

# Immune-related cholangitis induced by immune checkpoint inhibitors: a systematic review of clinical features and management

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**Background & Aims** Immune checkpoint inhibitors (ICIs) improve the survival of patients with advanced tumors.

However, immune-related adverse events limit the use of ICIs. Although liver toxicity has been concerned gradually, little is known about bile duct injury associated with ICIs. Hence, this review aims to describe clinicopathological features, imaging, and management of immune-mediated cholangitis (IMC) induced by ICIs.

**Methods** We retrieved the literature from the PubMed database for case reports and series of IMC induced by ICIs. IMC was then classified as small-ducts type, large-ducts type and mixed type. Biochemical parameters, pathological characteristics, imaging features, treatment and response were evaluated and compared among three patterns.

**Results** Fifty-three cases of IMC were enrolled. The median values of alkaline phosphatase and alanine transaminase of IMC were 1328 and 156 IU/L. The ALP level of the large-ducts type was higher than that of the small-ducts type ( $P = 0.021$ ).

The main pathological characteristics of small-ducts cholangitis were portal inflammation, bile duct injury and ductular reaction. The imaging features of large-duct cholangitis were bile duct dilatation, stenosis and bile duct wall thickening and irregularity. Forty-eight (90%) cases received immunosuppression therapy. Biliary enzymes reduced in 79% of cases receiving immunosuppression therapy, but only 8.5% of cases returned to normal. It took a long time for biliary enzymes to recover.

**Conclusions** The clinicians should be aware of the possibility of IMC if the biliary enzymes increase significantly after the use of ICIs. The liver function can be improved partially by immunosuppressive therapy in the majority of IMC. *Eur J Gastroenterol Hepatol* 33: e858–e867

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## Introduction

Immune checkpoint inhibitors (ICIs) have dramatically changed the landscape of cancer therapy and improved the survival of patients with advanced tumors. ICIs targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 receptor (PD-1) and its ligand (PD-L1) promote T cell response against the tumor-specific antigens [1]. Due to the increasing use of ICIs in oncohaematology, immune-related adverse events (irAEs) associated with ICIs are rising correspondingly, which can involve any organ or tissue [2]. Some irAEs are severe and even fatal, limiting the use of ICIs. Rapid identification

and reasonable management of irAEs are important to ameliorate clinical outcomes and bring new challenges for oncology and other specialists.

ICI-associated liver toxicity is referred to as immune-mediated hepatitis (IMH) [3]. The incidences of IMH are 4–7% in patients with monotherapy and 37% in patients with the combination of anti-PD-1 and anti-CTLA-4 therapy [4–6]. In comparison with IMH, cholangitis induced by ICIs is rarely reported. In 2017, two different patterns of nivolumab-related cholangitis were reported for the first time [7,8]. In the case reported by Gelsominon *et al.*, interlobular bile ducts aggression, intraductal microabscesses and ductular proliferation were identified by liver biopsy, but there were no significant changes in intra- or extrahepatic bile duct by imaging [7,9]. The cases described by Kawakami *et al.* presented as dilation and hypertrophy of extrahepatic bile duct on imaging, while the pathology did not show any signs of interlobular bile duct injury [8]. Gelsominon referred to the former as ‘small-ducts cholangitis’ and the latter as ‘large-ducts cholangitis’ [9].

The terms used for cholangitis induced by ICIs are confused. Large-ducts cholangitis has often been termed as ‘sclerosing cholangitis’ and ‘secondary sclerosing cholangitis (SSC) [10–15]. Small-ducts cholangitis has been named ‘cholangitis liver disease’, ‘cholangiopathy’, ‘biliary injury’ and so on [7,16–19]. In order to correspond with IMH, ICIs-related cholangitis is referred to ‘immune-mediated cholangitis’ (IMC) in this review.

At present, there is limited knowledge about the clinical features of IMC induced by ICIs. This study reviewed

*European Journal of Gastroenterology & Hepatology* 2021, 33:e858–e867

**Keywords:** cholangitis, hepatitis, immune checkpoint inhibitors, immune-related adverse events

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**Received** 1 June 2021 **Accepted** 28 July 2021

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the published cases of IMC, with a focus on biochemical results, pathological characteristics, imaging features, treatment strategies and outcomes, to provide new insights into the diagnosis and therapy of IMC.

## Materials and methods

This review was carried out following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

### Eligibility criteria

We aimed to search for the case reports and case series of IMC induced by ICIs. The inclusion criteria were as followed: (1) case reports and case series of IMC induced by ICIs, (2) the diagnosis of cholangitis was determined by imaging or pathology and (3) the cases were published in English.

