Abdominal pain accompanied by elevated serum inflammatory markers and biliary enzymes for diagnosing immune checkpoint inhibitor-induced sclerosing cholangitis

Takafumi Yamamoto
Nagoya University Graduate School of Medicine
Kazuyuki Mizuno
Nagoya University Graduate School of Medicine
Takanori Ito (tahkun56@med.nagoya-u.ac.jp)
Nagoya University Graduate School of Medicine
Shinya Yokoyama
Nagoya University Graduate School of Medicine
Kenta Yamamoto
Nagoya University Graduate School of Medicine
Norihiro Imai
Nagoya University Graduate School of Medicine
Yoji Ishizu
Nagoya University Graduate School of Medicine
Takashi Honda
Nagoya University Graduate School of Medicine
Takuya Ishikawa
Nagoya University Graduate School of Medicine
Akira Kanamori
Ogaki Municipal Hospital
Satoshi Yasuda
Ogaki Municipal Hospital
Hidenori Toyoda
Ogaki Municipal Hospital
Kenji Yokota
Nagoya University Graduate School of Medicine
Tetsunari Hase
Nagoya University Graduate School of Medicine
Naoki Nishio
Nagoya University Graduate School of Medicine
Osamu Maeda
Nagoya University Hospital
Makoto Ishii
Nagoya University Graduate School of Medicine
Michihiko Sone
Nagoya University Graduate School of Medicine
Yuichi Ando
Nagoya University Hospital
Masashi Akiyama
Nagoya University Graduate School of Medicine
Masatoshi Ishigami
Nagoya University Graduate School of Medicine
Hiroki Kawashima
Nagoya University Graduate School of Medicine

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Abstract

Background: Immune-related sclerosing cholangitis (irSC) is relatively rare and its clinical characteristics are not well known. In this study, we aimed to summarize the clinical features of irSC.

Methods: Clinical data were collected retrospectively from 1,393 patients with advanced malignancy treated with immune-checkpoint inhibitors (ICIs) between August 2014 and October 2021. We analyzed patients with immune-related adverse events of liver injury (liver-irAEs) and compared irSC and non-irSC groups.

Results: Sixty-seven patients (4.8%) had a liver-irAE (≥ grade 3) during the follow-up period (median, 262 days). Among these, irSC was observed in eight patients (11.9%). All patients in the irSC group were treated with anti-PD-1/PD-L1 antibodies. Compared with the non-irSC group, the irSC group showed mainly non-hepatocellular liver injury (87.5 % vs 50.8 %, $P = 0.065$), and had elevated serum inflammatory markers (e.g., CRP and NLR) and biliary enzymes (e.g., GGTP and ALP) at the onset of liver-irAEs. Furthermore, most patients with irSC had abdominal pain. In the non-irSC group, the liver injury of 23 patients improved only with the discontinuation of ICIs, and 22 patients improved with medication including prednisolone (PSL). Conversely, almost all patients (n=7) in the irSC group were treated with PSL, but only two patients experienced an improvement in liver injury.

Conclusion: We found that irSC is characterized by a non-hepatocellular type of liver injury with abdominal pain and a high inflammatory response and is refractory to treatment. Further examination by imaging is recommended to detect intractable irSC in cases with these characteristics.

Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target intrinsic immune regulatory pathways in T cells, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1), to release the brakes on T cell damage to tumor cells.[1] Despite these benefits, ICIs can cause immune-related adverse events (irAEs), which are autoimmune side effects in various organ systems. [2] The frequency of irAEs and the risk of mortality vary according to the type of irAEs. Endocrine abnormalities and mild skin rashes are frequent and are positively correlated with prognosis, whereas myocarditis and pneumonia are less frequent and are not necessarily correlated with a good prognosis. [3] [4] Severe immune-related liver injuries (liver-irAEs) can be fatal in some cases by themselves, whereas the inability to treat malignancy owing to steroid treatment for a period may also have a negative prognostic effect. [5] Therefore, diagnostic biomarkers for predicting early diagnosis as well as appropriate treatment algorithms for liver-irAEs are important for improving the prognosis of patients with malignancies treated by ICIs.

