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CASE REPORT

Elevated pancreatic enzymes during immunotherapy for malignant pleural mesothelioma: a case report

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ABSTRACT

We report a patient with malignant pleural mesothelioma who developed pancreatic enzyme elevations and pancreatitis during immune checkpoint inhibitor treatment. A male in his eighties visited his family clinic because of respiratory distress on exertion and was pointed out a left pleural effusion. A thoracoscopic pleural biopsy gave a diagnosis of desmoplastic pleural mesothelioma. The patient was started a combination immunotherapy of ipilimumab and nivolumab. At a routine visit of 32 days after the start of the treatment, blood tests revealed elevated amylase and lipase. The patient had no subjective symptoms such as abdominal or back pain or loss of appetite. Contrast-enhanced computed tomography imaging revealed decreased contrast uptake in the pancreas, and magnetic resonance imaging revealed edematous changes in the pancreas. These findings led us to the diagnosis of asymptomatic immune mediated acute pancreatitis. Extracellular fluid replacement and steroid treatment were initiated. Both amylase and lipase quickly decreased close to normal range but began to rise again when the prednisolone dose was reduced. Infliximab was administered, then amylase and lipase decreased again. Follow-up magnetic resonance imaging demonstrated that the edematous changes in the pancreas had resolved. During the treatment of pancreatitis, mesothelioma demonstrated no exacerbation. There is no established treatment strategy for immune mediated pancreatitis. Appropriated management of asymptomatic elevation of pancreatic enzymes during ICI treatment should be established.

Keywords: amylase, lipase, mesothelioma, pancreatitis.

Introduction

Immune checkpoint inhibitors (ICIs) have been currently applied in the treatment of many cancers. Among them, nivolumab and ipilimumab are monoclonal antibodies against programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), respectively. The combination of ipilimumab and nivolumab was approved in 2021 as a first-line therapy for unresectable malignant pleural mesothelioma (MPM) based on a phase 3 study[1]. These ICIs exhibit potent antitumor activity, however, could cause cross-organ immune-related adverse events (irAEs).

Immune mediated pancreatitis due to ICI treatment is a relatively rare adverse event. However, asymptomatic elevation of pancreatic enzymes during ICI treatment are more common, and the mechanisms, clinical significance and proper management are not established. We report a patient with MPM who developed pancreatic enzyme elevations and pancreatitis during ICI treatment.

Case Presentation

A man in his eighties visited his family clinic because of respiratory distress on exertion. The patient was pointed out a left pleural effusion and referred to our hospital for further examination. The patient had a history of smoking of 15 cigarettes/day for 45 years from the age of 20 and had been exposed to asbestos as an interior decorator. The patient had been diagnosed with cerebral infarction in his seventies. A thoracoscopic pleural biopsy was performed under general anesthesia and gave a diagnosis of desmoplastic pleural mesothelioma. The patient was started a combination immunotherapy of ipilimumab (1 mg/kg/day) every 6 weeks and nivolumab (240 mg/day) every 2 weeks. At a routine visit of 32 days after the start of the treatment, blood tests revealed elevated amylase of 470 IU/L and lipase of 577 IU/L. The patient had no subjective symptoms such as abdominal or back pain or loss of appetite, but we decided to discontinue the treatment. One week later, follow-up blood tests showed more elevated amylase of 883 IU/L and lipase of 2280 IU/L, then the patient was admitted for further examination and treatment. His temperature was 36.3°C, and there were no particular findings in blood pressure, pulse rate, or oxygenation. Physical examination revealed no tenderness in the abdomen or back. Blood tests showed elevated pancreatic enzymes but no elevated blood glucose levels; both HBs/HBc antibodies were positive, but HBV-DNA was negative.