### Search strategies

We performed literature search by use of PubMed database, with the search strings as follow: ('immune checkpoint inhibitors'[All Fields] OR 'cytotoxic t lymphocyte-associated antigen 4'[All Fields] OR 'programmed cell death'[All Fields] OR 'immune-related adverse events'[All Fields]) AND ('cholangitis'[All Fields] OR 'cholangitides'[All Fields] OR 'cholangiopathy'[All Fields] OR 'biliary injury'[All Fields] OR 'cholestatic'[All Fields]). The final search was performed in February 2021. The reference lists of relevant cases were also searched.

### Study selection and data collection

All titles and abstracts were assessed for inclusion. Full texts of relevant articles were independently assessed by two reviewers. Disagreements were resolved by discussion. Data items extracted included country, patient demographics, primary cancer type, ICIs type, ICIs cycles until onset, classification of IMC, biochemical parameters, pathological and radiological findings, treatment of IMC and response to the treatment.

IMC was classified as three patterns, on the basis of the anatomy of the biliary system [20]. (1) Small-ducts type: the lesions were located at the intrahepatic small bile ducts, including septal ducts, interlobular ducts, ductules, and canal of Hering. (2) Large-ducts type: the lesions were located at the intrahepatic and extrahepatic large bile ducts, including segmental ducts, area ducts, the left and right hepatic duct, common hepatic duct and common bile duct. (3) Mixed type: both the small and larger bile ducts were involved.

The definition of the biochemical response was according to the Barcelona criteria of primary biliary cirrhosis (PBC) [21]. The completed response was defined as a normalization of alkaline phosphatase (ALP). The poor response was defined as a decrease of ALP <40%. The partial response was defined as a decrease of ALP ≥40%, but not to the normal level. For a few cases without detailed information of ALP level, it was considered as a partial response if the improvement of ALP was judged by the authors themselves.

### Statistics and analysis

Continuous variables were presented as median with range and compared using Mann–Whitney *U* test or

Kruskal–Wallis *H* test. Categorical variables were presented as a number with percentage and compared using Fisher's exact test or Chi-square tests. The two-tailed *P* value less than 0.05 was considered statistically significant.

## Results

### Retrieved results

The process of literature selection is shown in Fig. 1. Seventy-three articles were identified through the search from the PubMed database. An additional four articles were identified by browsing the reference lists of the selected articles. Thirty-seven articles were excluded by screening the titles and abstracts: 22 were nonrelevant, eight were reviews, four were commentaries and three were not published in English. Forty full-text articles were assessed for eligibility further. Two articles of pathology without primary clinical data were excluded. At last, 26 cases and 12 case series with a total of 53 patients from March 2017 to February 2021 were enrolled in this study.

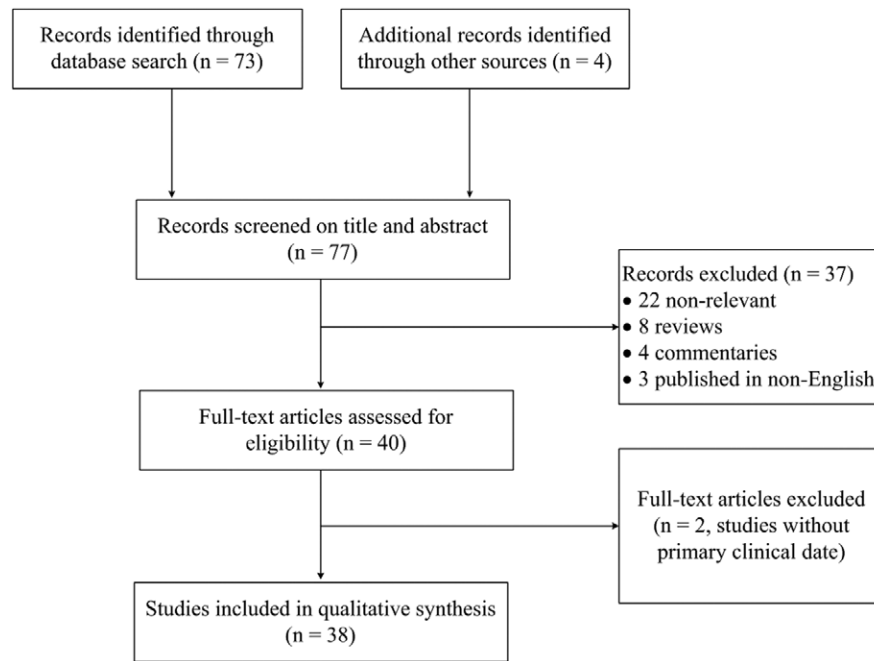
### General characteristics

A total of 53 cases of IMC induced by ICIs were included in this review, consisting of 12 with small-ducts type, 29 with large-ducts type and 12 with mixed type. There were 31 cases from Japan, five cases from the United Kingdom (UK), five cases from France, three cases from Switzerland, two cases from the USA and one case from Australia, Belgium, Canada, Italy, Korea, Norway and Turkey, respectively.