In our previous study, we reported that approximately half of liver-irAEs were non-hepatocellular type (cholestatic or mixed type), and approximately half of these were resistant to steroid therapy. In addition, liver-irAEs of the non-hepatocellular type include a unique form of cholangitis resembling primary sclerosis cholangitis, namely immune-related sclerosing cholangitis (irSC). [6] [7]

Like the other types of irAE (e.g., myocarditis), the pathogenesis of irSC is mainly characterized by inflammation with infiltration of cluster of differentiation 8 (CD8)-positive T cells into the bile ducts. [8] Kawakami et al. described the features of irSC as follows: (1) localized extrahepatic bile duct dilation without obstruction; (2) diffuse hypertrophy of the extrahepatic bile duct wall; (3) a dominant increase in the biliary tract enzymes alkaline phosphatase and gamma-glutamyl transpeptidase relative to the hepatic enzymes aspartate and alanine aminotransferase; (4) normal or reduced levels of the serum immunological markers anti-nuclear antibody, anti-mitochondrial antibody, smooth muscle antibody, and immunoglobulin G4; (5) a pathological finding of biliary tract CD8-positive T cell infiltration from a liver biopsy; and (6) a moderate to poor response to steroid therapy. [9] Furthermore, it has been reported that steroid treatment responsiveness of irSC may vary according to the subtype of irSC. Compared with the intrahepatic bile duct type, the extrahepatic bile duct type and the diffuse type may have a poor response to steroid treatment. [10] [11]

However, because irSC is relatively rare among irAEs, accounting for 0.05–0.7% of ICI-treated patients [6] [12] [13], its clinical characteristics are not well known compared with other irAEs. In this study, we aimed to summarize the clinical features and outcomes of irSC by comparing them with those of non-irSC in liver-irAEs.

Materials And Methods

Study population

We retrospectively collected and analyzed clinical data from 1,393 patients with advanced malignant tumors treated with ICIs at Nagoya University Hospital (n = 819) and Ogaki Municipal Hospital (n = 574) between August 2014 and October 2021. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of Nagoya University Hospital and Ogaki Municipal Hospital (approval no. 2018 – 0438 and 15,006).

Diagnosis of immune-related liver injury

We assessed the patients' general condition and blood test data at least every 3 weeks after ICI administration. When adverse events occurred, their severity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In cases of liver injury, we confirmed that there were no other factors causing liver injuries, such as hepatitis A, B, or C virus infection, autoimmune liver disease, metabolic liver disease, use of hepatotoxic drugs other than ICIs, or consumption of large amounts of alcohol. Abdominal ultrasonography, contrast-enhanced computed tomography (CT), and/or magnetic resonance imaging (MRI) was also performed to rule out exacerbation of liver metastases or bile duct obstruction. Pathological tests such as liver biopsy was performed in cases deemed necessary for diagnosis, considering the risk of complications such as hemorrhage. Based on previous reports, the pattern of liver injury was defined as follows: (i) hepatocellular type, alanine aminotransferase (ALT) ≥ 5 times upper limit of normal (ULN) or ALT/ alkaline phosphatase (ALP) ≥ 5; (ii) cholestatic type, ALP level ≥ 2 ULN or ALT/ALP ≤ 2; and (iii) mixed type, ALT/ALP > 2 and < 5. [14] [15] In this study, irSC was

defined as having extrahepatic bile duct changes, as proposed by Kawakami et al. (localized dilation of the extrahepatic bile ducts without obstruction or diffuse thickening of the bile duct wall), and/or intrahepatic bile duct change (dilation or hypertrophy) in imaging studies such as CT or MRI. [9]

Treatment of immune-related liver injury

In this study, treatment of liver-irAEs was generally conducted according to the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL). [1] [16] Briefly, in the case of grade 3 liver-irAEs, oral prednisolone (PSL) 0.5–1 mg/kg/day was started only if liver-irAEs did not improve when the ICI was withheld. In cases of grade 4 liver-irAEs, a steroid pulse with methylprednisolone was administered immediately, followed by oral treatment with PSL 1.0–2.0 mg/kg/day. In cases of cholestatic type and mixed type, the use of ursodeoxycholic acid (UDCA) was considered when imaging studies ruled out bile duct obstruction. In our study, improvement of liver-irAEs was defined as follows: (i) if baseline data at the start of the ICI were normal, improvement was recorded if liver injury had recovered to below the upper limit of normal; (ii) if baseline data at the start of the ICI were abnormal, improvement was recorded if liver injury had recovered to baseline levels based on CTCAE v5.0. In our study, several patients received the best supportive care without PSL treatment for irAEs because of the progression of malignancy after the onset of liver-irAEs.

