Durable benefit from immunotherapy and accompanied lupus erythematosus in pancreatic adenocarcinoma with DNA repair deficiency

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ABSTRACT

Background Clinical trials showed limited benefit of anti-PD-1 (programmed cell death 1) monotherapy in pancreatic adenocarcinoma patients and immune-related adverse events caused by immune checkpoint inhibitors were rarely reported in pancreatic adenocarcinoma. Here, we report the first case of durable benefit along with systemic lupus erythematosus following immunotherapy in mismatch repair-proficient pancreatic cancer.

Case presentation We describe a 57-year-old woman with resected stage IIIB pancreatic cancer who underwent several lines of conventional chemotherapy after multiple lymph node metastases. When the disease progressed again, the patient received an off-label treatment with pembrolizumab (100 mg every 3 weeks). After four cycles of immunotherapy treatment, CA19-9 level rapidly decreased to normal and the lymph node metastases reduced dramatically in volume, demonstrating a partial response to the therapy by RECIST 1.1 criteria. She continued on pembrolizumab and a total of eight cycles of administration she had received. Her lesions showed consistent reduction in size even when the medication had been stopped. Actually the patient experienced durable benefit from anti-PD-1 therapy for more than 4 years and she is still in good condition without tumor relapses to date. Besides, she was diagnosed with systemic lupus erythematosus 2 months after the last dose of pembrolizumab. Molecular profiling identified two deleterious *PALB2* alterations including a germline mutation (*PALB2* c.3114–1G>A) and a somatic mutation (*PALB2* c.2514+1G>C) in this patient, suggesting the potential of DNA homologous recombination deficiency. Multiplex immunohistochemistry and RNA-seq results revealed a brisk immune cell infiltration in her resected primary lesion. Additionally, human leukocyte antigen (HLA) typing assay identified two previously reported systemic lupus erythematosus risk alleles HLA-DRB1*15:01 and HLA-DQB1*06:02 in this patient.

Conclusions The deleterious mutations of *PALB2* closely related to homologous recombination deficiency or alterations of DNA damage response and repair genes might be promising biomarkers for predicting efficacy of immune checkpoint inhibitors in pancreatic adenocarcinoma. Genetic correlation behind immunotherapy-induced systemic lupus erythematosus and associated mechanism remain to be elucidated.

INTRODUCTION

Pancreatic adenocarcinoma (PAAD) is one of the most refractory malignancies with poor prognosis after radical surgery. In recent years, immune checkpoint blockade-based immunotherapies have gained encouraging success in multiple solid tumors, however, single-agent immune checkpoint inhibitors (CPIs) fail to elicit efficacy in PAAD patients except pembrolizumab in certain individuals with mismatch repair deficiency.^{1 2} There is little known about whether there are other biomarkers for predicting response to CPI treatment in PAAD. It should be noted that 3.9% to 9.7% of pancreatic ductal adenocarcinoma individuals carry pathogenic/likely pathogenic germline alterations, especially those alterations involved in homologous recombination deficiency (HRD) or DNA damage response and repair (DDR) genes including *BRCA1/2*, *PALB2*, *ATM*, etc.^{3 4} Moreover, the deleterious DDR gene variants have revealed the potential of predicting responsiveness to anti-PD-1 (programmed cell death 1)/PD-L1 (programmed death-ligand 1) therapy in bladder urothelial carcinoma⁵ and non-small cell lung cancer patients,⁶ whereas there are few reports of survival benefit in PAAD patients receiving CPIs.

As the increasing prevalence of CPI treatment in solid tumors, the special feature of side effects, that is, the immune related adverse events (irAEs), have gained wide attention. The diverse irAEs bring challenges in management of cancer patients during immunotherapy treatment. On the other hand, studies have found that certain irAEs are associated with improved response and prognosis in cancer patients treated with CPIs.^{7 8} In general, it is vital to explore the underlying mechanisms of irAEs, especially genetic factors.⁹

Figure 1 Clinical course of the patient. (A) Histological characteristic of the moderately differentiated adenocarcinoma of the pancreas (hematoxylin-eosin stain; original magnification×400). (B) Serum CA19-9 levels during and after treatment with pembrolizumab (red arrow indicates the last dose of pembrolizumab). (C) Representative contrast-enhanced CT images of the abdomen in venous phase, showing patient's recurrent lymph node lesions during and after treatment with pembrolizumab. A 2.5-month follow-up scan demonstrated partial response of the disease. (the top row: retroperitoneal lymph nodes; the bottom row: abdominal para-aortic lymph node; lesions are marked by red triangle). (D) Time line of clinical events. PD, progressive disease; PR, partial response.