The characteristics of the enrolled cases are summarized in Table 1. There were 35 men and 18 women, with a median age of 68 years (range, 43–89). The most common primary diseases were lung cancer ( $n = 37$ ). Forty-seven patients received anti-PD-1 therapy, three received anti-PD-L1 therapy, once received anti-CTLA-4 therapy and two received the combination of anti-PD-1/PD-L1 and anti-CTLA-4 therapy. There were no reports of large-ducts cholangitis caused by anti-CTLA-4 monotherapy so far. There were no differences in sex, age, primary disease and ICIs type among the three patterns of IMC. The median numbers of ICIs cycles until IMC onset were five (range, 1–27). The earliest and latest onset time was 8 days and 2 years after the initiation of the ICIs therapy respectively [16,22]. The ICIs cycles until onset were different among the three patterns of IMC ( $P = 0.025$ ). Pairwise comparisons indicated that the ICI cycles in patients with large-ducts type were significantly longer than those in patients with small-ducts type (7 vs. 2.5;  $P = 0.027$ ). The mixed type had no significant difference in ICI cycles from large-ducts types or small-ducts type ( $P = 1.000$ ;  $P = 0.125$ ).

### Biochemical results

The values of ALP and alanine aminotransferase (ALT) were obtained in 37 cases at the same time. The median values of ALP and ALT were 1328 IU/L (range, 237–4635) and 156 IU/L (range, 31–1536) respectively. ALP level was different among the three patterns of IMC ( $P = 0.025$ ). Pairwise comparisons indicated that ALP in the patients with large-ducts type was higher than that with small-ducts type (1683 vs. 678 IU/L;  $P = 0.021$ ). The mixed type



**Fig. 1.** Flowchart for the selection of the cases of immune-mediated cholangitis induced by immune checkpoint inhibitors in this review.

had no significant difference in ALP level from large-ducts types or small-ducts type ( $P = 1.000$ ;  $P = 0.189$ ). There was no significant difference in ALT level among the three types.

### Pathological findings

Liver biopsies were performed in 30 cases, 24 of which had evidence of cholangiopathy. The pathological findings included portal inflammation ( $n = 21$ , 87.5%), bile duct injury ( $n = 24$ , 100%), ductular reaction ( $n = 13$ , 54.2%), bile duct loss ( $n = 4$ , 16.7%), cholestasis ( $n = 7$ , 29.2%) and lobular injury ( $n = 11$ , 45.8%). The biopsies of extrahepatic bile ducts were performed in nine cases. The pathology was characterized by inflammatory infiltration in the lining epithelium ( $n = 9$ , 100%) and noncentricular diffuse fibrosis ( $n = 3$ , 33.3%).

### Imaging findings

Twenty-nine cases of IMC with large-ducts type and 12 with mix type were diagnosed by imaging. The main findings were bile duct dilatation, stenosis and bile duct wall thickening and irregularity, which could be segmental or diffuse. Except for three cases without detailed information, the remaining 38 cases had abnormalities at different anatomical levels of bile ducts. Five cases were at the intrahepatic bile duct, 15 at the extrahepatic bile duct, and 18 at both intra- and extrahepatic bile duct. The patients with large-ducts type had a higher proportion of abnormality at extrahepatic bile duct (53.8 vs. 8.3%,  $P = 0.012$ ) and lower at intrahepatic bile duct (3.8 vs. 33.3%,  $P = .027$ ), concerning those with mixed cholangitis.

Positron-emission tomography-computed tomography (PET-CT) was performed in two cases, one of which had increased fluorodeoxyglucose (FDG) uptake in the gallbladder and bile ducts [14]. The other patient had a negative result, probably because PET-CT was carried out 6 weeks before the abnormality of liver function test (LFT)

[23]. Peroral cholangioscopy was performed in five cases. Band-like narrowing of the biliary tract wall was revealed in three cases, two of which were accompanied by diverticulum-like outpouching [13]. Ulcerative lesions with the ‘burned-out’ epithelium were detected in one case [24]. Multiple scarred lesions with hemorrhage and narrowing of second-order biliary branches were found in another case [25].

### Treatment strategies

The treatment strategies of IMC cases are shown in Table 2. ICIs were discontinued in all of the 53 cases. Five cases did not receive immunosuppression therapy. Two out of the five patients received ursodeoxycholic acid (UDCA) and two underwent biliary drainage. Forty-eight cases were treated with immunosuppression therapy, 32 with glucocorticoid (GC) monotherapy, 11 with GC and immunosuppressive agents, three with GC and immunomodulators, two with the combination of GC, immunosuppressive agents and immunomodulators. UDCA was used in 18 cases concurrently. Most patients were treated with (methyl)prednisone of 0.5–2 mg/kg/day, seven with high dose methylprednisolone of 500–1000 mg/day. The immunosuppressive agents used for the treatment of IMC were mycophenolate mofetil, azathioprine and tacrolimus. Immunomodulators included interleukin-6 receptor neutralizing antibody (tocilizumab) and plasmapheresis.