Statistical analysis

Categorical variables, described as numbers (percentages), were compared using Fisher's exact test, and continuous variables, described as median (first to third quartiles), were compared using the Mann–Whitney U test. The incidence of liver-irAEs was estimated using the cumulative incidence method and compared using the Gray test. For all tests, statistical significance was set at $P < 0.05$. The cut-off value for each test was the lower or upper limit of the reference value at Nagoya University Hospital and Ogaki Municipal Hospital. GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R, were used for statistical analyses. [17]

Results

Clinical characteristics of immune-related liver injury

The clinical characteristics of liver-irAEs in this study are shown in Table 1. During the follow-up period (median, 262 days), liver-irAEs (≥ grade 3) occurred in 67 (4.8%) patients. The median age of patients with liver-irAEs was 64 (55–71) years, with 37 (55.2%) male patients and 30 (44.8%) female patients. Regarding the type of malignancy, lung cancer (40.3%) was the most common, followed by malignant melanoma (23.9%) and renal cell cancer (17.9%) (Supplemental Fig. 1). Sixty patients (89.6%) received anti PD-1 antibody (Ab) or anti programmed death receptor ligand 1 (PD-L1) Ab, and 17 patients (25.4%) received anti CTLA-4 Ab (Table 1). The types of liver injury that occurred in our study were hepatocellular type in 30 (44.8%) patients, mixed type in 13 (19.4%) patients, and cholestatic type in 24 (35.8%) patients. Additional imaging studies led to the diagnosis of irSC in 8 patients, 0.6% of patients receiving ICIs, and 11.9% of patients with liver-irAEs (≥ grade 3). The median time from the first ICI administration to the onset of liver-irAEs was 53 days (95% CI: 36–81 days) (Supplemental Fig. 2), and the number of ICI cycles was 2 (range, 1–4) (Table 1). Twenty-six (38.8%) patients had other types of irAEs (≥ grade 3) before the onset of liver-irAEs, and 40 (59.7%) patients had some symptoms at the onset of liver-irAEs. As for treatment of liver-irAEs, 34 patients (50.7%) were treated with PSL and 33 patients (49.3%) were treated without PSL. Among patients without PSL, some cases could not undergo PSL therapy owing to deterioration of their general condition, but 23 patients had improved liver-irAEs only after discontinuation of ICIs. In the 34 patients who required PSL, improvement was observed in 24 patients.

Table 1
Baseline characteristics

Factor	Group	All (n = 67)	non-irSC (n = 59)	irSC (n = 8)	*p* - value
Follow-up period (days)		262 (121, 538)	262 (121, 557)	242 (162, 342)	
Age (years)		64 (55, 71)	64 (55, 71)	66 (60, 69)	0.786
Gender	F	30 (44.8)	27 (45.8)	3 (37.5)	0.722
	M	37 (55.2)	32 (54.2)	5 (62.5)	
Using anti-PD-1/PD-L1 Ab	Yes	60 (89.6)	52 (88.1)	8 (100.0)	0.586
	No	7 (10.4)	7 (11.9)	0 (0.0)	
Using anti-CTLA-4 Ab	Yes	17 (25.4)	16 (27.1)	1 (12.5)	0.669
	No	50 (74.6)	43 (72.9)	7 (87.5)	
Type of ICI	aPD-1 Ab	40 (59.7)	34 (57.6)	6 (75.0)	
	aPDL-1 Ab	10 (14.9)	9 (15.3)	1 (12.5)	
	aCTLA-4 Ab	7 (10.4)	7 (11.9)	0 (0.0)	
	aPD-1 Ab + aCTLA-4 Ab	10 (14.9)	9 (15.3)	1 (12.5)	
ICI cycles until onset		2 (1, 4)	2 (1, 4)	5 (3, 6)	0.024
hepatocellular type of liver injury	Yes	30 (44.8)	29 (49.2)	1 (12.5)	0.066
	No	37 (55.2)	30 (50.8)	7 (87.5)	
Type of liver injury	Hepatocellular	30 (44.8)	29 (49.2)	1 (12.5)	
	Mixed	13 (19.4)	10 (16.9)	3 (37.5)	
	Cholestatic	24 (35.8)	20 (33.9)	4 (50.0)	
Pre-Treatment AST (U/L)		20.0 (15.5, 24.0)	20.0 (16.0, 24.0)	15.5 (14.5, 17.0)	0.018
Pre-Treatment ALT (U/L)		15.0 (11.0, 22.0)	16.0 (12.5, 22.5)	9.0 (8.8, 14.3)	0.062
Pre-Treatment ALP (U/L)		251 (212, 301)	224 (212, 300)	275 (229, 312)	0.637
Pre-Treatment GGTP (U/L)		33.0 (19.0, 49.0)	31.0 (19.0, 47.0)	40.0 (30.8, 54.5)	0.235
Pre-Treatment TB (mg/dL)		0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.5 (0.3, 0.5)	0.329
Pre-Treatment CRP (mg/dL)		0.46 (0.08, 2.48)	0.33 (0.06, 1.88)	2.18 (0.56, 5.76)	0.106
Pre-Treatment NLR		3.26 (2.20, 4.85)	3.26 (2.16, 4.87)	2.79 (2.23, 4.69)	1
Pathology of liver	Presence	19 (28.4)	15 (25.0)	4 (50.0)	0.206
	Absence	48 (71.6)	45 (74.6)	4 (50.0)	
Multi-system irAE	Presence	26 (38.8)	25 (57.6)	1 (12.5)	0.138
	Absence	41 (61.2)	34 (42.4)	7 (87.5)	
Type of other irAEs (Grade ≥ 3)	Thyroid dysfunction	6 (9.0)	6 (10.2)	0 (0.0)	
	Colitis	6 (9.0)	6 (10.2)	0 (0.0)	
	Rash	5 (7.5)	5 (8.5)	0 (0.0)	
	Pituitary dysfunction	4 (6.0)	4 (6.8)	0 (0.0)	
	Pulmonary disorder	3 (4.5)	3 (5.1)	0 (0.0)	
	Type 1 diabetes	2 (3.0)	2 (3.4)	0 (0.0)	
	Pancreatitis	2 (3.0)	1 (1.7)	1 (12.5)	