Amylase isozymes were measured, and about 85% were pancreatic origin. Contrast-enhanced computed tomography imaging revealed no pancreatic enlargement or peripancreatic fat stranding, but hypoenhancement in the pancreas in the early phase of the contrast (Figure 1A), and magnetic resonance imaging (MRI) revealed low signal in fat-suppressed T1 weighted image (Figure 1B), modest increased signal in T2 weighted image (Figure 1C), and high intensity in diffusion weighted image (Figure 1D), which suggested edematous changes in the pancreas. There were no other potential causes of pancreatitis such as excessive alcohol use, hypertriglyceridemia, use of culprit drugs, or gallstones or dilated bile ducts on imaging. These findings led us to the diagnosis of asymptomatic immune mediated acute pancreatitis, which was grade 2 of Common Terminology Criteria of Adverse

Event Version 5. Intravenous fluid and steroid treatment (1 mg/kg of prednisolone) were initiated. Both amylase and lipase quickly decreased close to normal range but began to mildly rise again when the prednisolone dose was reduced to 0.5 mg/kg. Worrying about the recurrence of pancreatitis, infliximab was administered, then amylase and lipase decreased to the grade 1 range, and the prednisolone dose was reduced finally to 2.5 mg/body (Figure 2). Follow-up MRI demonstrated that the edematous changes in the pancreas had resolved. During the treatment of pancreatitis, MPM demonstrated no exacerbation.

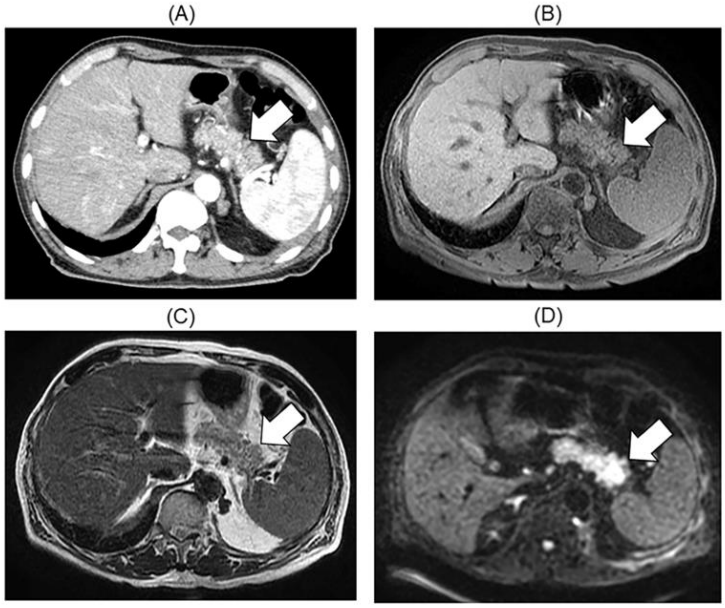

Figure 1. Contrast-enhanced computed tomography imaging revealed hypoenhancement in the pancreas in the early phase of the contrast (A), and magnetic resonance imaging revealed low signal in fat-suppressed T1 weighted image (B), modest increased signal in T2 weighted image (C), and high intensity in diffusion weighted image (D).

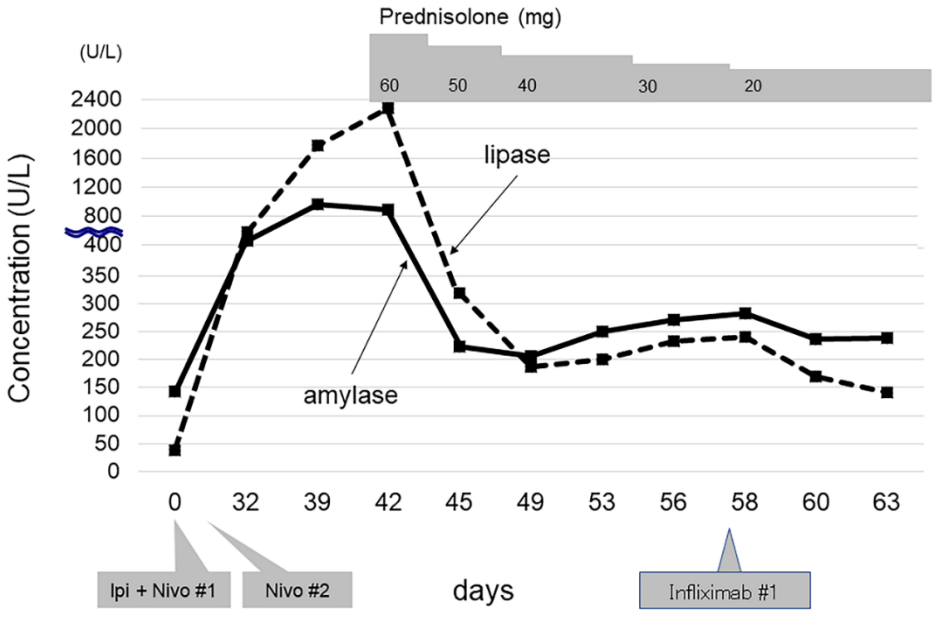

Figure 2. Clinical course of the case.

