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Letter to the Editor

Development of mild drug-induced sclerosing cholangitis after discontinuation of nivolumab

Shoko Noda-Narita [a], Suguru Mizuno [b], Satoshi Noguchi [a], Kousuke Watanabe [a], Yousuke Nakai [b], Kazuhiko Koike [b], Hidenori Kage [a,*], Takahide Nagase [a]

[a] *Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Japan*
[b] *Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Japan*

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Dear Editor,

Immune check point inhibitors (ICIs) have shown remarkable success in medical oncology and are being used in many types of tumours including non–small-cell lung carcinoma (NSCLC). However, activation of host T cells can cause immune-related adverse events (irAEs), which can make treatment decisions difficult. Immune-related liver injury is a common form of irAEs and is known to occur in 1–3% of patients treated with ICIs [1]. In contrast, only eight cases of immune-related cholangitis have been reported, most of whom required extensive treatment [2–7]. In addition, the typical presentation of immune-related cholangitis is still unknown. Sclerosing cholangitis is a chronic inflammatory disease of the bile duct and is diagnosed by clinical presentation, presence of diffuse or segmental narrowing of bile duct associated with thickening of the bile duct wall and exclusion of other diseases. The disease is classified into three different etiologies: primary sclerosing cholangitis, IgG4-related sclerosing cholangitis and secondary sclerosing cholangitis (SSC), which can be caused by bile duct stones, malignancy and drugs [8,9]. Here, we report a case of SSC which developed seven months after discontinuation of nivolumab and resolved without corticosteroid treatment.

1. Case report

A 57-year-old woman with stage IV squamous-cell NSCLC received nivolumab as second-line treatment after failing combination chemotherapy with carboplatin and tegafur/gimeracil/oteracil (S-1). Pulmonary metastasis progressed after seven cycles, and she received docetaxel as third-line chemotherapy. Five months after her last administration of nivolumab, she started her fourth-line chemotherapy, nab-paclitaxel (nab-PTX). Her past medical history included gallstones and non-alcoholic fatty liver disease, but she had no hepatic or biliary adverse events during previous systemic chemotherapies.

After two cycles of nab-PTX, and seven months after discontinuation of nivolumab, she complained of

* *Corresponding author*: Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655 Japan Fax: +81 3 3815 5954.
E-mail addresses: s91063notsuko@gmail.com (S. Noda-Narita), smizuno-tky@umin.ac.jp (S. Mizuno), snoguchi-tky@umin.ac.jp (S. Noguchi), kwatanabe-tky@umin.ac.jp (K. Watanabe), ynakai-tky@umin.ac.jp (Y. Nakai), kkoike-tky@umin.ac.jp (K. Koike), kageh.tky@umin.ac.jp (H. Kage), takahide-tky@umin.ac.jp (T. Nagase).

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postprandial abdominal pain without fever. Alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GTP) were slightly elevated, and we initiated oral ursodeoxycholic acid (UDCA) at a dose of 150 mg/day for possible biliary colic. Abdominal and endoscopic ultrasound demonstrated hyperplasia and a slight dilation of the extrahepatic biliary duct with diffuse dilation of the intrahepatic biliary ducts without any findings of malignancy or stones in the common bile duct (Fig. 1A), suggestive of sclerosing cholangitis. Continuing oral UDCA resolved her abdominal pain, but her biliary enzymes remained elevated. After four cycles of nab-PTX, she complained of fever with abdominal pain, and computed tomography (CT) showed diffuse narrowing and dilation of the intrahepatic biliary ducts and thickening of the extrahepatic biliary duct walls (Fig. 1C). We initiated antibiotics for possible biliary infection, and her fever subsided the next day. However, her biliary enzymes continued to elevate, peaking at ALP 1065 U/l and γ-GTP 304 U/l, and we delayed the fifth cycle of nab-PTX and increased UDCA to 300 mg/day. Thereafter, ALP and γ-GTP gradually improved, and we resumed administration of nab-PTX with only 2 weeks of withdrawal. Magnetic resonance cholangiopancreatography taken at the start of the fifth cycle also showed diffuse stenosis and dilation of the intrahepatic biliary ducts (Fig. 1B), confirming sclerosing cholangitis. Follow-up CT taken after 3 months at the time of disease progression showed resolution of the biliary lesions. None of the imaging studies showed liver or biliary metastasis, immunoglobulin G4 (IgG4) level was normal and both anti-nuclear and anti-mitochondrial antibodies were negative. We made a diagnosis of nivolumab-induced SSC.