### Treatment outcomes

Of the five cases without immunosuppressive therapy, liver function tests (LFTs) returned to normal in one patient and got improved in three patients. The outcome was unavailable in the remaining one patient. For the cases with immunosuppressive therapy, the responses were evaluated from biochemical, imaging and histological aspects (Table 2).

**Table 1.** Clinical characteristics of the patients with IMC of three types induced by ICIs

Characteristics	All patients (n = 53)	Small-ducts type (n = 12)	Large-ducts type (n = 29)	Mixed type (n = 12)	P value
Sex, men (%)	35 (66.0%)	8 (66.7%)	17 (58.6%)	10 (83.3%)	0.318
Age, median (range, year)	68 (43–89)	64.5 (43–83)	68.5 (50–89)	67.5 (43–80)	0.704
Primary cancer type					0.068
Lung cancer	37	5	23	9	
Melanoma	7	4	2	1	
Gastric cancer	4	1	1	2	
Bladder cancer	2	0	2	0	
Other cancers	3	2	1	0	
ICIs type					0.577
Nivolumab	28	4	17	7	
Pembrolizumab	19	6	9	4	
Atezolizumab	2	1	1	0	
Avelumab	1	0	1	0	
Ipilimumab	1	1	0	0	
Nivolumab + Ipilimumab	1	0	0	1	
Durvalumab + tremelimumab	1	0	1	0	
ICIs cycles until onset, median (range)	5 (1–27)	2.5 (1–13)	7 (1–25)	5 (3–27)	0.025†; 0.027‡
Biochemical parameters					
ALP, median (range, IU/L)	1328 (237–4635)	678 (237–2837)	1683 (550–4635)	1652 (545–2427)	0.025†; 0.021‡
ALT, median (range, IU/L)	156 (31–1536)	217 (31–1536)	101 (45–516)	162 (68–331)	0.105
Pathological findings					
Small-ducts cholangitis	24	12	-	12	
Portal inflammation, n (%)	21 (87.5%)	10 (83.3%)	-	11 (91.7%)	1.000
Bile duct injury, n (%)	24 (100%)	12 (100%)	-	12 (100%)	-
Ductular reaction, n (%)	13 (54.2%)	5 (41.7%)	-	8 (66.7%)	0.401
Bile duct loss, n (%)	4 (16.7%)	3 (25%)	-	1 (8.3%)	0.590
Cholestasis, n (%)	7 (29.2%)	5 (41.7%)	-	2 (16.7%)	0.371
Large-ducts cholangitis	9	-	7	2	
Inflammatory infiltration	9 (100%)	-	7 (100%)	2 (100%)	-
Noncentricular diffuse fibrosis	3 (33.3%)	-	1 (14.3%)	2 (100%)	0.083
Imaging of large bile ducts	38	-	26	12	
Intrahepatic bile ducts	5 (13.2%)	-	1 (3.8%)	4 (33.3%)	0.027§
Extrahepatic bile duct	15 (39.5%)	-	14 (53.8%)	1 (8.3%)	0.012§
Intra- and extrahepatic bile duct	18 (47.4%)	-	11 (42.3%)	7 (58.3%)	0.489
Treatment					
Without immunosuppression therapy	5	0	5	0	-
GC monotherapy	32	6	18	8	-
GC + MMF	8	3	4	1	-
GC + AZA	2	0	1	1	-
GC + MMF + TAC	1	0	0	1	-
GC + TCZ	3	2	0	1	-
GC + MMF + TAC + TCZ	1	0	1	0	-
GC + MMF + plasmapheresis	1	1	0	0	-
UDCA	20	6	9	5	-
Response to immunosuppressive therapy					
Biochemical response	47	12	23	12	
Complete response	4 (8.5%)	1 (8.3%)	2 (8.7%)	1 (8.3%)	1.000
Partial response	33 (70.2%)	8 (66.7%)	18 (78.3%)	7 (58.3%)	0.505
Poor response	10 (21.3%)	3 (25%)	3 (13.0%)	4 (33.3%)	0.277
Imaging response	6	-	6	NA	
Improve / worsen	4/2	-	4/2	NA	-
Histological response	4	2	1	1	
Reduced inflammation	4	2	1	1	-
Progressive bile duct injury	2	2	0	0	-

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AZA, azathioprine; GC, glucocorticoid; ICIs, immune checkpoint inhibitors; IMC, immune-mediated cholangitis; MMF, mycophenolate mofetil; NA, unavailable; UDCA, ursodeoxycholic acid.

†P < 0.05 among the three types

‡P < 0.05 small-ducts type vs. large-ducts type

§P < 0.05 large-ducts type vs. mixed type.