Discussion

Acute pancreatitis is diagnosed when a patient fulfill at least two of the following three criteria, 1) elevated pancreatic enzymes (>3 times the upper limit of normal), 2) Clinical symptoms such as vomiting, abdominal pain, back pain, fever, diarrhea, and 3) Imaging findings including pancreatic enlargement or hypoenhancement in the pancreas[2]. Although the patient in the current report was asymptomatic, he was diagnosed of immune related pancreatitis based on markedly elevated pancreatic enzymes and typical imaging findings. The patient was successfully treated with fluid replacement, steroid, and infliximab and had no late complications such as diabetes mellitus so far. The strength of our approach to the current case was to make an early diagnosis of immune related acute pancreatitis based on regular monitoring of pancreatic enzymes and imaging and to offer proper treatment.

In the phase III study of MPM, elevation of serum lipase was one of the most frequently observed adverse events with 3.7% of patients demonstrated grade 3 or higher lipase elevation[1]. However, elevated pancreatic enzymes during ICI treatment are often asymptomatic, and their clinical significance and mechanisms are largely unknown. In a single-center retrospective study, 82 patients experienced grade 3 or higher lipase elevations out of 2279 ICI-treated patients. Of those, 32 had clinical symptoms of pancreatitis, and only 11 of the 62 patients who underwent imaging studies demonstrated abnormal radiologic findings[3]. Therefore, diagnosis of pancreatitis as an immune-related adverse event is often challenging.

There is no established treatment strategy for immune mediated pancreatitis. Immunosuppressive therapy including steroids is commonly used as in other irAEs, but its usefulness is unclear[4-6]. Fluid replacement and the use of steroids resulted in rapid improvement in the current case; however, they could not improve the pancreatic enzymes below grade 2. Therefore, we used infliximab. The National Comprehensive Cancer Network Guidelines recommend the use of steroids for moderate to severe ICI-associated pancreatitis[7]. The use of infliximab is recommended if ICI-associated adverse events showed no improvement with the use of steroid. In contrast, Abu-Sbeih reported that steroid did not have any value in the management of ICI-associated pancreatitis[3]. The appropriated management in those setting should be established.

In the first place, several guidelines do not recommend regular monitoring of pancreatic enzymes in the absence of symptoms of pancreatitis[7,8]. Those guidelines suggest that if there is an incidental elevation of asymptomatic pancreatic enzymes, ICIs can be continued. However, we suppose that detailed examination of pancreatitis or diabetes, such as imaging examination including MRI would be essential in such cases with asymptomatic elevation of pancreatic enzymes. We understand the limitation of our report based on just a single case.

Conclusion

We reported a patient with MPM who developed asymptomatic immune related pancreatitis during ICI treatment. Appropriated management of asymptomatic elevation of pancreatic enzymes during ICI treatment should be established.

Conflict of Interest Statement:

Dr. Fujimoto received honoraria from Ono Pharmaceutical, AstraZeneca, and Nippon Kayaku. All other authors declare no conflict of interest.

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None

References:

1. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2021; 397(10272):375-386. DOI: 10.1016/S0140-6736(20)32714-8

2. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol* 2016; 2(10):1346-1353. DOI: 10.1001/jamaoncol.2016.1051

3. Abu-Sbeih H, Tang T, Lu Y, et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *J Immunother Cancer* 2019; 7(1):31. DOI: 10.1186/s40425-019-0502-7

4. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* 2018; 378(2):158-68.

5. Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28(suppl_4):iv119-iv42.

6. Abu-Sbeih H, Tang T, Lu Y, et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *J Immunother Cancer* 2019; 7(1):31.

7. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; 36(17):1714-68.

8. Thompson JA, Schneider BJ, Brahmer J, et al. Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw* 2020; 18:230-241. DOI: 10.6004/jnccn.2020.0012.