

[CASE REPORT]

The Simultaneous Onset of Pancreatitis and Colitis as Immune-related Adverse Events in a Patient Receiving Nivolumab Treatment for Renal Cell Carcinoma

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Abstract:

Immune checkpoint inhibitors (ICIs), which have anti-tumor effects, are currently approved for treatment of several kinds of advanced malignancies. However, with their increasing use, a variety of immune-related adverse events (irAEs) in administered patients have been reported. We herein report a rare case of the simultaneous onset of acute pancreatitis and colitis as irAEs during nivolumab treatment given to a patient with renal cell carcinoma, who then shown marked improvement with corticosteroid therapy.

Key words: immune checkpoint inhibitor, immune-related adverse event, pancreatitis, colitis

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Introduction

Based on accumulating evidence showing anti-tumor effects, immune checkpoint inhibitors (ICIs) have received approval for treatment of various advanced malignancies, including melanoma (1), gastric cancer (2), non-small-cell lung cancer (3), hepatocellular carcinoma (4), and renal cell carcinoma (5). Various ICI-based treatment regimens have also been developed, such as combination therapy with conventional chemotherapy and an ICI (6, 7), therapy with a combination of ICIs (8), and ICI maintenance therapy following chemoradiotherapy (9). Thus, anti-tumor therapy with an ICI is presently considered to be an indispensable treatment option for patients with advanced malignancy.

However, with increasing use of ICIs, various immune-related adverse events (irAEs) specific to several organs have become more prevalent. In this regard, an appropriate

management strategy that differs from those used in cases with side effects of conventional chemotherapy should be considered.

We herein report a case of simultaneous onset of pancreatitis and colitis accompanied by irAE features during nivolumab infusion in a patient with postoperative recurrence of renal cell carcinoma.

Case Report

The patient was a 62-year-old man with medical comorbidities related to controlled hypertension who had undergone aortic replacement for an abdominal aortic aneurysm 2 years earlier. There was no history of heavy alcohol drinking or hyperlipidemia. Left nephrectomy for left renal cell carcinoma with bone metastasis was also performed two years previously, with postoperative chemotherapy with sunitinib and denosumab started immediately after that pro-

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Table. Laboratory Findings on Admission.

<Blood count>		<Biochemistry>			
WBC	4,660 / μ L	TP	5.5 g/dL	TSH	3.4 μ U/mL
Neut	74.3 %	Alb	2.8 g/dL	FT3	1.8 pg/mL
Lymph	12.5 %	T-Bil	0.4 mg/dL	FT4	1.1 ng/dL
Mono	11 %	AST	11 U/L	IgG	769 mg/dL
Eosino	0.7 %	ALT	7 U/L	IgA	237 mg/dL
RBC	312 \times 10 ⁴ / μ L	ALP	159 U/L	IgM	38 mg/dL
Hb	9.5 g/dL	LDH	69 U/L	IgG4	23.4 mg/mL
Ht	27.5 %	γ -GTP	17 U/L		
Plt	19.9 \times 10 ⁴ / μ L	Amy	200 U/L	<Tumor marker>	
		Lipase	248 U/L	CEA	1.9 ng/mL
<Coagulation>		BUN	20.5 mg/dL	CA19-9	8 U/mL
PT	79.4 %	Cre	0.89 mg/dL		
APTT	30.3 s	Na	139 mEq/L		
FDP	56.7 μ g/mL	K	3.8 mEq/L		
D-dimer	24.2 μ g/mL	Cl	107 mEq/L		
		Ca	7.7 mg/dL		
		CRP	12 mg/dL		