Here we report an exceptional case of recurrent PAAD individual with microsatellite stability (MSS)/proficient mismatch repair who experienced durable survival benefit (more than 4years) along with systemic lupus erythematosus (SLE) after receiving pembrolizumab. Two deleterious *PALB2* mutations including a germline mutation in combination with several humanleukocyte antigen (HLA) class II risk *loci* for SLE identified in this patient may account for her outcomes under CPI treatment.

CASE PRESENTATION

A 57-year-old Chinese woman was diagnosed with a stage IIIB moderately-differentiated pancreatic adenocarcinoma (figure 1A) and underwent distal pancreatectomy and en-bloc splenectomy in September 2014. Eight months later, a follow-up contrast-enhanced CT scan revealed enlargement of her multiple abdominal lymph

nodes. Then the patient was treated with two cycles of chemotherapy with gemcitabine (1200mg) plus paclitaxel liposome (180mg) on days 1 and 8, every 3 weeks. However, the re-examination of CT demonstrated progression of disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST, V.1.1). Next, she started receiving docetaxel (110mg) intravenously on days 1, plus tegafur (50mg, two times per day) orally on days 1 to 14, every 3 weeks. CT scan showed a partial response (PR) following six cycles of the chemotherapy. In November 2015, docetaxel was discontinued and tegafur regimen was used for maintenance chemotherapy. After two cycles of tegafur monotherapy, a follow-up CT scan showed the PD again. CT imaging revealed the presence of retroperitoneal lymph node metastases with two nodes of 2.4×2.1 cm and 2.9×1.7 cm, respectively, as well as abdominal para-aortic lymph node metastasis with a node of 2.4×2.2 cm. Whereafter, this patient decided to pursue an off-label use of pembrolizumab (100mg, every 3 weeks) on January 21, 2016. Fortunately, radiological results demonstrated a PR after four cycles of immunotherapy. Moreover, her serum level of CA19-9 rapidly dropped down to normal (below 37U/mL) (figure 1B). Next, she continued to receive another four cycles of pembrolizumab with the same dosage and administration as before and durable benefit was observed (figure 1C). Notably, after her last cycle of pembrolizumab treatment in July 2016, the adverse effects started to appear, characterized by allergic dermatitis, fever, nausea and vomiting. In September 2016, she was diagnosed with SLE based on her clinical features and autoantibody in serum, positive antinuclear antibody of 1:320 titer (speckled patterns) and antibodies to Sjögren's-syndrome-related antigen A (SS-A). Subsequently, she was administrated with hydroxychloroquine (200mg, daily) to control SLE until March 2019. In the meantime, her recurrent tumor lesions of retroperitoneal nodes achieved near complete remission and the para-aortic nodes maintained a reduced size. This patient has neither history of autoimmune disease nor family history of cancer. Her whole disease course and clinical outcomes were summarized in figure 1D. From initiation of the immunotherapy to date, the patient experienced durable survival benefit of more than 4years, and she had a good performance status when this case report was revised.

METHODS

To identify the involvement of genomic features as well as tumor immune microenvironment signature in this unexpected response to immune checkpoint blockade and underlying genetic association with pembrolizumab-induced systemic lupus erythematosus. We performed molecular analyzes of the patient's resected primary tumor tissue, paracancerous tissue and peripheral blood sample in a College of American Pathologists accredited laboratory (GeneCast Biotechnology Co, Beijing) with consent of the patient.

Tumor immune microenvironment was examined by multiplex immunohistochemistry (mIHC) and RNA sequencing. Two resected tumor tissue sections were used for mIHC staining: one for anti-CD3 (clone LN10), anti-CD8 (clone SP16), anti-PD-1 (clone UMAB199); the other for anti-CD4 (clone UMAB64), anti-CD68 (clone KP1), anti-CD163 (clone 10D6); all the primary antibodies were from ZSGB-BIO, Beijing, China. The stained slides were scanned using the PerkinElmer Vectra and analyzed by inForm Advanced Image Analysis software (PerkinElmer, Massachusetts, USA). Positive cells were defined as cells with true immunofluorescence signal detected and with right expression pattern. More than 12 fields per slide were selected to calculate the number, percentage and density of positive cells under the 200×magnification. Mean percentage of specific positive cells in all nucleated cells of the tumor stroma from the selected fields was used for analyzes. RNA sequencing based gene expression profiling was performed on resected tumor tissue and paracancerous tissue by the OncoPrint Immune Response Research Assay (Thermo Fisher Scientific, USA). Gene expression levels of approximately 400 genes relevant to oncology and immunology were analyzed. Five immune signatures were defined to represent T cell-inflamed features, including T cell markers (CD2, CD3D, CD3E, CD4, CD40LG, CD8A and CD8B), cytolytic markers (GNLY, GZMA, GZMB and PRF1), IFN- γ signature (CXCL10, CXCL9, HLA-DRA, IDO1, IFNG and STAT1), HLA molecules and chemokines. The signature scores were calculated by averaging the log10 transformed expression value of the involved genes.

