【 CASE REPORT 】

Fatal Immune Checkpoint Inhibitor-related Pancreatitis

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Abstract:

We herein report a case of fatal pancreatitis induced by an immune checkpoint inhibitor. A 62-year-old man with cancer of unknown primary was treated with pembrolizumab. After 12 cycles, immune-related pneumonitis developed and was treated with prednisolone. Three months later, pancreatitis developed, which was successfully treated with hydration and protease inhibitors. Eight months later, another attack of pancreatitis occurred, which did not respond to therapy, including high-dose corticosteroids, and he eventually died. This is the first report describing fatal immune checkpoint inhibitor-related pancreatitis. Despite the rarity of this complication, attention should be paid to its potential severity and treatment.

Key words: immune-related adverse event, acute pancreatitis, pembrolizumab, drug-induced pancreatitis, immune checkpoint inhibitor

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Introduction

Immune checkpoint inhibitors (ICIs) are being increasingly used. ICIs enhance the antitumor T-cell activity by blocking negative regulators of immunity, and they provide a survival benefit in many cancers (1). However, they also induce distinct adverse inflammatory reactions known as immune-related adverse events (irAEs) (2). ICI-related pancreatitis is rare among irAEs and is mostly asymptomatic or mild; no life-threatening case of ICI-related pancreatitis has been reported (3). We herein report a patient with cancer of unknown primary who died from recurrent pancreatitis after treatment with pembrolizumab. To the best of our knowledge, this is the first case report of fatal pancreatitis induced by ICI. This case report was prepared according to the CARE Guidelines (4) and the protocol of the Medical Ethics Committee of Kurashiki Central Hospital; ethics review was not required.

Case Report

A 53-year-old man presented with a history of asthma, chronic obstructive pulmonary disease, and depression. Non-small cell lung carcinoma in the right lung was diagnosed. The right lower lobe was resected with lymph node dissection, followed by adjuvant chemotherapy (paclitaxel plus carboplatin, 4 cycles). Nine years later (age 62), swollen lymph nodes around the aorta were found on computed tomography (CT) (Fig. 1a). There were no abnormal findings in the pancreas and biliary tract on the image (Fig. 1b). Positron emission tomography revealed an uptake of fluorine-18-fluorodeoxyglucose (Fig. 1c), and adenocarcinoma cells were detected by endoscopic ultrasound-guided fine-needle aspiration. Because the pathological features and immunohistochemical staining patterns were different from those of the resected lung cancer, other primary lesions were searched with whole-body contrast-enhanced CT, esophagogastroduodenoscopy, and colonoscopy, but no primary lesion was detected; cancer of unknown primary was thus diagnosed. The lymph node-tumor cells highly expressed programmed cell-death ligand 1, and he was treated with pembrolizumab (200 mg, every 21 days). Immune-related hypothyroidism (grade 2) developed during the 5th cycle, and pneumonitis (grade 3) during the 12th cycle of treatment. Because of immune-related pneumonitis, pem-
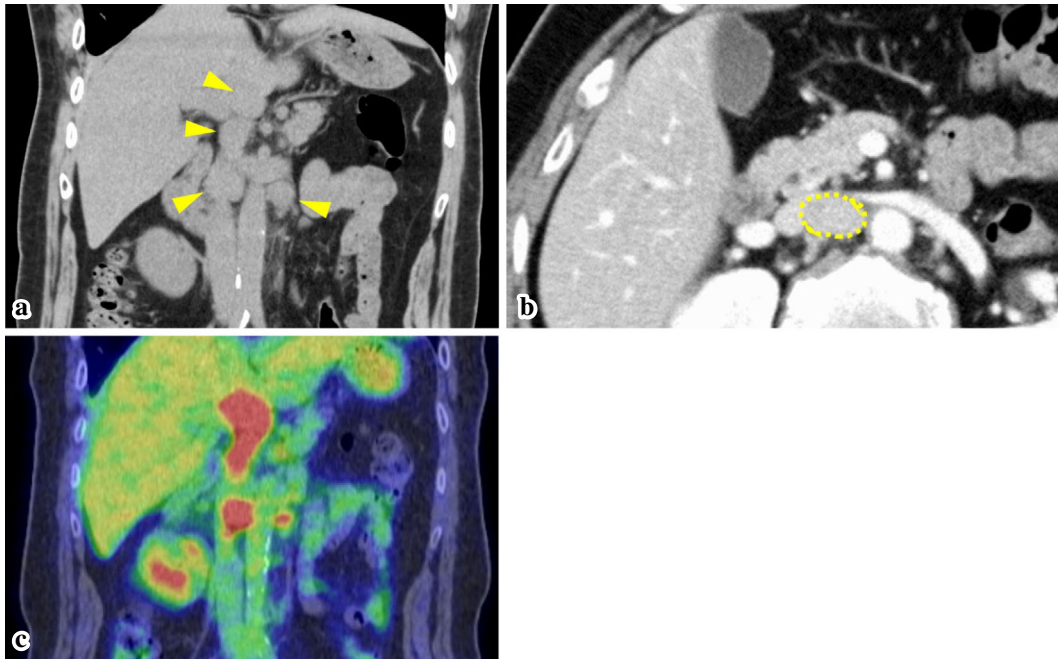
Figure 1.   Pretreatment radiological findings. (a) CT reveals swollen lymph nodes (arrowheads) around the aorta. (b) No abnormal findings are seen in the pancreas. The yellow circle represents a swollen lymph node. (c) PET reveals an increased uptake of FDG in the lymph nodes; the maximum standardized uptake value (SUVmax) is 11.7.
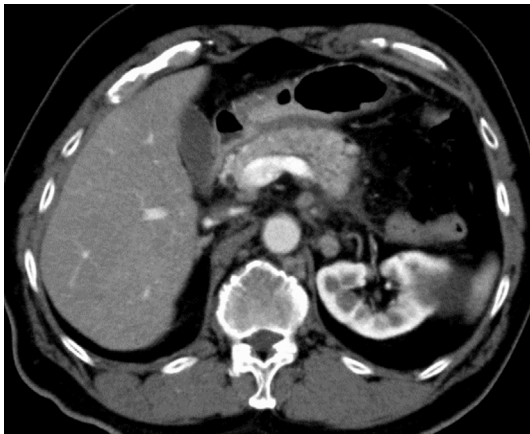

