



Case Report

Pancreatitis as immune-related adverse event during pembrolizumab therapy for multiple lung metastases from renal pelvic cancer

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Abbreviations & Acronyms

CR = complete response
 CT = computed tomography
 CTCAE = Common Terminology Criteria for Adverse Event
 ICI = immune checkpoint inhibitor
 irAE = immune-related adverse event
 NCCN = National Comprehensive Cancer Network
 PD = progressive disease
 TURBT = transurethral resection of bladder tumor

Introduction: Pembrolizumab administration has become the standard of care for patients with urothelial carcinoma, though a variety of adverse events have been reported. Presented here is a rare case of pancreatitis that occurred as an immune-related adverse event.

Case presentation: An 81-year-old man undergoing treatment with pembrolizumab for multiple lung metastases from renal pelvic cancer was presented with a fever and diagnosed with pancreatitis based on elevated pancreatic enzyme levels and imaging findings. There was no history of alcohol consumption or findings indicating gallstones, elevated liver enzymes, or abdominal complications. The patient was diagnosed with immune-related adverse event pancreatitis and treated with Lactate Ringer's solution (3000 mL/day) and steroids, during which his condition improved.

Conclusion: Although pancreatitis is a rare complication, it should always be considered as a potential immune-related adverse event in patients treated with an immune checkpoint inhibitor such as pembrolizumab.

Key words: immune checkpoint inhibitor, immune-related adverse event, pancreatitis, pembrolizumab, renal pelvic cancer, urothelial carcinoma.

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Keynote message

In the case of irAE pancreatitis, there are often no typical symptoms of pancreatitis, and it is important to follow up the patient's progress with blood tests and imaging studies.

Introduction

ICI treatment is given for a variety of cancers, though reports of associated irAEs have also increased as usage has become more common. Presented here is a case of irAE pancreatitis that occurred in association with administration of pembrolizumab, including a review of related literature.

Case presentation

An 81-year-old man underwent a retroperitoneoscopic nephroureterectomy procedure for right renal pelvic cancer, cT2N0M0, 1 year prior. Results of a pathological examination showed pT2 and were suggestive of venous invasion, thus postoperative chemotherapy with gemcitabine + carboplatin was started about 1 month after surgery, during which hematuria appeared. Though preoperative cystoscopic findings did not reveal any tumor in the bladder, postoperative examination revealed recurrence of tumor in the bladder, thus a TURBT procedure was performed after the first course of chemotherapy. A post-operative imaging evaluation done after that procedure showed some lung metastases (Fig. 1), thus the chemotherapy was continued. After three additional courses, recurrence of tumor in the bladder was noted and TURBT was again performed. Imaging findings showed worsening of the lung metastasis and PD was diagnosed (Fig. 2a), thus pembrolizumab was started as second-line therapy. At the end of the three courses of pembrolizumab, recurrence of tumor in the bladder was noted,

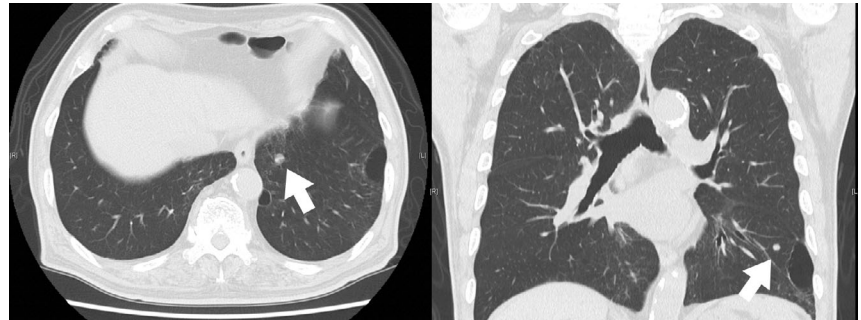


Fig. 1 After one course of adjuvant chemotherapy, new metastatic lesion was found in the lung.