Categorical variables were described as numbers (percentages), and continuous variables were described as median (first-third interquartile).

PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGTP, gamma-glutamyltransferase; TB, total bilirubin; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PSL, prednisolone; UDCA, ursodeoxycholic acid; MMF, mycophenolate mofetil. *P*-values are for comparison between the irSC and non-irSC groups.

Factor	Group	All (n = 67)	non-irSC (n = 59)	irSC (n = 8)	*p* - value
Follow-up period (days)		262 (121, 538)	262 (121, 557)	242 (162, 342)	
Age (years)		64 (55, 71)	64 (55, 71)	66 (60, 69)	0.786
	Neuritis	1 (1.5)	1 (1.7)	0 (0.0)	
	Uveitis	1 (1.5)	1 (1.7)	0 (0.0)	
	Arthritis	1 (1.5)	0 (0.0)	1 (12.5)	
Presence of symptom	Yes	40 (59.7)	32 (54.2)	8 (100)	0.018
	No	27 (40.3)	27 (45.8)	0 (0.0)	
Type of symptoms	Anorexia or malaise	23 (34.3)	21 (35.6)	2 (25.0)	
	Fever	14 (20.9)	13 (22.0)	1 (12.5)	
	Abdominal pain	9 (13.4)	2 (3.4)	7 (87.5)	
	Rash	5 (7.5)	5 (8.5)	0 (0.0)	
Using PSL for liver-irAE	Yes	34 (50.7)	27 (45.8)	7 (87.5)	0.054
	No	33 (49.3)	32 (54.2)	1 (12.5)	
Using UDCA for liver-irAE	Yes	19 (28.4)	14 (25.0)	6 (75.0)	0.007
	No	48 (71.6)	45 (76.3)	2 (25.0)	
Using MMF for liver-irAE	Yes	3 (4.5)	2 (3.4)	1 (12.5)	0.321
	No	64 (95.5)	57 (96.6)	7 (87.5)	
Improvement of liver irAE	Yes	47 (70.1)	45 (76.3)	2 (25.0)	0.007
	No	20 (29.9)	14 (23.7)	6 (75.0)	
Outcome of liver-irAE	Improvement without medication	23 (34.3)	23 (39.0)	0 (0.0)	
	Improvement with medication	24 (35.8)	22 (37.3)	2 (25.0)	
	Not improvement or relapse	20 (29.9)	14 (23.7)	6 (75.0)	

Categorical variables were described as numbers (percentages), and continuous variables were described as median (first-third interquartile).

PD-1, programmed death receptor 1; PD-L1, programmed death receptor ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGTP, gamma-glutamyltransferase; TB, total bilirubin; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PSL, prednisolone; UDCA, ursodeoxycholic acid; MMF, mycophenolate mofetil. *P*-values are for comparison between the irSC and non-irSC groups.