Figure 2.   CT findings at the first pancreatitis episode (pancreatic phase of dynamic enhanced CT). Fluid collection is present around the pancreas.

brolizumab was discontinued, and he received a 3-day course of methylprednisolone (1,000 mg/day) followed by oral prednisolone [30 mg (0.5 mg/kg) /day]. Despite a radiological improvement of pneumonitis, he required permanent home oxygen therapy.

Three months after the discontinuation of pembrolizumab (age 63), he presented to the emergency department with severe epigastric pain. The dose of prednisolone had been reduced to 15 mg/day. He was afebrile, and physical examination revealed tenderness in the upper abdomen. Laboratory studies revealed a mild elevation of C-reactive protein (0.99 mg/dL) (normal range, 0.00-0.14), amylase 179 U/L (44-132), lipase 105 U/L (13-55), white blood cells 13,500/µL

(3,300-8,600), and immunoglobulin (Ig) G4 133 mg/dL (11-121). Contrast-enhanced CT revealed an enlarged pancreas, surrounding fluid collection but no biliary abnormalities (Fig. 2). Although the screening of common causes of acute pancreatitis, such as alcohol, gallstones, or dyslipidemia were performed, all of them were ruled out. According to the clinical course and the result of screening, we judged that he had ICI-induced acute pancreatitis (grade 3). After treatment with hydration, a protease inhibitor (nafamostat mesylate), and fentanyl, the abdominal pain disappeared. Although amylase and lipase did not normalize, inflammatory markers (white blood cells, C-reactive protein) (Fig. 3) and the peripancreatic fluid collection on CT improved.