### Biochemical response to immunosuppressive therapy

Apart from one case unable to obtain the treatment outcome, 8.5% (4/47) of the cases with immunosuppressive therapy had complete biochemical responses, 70.2% (33/47) had partial biochemical responses and 21.3% (10/47) had poor biochemical responses. There was no difference in the biochemical response among the three types of IMC ( $P = 0.656$ ). The follow-up time of LTFs could be estimated in 21 cases. The abnormality of biliary enzymes persisted for more than 3 months in nine cases and more than 6 months in another ten cases.

### Imaging response to immunosuppressive therapy

The imaging was reexamined in six cases with large-duct cholangitis, four of which ameliorated and two progressed. The reexamination time of the imaging ranged from 1.5 to 3 months.

### Histological response to immunosuppressive therapy

Liver biopsies were repeated in four cases. The amounts of inflammatory cells in portal tracts decreased in all four patients. While the bile duct injury in two cases was ongoing after 2–4 weeks of GC therapy.

**Table 2.** Treatment and response of the cases of IMC induced by ICIs

Case	References	IMC patterns	Location of abnormal imaging	Treatment	Biochemical response	Time for recovery of LTFs	Imaging response	Histology response
1	Gelsomino <i>et al.</i> [7]	Small-ducts type	-	PSL (1 mg/kg) + UDCA (15 mg/kg)	Partial	>3 months	-	-
2	Kawakami <i>et al.</i> [8]	Large-ducts type	EBD	PSL (0.5 mg/kg)	Partial	>3 months	-	-
3	Kawakami <i>et al.</i> [8]	Large-ducts type	EBD	PSL (0.5 mg/kg) + biliary drainage	Partial	>6 months	-	-
4	Kawakami <i>et al.</i> [8]	Large-ducts type	IEBD	Biliary drainage	-	NA	-	-
5	Yildirim <i>et al.</i> [62]	Small-duct type	-	PSL (2 mg/kg)	Partial	NA	-	-
6	Doherty <i>et al.</i> [16]	Small-duct type	-	PSL (1 mg/kg) + MMF (2g) + UDCA (NA)	Poor	-	-	-
7	Doherty <i>et al.</i> [16]	Small-duct type	-	PSL (1 mg/kg) + UDCA (NA)	Partial	>6 months	-	-
8	Doherty <i>et al.</i> [16]	Small-duct type	-	mPSL (2 mg/kg) + MMF (1g) + UDCA (NA)	Partial	>3 months	-	Reduced inflammation and progressive bile duct injury
9	Kashima <i>et al.</i> [26]	Large-ducts type	EBD	PSL (2 mg/kg) + biliary drainage	Partial	>3 months	Improve	-
10	Cho <i>et al.</i> [63]	Large-ducts type	EBD	mPSL (1 mg/kg)	Partial	NA	-	-
11	Kuraoka <i>et al.</i> [24]	Large-ducts type	EBD	PSL (60 mg) / mPSL (0.5g)	Poor	-	-	-
12	Hamoir <i>et al.</i> [17]	Mixed type	IBD	mPSL (0.5 mg/kg) + UDCA (10 mg/kg)	Complete	3 months	-	-
13	Noda-Narita <i>et al.</i> [12]	Large-ducts type	IEBD	UDCA (300 mg)	-	NA	Improve	-
14	Le Taillec <i>et al.</i> [64]	Large-ducts type	IEBD	GC (NA)	NA	NA	-	-
15	Oda <i>et al.</i> [57]	Small-ducts type	-	PSL (1 mg/kg) / mPSL (1g) + MMF (2g)	Poor	-	-	-
16	Ogawa <i>et al.</i> [10]	Large-ducts type	IEBD	-	-	<3 months	Improve	-
17	Kono <i>et al.</i> [11]	Large-ducts type	EBD	Biliary drainage	-	NA	-	-
18	Sawada <i>et al.</i> [30]	Mixed type	EBD	PSL (0.5 mg/kg) + UDCA (NA)	Partial	>3 months	-	-
19	Fouchard <i>et al.</i> [61]	Large-ducts type	NA	PSL (0.5 mg/kg) + UDCA (NA) + cholecystectomy	Partial	>6 months	-	-
20	Fouchard <i>et al.</i> [61]	Large-ducts type	NA	PSL (120 mg) + UDCA (NA) + cholecystectomy	Partial	>6 months	-	-
21	Fouchard <i>et al.</i> [61]	Large-ducts type	NA	PSL (1 mg/kg)	Complete	>6 months	-	-
22	Koya <i>et al.</i> [25]	Mixed type	IEBD	mPSL (0.5g) / PSL (1 mg/kg) + UDCA (900 mg) + biliary drainage	Poor	-	-	-
23	Çallıgüreanu <i>et al.</i> [23]	Mixed type	IEBD	PSL (1 mg/kg)	Partial	>6 months	-	-
24	Anderson <i>et al.</i> [65]	Mixed type	IEBD	PSL (50 mg) + MMF (NA) + TAC (NA)	Poor	-	-	-
25	Cheung <i>et al.</i> [28]	Large-ducts type	IBD	PSL (40 mg/kg) + UDCA (75 mg)	Partial	>3 months	-	-
26	Izumi <i>et al.</i> [66]	Large-ducts type	EBD	mPSL (2 mg/kg) + MMF (2g)	Partial	NA	-	-
27	Izumi <i>et al.</i> [66]	Large-ducts type	EBD	mPSL (2 mg/kg) + MMF (2g)	Partial	NA	-	-
28	Izumi <i>et al.</i> [66]	Large-ducts type	EBD	mPSL (2 mg/kg)	Partial	NA	-	-
29	Onoyama <i>et al.</i> [13]	Large-ducts type	EBD	PSL (1 mg/kg) + UDCA (600 mg)	Partial	NA	-	-
30	Onoyama <i>et al.</i> [13]	Large-ducts type	EBD	UDCA (600 mg)	-	NA	-	-
31	Onoyama <i>et al.</i> [13]	Large-ducts type	EBD	PSL (1 mg/kg) + UDCA (600 mg)	Partial	NA	-	-
32	Reddy <i>et al.</i> [67]	Large-ducts type	IEBD	PSL (0.85 mg/kg) + MMF (2g) + TAC (2 mg) + TCZ (4 mg/kg) + UDCA (1500 mg)	Poor	-	Worsen	-
33	Williams <i>et al.</i> [22]	Large-ducts type	IEBD	GC (NA)	Complete	>3 months	-	-
34	Kurokawa <i>et al.</i> [19]	Small-ducts type	-	PSL (1 mg/kg) + UDCA (900 mg)	Partial	>3 months	-	-
35	Imoto <i>et al.</i> [68]	Mixed type	IEBD	mPSL (1g) / PSL (0.6 mg/kg) + UDCA (600 mg)	Partial	NA	-	-
36	Onoyama <i>et al.</i> [69]	Large-ducts type	IEBD	mPSL (2 mg/kg) + MMF (2g)	Partial	NA	-	-
37	Onoyama <i>et al.</i> [69]	Large-ducts type	EBD	mPSL (2 mg/kg) + MMF (2g) + biliary drainage	Partial	NA	-	-
38	Onoyama <i>et al.</i> [69]	Large-ducts type	EBD	mPSL (1.6 mg/kg)	Partial	NA	-	-
39	Zen <i>et al.</i> [32]	Mixed type	IEBD	PSL (50 mg)	Partial	NA	-	-
40	Zen <i>et al.</i> [32]	Mixed type	IEBD	PSL (40 mg)	Poor	NA	-	-
41	Zhang <i>et al.</i> [70]	Small-ducts type	-	GC (NA)	Partial	NA	-	-

