Case Report

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Case Report – A Patient with Pancreatitis as a Side Effect of Immunotherapy

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Introduction

Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1 and anti-CTLA-4) contribute to the immune response and antitumor immunity. Immunotherapy is associated with more immune-related adverse events, with pancreatitis being among the rarer [1]. Early signs of pancreatitis may include only an increase in lipase and amylase. The NCCN guidelines for the management of ICI-associated pancreatitis state that laboratory blood tests and abdominal radiography should be performed when potential symptoms of pancreatitis appear. The guidelines do not recommend intervention for asymptomatic elevation of pancreatic enzymes. Immunotherapy can be continued with monitoring of pancreatic enzymes. For moderate pancreatitis, immunotherapy should be temporarily stopped and glucocorticosteroids should be administered until the symptoms subside and the pancreatic enzyme findings improve. For severe and life-threatening pancreatitis, immunotherapy should be permanently discontinued and treatment with a double daily dose of glucocorticosteroids and iv. liquid [1].

Case Report

56-year-old patient in 6/2021. a diagnosis of metastatic lung adenocarcinoma was made (PD-L1 >50%). According to the recommendation of the MDT, treatment with pembrolizumab was started. On the same, disease regression and radiologically stable disease over time are recorded. Until 10. /2022. he received 21 cycles of pembrolizumab, after which he underwent MSCT and was hospitalized. A more voluminous pancreas with denser surrounding fatty tissue in terms of pancreatitis is described as a new moment. Laboratory findings showed significantly elevated values of alpha-amylase (358 U/l) and lipase (433 U/L). Since he was asymptomatic, we decided to continue immunotherapy with regular monitoring of pancreatic enzymes. He was examined by a gastroenterologist and had an abdominal ultrasound (homogeneous and non-enlarged pancreas). From 12/2022. replacement of exogenous pancreatic enzymes was introduced into his therapy. At the beginning of 1/2023. blood tests showed a drop in alpha-amylase and lipase values, and at the end of 2/2023. they returned to normal. The therapy with pembrolizumab was not interrupted and the patient was asymptomatic. It was agreed to stop taking the replacement of exogenous pancreatic enzymes.

Discussion

Programmed death 1 (PD-1) receptors bind to programmed death-ligand 1 (PD-L1), transport negative signals to T cells, and regulate functions of effector T cells. These receptors are expressed by T cells, B cells, and natural killer cells. In addition to normal T cells, several tumor cells upregulate PD-L1 on their surface, thus evading antitumor immune response and promoting immune tolerance by inactivating T cells through the PD-1/PD-L1 axis. These processes cause delay in the immune activation cycle. Cytotoxic T lymphocyte antigen 4 (CTLA-4) expressed on the surface of T cells downregulates immune responses

against cancer cells in the early stages of the immune activation cycle. The mechanism of action is by interacting with the surface molecules B7.1 (CD80) and B7.2 (CD86) on antigen-presenting cells [1-4]. These interactions promote tumor cells and aid in evasion of immunosurveillance. Therefore, use of immune checkpoint inhibitors (ICIs), including anti-PD-1 monoclonal antibodies (nivolumab and pembrolizumab), anti-PD-L1 monoclonal antibodies (atezolizumab, avelumab, and durvalumab), and anti-CTLA-4 monoclonal antibodies (ipilimumab and tremelimumab), triggers activation and expansion of T lymphocytes. These inhibitors act by blocking inhibitory signals of T cells and enhancing the ability of the immune system to fight cancer cells. Incidence rate of ICIs-associated pancreatic AEs (pancreatitis, hyperglycaemia, elevated amylase/lipase, and exocrine pancreatic insufficiency) is relatively low.

Most of these events have been described as a case report. Cancer patients treated with ICIs present with symptoms collectively described as ICIs-associated pancreatic AEs including abdominal pain, vomiting, dyspepsia, irregular stools, and large daily glucose fluctuations [5,6]. ICIs-associated pancreatic AEs are rare; however, they result in poor quality of life and affect safety of patients. ICIs associated with pancreatitis (ICIs-P) are extremely rare irAEs, making diagnosis a clinical challenge. Diagnosis of ICIs-P requires at least 2 criteria among the significant symptoms of pancreatitis, including radiographic evidence, and changes in laboratory data. George et al. evaluated 33 trials in a meta-analysis and reported that incidence of pancreatitis in the CTLA-4 group was higher compared with that of the PD-1 group (4% vs. 1%). Moreover, incidence of grade 2 pancreatitis in CTLA-4-PD-1 combination group was 10.6%, significantly higher compared with that of mono-immunotherapy [7]. Kohlmann et al. reported a case of ICIs-P within the first 4 months of immunotherapy. The patient had band-shaped epigastric pain with elevated levels of amylase and lipase in the blood. In addition, a CT scan of the pancreas showed edema within the tail of the pancreas. Immunotherapy was stopped immediately, and methylprednisolone (1.3 mg/kg) was administered to the patient. The symptoms gradually subsided, and the dose of glucocorticosteroids was reduced. When the dose was reduced to 8 mg, symptoms returned, and serum lipase levels rose again. For this reason, the patient was treated for a longer period with a high dose of methylprednisolone with a slow reduction of the daily dose until the disappearance of clinical symptoms and the achievement of a normal level of serum pancreatic enzymes [8].