and a third TURBT procedure was performed. Imaging evaluation at the end of three courses of pembrolizumab showed good response and resolution of lung lesions, thus CR was determined (Fig. 2b). However, end of four courses, there was onset of fever and fatigue, and blood test results showed elevated pancreatic enzymes, including amylase at 800 U/L (normal 35–165 U/L), P-amylase at 755 U/L (normal 0–115 U/L), and lipase at 755 U/L (normal 13–55 U/L). In addition, a CT scan revealed an enlarged pancreas, and a diagnosis of pancreatitis was determined. While the patient had no symptoms of abdominal pain or vomiting, fever, markedly elevated pancreatic enzymes, and diffuse enlargement in CT images were noted (Fig. 3a). Since there was no history of alcohol consumption nor evidence of obstruction such as gallstones, he was diagnosed with Grade 3 irAE pancreatitis, and treatment was initiated with a high volume of supplemental IV fluids of Lactate Ringer's solution (3000 mL/day) and steroids at 40 mg/day orally. Pancreatic enzymes gradually improved with the use of steroids, and after 4 weeks, the dose could be reduced to 25 mg/day, and CT scans showed improvement in pancreatic enlargement (Fig. 3b). Thereafter, the dose of steroids was gradually

reduced, and now he is taking 7.5 mg/day of steroids while resuming pembrolizumab.

Discussion

ICIs have proven to be effective for the treatment of a variety of cancers, with improved prognosis in many treated cases, thus their indications are being expanded. During treatment with an ICI, activation of the immune system can cause unpredictable irAEs in various organs, which can be life-threatening, making early detection and treatment, as well as strict management important. Due to the rarity and infrequency of irAE pancreatitis, the NCCN guidelines no longer require routine pancreatic enzyme monitoring. The rate of incidence of irAE pancreatitis The CTCAE Grade 2 or higher is 1.9%, while that is 0.94% for cases given a PD-1 inhibitor alone, while reports of increased incidence of irAE pancreatitis in patients that received that in combination with CTLA-4 inhibitors have also been presented.¹ Compared to patients with generalized acute pancreatitis, those with irAE pancreatitis are reported to have lower incidence of abdominal pain and fever, as well as nausea and vomiting, while CT findings

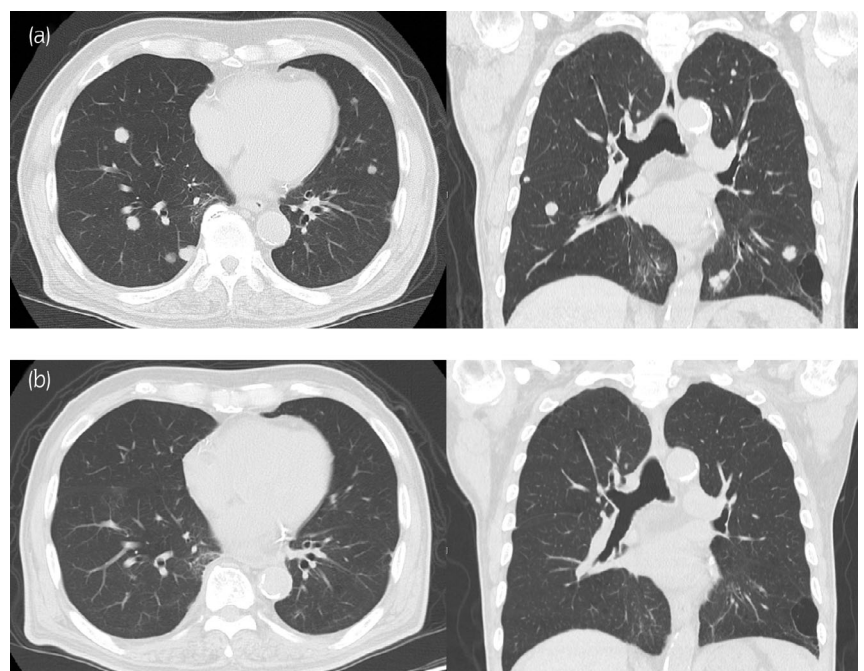


Fig. 2 (a) After three additional chemotherapy with gemcitabine + carboplatin, CT shows multiple metastatic tumors in the lungs. (b) The end of three courses of pembrolizumab showed good progress and resolution of lung lesions.