(Continued)

Table 2. (Continued)

Case	References	IMC patterns	Location of abnormal imaging	Treatment	Biochemical response	Time for recovery of LTFs	Imaging response	Histology response
42	Thorsteinsdottir et al. [18]	Small-ducts type	-	PSL (120 mg) + MMF (2g) + plasmapheresis	Poor	NA	-	-
43	Mizuno et al. [27]	Large-ducts type	IEBD	PSL (40 mg)	Poor	NA	Worsen	-
44	Matsumoto et al. [14]	Large-ducts type	IEBD	PSL (80 mg)/mPSL (1 g) + AZA (50 mg)	Partial	NA	Improve	-
45	Ooi et al. [58]	Mixed type	IBD	PSL (40 mg)/mPSL (1 g) + AZA (50 mg)	Partial	>6 months	-	Reduced inflammation and progressive bile duct injury
46	McClure et al. [34]	Mixed type	IBD	PSL (50 mg)	Partial	>6 months	-	-
47	Yoshikawa et al. [71]	Mixed type	IEBD	PSL (1–1.5 mg/kg) + UDCA (600 mg) + MMF (2g)	Poor	NA	-	-
48	Fuji et al. [72]	Large-ducts type	IEBD	PSL (30 mg)	Partial	>3 months	Improve	-
49	Sato et al. [15]	Large-ducts type	IEBD	mPSL (30 mg) + UDCA (300 mg)	Partial	>6 months	Improve	Reduced inflammation
50	Moi et al. [35]	Small-ducts type	-	mPSL (125 mg)/mPSL (0.5g) + TCZ (500 mg)	Complete	<3 months	-	Reduced inflammation
51	Moi et al. [35]	Mixed type	IBD	mPSL (62.5–125 mg) + TCZ (500 mg)	Partial	NA	-	-
52	Moi et al. [35]	Small-ducts type	-	mPSL (125 mg) + TCZ (500 mg)	Partial	NA	-	-
53	Nabeshima et al. [36]	Small-ducts type	-	PSL (0.5 mg/kg) + UDCA (NA)	Partial	>6 months	-	-

AZA, azathioprine; EBD, extrahepatic bile duct; IBD, intrahepatic bile duct; ICIs, immune checkpoint inhibitors; IEBCD, intra- and extrahepatic bile duct; IMC, immune-mediated cholangitis; MMF, mycophenolate mofetil; mPSL, methylprednisolone; NA, unavailable; PSL, prednisone; TCZ, tacrolimus; UDCA, ursodeoxycholic acid.