Differentiation between irSC and non-irSC with clinical characteristics

Next, we compared the clinical characteristics of irSC (n = 8) and non-irSC (n = 59) patients. Detailed information on the eight patients with irSC is summarized in Table 2. Approximately 10% of non-irSC patients were treated without anti-PD-1/PD-L1 Abs, whereas all patients who developed irSC were treated with anti-PD-1/PD-L1 Abs in our study. The median time from the first administration of ICIs to the onset of irSC was 77 days (95%CI: 35–245) days (Fig. 1A) and the number of ICI cycles was 5 (range, 3–6). The time to onset of irSC was no difference between the two groups ($P = 0.237$) (Fig. 1A), but the number of cycles was higher in the irSC group ($P = 0.024$) (Table 1). As for baseline laboratory data, AST was lower in the irSC group, but there were no significant differences in other hepatobiliary enzymes or inflammatory markers between the two groups (Table 1). However, for laboratory data at the onset of liver-irAEs, AST, ALT, and TB were comparable between the two groups, whereas the values of gamma glutamyltransferase (GGTP), ALP, C-reactive protein (CRP), and neutrophil to lymphocyte ratio (NLR) were significantly higher in the irSC group (Fig. 1B–H). The type of liver injury in the irSC group was hepatocellular type in one (12.5%) patient, mixed type in three (37.5%) patients, and cholestatic type in four (50.0%) patients. Compared with the non-irSC group, the non-hepatocellular type tended to be more common in irSC ($P = 0.065$). The imaging findings of irSC were intrahepatic bile duct type in one case, extrahepatic bile duct type in one case, and diffuse type in six cases (Table 2).

Table. 2 Clinical characteristics of immune-related sclerosing cholangitis

Case no	Age	Gender	Type of Cancer	Type of ICI	Symptom	Type of liver injury	Grade	Type of cholangitis	Extrahepatic duct	Intrahepatic duct	Gallbladder
1	52	F	Head and Neck	aPD-1 Ab	Abdominal pain, Anorexia	Mix	4	Diffuse	dilation, diffuse hypertrophy	dilation	hypertrophy
2	64	F	Lung	aPD-1 Ab	Fever, Fatigue	Cholestatic	4	Diffuse	dilation, diffuse hypertrophy	dilation	NA
3	74	M	Lung	aPD-1 Ab	Abdominal pain	Cholestatic	4	Diffuse	dilation, diffuse hypertrophy	dilation	hypertrophy
4	68	M	Malignant pleural mesothelioma	aPD-1 Ab	Abdominal pain	Cholestatic	4	Diffuse	dilation, diffuse hypertrophy	dilation, irregular narrowing	hypertrophy
5	69	F	Lung	aPDL-1 Ab	Abdominal pain	Mix	3	Extrahepatic	dilation, diffuse hypertrophy	None	hypertrophy
6	62	M	Head and Neck	aPDL-1 Ab	Abdominal pain	Cholestatic	3	Diffuse	dilation, diffuse hypertrophy	dilation	hypertrophy
7	47	M	Lung	aPD-1 Ab + aCTLA-4 Ab	Abdominal pain	Hepatocellular	3	Intrahepatic	None	dilation, irregular narrowing	None
8	69	M	Malignant melanoma	aPD-1 Ab	Abdominal pain, Diarrhea, Nausea	Mix	4	Diffuse	dilation, diffuse hypertrophy	dilation	hypertrophy

ICI, immune checkpoint inhibitor; aPD-1Ab, anti-programmed death receptor 1 antibody; aPD-L1 Ab, anti-programmed death receptor ligand 1 antibody; aCTLA-4 Ab, anti-cytotoxic T-lymphocyte antigen 4 Ab; NA, not available; PSL, prednisolone; UDCA, ursodeoxycholic acid; MMF, mycophenolate mofetil.

Regarding the symptoms at the onset of liver-irAEs, all patients were symptomatic in the irSC group, whereas only half of the patients (n = 32, 54.2%) were symptomatic in the non-irSC group (P = 0.018). The types of symptoms in irSC were abdominal pain in seven patients (87.5%), anorexia/malaise in two patients (25.0%), and fever in one patient (12.5%). However, abdominal pain was not prominent in the non-irSC group (n = 2, 3.4%).

There were 25 patients in the non-irSC group with multisystem irAEs (≥ grade 3) until the onset of liver-irAEs. Six patients had thyroid dysfunction, six patients had colitis, five patients had skin rash, four patients had pituitary dysfunction, and three patients had lung injury, and there were two cases of type 1 diabetes, one case of pancreatitis, one case of neuritis, and one case of uveitis. In the irSC group, there was one case of multisystem irAEs with arthritis and pancreatitis.