Pathophysiological features underlying ICIs-P remain elusive. Like other irAEs, mechanisms can be thourgh inflammatory responses in the pancreas after ICIs administration. A few studies report on functional T cell activation induced by ICIs treatment. Immunohistochemical analysis shows that CD3+ T lymphocytes densely infiltrate pancreatic islets in "healthy" (nontumoral) areas, thereby increasing the ratio of CD8+/CD4+ T lymphocytes in peritumoral areas. These findings imply that immune T cell infiltrates might be the prevalent cytotoxic components of ICIs treatment [9]. NCCN guidelines for management of ICIs-P state that when potential symptoms of ICIs-P appear, laboratory tests and abdominal imaging should be performed. Once the diagnosis of ICIs-P is confirmed, hospital admission is recommended, however, other management approaches depend on grading. For grade 2 pancreatitis (moderate), treatment with ICIs should be discontinued, and 0.5–1 mg/kg/day prednisone/methylprednisolone should be administered until symptoms improve to grade ≤1. After achieving grade ≤1, the dose should be tapered for 4-6 weeks, and IV hydration should be administered. For grade 3–4 of pancreatitis (severe and life-threatening), immunotherapy should be permanently discontinued, and treatment with a double daily dose of glucocorticosteroids rather than moderate grade and IV fluids should be started [10].

Conclusion

Clinical trials reported a less than 1% incidence of more serious pancreatitis. The incidence of pancreatitis associated with anti-CTLA-4 was noted to be higher than that associated with PD-1 and PD-L1 antibodies ranging from approximately 1.8% to 2, 6%. In combined immunotherapy, the incidence can be as high as 6%. We presented an asymptomatic patient on pembrolizumab therapy in whom MSCT verified pancreatitis followed by elevation of alpha-amylase and lipase (according to CTCAE grade 2 pancreatitis). Considering everything, we decided to continue pembrolizumab therapy with regular monitoring of pancreatic enzymes. Until the beginning of 5/2023. he received 29 cycles of pembrolizumab.

References

1. Liu Y, Zhang H, Zhou L, Li W, Yang L, et al. (2021) Immunotherapy-Associated Pancreatic Adverse Events: Current Understanding of Their Mechanism, Diagnosis, and Management. Front Oncol 25 (11): 627612.
2. Hickmott L, De La Peña H, Turner H, Ahmed F, Protheroe A, et al. (2017) Anti-PD-L1 atezolizumab-Induced Autoimmune Diabetes: A Case Report and Review of the Literature. Targeted Oncol 12(2): 235-241.
3. Pardoll DM (2012) The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12(4): 252-264.
4. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, et al. (2006) Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med 203(4): 883-895.
5. Porntharukchareon T, Tontivuthikul B, Sintawichai N, Srichomkwun P (2020) Pembrolizumab- and ipilimumab-induced diabetic ketoacidosis and isolated adrenocorticotropic hormone deficiency: a case report. J Med Case Rep 14(1): 171.
6. Kusuki K, Suzuki S, Mizuno Y (2020) Pembrolizumab-induced fulminant type 1 diabetes with C-peptide persistence at first referral. Endocrinol Diabetes Metab Case Rep 2020: 19-0152.
7. George J, Bajaj D, Sankaramangalam K, Yoo JW, Joshi NS, et al. (2019) Incidence of pancreatitis with the use of immune checkpoint inhibitors (ICI) in advanced cancers: A systematic review and meta-analysis. Pancreatology 19(4): 587-594.

8. Kohlmann J, Wagenknecht D, Simon JC, Ziemer M (2019) Immune-related pancreatitis associated with checkpoint blockade in melanoma. Melanoma Res 29(5): 549-552.

9. Yoneda S, Imagawa A, Hosokawa Y, Baden MY, Kimura T, et al. (2019) T-Lymphocyte Infiltration to Islets in the Pancreas of a Patient Who Developed Type 1 Diabetes After Administration of Immune Checkpoint Inhibitors. Diabetes Care 42(7): e116-e118.

10. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, et al. (2020) NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1. J Natl Compr Cancer Netw: JNCCN 18(3): 230-241.

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