Discussion

Epidemiology

IMC has been recently perceived as an uncommon form of irAEs. To date, the limited data indicate the incidence of IMC with large-ducts type was between 0.05 and 0.7% [26–28]. In a retrospective study during 2011–2018 in the UK, 0.2% (1/453) of the patients receiving immunotherapy for cancer was found with stricture and ectasia of the bile duct [28]. In a real world study during 2014–2019 in Japan, nonobstructive biliary duct dilation was reported in 0.7% (4/546) of the patients treated with ICIs [27]. According to the postmarketing surveillance of nivolumab during 2014–2017 in Japan, ten cases of sclerosing cholangitis were reported, with an incidence of 0.05% [26]. The incidence of IMC with small-ducts type is still unknown and likely to be underestimated because its diagnosis depends on liver biopsy. In the retrospective pathological study of 60 patients treated with ICIs who underwent liver biopsy attributable to abnormal LTFs from 2014 to 2018 in Boston, 16 (27%) patients had a predominantly cholangitic pattern. Twelve (20%) patients confirmed with the presentation of IMC with small-ducts type, 4 (6.7%) patients coincided with that of mixed type entailing large and small bile ducts simultaneously [29]. In our review, a total of 54 cases of IMC were identified from March 2017 to February 2021, comprised of 12 cases with small-ducts type, 29 with large-ducts type and 12 with mixed type. More than half of the cases came from Japan, which perhaps related to the fact that the Japanese scholars paid more attention to IMC. As early as 2017, the Ministry of health, welfare and labor of Japan had already called for more researches on nivolumab-related cholangitis [30]. Hepatologists and oncologists in all countries should pay more attention to IMC induced by ICIs.

Biochemical presentations

The common biochemical feature of IMC was a significant elevation of biliary enzymes relative to hepatic enzymes. Our study showed that the later onset time and higher ALP level were found in the patients with large-ducts cholangitis, as compared to those with small-ducts cholangitis. This was consistent with Hafsteinn O’s research on SSC in patients with drug-induced liver injury (DILI) [31]. In their study, ten out of 102 unselected DILI patients had ductal stricture, irregularity and dilatation on MRCP, conforming to the features of SSC. The SSC group had higher ALP than the patients with the cholestatic pattern.

Histopathologic characteristics

Pathologists and hepatologists are needed to be familiar with the histopathologic characteristics of IMC, which helps to make a timely pathological diagnosis and appropriate treatment decision. Generally, pathological findings of IMC were nonspecific and similar to the biliary injury in DILI. The pathological findings of small-ducts cholangitis were: (1) portal inflammation. Mixed inflammatory cells were mainly composed of lymphocytes with casual neutrophils, eosinophils, macrophages. A predominance of CD8+ T cell infiltration is a characteristic of IMC, which is verified by Zen’s research and coincides with IMH [32,33]. Moreover, Zen et al. compared the ratio of CD8+/CD4+ T

cells among IMH, IMC, autoimmune hepatitis (AIH) and heterogeneous DILI. The results showed that the ration of CD8<sup>+</sup>/CD4<sup>+</sup> T cells in the IMH/IMC group was  $12.2 \pm 5.1$ , which was much higher than that of the AIH group ( $2.7 \pm 1.1$ ) and DILI group ( $5.0 \pm 1.1$ ) [32]. (2) Small bile duct injuries, such as irregularity of bile duct epithelium, cytoplasmic vacuolization, degeneration of ducts, intraepithelial lymphocytes infiltration, periductal lymphocytes infiltration and periductal fibrosis. Florid duct lesions ( $n = 4$ ) [23,32,34,35] and concentric periductal fibrosis ( $n = 2$ ) [16,36] were found in some cases, which are similar to the characteristics of PBC and PSC respectively. (3) Ductular reaction. Proliferative ductules were often located in the periportal areas, which was a repair response to the bile ducts injury. (4) Bile duct loss, a less common pathological finding in DILI. The Drug-Induced Liver Injury Network reported that 7% of the patients with DILI had different extents of bile duct loss [37]. In our review, bile duct loss was found in four cases, one of which had only one small bile duct left and was diagnosed as vanishing bile duct syndrome. To date, only six cases of VBDS related to ICIs were recorded in the US FDA Adverse Event Reporting System [38]. There are two different outcomes of bile duct loss, decided by the balance between biliary apoptosis and regeneration [39]. The one is progressive, irreversible loss leads to biliary cirrhosis and liver failure. The other is the bile ducts regenerate and recover over months to years [39]. The prognosis of drug-induced bile duct loss is slightly better than that of other causes [39,40]. In our review, two of the four patients with bile duct loss had poor outcomes, two improved gradually. (5) Cholestasis and lobular injury. Approximately half of the patients were complicated with various levels of lobular inflammation, necrosis and cholestasis.