Eight months later, he presented again with mild abdominal pain lasting for 2 weeks; the dose of prednisolone had been reduced to 4 mg/day. Physical examination revealed tenderness throughout the abdomen with multiple erythematous areas in the upper limbs, which a dermatologist suspected were a manifestation of irAE. Laboratory tests revealed elevated values of C-reactive protein, 3.10 mg/dL; amylase, 325 U/L; lipase, 589 U/L; and IgG4, 142 mg/dL. The white blood cell count was 8,400/µL. Contrast-enhanced CT revealed an enlarged pancreas and peripancreatic fluid; recurrence of acute pancreatitis was diagnosed. The severity of the acute pancreatitis was classified as mild according to the Japanese criteria (5). His symptoms and CT findings improved after admission and treatment with hydration and protease inhibitor, and he was discharged on day 8. However, only a few hours later, he was readmitted because of severe abdominal pain. According to contrast-enhanced CT image, we diagnosed a recurrence of acute pancreatitis with
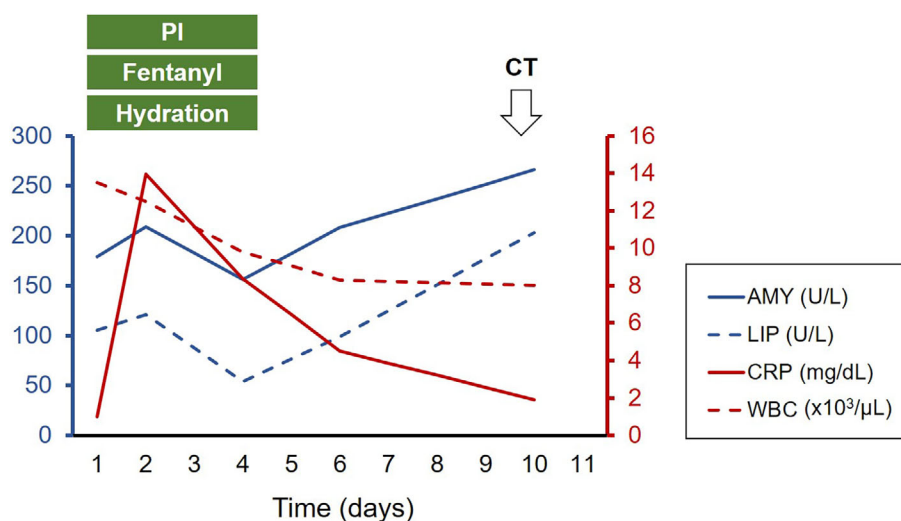
Figure 3. Clinical course for the first bout of pancreatitis. After admission, the patient was treated with hydration and fentanyl. CRP and WBC decreased, but the pancreatic enzyme values did not normalize. PI: protease inhibitor
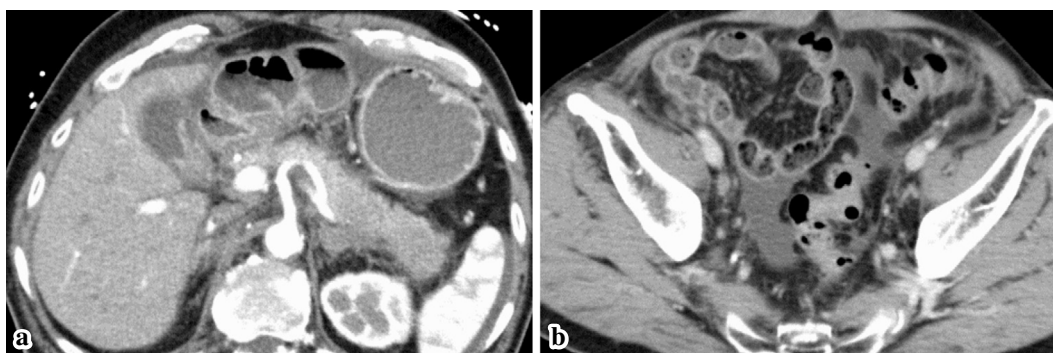

Figure 4. CT findings for the second pancreatitis episode (on day 8, dynamic enhanced CT). (a) Arterial phase. Fluid collection is present around the pancreas. The attenuation of the pancreatic body and tail is relatively low. (b) Delayed phase. The fluid collection extends to the pelvis.