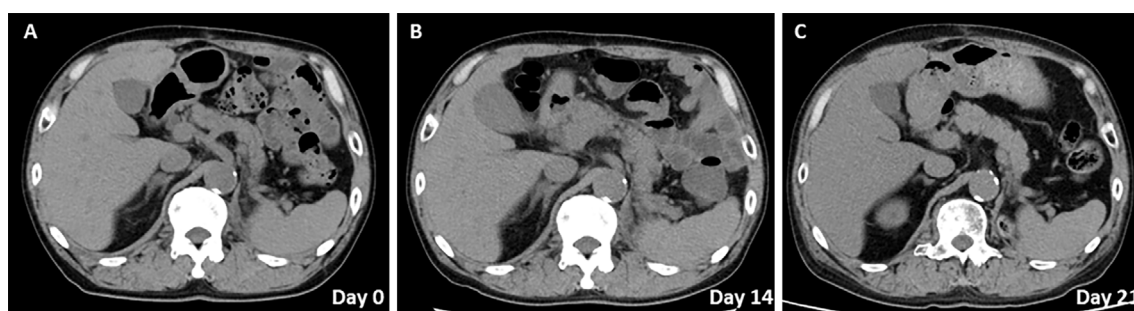


Figure 1. Plain computed tomography images. (A) Day 0. No remarkable findings in the pancreas. (B) Day 14. Edematous pancreas with inflammation spread to surrounding areas. (C) Day 21. Marked improvement of pancreatitis findings following prednisolone treatment.

cedure. Since the metastatic lesions were reduced by chemotherapy, resection of the 6th rib was performed, and the patient was subsequently followed without additional treatment. However, multiple lung and bone metastases appeared, and treatment with nivolumab (3 mg/kg, every 2 weeks) as third-line chemotherapy was instituted.

After nine cycles of nivolumab administration over a period of four months, the patient visited our emergency room due to various symptoms, including a fever, nausea, and abdominal fullness. A blood examination revealed grade 2 amylase elevation (200 U/L), grade 3 lipase elevation (248 U/L), and severely elevated C-reactive protein (CRP; 12 mg/dL). The serum levels of immunoglobulin G (IgG), IgG4, and IgM were normal (Table). Due to a history of allergy to contrast media, contrast-enhanced computed tomography (CT) could not be performed, while plain CT did not show positive findings indicating acute pancreatitis at that time (Fig. 1A; Day 0). However, the presence of acute pancreatitis was suspected due to upper abdominal pain and elevated pancreatic enzymes.

Since other causes of pancreatitis were ruled out, development of acute pancreatitis as an irAE due to nivolumab

treatment was considered in this case. Nivolumab administration was discontinued, and conservative treatment, including fasting and an intravenous drip, was started, after which the serum CRP level decreased. However, the serum levels of amylase and lipase did not improve, and the abdominal fullness symptoms worsened (Fig. 2). Furthermore, plain CT abdominal findings showed edematous pancreatitis with inflammation that spread to the surrounding areas (Fig. 1B; Day 14). Magnetic resonance cholangiopancreatography (MRCP) was performed on day 15 after admission, revealing no obvious abnormalities in the common bile duct or main pancreatic duct. A simple cyst with a diameter of approximately 20 mm was found in the tail of the pancreas without involvement of the main pancreatic duct, suggesting that the lesion was a branch duct intraductal papillary mucinous neoplasm (IPMN). Despite performing conventional treatments of fasting and administration of a proteolytic enzyme inhibitor, pancreatitis did not improve, suggesting that any association between the pancreatitis onset and the IPMN cystic lesion was extremely weak.

In addition, from four days after admission, non-bloody diarrhea, up to eight stools per day, and vomiting symptoms