Treatment and outcome of irSC and non-irSC

Seven patients in the irSC group (87.5%) and 27 patients (45.8%) in the non-irSC group underwent PSL treatment. UDCA was used in 6 patients (75.0%) in the irSC group and 14 patients (25.0%) in the non-irSC group. MMF was used one patient (12.5%) in the irSC group and two patients (3.4%) in the non-irSC group. Improvement of liver-irAEs was achieved in 2 patients (25.0%) in the irSC group and in 45 patients (76.3%) in the non-irSC group (P = 0.007). Here, we describe a typical case of steroid-resistant irSC (Patient No. 6) (Fig. 2). A 62-year-old male with head and neck cancer was administered anti-PD-L1 Ab. After two cycles of ICI, he presented to our clinic complaining of abdominal pain. Abdominal CT showed wall thickening with dilatation of extra- and intrahepatic lesions (Fig. 2A). From CT imaging, irSC was suspected, but he had a history of gallstones. We performed a liver biopsy and endoscopic retrograde cholangiopancreatography (ERCP) with bile duct biopsy. ERCP showed bile duct dilatation and narrowing of the intrahepatic bile ducts, but no obstruction due to stones or other factors (Fig. 2B). Liver and bile duct tissues stained with hematoxylin–eosin revealed portal inflammation with interface hepatitis and severe bile duct inflammation. Immunohistological staining in liver and bile duct samples showed the infiltration of T cells with anti-CD3 and anti-CD8 positivity (Fig. 2C) Based on these results, we diagnosed this case as irSC. Endoscopic nasobiliary drainage (ENBD) was performed, but liver injury could not be improved. Anti-PD1 Ab was withdrawn immediately and PSL 35 mg/day and UDCA 600 mg/day were started. However, biliary enzymes again increased during PSL tapering, and we added MMF 2 g/day. (Fig. 2D) Thereafter, treatment with anti-cancer drugs for head and neck cancer could not be resumed and the patient was transferred to a hospital for palliative treatment.

Discussion

All cases were induced using anti-PD-1 Ab or anti-PDL-1 Ab and the onset of irSC was characterized by the appearance of abdominal pain with elevated biliary enzymes and inflammatory markers. Approximately half of the patients were resistant to PSL therapy.

As the present study showed that irSC was resistant to steroid therapy, Onoyama et al. reported that the response rate to steroid therapy for irSC was 11.5% [11], and Berry et al. reported that only 40% cases achieved a clinical response to immunosuppressive therapy including PSL. [18] The pathogenesis of irSC is currently not fully understood, and there is no drastically effective treatment for irSC.

We previously reported that the response rate of PSL was only 44% in non-hepatocellular types liver-irAEs (≥ grade 3). [7] Takinami et al. also reported that in a study of ≥ grade 2 liver-irAEs, comparing with non-irSC biliary enzymes at the onset of liver-irAEs were higher in irSC. [19] Because most of the irSC patients in our study also presented with non-hepatocellular type, this characteristic was the one of the critical factors in considering the possibility of irSC. The appropriate steroid dosage for such a non-hepatocellular type of liver-irAE has not yet been established. However, if steroids are not effective, we need to taper PSL earlier and add alternative treatment options such as UDCA or immunosuppressive agents.

Biliary drainage has also been performed in some irSCs but has been reported to be ineffective. [9][12][20][21] We also experienced a refractory case in which biliary drainage was performed but the liver injury did not improve, and liver-irAE was relapsed during PSL reduction (Fig. 2). On the basis of these reports, we recommend biliary drainage for irSC only in suspected cases with complications of acute pyogenic cholangitis or bile duct stones.

In ICI treatment of patients with malignant melanoma, CRP and interleukin-6 (IL-6) are elevated when irAEs occur. [22] [23] Regarding HCC treatment with anti-PD-1 Ab, the severity of irAEs is positively correlated with CRP and IL-6 and negatively correlated with the frequency of T and B lymphocyte subsets. [24] Our study found that CRP and NLR levels at the onset of liver-irAEs were higher in the irSC group. IL-6, which triggers the synthesis of CRP, is an inflammatory cytokine that plays an important role in immune processes and is involved in a variety of diseases including cancer. [25] Tocilizumab, an IL-6 receptor Ab that inhibits IL-6-mediated signaling, has been reported to be effective in steroid-resistant irAEs in malignant melanoma. [26] Moi et al. reported that inflammatory cytokines such as IL-6 were elevated in three PSL-resistant irSC patients, and tocilizumab was effective for steroid-resistant irSCs. [27] These findings suggest that these inflammatory markers may be strongly correlated with the pathogenesis of irSC and may help to elucidate the pathogenesis of steroid resistance and effective therapies after secondary treatment.