Genetic analyzes were used to explore the mechanism of immunotherapy response and the induced autoimmune disease. HLA genotyping of the peripheral blood lymphocytes was performed via PCR amplification with sequence based typing methodology and DNA sequencing analysis of resected tumor and peripheral blood sample was performed using next generation sequencing of a customized gene panel, including 543 cancer related genes.

PD-L1 expression and mismatch repair protein expression were also examined with regular methods. For more details of the experimental methods, please see the online additional file 1. No statistical test was performed as there is only one patient and we did not investigate the differences between samples.

RESULTS

Targeted sequencing results show a common driver mutation *KRAS* p.G12V (8.72%) along with two splicing mutations of *DDR* gene *PALB2* in her resected primary lesion (online supplementary table S1). No alterations of other major driver genes (ie, *TP53*, *CDKN2A*, *SMAD4*) in PAAD were identified. Of note, both of the two *PALB2* mutations are viewed as likely pathogenic based on ClinVar database, suggesting the probable deficiency of DNA homologous recombination. Among them, *PALB2* c.3114-1G>A

Figure 2 *PALB2* mutations and immunologic characteristics of the patient. (A) Schematic representation of *PALB2* gene with the two splicing mutations indicated. (B) Immune response signature scores of primary tumor and matched paracancerous tissue. (C) Quantitative distribution of tumor infiltrated T cell and macrophage in the stroma of the primary tumor. (D) Distribution of PD-1 expression on CD3 or CD8 positive T cells and CD163 expression on CD68 positive macrophages in stroma. (E and F) Representative histological images of the resected tumor stained by multiplex immunofluorescence, showing the brisk immune cell infiltration in tumor microenvironment. Original magnification×200. HLA, human leukocyte antigen; PD-1, programmed cell death 1.

was a germline mutation simultaneously detected in her peripheral blood cells, while *PALB2* c.2514+1G>C (8.32%) was a somatic mutation (figure 2A).

Tumor immune microenvironment signature of this patient was examined by expression profiling of 395 immune related genes and analysis of immune cell subsets in situ by mIHC. Compared with paracancerous tissue, higher expression levels of cytolytic markers, T cell markers, IFN- γ signature, chemokines as well as HLA molecules were observed in cancer tissue, demonstrating a T cell-inflamed tumor microenvironment (figure 2B). Global expression levels of 35 pre-set gene function signatures were also evaluated and immune signature scores of 21 functional pathways are at least 1.5-fold differentially changed in cancer tissue relative to paracancerous tissue, most of which are favorable for antitumor immune (online supplementary figure S1). In consistent with the expression profiling results, there were relatively high infiltration degrees of CD3 or CD8 positive T cells in stroma of cancer specimen examined by multiplex immunohistochemistry (figure 2C-F). Cytotoxic T cells (CD8+)

Table 1 Human leukocyte antigen alleles of the patient

HLA loci	Allele	Association with SLE susceptibility	Population (reference)
HLA-A	A*02:01	–	NA
	A*11:01	Uncertain	Malays and Chinese ¹⁸
HLA-B	B*15:01	–	NA
	B*54:01	–	NA
HLA-C	C*03:03	–	NA
	C*01:02	–	NA
HLA-DQ	DQB1*05:01	Risk factor	Chinese Taiwan ¹⁹
	DQB1*06:02	Risk factor	Eastern Asians ¹¹ European ^{10 20} Saudis ²¹
HLA-DR	DRB1*01:01	–	NA
	DRB1*15:01	Risk factor	Eastern Asians ¹¹ Chinese Taiwan ^{19 22} Japanese ²³ Koreans ²⁴ European ^{10 20}
HLA-DP	DPB1*04:02	–	NA
	DPB1*05:01	Uncertain	Japanese ²⁵

Alleles in bold font are considered to be more likely to increase the risk of SLE.

–, unknown; HLA, human leukocyte antigen; NA, not available; SLE, systemic lupus erythematosus.

and helper T cells (CD4+) account for about 10% of all cells in tumor stroma, respectively, and macrophages (CD68+) has a proportion of 4% (figure 2C). Moreover, exhausted or inhibitory cells such as PD-1 positive CD3 or CD8 T cells or CD68⁺ CD163⁺ cells were also explored, each accounts for tiny proportion in corresponding immune cell subset (figure 2D; online supplementary figure S2), indicating good activity and antitumor potential of the tumor infiltrating lymphocytes or macrophages. Collectively, primary tumor of this pancreatic patient has a favorable baseline immune microenvironment.