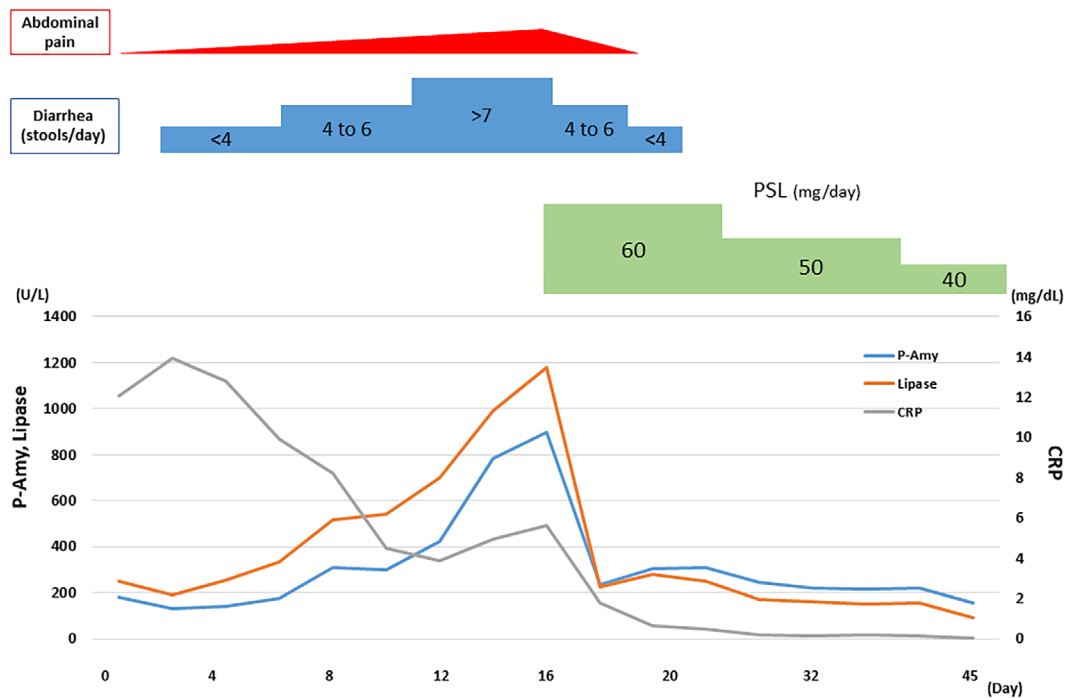


Figure 2. Clinical course in patient with colitis and pancreatitis, including symptoms, laboratory data, and therapy. P-Amy: pancreatic amylase, PSL: prednisolone, CRP: C-reactive protein

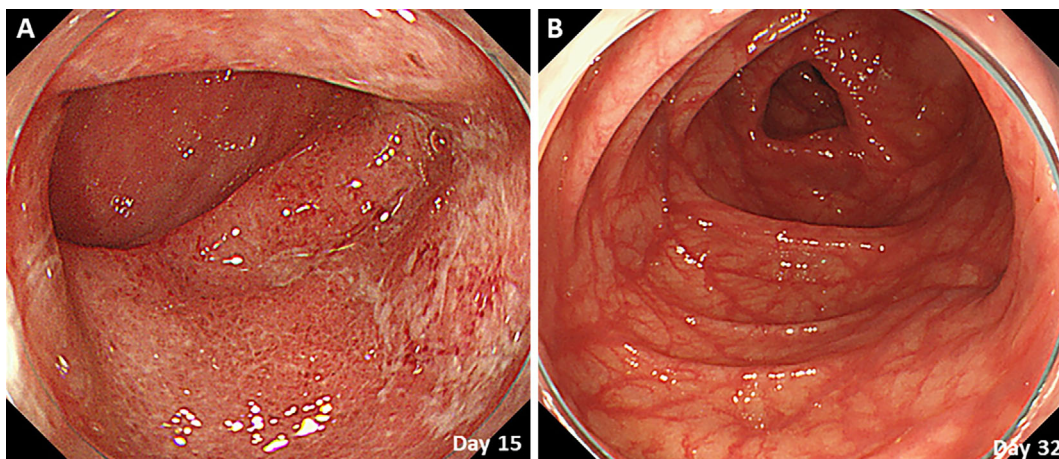


Figure 3. Colonoscopy findings. (A) Day 15. Edematous pattern, exudates, loss of vascular pattern, and erosion and ulcerations similar to ulcerative colitis (16, 17). (B) Day 32. Marked improvement of colitis findings following prednisolone treatment.

appeared and gradually worsened (Fig. 2). A colonoscopy examination indicated colitis with exudates, edematous mucosa, and loss of vascular pattern mainly in the left colon (Fig. 3A; Day 15), while histological results showed infiltration of polymorphonuclear and mononuclear inflammatory cells, and the presence of crypt abscesses (Fig. 4A; yellow arrows), as well as apoptotic epithelial cells (Fig. 4B; yellow arrow). There were no changes seen in the rectal or ileocecal valve. A stool culture test was negative, and other causes of diarrhea or colitis, such as infectious or pseudomembranous enterocolitis, were excluded. Based on these findings, this case was diagnosed as acute pancreatitis and colitis as

irAEs associated with nivolumab treatment.

