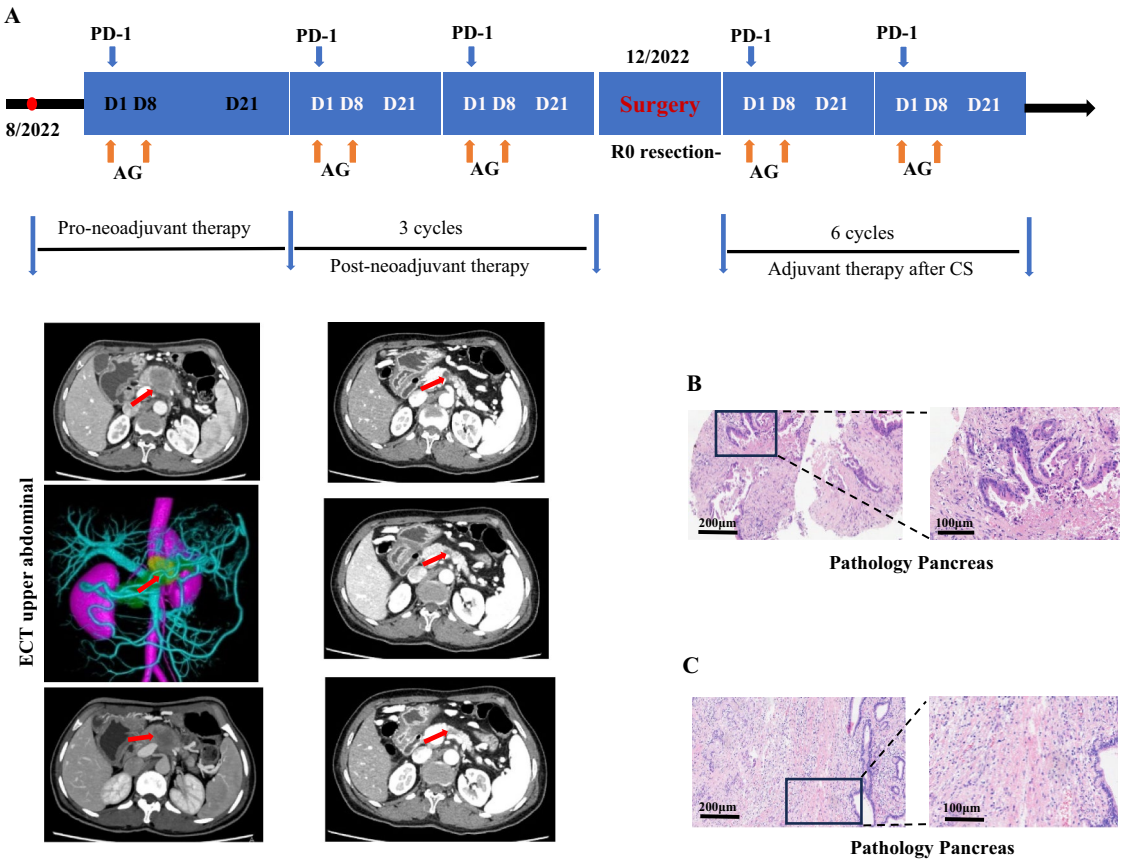

Fig. 2 Case presentation of patient. **A** Timeline of disease status. Medication regimens of neoadjuvant therapy and postoperative adjuvant therapy. Tumor responses shown by ECT of pre- and post-neoadjuvant therapy. **B** Pathological diagnosis of the pancreas with fine needle aspiration. **C** H&E staining of the isolated pancreas tissues after surgery. PD-1, programmed cell death protein 1. *AG* gemcitabine and albumin paclitaxel. *CS* conversion surgery

no metastatic carcinoma in peripancreatic lymph nodes. The Tumor Regression Grade (TRG) score was 0, and the pathological stage was ypT0N0M0 (Fig. 2C).

Subsequently, 2 courses of PD-1 inhibitor plus AG were implemented, and because the patient developed severe gastrointestinal reactions (nausea and vomiting), chemotherapy (AG) was discontinued, and the patient continued to receive 4 cycles of 200 mg PD-1 antibody combined with Tegretol (S-1): 60 mg/m^2 orally twice a day on days 1–14 for 21 days in each cycle. There was no recurrence 24 months after resection and follow-up was continued.

Discussion

Pancreatic ductal adenocarcinoma (PDAC) is highly malignant and has a very poor prognosis, making it a very difficult digestive malignancy. Surgical resection is the only possible cure, but only 10–20% of patients have a chance of surgical radicalization. Radical surgery is a major prognostic factor, and for patients who undergo radical surgery, their chances of long-term survival are significantly increased (Ferrone et al. 2012). Clinically, our choice of treatment for patients with PDAC is based more on whether the tumor can be resected than on the stage of the tumor. Therefore, the National Comprehensive Cancer Network (NCCN) proposed a resectable classification of PDAC based on the degree of vascular involvement, especially venous (portal vein or superior mesenteric vein) and arterial (superior mesenteric artery or celiac trunk and its branches), and recommended the optimal treatment regimen based on each resectable classification (Park et al. 2024). However, approximately 35% of patients have unresectable pancreatic ductal adenocarcinoma (UR-PDAC) at the time of first diagnosis. UR -PDAC is further subdivided according to anatomical and biological criteria into unresectable locally advanced carcinoma (UR-LA, 35%) and unresectable metastatic carcinoma (UR-M, 50%).