peripancreatic fluid collection that extended to the pelvis (Fig. 4). Thereby, it was classified as severe acute pancreatitis on the Japanese criteria. At the timing of this recurrence, there were no signs of new-onset organ failure or infection. We restarted hydration, fasting and analgesia with fentanyl. However, his symptoms did not improve, and the serum bilirubin levels gradually increased (Fig. 5); the laboratory tests on day 18 showed the elevation of total bilirubin, 3.4 mg/dL; alanine transaminase, 173 U/L; and alkaline phosphatase, 2,759 U/L. Magnetic resonance imaging revealed a narrowing of the main pancreatic duct and intrapancreatic bile duct, with dilation of the supra-pancreatic biliary tree (Fig. 6). Stenosis was located only in the lower part of common bile duct, mimicking type 1 IgG4-related sclerosing cholangitis (6). Due to respiratory deterioration, a detailed endoscopic evaluation and the biliary drainage could not be performed. Methylprednisolone (1,000 mg/day) for 3 days followed by oral prednisolone [60 mg (1 mg/kg) /day] were administered. However, the abdominal pain and dilatation of intrahepatic duct still worsened (Fig. 7). He showed severe

hypoxia associated with acute pancreatitis, thereby requiring oxygenation with a non-rebreather mask. He and his family did not want further invasive therapy, and he died on day 33. It was considered that the cause of death was ICI-related pancreatitis, not liver failure, because the laboratory data on day 32 showed that pancreatic isozymes was more activated (amylase, 536 U/L; lipase, 809 U/L) and liver synthetic function was maintained (albumin, 3.0 g/dL; cholinesterase, 173 U/L; bilirubin, 16.5 mg/dL; international normalized ratio of prothrombin time, 1.23).

Discussion

We herein described a case of recurrent pancreatitis after ICI therapy for cancer of unknown primary. Fluid therapy was effective treatment for the first attack of pancreatitis, but the second attack did not improve with fluid therapy together with corticosteroids. Although the patient was complicated by severe obstructive jaundice, persistent pancreatitis was considered to be the main cause of death. As far as
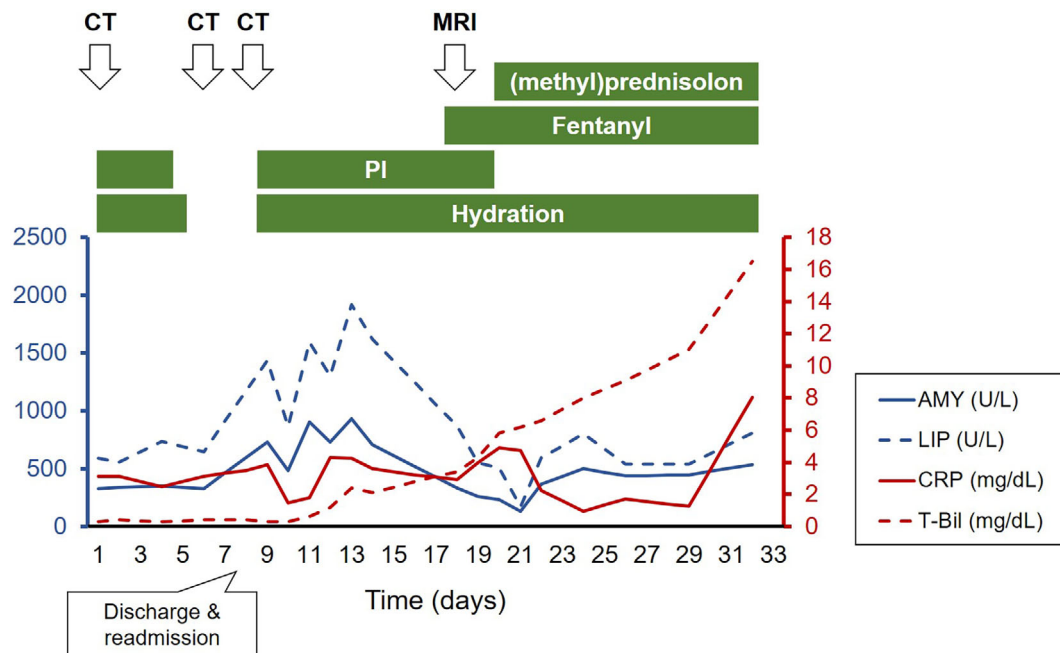
Figure 5. **Clinical course of the second episode of pancreatitis. The patient was discharged and re-admitted on day 8. Thereafter, the total bilirubin values continued to increase. On day 20-22, intravenous methylprednisolone (1,000 mg/day for 3 days) was given, followed by oral prednisolone (60 mg/day). The patient died on day 33. PI: protease inhibitor**
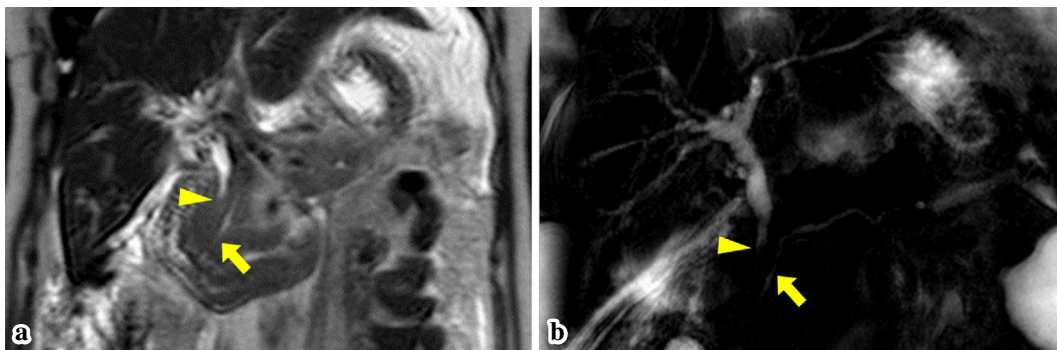