The intravenous administration of prednisolone (PSL; 1 mg/kg/day) was started, which immediately reduced the levels of serum amylase and lipase, while clinical symptoms of diarrhea and abdominal pain were also significantly improved (Fig. 2). In addition, marked improvement in the pancreatitis findings on plain CT (Fig. 1C; Day 21) as well as the colonoscopy findings of colitis (Fig. 3B; Day 32) were noted. Thus, the effectiveness of PSL suggested that development of pancreatitis and colitis in this case was related to irAEs. Thereafter, the dose of PSL was tapered, with no relapse of symptoms seen for up to 18 months

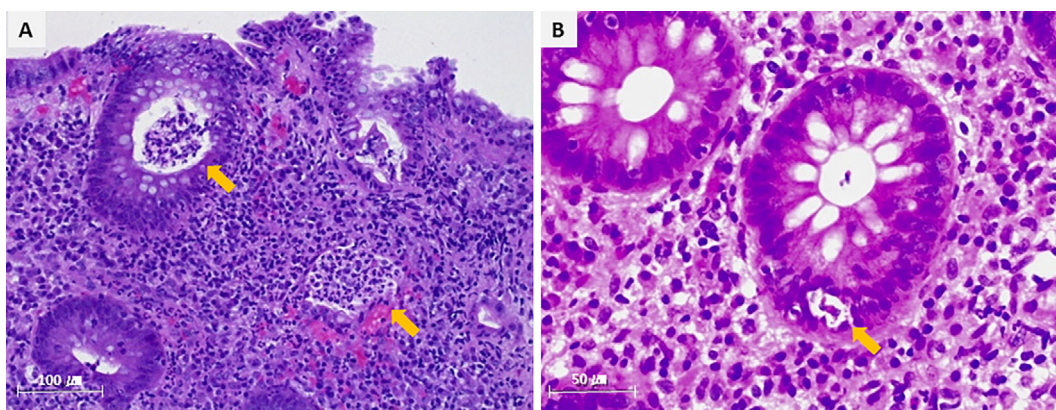


Figure 4. Histological examination results (Hematoxylin and Eosin staining). (A) Day 15. Diffuse infiltration of inflammatory cells, including neutrophils and crypt abscesses (yellow arrows). (B) Day 15. Apoptotic epithelial cell (yellow arrow).

thereafter.

Discussion

Nivolumab, a human immunoglobulin G4 monoclonal antibody, inhibits interactions between the programmed cell death-1 (PD-1) receptor and its ligands (PD-L1, PD-L2). Proliferation and activation of T cells specific for cancer antigens are induced by an anti-PD-1 antibody, leading to a sustained antitumor effect (10, 11). Drugs with such anti-tumor mechanisms, including nivolumab, are used as ICIs, which have received approval for treatment of various advanced malignant tumors.

Unlike conventional chemotherapy, anti-tumor immunotherapy with an ICI regimen has been reported to cause various irAEs (12), with gastrointestinal (GI) injury, acute hepatitis, skin rash, endocrinopathies, and pneumonitis occurring relatively frequently. Severity in most irAE cases is mild and the conditions are considered reversible, so treatment for related symptoms is often sufficient. In contrast, though rare, irAEs such as encephalitis, meningitis, polymyositis, myocarditis, hypopituitarism, and type 1 diabetes mellitus can be serious or even fatal, so a rapid diagnosis and therapeutic intervention are required in affected patients.