Reports of surgical resection of advanced pancreatic cancer after NAT have been increasing since the 2010s (Klaiber et al. 2021). According to the latest NCCN guidelines (2020 NCCN Clinical Practice Guidelines, 2nd edition) (Park et al. 2024), surgical resection is the follow-up treatment of choice for patients with advanced tumors with good outcome after NAT and without disease progression. Retrospective studies have shown that patients with UR-PDAC may benefit from surgery and that patients who undergo systemic therapy followed by surgery have a better prognosis than those who undergo surgery only. Failure to achieve R0 resection and absence of NAT are independent factors for poor prognosis in patients with UR-PDAC (Versteijne et al. 2020). Although two chemotherapeutic regimens, FOLFIRINOX and gemcitabine plus albumin-conjugated paclitaxel (AG), are considered to the standard regimens for NAT in patients with UR-PDAC and have achieved a certain degree of efficacy, the abundance of interstitial stroma in pancreatic cancers makes it difficult for chemotherapeutic agents to penetrate, resulting in patients seldom achieving partial remission with chemotherapy alone (Smyth et al. 2016).

Immune checkpoint inhibition has revolutionized cancer treatment in the last decade. Immunotherapy is now approved by the US Food and Drug Administration (FDA) for nearly 70 different indications across 18 histologies (Sharma et al. 2021). However, with the exception of a very small number (< 1%) of patients with high tumor microsatellite instability-high (MSI-H), immunotherapy has not shown better efficacy in PDAC, which exhibits an immunologically "cold" tumor microenvironment. PDAC exhibits an immunologically "cold" tumor microenvironment (TME), with the exception of < 1% defective Mismatch Repair (dMMR)/Microsatellite Instability-High (MSI-H) (O'Reilly et al. 2019), where PDAC shows near-universal tolerance to Immune Checkpoint Blockade (ICB) near universal tolerance. Treatment of pancreatic cancer with immune checkpoint inhibitors alone is not effective and lacks markers that effectively predict the likelihood of a response to ICB therapy. The patient in this report had microsatellite stability (MSS) and was negative for PD-L1 antibodies (CPS < 1) (Table 1). Although PD-L1 is a strong predictive marker of treatment response in non-small cell lung cancer (NSCLC), there is insufficient evidence to suggest that PD-L1 can serve as a marker of treatment response in pancreatic cancer. However, combination regimens of immune checkpoint inhibitors with chemotherapy have shown encouraging results. A phase I study of patients with advanced pancreatic cancer without systemic therapy demonstrated a 50% objective remission rate after nabumab in combination with AG. Despite the small sample size, this suggests that immunotherapy plus chemotherapy may have clinical benefit (Springfeld et al. 2023). In contrast, the results of a phase Ib study of Pembrolizumab (anti-PD-1 antibody) in combination with AG showed a clinical efficiency of approximately 92% with no increase in serious complications (Daunke et al. 2023). In our case, moderate myelosuppression (decreased WBC) was observed during the second cycle of NAT, which was alleviated after administration of granulocyte colony-stimulating factor and did not interfere with subsequent treatment. The immunostimulatory effect of chemotherapy contributes to the antitumor effect by generating neoantigens, changing pancreatic cancer from a "cold tumor" to a "hot tumor" and enhancing the sensitivity of pancreatic tumors to immunotherapy.

Table 1 The molecular background of cases

	PD-L1	Microsatellite	Mutant gene	
			I	II
Case	Negative (TPS < 1%, CPS < 1)	MSS	KRAS	MSH2 PTEN KDR

MSS microsatellite stability, *CPS* combined positive score, *TPS* tumor cell proportion score. *I* mutations with clear clinical significance corresponding to drug sensitivity grade 1. *II* mutations with potential clinical significance corresponding to drug susceptibility grade 2–4

Tirelizumab is a humanized recombinant immunoglobulin G4 monoclonal antibody against PD-1 that blocks the PD-1/PD-L1 signaling pathway, releasing the "brakes" of the immune system. It is currently the only PD-1 monoclonal antibody successfully modified on Fc to minimize binding to the macrophage surface Fcγreceptor (FcγR), avoiding T-cell depletion caused by antibody-dependent cell-mediated phagocytosis (ADCP) (Zhang et al. 2018). With low toxicity and long half-life, tirilizumab has been approved in China for the treatment of 14 indications including relapsed or refractory classic Hodgkin's lymphoma, locally advanced or metastatic uroepithelial carcinoma, advanced non-small cell lung cancer, esophageal cancer, gastric cancer and hepatocellular carcinoma, making it the PD-1 monoclonal antibody with the largest number of clinical indications.

Sensitive tumor markers are critical for predicting treatment outcomes. pD-1 antibodies have received FDA approval for the treatment of defective mismatch repair/high microsatellite instability (dMMR/MSI-H) or non-high tumor mutation burden (TMB-H) tumors. However, the clinical efficacy of immune checkpoint inhibitors in the treatment of PDAC is still poorly understood, and there is a lack of markers that effectively predict the likelihood of a response to ICI therapy. Although, PD-LI expression is currently one of the most effective predictors of PD-1/PD-L1 therapy. Moreover, PD-L1 is a strong predictive marker for response to treatment in NSCLC, but there is no evidence that PD-L1 can be used as a marker for predicting response to PDAC therapy. In our case, PD-L1 was negative (CPS < 1) (Table 1), so more sensitive markers

are needed to predict the effect of immunotherapy in patients with PDAC.

This study provides a new idea on how to better treat patients with UR-PDAC. In this study, we observed a patient who underwent NAT (PD-1 antibody immunotherapy combined with chemotherapy) and ultimately achieved R0 resection and had complete tumor regression with a pathological stage of ypT0N0M0. However, because of limitations such as the lack of control cases and a short follow-up period, it was not possible to observe the effect of the immune-combination therapy on the postoperative overall survival. Future clinical trials with large samples are needed to test the clinical efficacy of this neoadjuvant therapy in patients with UR-PDAC.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Written informed consent was obtained from all patients for the publication of any potentially identifiable images or data included in this article.

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