Additionally, PD-L1 (SP142 staining) was absent and four mismatch repair proteins (MLH1, MSH2, MSH6 and PSM2) were proficient in this patient's tumor (online supplementary figure S3). Likewise, her microsatellite instability status was MSS (online supplementary figure S4). Given the close relationship of HLA alleles with the susceptibility to SLE,¹⁰ we performed HLA genotyping of normal DNA from her peripheral blood cells. Not surprisingly, two SLE risk alleles HLA-DRB1*15:01 and HLA-DQB1*06:02 previously reported in the Eastern Asians¹¹ were identified. Besides, there were some other HLA alleles potentially related to SLE in this patient (table 1).

DISCUSSION AND CONCLUSIONS

The pancreatic ductal adenocarcinoma patients with HRD have shown association with enhanced expression of antitumor immunity related molecules and active immune status in previous research,¹² which is in agreement with our findings of this pancreatic cancer patient harboring deleterious *PALB2* mutations. There were obviously higher levels of cytolytic markers in her resected cancer tissue than in paracancerous tissue as well as more infiltrates of CD8⁺ T cells in tumor stroma. Correspondingly, she responded well to CPI treatment with pembrolizumab and achieved more than 4-year survival benefit. It should be noted that this individual had paired deleterious mutations of *PALB2*, each one for germline and somatic, while about half of PAAD patients arising from pathogenic germline alterations of homologous recombination (HR) genes lack somatic variants of HR genes ('second hit') in their tumors and these patients may not be true HRD.¹³ Theoretically, co-occurrence of germline and somatic HR gene alterations might bring about higher number of tumor-specific neoantigens along with relatively activated immune environment.¹² Given this, we speculated that this patient's paired *PALB2* mutations probably contributed to her exceptional good outcomes after pembrolizumab treatment, although to our knowledge there are hardly any clinical studies reporting HR gene variants as predictive biomarkers for CPI monotherapy in PAAD patients to date.

During cancer immunotherapy, irAEs consisting of rash, colitis, pneumonitis, and so on, are not uncommon as the increasing clinical use of CPIs.¹⁴ Nonetheless, secondary lupus erythematosus following CPI treatment is fairly rare. In terms of mechanism, two aforementioned known HLA class II (HLA-II) germline alleles susceptible to SLE in combination with the exposure to pembrolizumab may jointly lead to the unusual adverse event of this patient. The two SLE risk alleles HLA-DRB1*15:01 and HLA-DQB1*06:02 might confer a high level of immunity to this patient or even put her in a pre-autoimmunity state. As an external factor, CPI could just trigger the development of SLE. Interestingly, a substantial association between the development of irAEs and survival benefit from anti-PD-1/PD-L1 antibodies has been recently identified in 1747 patients.⁸ In addition, it was previously reported that among five efficacy evaluable cancer patients with the occurrence of lupus erythematosus after receiving CPIs, three individuals had complete or partial remission and two of them were treated with pembrolizumab.¹⁵ It is impressive that CPI showed remarkable efficacy in this patient with HRD pancreatic cancer carrying two SLE risk alleles, which may inspire future investigation of the intrinsic correlation between efficacy and side effects of checkpoint inhibitors in tumors. Predictive biomarkers of immunotherapy-related toxicity are worth studying, like autoantibodies¹⁶ or genetic factors.⁹

Notably, the duration of exposure to pembrolizumab in this PAAD patient was just 6 months (100 mg, every three weeks). However, she gained lasting survival benefit along

with lupus erythematosus until now. In consideration of the potential role of HLA-II molecules in immunotherapy,¹⁷ it is plausible that her specific HLA-II genotype perhaps not only involves in irAEs but also is beneficial for CPI treatment.

In summary, DNA repair deficiency characterized by deleterious germline and somatic alterations of *PALB2* as well as certain HLA-II germline alleles related to lupus erythematosus may be promising biomarkers for anti-PD-1/PD-L1 therapy in PAAD patients.

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Contributors XP, JQ and HJ contributed equally to this work and are co-first authors. XP and JQ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. XP, JQ and HJ designed the study. LL, ZZ, and ML collected the data. YW and YL performed radiological data analysis and provided the imaging figures. JQ, HJ, LL, ZZ and ML analyzed the data. JQ drafted the manuscript. XP was the main treating physician. LZ, XP and HZ contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors have read and approved the final version manuscript. XP and HZ are the study guarantors.

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