Editorial

Immunotherapy for deficient mismatch repair (dMMR) pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging cancers to treat due to its late stage at diagnosis in the absence of early signs and symptoms, lack of effective screening or prevention strategies, and overall poor prognosis. More than 50% of patients present with locally advanced or metastatic disease at the time of diagnosis (1,2). In 2022, the American Cancer Society estimated that 62,210 new cases of PDAC will be diagnosed and about 49,380 Americans will die from pancreatic cancer (2). Not surprisingly, PDAC is projected to be the second leading cause of cancer-related death by 2030 in the United States, surpassing prostate, breast and colorectal cancer (3).

Surgical resection is the only curative option for PDAC especially in early stages at initial diagnosis, though careful review should be undertaken to assess for potential locally advanced or metastatic disease. Neoadjuvant chemotherapy with modified FOLFIRINOX (combination 5-fluorouracil, leucovorin, irinotecan, oxaliplatin) (4) or gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel (5) remain the standards of care by providing an overall survival advantage in locally advanced and metastatic PDAC. In the borderline resectable and locally advanced settings, either regimen is used at times in combination with radiation therapy, to potentially downstage a tumor and achieve a desirable R0 resection. Surgery followed by adjuvant systemic therapy reduces the risk of recurrence though subsequent cycles of treatment are often limited by patient tolerance and toxicity.

In the case reported by Han and Borazanci (6), the authors described a 57-year-old male with metastatic PDAC whose tumor profile revealed a high tumor mutational burden (TMB), microsatellite instability-high (MSI-H), and a non-germline deficient mismatch repair (dMMR) tumor, who ultimately achieved an ongoing response to combination immune checkpoint inhibition (ICI) with ipilimumab and nivolumab. In addition, this case reports detailed a heavily pre-treated tumor which progressed on FOLFIRINOX, gemcitabine/nab-paclitaxel, and clinical trial prior to ICI. Pancreatic tumors characterized by MSI-H or dMMR status, unlike their microsatellite stable and MMR proficient counterparts, are less sensitive to gemcitabine or 5-fluorouracil based regimens (7). Moreover, it is known that dMMR cancers are sensitive to programmed cell death-1 (PD-1) blockade, regardless of tissue of origin, due to the higher number of somatic mutations and potential neoantigens that allow for a more robust and

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durable anti-tumor response (8). Following the U.S. Food and Drug Administration's approval of pembrolizumab, a PD-1 inhibitor, for the treatment of MSI-H or dMMR solid tumors, as in this case, knowing the MMR deficiency status can have profound effects on treatment options and it should be tested for in all pancreatic tumors regardless of stage.

The authors described the PDAC in this case report as a manifestation of sporadic MMR deficiency, although the molecular basis for this was not defined. Neither germline pathogenic variants associated with hereditary cancer-predisposing syndromes (including Lynch syndrome) nor somatic mutations of the MMR genes were identified to account for the dMMR noted (on the comprehensive molecular profiling tumor tissue and tumor DNA panel by Caris Life Sciences). Somatic *ARID1A* mutation, as detected in this patient's tumor, has been associated with epigenetic inactivation of *MLH1* via promoter hypermethylation in other cancer types (9-11). It is therefore possible that the MMR deficiency in this PDAC was associated with *MLH1* hypermethylation, although this does not appear to have specifically been tested for. Irrespective of precise molecular mechanism, concordant high TMB and MSI in the absence of a germline pathogenic variant corroborate a sporadic occurrence of MMR deficiency. For patients with dMMR or MSI-H tumors, irrespective of site, it is crucial that germline genetic testing also be performed as this may influence the need for closer surveillance and preventive measures for metachronous cancers, as well as cascade genetic testing in relatives (12). In contrast, one case report of a patient with a pathogenic *MSH2* germline mutation and history of Lynch syndrome-type cancers (endometrial, colorectal, urothelial) that lacked *MSH2* and *MSH6* expression, presented with a PDAC with intact expression of both *MSH2* and *MSH6*, which rendered the patient ineligible for immunotherapy with pembrolizumab (13). This case underscores the importance of testing for MMR gene expression in all tumors of patients with Lynch syndrome especially pancreatic tumors.

Aside from systemic therapy, the biology of pancreatic tumors allows us to explore other therapeutic options. The pathogenesis of PDAC is typically driven by somatic mutations in oncogenes, namely *KRAS*, and tumor suppressor genes, including *CDKN2A*, *TP53*, and *SMAD4* (1). Additionally, alterations in the tumor microenvironment by pancreatic neoplastic cells, surrounding desmoplastic stroma, and the presence of other immune cells including carcinoma associated fibroblasts, immunosuppressive myeloid cells, and regulatory T-cells have significant implications for mechanisms of treatment resistance leading to tumor cell proliferation and subsequent metastasis (14). Despite this complexity, there has been progress in identifying new targets including CD40 agonists, focal adhesion kinase inhibitors, vaccines, and combination regimens of standard chemotherapy, radiotherapy, immunotherapy, and targeted agents being studied in clinical trials (14).

In summary, PDAC is challenging to treat but a subset of pancreatic tumors namely those with high TMB, MSI-H, and/or deficient MMR expression appear to have promising results when treated with ICIs, as demonstrated in this case report. Though these tumors are rare, it is highly recommended that all cases of PDAC undergo tumor and germline testing to determine candidacy for immunotherapy or other potential treatment options.

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References

1. Wood LD, Canto MI, Jaffee EM, et al. Pancreatic Cancer: Pathogenesis, Screening, Diagnosis, and Treatment. Gastroenterology 2022;163:386-402.e1.
2. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
3. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-25.
5. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.
6. Han MY, Borazanci E. A rare case of sporadic mismatch repair deficient pancreatic ductal adenocarcinoma that responded to ipilimumab and nivolumab combination treatment: case report. J Gastrointest Oncol 2023;14:458-62.
7. Riazy M, Kalloger SE, Sheffield BS, et al. Mismatch repair status may predict response to adjuvant chemotherapy in resectable pancreatic ductal adenocarcinoma. Mod Pathol 2015;28:1383-9.
8. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
9. Bosse T, ter Haar NT, Seeber LM, et al. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations, TP53 and microsatellite instability in endometrial cancer. Mod Pathol 2013;26:1525-35.
10. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
11. Zhang K, Liu Y, Liu X, et al. Clinicopathological significance of multiple molecular features in undifferentiated and dedifferentiated endometrial carcinomas. Pathology 2021;53:179-86.
12. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. J Clin Oncol 2019;37:286-95.
13. Hendifar AE, Larson BK, Rojansky R, et al. Pancreatic cancer 'mismatch' in Lynch syndrome. BMJ Open Gastroenterol 2019;6:e000274.
14. Anderson EM, Thomassian S, Gong J, et al. Advances in Pancreatic Ductal Adenocarcinoma Treatment. Cancers (Basel) 2021;13:5510.

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