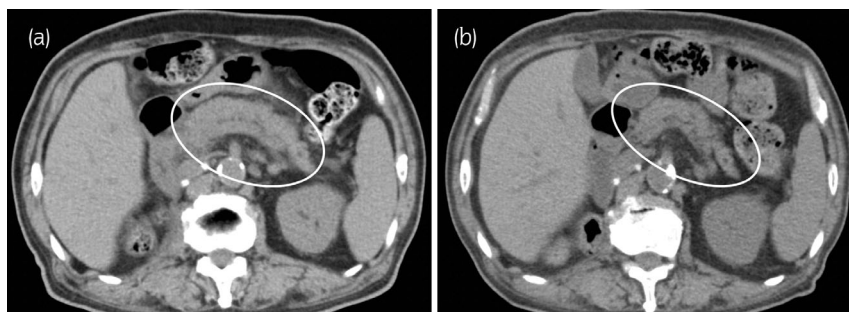


Fig. 3 (a) Pancreas is diffusely enlarged. (b) Pancreatic enlargement has improved and there are no obvious abnormal findings.

are limited to diffuse enlargement of the pancreas in 17% of the cases.² As for treatment, high-volume infusion and nutritional management such as for acute pancreatitis, and also steroids are recommended, as noted for other irAEs that are moderate or above.³ In addition, Pancreatic atrophy and pancreatic exocrine dysfunction may develop after healing of irAE pancreatitis.⁴

There is insufficient evidence regarding whether to continue with an ICI as the next treatment for irAE pancreatitis. Michot *et al.* recommended considering resumption of an ICI or alternative treatment after noting improvement in lipase condition.⁵ In addition, NCCN guidelines state that when irAE pancreatitis is initially shown to be CTCAE Grade 2 or 3, re-administration should be considered once the steroid dose has been reduced to 10 mg/day, after consultation with a specialist department. As for cases of CTCAE Grade 4 or higher with recurrence, the guidelines state that re-administration should not be done.⁵ There have been reports of death due to treatment resumption, making it necessary to select an appropriate drug for individual cases.⁶

Only one case of irAE pancreatitis in urothelial carcinoma has been reported. In this case, as in our case, there were no typical symptoms of pancreatitis such as abdominal pain or vomiting, and the only imaging findings were an enlarged pancreas. However, in this case, there was no increase in amylase or lipase, only a decrease in elastase, and the only treatment was elastase replacement.⁷ The present patient with CTCAE Grade 3 irAE pancreatitis was treated with steroids and a high volume of supplemental IV fluids. At the time of writing, the steroid dose has been reduced to 7.5 mg or less and progress is good, and neither pancreatic atrophy nor pancreatic exocrine dysfunction has been observed. Although recurrence of tumor in the bladder was noted, multiple lung metastases, found to be evaluable lesions, showed CR after administration of pembrolizumab. Effect on recurrence of tumor in the bladder would be limited. But a higher overall survival rate for patients who resume as compared to those who discontinue treatment has been potentially reported,² given that the next scheduled treatment is Enfortumab Vedotin therapy only, we consider that continued use of pembrolizumab is necessary and have resumed that under an oral steroid therapy regimen.

Conclusion

irAEs are difficult to predict and potentially fatal. The present patient developed irAE pancreatitis, a rare complication,

during pembrolizumab use. Caution is needed when administering ICIs for such cases.

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Author contributions

Kazuki Kokura: Writing – original draft; writing – review and editing. Jun Watanabe: Writing – review and editing. Takaaki Takuma: Writing – review and editing. Hitoshi Yokozeki: Writing – review and editing. Shoko Uketa: Writing – review and editing. Yuichi Uemura: Writing – review and editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Not applicable.

Registry and the Registration No. of the study/trial

Not applicable.

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