Figure 6. **MRI findings for the second bout of pancreatitis. A coronal T2-weighted MR image (a) and magnetic resonance cholangiopancreatography (b) demonstrate the narrowing of the intrapancreatic bile duct (arrowhead) and main pancreatic duct (arrow) in the enlarged pancreatic head.**

Figure 7. **CT findings after treatment with corticosteroids. Dilatation of the intrahepatic biliary ducts is seen. Stricture of the supra-pancreatic biliary tree is absent.**

we know, this is the first report of fatal pancreatitis induced by an ICI.

Fatal irAEs occur in 0.36% of patients who receive ICI. Death is often due to pneumonitis, hepatitis, and neurotoxic adverse events (7), but life-threatening pancreatitis is rare (3). According to a recent systematic review, the incidence of asymptomatic lipase elevation was 2.7% and grade 2 pancreatitis 1.9% after ICI treatment (8); the incidence was similar in a real-world retrospective study (9). In both studies, no fatal case was reported. Our literature search found 12 case reports of ICI-induced pancreatitis (Table) (10-21), and all patients improved with cessation of the ICIs or corticosteroid therapy.

Making an accurate diagnosis of ICI-related pancreatitis may be challenging because the clinical manifestations may be subtle (3). Abu-Sbeih et al. (9) reported that more than

Table. Reported Cases of Immune Checkpoint Inhibitor-related Pancreatitis.