Fever, abdominal pain, general malaise, and vomiting are reported to be the most common symptoms at the time of irSC diagnosis. [28] Notably, in our study, approximately half of the non-irSC patients were asymptomatic, whereas all irSC patients were symptomatic. Although fever occurred in 10–20% of cases in both groups, abdominal pain was more common in the irSC group (n = 7, 87.5%). We believe that the presence of abdominal pain can help the early diagnosis of irSC.

Some cases (25%) with irSC can relapse after the introduction of steroid therapy (Table 2). The findings of bile duct at recurrence are variable; in some cases, intrahepatic bile duct stenosis is predominant, with thickened bile duct wall being less prominent. [29] In one previous report with repeated liver biopsy, the infiltration of inflammatory cells in the liver had decreased but bile duct injury had progressed, even after steroid therapy. [30] Fibrosis as well as inflammation may be involved in the narrowing of the bile ducts, making it important to assess not only the degree of inflammation by liver biopsy but also to re-evaluate MRI and CT imaging during the clinical course.

There are several limitations of this study. First, because it was a retrospective study, the methods of imaging assessment and treatment of liver-irAEs were not completely uniform: when liver-irAE develops, there are differences of opinion between attending physicians, such as whether to use UDCA based on limited evidence.

Second, the number of cases with ≥ grade 3 irSC was small because irSC is rare. The detailed assessment of grade 1–2 liver injury was difficult because many patients in this study had multiple concomitant medications and treatments for various advanced malignancies. However, we rigorously performed imaging examinations to exclude other liver diseases and to assess the bile duct imaging in patients with ≥ grade 3 liver injury.

Conclusion

We found that irSC is characterized by a non-hepatocellular type of liver injury with abdominal pain and a high inflammatory response. irSC is refractory to PSL treatment, as previously reported, and early diagnosis is recommended with aggressive screening to assess the bile duct imaging. In the future, prospective studies in more cases with irSC are needed to analyze the appropriate concentration of steroids as initial treatment, the timing of tapering, and the need for immunosuppressive treatment for relapsed cases with irSC.

Declarations

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Data availability statement: Original data can be requested from the corresponding author.

Disclosure of Ethical Statements

Approval of the research protocol: This study was conducted by the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of Nagoya University Hospital (no. 2018-0438).

Informed Consent: Informed consent for this study was obtained from the website of Nagoya University Hospital.