GI injury conditions, such as diarrhea and colitis, are reported to be found in 30-40% of all severe irAE cases, with the frequency of Grade ≥ 3 approximately 10% in those cases (13-15). When diarrhea is observed during ICI treatment, it is important to distinguish the cause as different from infectious enteritis and other inflammatory bowel diseases. After excluding infectious enteritis by stool culture examination findings, CT and colonoscopy are useful methods for diagnosing GI injury as an irAE. That is shown by CT as mesenteric edema and thickening of the intestinal wall, while colonoscopy findings indicate a granular or edematous pattern, exudates, loss of vascular pattern, aphtha, and ulcerations similar to ulcerative colitis (UC) (16, 17). However, those findings are not always specific to ICI-related colitis. In addition, a histological examination com-

monly shows acute to chronic nonspecific inflammatory cell infiltration, including cryptitis and crypt abscesses. In the present case, UC-like endoscopic findings were found mainly in the left-side colon (Fig. 3A), and a histological examination revealed diffuse infiltration of inflammatory cells, including neutrophils, crypt abscesses (Fig. 4A), and apoptotic epithelial cells (Fig. 4B). Notably, the presence of apoptotic epithelial cells has been observed as a typical histological finding of ICI-related colitis (18). In addition, ICI-related colitis is often reported to be found in the descending colon (19), as similarly observed in our case. Taken together, these findings suggest that the GI injury observed in the present patient was colitis due to a nivolumab-related irAE.

The serum levels of pancreatic enzymes are reportedly elevated as irAEs in patients receiving ICIs (20), although the frequency is not high. In clinical practice, when no symptoms are observed, even in cases with elevated pancreatic enzymes, ICI treatment should be continued. In contrast, when a patient has symptoms as well as Grade ≥ 3 pancreatic enzyme elevation, ICI treatment should be discontinued and treatment for pancreatitis given. A blood examination revealed Grade 3 pancreatic enzyme elevation in the present patient, who also had upper abdominal pain, but there was no history of heavy drinking or hyperlipidemia, and the possibility of another disease, such as autoimmune pancreatitis, was low. The diagnosis was the simultaneous onset of pancreatitis and colitis as irAEs during nivolumab treatment. Despite discontinuing nivolumab and providing general conservative treatment for pancreatitis, we noted exacerbation of the abdominal symptoms and increased pancreatic enzymes (Fig. 2), while swelling of the pancreas was revealed on CT (Fig. 1B). Thus, corticosteroid (CS) therapy was started, resulting in marked improvement of abdominal symptoms (Fig. 2) as well as colonoscopy (Fig. 3B) and CT (Fig. 1C) results. The efficacy of CS suggests that the clinical findings observed in this case might have been associated with irAEs resulting from nivolumab treatment.

Although few reports regarding colitis and pancreatitis as

irAEs in association with ICI treatment have been presented, especially for patients with a combination of both diseases, Pagen et al. reported a case of pembrolizumab-induced acute pancreatitis combined with colitis (21). The location and pathophysiology of colitis were similar in the present case, and the timing of the development of enteritis and pancreatitis was also nearly the same. Discontinuation of the ICI did not improve the symptoms, and a good response was seen with CS treatment in that previous report, although ICI administration was not resumed. In the present patient as well, no recurrence of symptoms has been observed since tapering of CS therapy. As in that other case, we also did not restart nivolumab treatment, as resumption was considered likely to again induce an excessive immune response in association with the development of serious irAEs. Alternative anticancer therapies should therefore be considered in patients with a history of serious irAEs induced by ICI treatment.

The main mechanism of irAE initiation is thought to be damage to autologous tissues and cells by lymphocytes that are misidentified as self-antigens. In particular, major histocompatibility complex (MHC) class I molecules involved in antigen recognition of cytotoxic T cells (CD8-positive T cells) are expressed nearly systemically, so it has been speculated that irAEs can occur anywhere in the body (22). Jamal et al. (23) also reported that the clinical spectrum of irAEs is broad, and multi-organ systems can be affected. Furthermore, the onset of skin and gastrointestinal disorders occurs relatively early as irAEs in each site, suggesting that the onset times may have overlapped in the present patient. However, there are few reports of cases in which irAEs develop in multiple organs at the same time, and the characteristics compared with cases with only a single affected organ are unknown at this time. The accumulation of additional case reports in the future is necessary.

In conclusion, we reported a rare case of nivolumab-related pancreatitis and colitis in a patient with a renal cell carcinoma who showed an immediate response to CS therapy. The number of cases treated with ICIs will likely increase in the future, with the frequency of irAEs increasing accordingly. In such cases, it is necessary to understand the medical condition at an early stage and perform appropriate therapeutic intervention.

The authors state that they have no Conflict of Interest (COI).

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