2. Discussion

The patient in this study developed cholangitis 7 months after discontinuation of nivolumab and during nab-PTX chemotherapy. Her fever developed a month after the onset of abdominal pain and was brief, and elevation of inflammatory markers was mild, making infectious

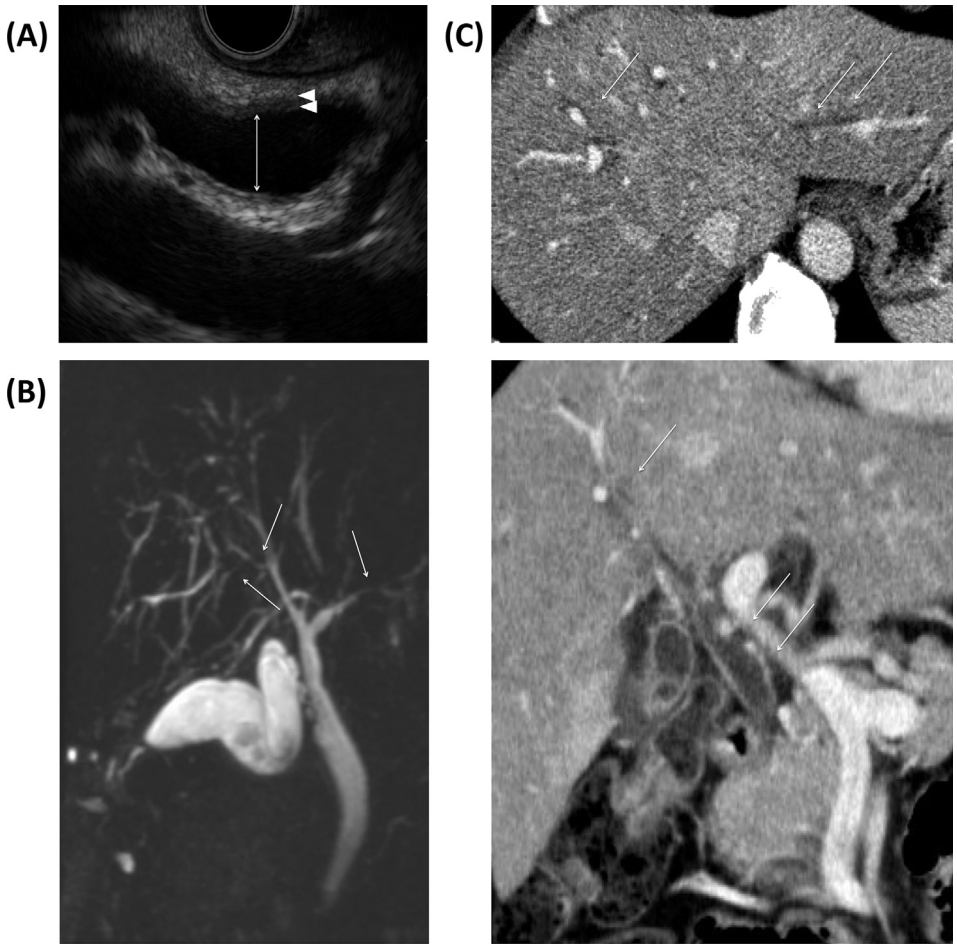

Fig. 1. (A) Endoscopic ultrasound showed wall thickening (1.6 mm, arrowheads) and slight dilation (10.8 mm, arrow) of the extrahepatic biliary duct. (B) Magnetic resonance cholangiopancreatography showed diffuse and multiple strictures (arrows) and slight dilation of the intrahepatic biliary ducts. (C) Computed tomography showed wall thickening of the extrahepatic biliary duct as well as diffuse strictures and dilation of the intrahepatic biliary ducts (arrows).