Registry and the Registration No. of the study/trial: N/A

Animal Studies: N/A

Research involving recombinant DNA: N/A

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Figures

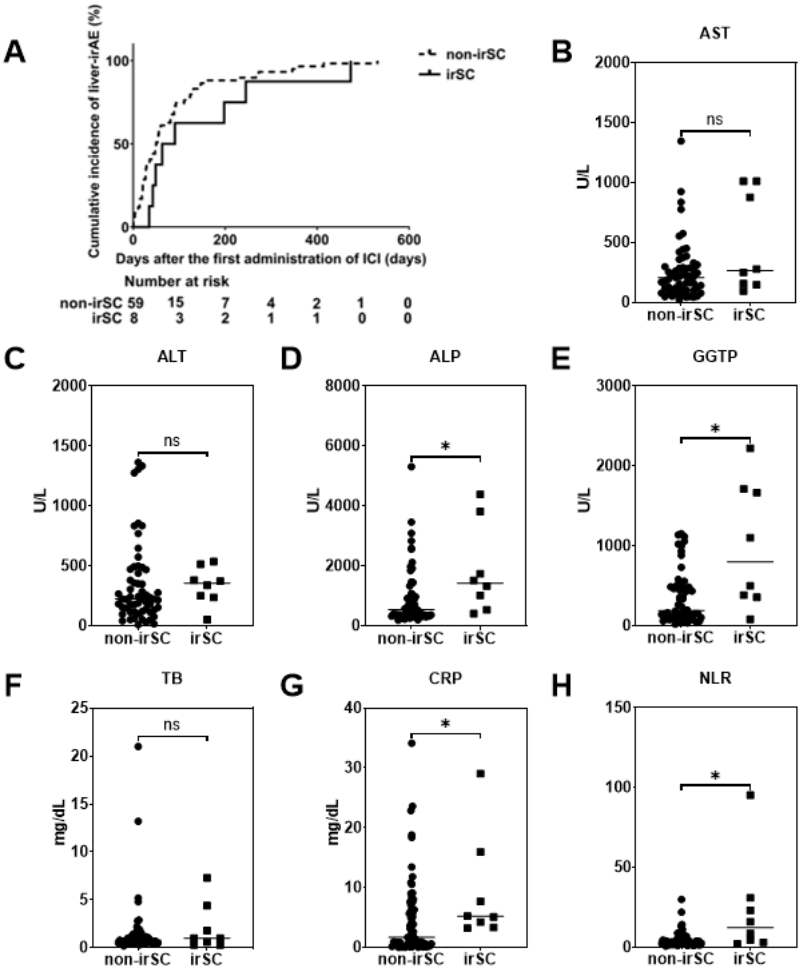

Figure 1

Onset pattern and laboratory features at the onset of immune-related liver injury (immune-related sclerosing cholangitis vs non- immune-related sclerosing cholangitis).

(A) Duration from the start of immunotherapy to the onset of severe immune-related liver injury (≥ grade 3). Comparison of laboratory data at the onset of an immune-related liver injury (≥ grade 3). (B) Aspartate aminotransferase (AST), (C) alanine aminotransferase (ALT), (D) alkaline phosphatase (ALP), (E) gamma-glutamyl transpeptidase (GGTP), (F) total bilirubin (TB), (G) C-reactive protein (CRP), and (H) neutrophil-lymphocyte ratio (NLR). * $P < 0.05$

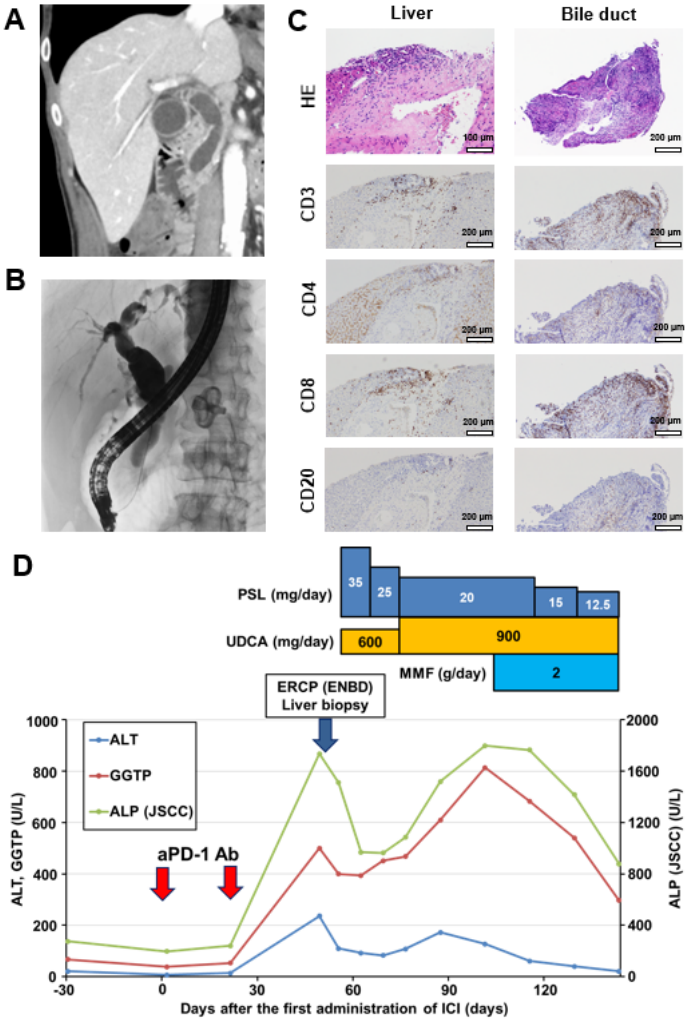

Figure 2

Representative case of immune-related sclerosing cholangitis (irSC).

(A) Abdominal computed tomography with contrast medium performed at the onset of abdominal pain and (B) endoscopic retrograde cholangiopancreatography. (C) Liver and bile duct samples stained with HE and anti-CD3, anti-CD4, anti-CD8, and anti-CD20 antibodies. (D) Graph showing the changes in hepatobiliary enzymes (ALT, ALP, and GGTP), with a summary of systemic treatments administered over time. The right *y*-axis refers to ALT and GGTP levels and the left *y*-axis refers to ALP levels (D).

HE: hematoxylin–eosin, CD: cluster of differentiation, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGTP: gamma-glutamyltransferase

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