Age	Sex	Cancer type	ICI regimen	Duration of ICI treatment	Symptoms	Elevation of AMY/LIP	Elevation of IgG4	CT/MRI findings	PET findings	Treatment for pancreatitis	Outcomes	Reference
36	F	Melanoma	Ipilimumab	6 weeks	Abdominal pain	Grade 3/4	NA	Acute pancreatitis	NA	DEX, PSL	Improved but relapsed	10
57	M	Melanoma	Ipilimumab followed by pembrolizumab	3 plus 3 cycles	Asymptomatic	Yes	NA	Fat stranding around pancreas	Increased FDG uptake	NA	NA	11
66	F	NSCLC	Nivolumab	4 weeks	Anorexia, vomiting and back pain	Grade 3	NA	Normal	NA	Fluid hydration, ulinastatin and PSL	Improved with PSL (4mg/kg/day)	12
43	M	Melanoma	Ipilimumab followed by pembrolizumab	36 weeks	NA	No	No	Small bowel obstruction	NA	Duodenal stent, DEX, surgery	Improved	13
76	F	Urothelial	Pembrolizumab	NA	Diarrhea and weight loss	No	No	Stricture and upstream dilation of MPD	NA	PERT	Improved	14
72	M	NSCLC	Nivolumab	NA	Asymptomatic	Yes	No	Enlarged pancreas	Increased FDG uptake	Cessation of ICI	Improved	15
46	M	NSCLC	Pembrolizumab	3 cycles	Epigastric pain	Yes	NA	Focal enlargement	Increased FDG uptake	Corticosteroids	Improved	16
58	M	Melanoma	Ipilimumab plus nivolumab	5 cycles	Epigastric pain	Grade 2/3	NA	Swelling of pancreatic tail	NA	mPSL	Improved but relapsed	17
70	M	Renal	Nivolumab	6 months	NA	Grade 4	NA	Diffuse enlargement of pancreas	NA	Discontinuation of ICI	Improved	18
65	M	SCLC	Pembrolizumab	2 cycles	Epigastric pain	Grade 2	NA	Diffuse enlargement of pancreas	NA	PSL	Improved	19
76	M	Renal	Pembrolizumab	NA	Abdominal pain, nausea and vomiting	Grade 3	NA	Edematous pancreas	NA	Corticosteroids	Improved	20
70	M	NSCLC	Pembrolizumab	14 months	Asymptomatic	Grade 2	NA	Swollen pancreas and MPD dilation	Focally increased FDG uptake	PSL	Improved	21

AMY: amylase, CT: computed tomography, DEX: dexamethasone, F: female, FDG: fluorine-18-fluorodeoxyglucose, ICI: immune-checkpoint inhibitor, IgG: Immunoglobulin G, LIP: lipase, M: male, MPD: main pancreatic duct, mPSL: methylprednisolone, MRI: magnetic resonance imaging, NA: not available, NSCLC: non-small cell lung cancer, PERT: pancreatic enzyme replacement therapy, PET: positron emission tomography, PSL: prednisolone, SCLC: small cell lung cancer

half of ICI-related pancreatic injury cases were asymptomatic, and typical CT findings were present in only 25%, even among symptomatic patients. As illustrated in Table, ICI-related pancreatitis could be asymptomatic even with abnormal laboratory and radiological abnormalities (11, 15, 21). In our case, the diagnosis was not difficult to make because the patient had epigastric pain, elevated pancreatic enzyme values, and fluid collection around the enlarged pancreas. In spite of acute pancreatitis, the C-reactive protein level was relatively low in this patient. This phenomenon may be due to an unusual condition of the immune response with ICI and prednisolone usage. Narrowing of the intrapancreatic bile duct and main pancreatic duct, which are characteristic findings of autoimmune pancreati-

tis (22), were present in our patient. Although an abnormality of the main pancreatic duct has not often been a feature of ICI-related pancreatitis (18, 23), it is possible that dysregulation of the immune system like that in autoimmune pancreatitis was involved in the development of pancreatitis in our patient.

No optimal treatment for ICI-related pancreatitis has yet been established. The National Comprehensive Cancer Network guideline recommends using prednisolone or methylprednisolone for grade ≥2 immune-related pancreatitis (24), whereas other guidelines offer no recommendations (25, 26). In previous reports, corticosteroids were used in 8 patients, whereas 3 patients improved without corticosteroids (Table). Pancreatitis relapsed in 2 cases, and the authors concluded that slow tapering of corticosteroids might help prevent a relapse of pancreatitis (17). Our patient experienced 2 attacks of pancreatitis during the tapering of the steroid dose: The first episode resolved with fluid therapy alone, but the second episode did not respond to either fluid therapy or high-dose methylprednisolone. Whether the use of other immunosuppressive agents, such as infliximab, may be useful in ICI-related pancreatitis is not known but this possibility deserves further investigation.

As a limitation associated with this report, a histological assessment of pancreatic parenchyma was not available in our patient. Therefore, although radiological examinations showed pancreatic damage, hepato-biliary pancreatic inflammation could not be assessed directly. To obtain stronger evidence regarding mortality from ICI-related pancreatitis, additional well-designed studies are needed.

In conclusion, fatal pancreatitis is a risk associated with ICI therapy. ICI-related pancreatitis may not respond to fluid therapy and corticosteroids.

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