Table 1
Previously reported cases of immune-related cholangitis.

Case	Age	Sex	Agent	Symptom	ALP/γ-GTP elevation (grade)	Bilirubin elevation (grade)	IgG4	Thickening of biliary duct wall	Other characteristics	Treatment
1 [2]	79	M	Nivolumab	Jaundice	4	4	−	−	CD8+ T-cell in pathology	mPSL 1 mg/kg, UDCA
2 [3]	64	M	Nivolumab	Fever, abdominal	4	0	−	+	CD8+ T-cell in pathology	Drainage, PSL 0.5 mg/kg
3 [3]	73	F	Nivolumab	pain	4	2	−	+		Drainage, PSL 0.5 mg/kg
4 [3]	82	F	Nivolumab		4	0	−	+	CD8+ T-cell in pathology	Antibiotics only
5 [4]	63	M	Nivolumab	Fever, abdominal pain	3	n/a	− (in pathology)	+	Obstruction in extrahepatic biliary duct	Drainage, PSL 2 mg/kg
6 [5]	69	M	Nivolumab	Rash	n/a	n/a	n/a	+	Ulcer in extrahepatic biliary duct	PSL 60 mg/day, mPSL 500 mg pulse
7 [6]	73	M	Pembrolizumab	None	3	n/a	n/a	+	Sclerosing cholangitis; CD8+ T-cell in pathology	Discontinuation
8 [7]	69	M	Avelumab	Abdominal pain	3	0	n/a	+	Recurrence after rechallenge	mPSL 1 mg/kg

ALP, alkaline phosphatase; IgG4, immunoglobulin G4; F, female; M, male; mPSL, methylprednisolone; n/a, not applicable; PSL, prednisolone; UDCA, ursodeoxycholic acid; γ-GTP, gamma-glutamyl transpeptidase.

cholangitis unlikely. Imaging studies revealed diffuse stenosis and dilation of the intrahepatic biliary ducts with hyperplasia of the extrahepatic biliary ducts which resolved after 3 months, suggestive of sclerosing cholangitis and ruling out drug-induced liver injury, bile duct stones and metastasis. We further made a diagnosis as drug-induced SSC because primary sclerosing cholangitis, IgG4-related sclerosing cholangitis and other SSCs were considered unlikely.

SSC has many causes. Drug-induced SSC is often reported after intra-arterial injection of fluorodeoxyuridine, presumably due to direct biliary duct injury by the drug [10]. Other anti-cancer agents, such as 5-fluorouracil, S-1, docetaxel and paclitaxel plus bevacizumab, have also been reported as rare causes of SSC [11,12]. We diagnosed her SSC to be nivolumab induced, and not nab-PTX induced, for two reasons: only one case of nab-PTX-induced SSC has been reported [13] and our patient could continue nab-PTX treatment. Our case was remarkable for its late onset after discontinuation of nivolumab, but onset was also late for the patient with avelumab-induced cholangitis (case 8 in Table 1), 12 months after initiation of the treatment [7]. IrAEs can occur long after ICI treatment, presumably due to the long PD-1 occupancy of T cells, which was reported to last for months [14].

Although we diagnosed our case as the first nivolumab-induced SSC to be reported, we found it striking that previously reported cases of ICI-induced cholangitis (Table 1) except for case 1 showed clinical features typical for SSC, with characteristic thickening of biliary duct walls and/or pathological findings of inflammatory cell infiltration. Obstruction and ulcers reported in cases 5 and 6 could be interpreted as features of sclerosing cholangitis. We suggest that ICI-induced SSC should be recognised as a form of irAE.

The current case had a better outcome compared with previous ICI-induced cholangitis. This might be due to the late onset after a long absence of nivolumab. On the other hand, some ICI-induced SSC may not need corticosteroid treatment. In addition, some mild forms of SSC caused by ICI treatment may have been diagnosed as drug-induced liver injury without being aware of the presence of cholangitis.

In conclusion, ICI-induced SSC is a rare irAE but warrants consideration in addition to immune-related hepatitis when we recognise elevation of biliary enzymes.

Conflict of interest statement

None declared.

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