The histopathological features of large-ducts cholangitis were inflammatory infiltration in the lining epithelium and noncentricular diffuse fibrosis of the extrahepatic bile duct. Zen *et al.* reported an interesting IMC case with mixed pattern induced by pembrolizumab [32]. Its intrahepatic duct injury was similar to PBC, with dense infiltration of inflammatory cells around the septal bile duct and a borderline granulomatous change. The pathology of the extrahepatic duct resembled those of IgG4-related cholangitis, with an extensive inflammatory infiltrate in the fibrotic duct wall. However, IgG4-positive plasma cells are <10/high power field.

### Imaging findings

Imaging examination is crucial for the diagnosis and differential diagnosis of IMC. Physicians should know the optimal imaging modality for the detection of IMC and be acquainted with the imaging features of IMC. The imaging findings of intrahepatic and extrahepatic large-ducts cholangitis were comprised of three aspects. (1) Nonobstructive dilatation, or stenosis of bile duct lumen, which could be segmental or diffuse. (2) Enhancement, hypertrophy, and irregularity of bile duct walls. (3) Changes of the adjacent structure, such as gallbladder edema, gallbladder wall thickening and Gleason's sheath edema. The typical imaging of IMC can be obtained in Fig. 1 in Ogawa *et al.*'s work [10]. Multiple imaging modalities had been used for the diagnosis and evaluation of the large-ducts type

of IMC [41,42]. Ultrasound is dependent on the operator and less sensitive for the lesions of the distal common bile duct. The normal presence of bile ducts on ultrasound does not completely exclude biliary obstruction [43]. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiography (ERCP) provide an overview of the biliary tree and assess the morphological changes of the ductal system sensitively, such as luminal dilatation, stricture and irregularity. Both contrast-enhanced MRI and computed tomography (CT) scans are useful in the evaluation of the bile duct walls, peribiliary or periportal masses and hepatic and pancreatic parenchymal diseases, while MRI had higher soft-tissue contrast resolution than CT. Contrast-enhanced MRI with MRCP is verified to offer the most comprehensive evaluation of biliary stricture [44]. Anderson *et al.* also suggested contrast-enhanced MRI with MRCP would be the optimal imaging modality for the detection of IMC [41]. Accumulation of FDG may be noted on PET-CT, even before the symptom appears [42]. Cholangioscopy can observe the lesions of the bile duct and take a biopsy under direct vision. Besides, imaging plays an important role in excluding other biliary diseases, such as stones and tumors.

### Differential diagnosis

IMC needs to be differentiated carefully from other causes of intrahepatic cholestasis and extrahepatic biliary obstruction, for instance, autoimmune cholangitis (PBC, PSC and IgG4-related cholangitis), malignant disorders, infections and other drug-induced biliary lesions [45,46]. In general, autoimmune cholangitis can be excluded on the basis of past history, past biochemical and imaging tests and negative immunological markers, including antinuclear antibodies, antimitochondrial antibody, antineutrophil cytoplasmic antibodies and IgG4 [45,46]. In clinical practice, it is more difficult to differentiate IMC from malignant diseases and chemotherapy and targeted therapy-induced biliary lesions. In a recent study on the hepatobiliary irAEs, ten out of 16 patients with a cholangitic pattern had competing causes for the biochemical abnormality, including primary disease progression in the liver, concomitant chemotherapy, other drugs and sepsis [29].

It should be noted that periductal-infiltrating cholangiocarcinoma and metastasis grow along the bile ducts, whose imaging manifestation mimics that of IMC [47]. The MRI findings of the periductal-infiltrating tumor were irregular narrowing of the involved bile duct, with and without a visible thickened wall, and dilation of the proximal bile duct. Sometimes, even CT scans are difficult to depict the periductal tumor mass [48]. We need to pay more attention to gastrointestinal cancers, which metastasize to the biliary tract most frequently [48,49]. Especially when the response to steroids of IMC is poor, we must re-review the imaging and carry out biopsies to exclude infiltrating cancers as far as possible.

Besides, although very rare, SSC induced by taxane drugs (paclitaxel, docetaxel and nab-paclitaxel) and bevacizumab have been reported, with similar biochemical and imaging findings with that of large-ducts type of IMC [50–54]. Taxol is mainly excreted through bile ducts,

and it was hypothesized that the increase of taxol concentration resulted in biliary injury [52]. Bevacizumab is supposed to induce a hypercoagulative condition and promote thrombosis of microvessels supplying biliary ducts, leading to bile duct ischemia [50]. In our review, ICIs were not concurrently combined with chemotherapy in any patients. However, 11 patients received paclitaxel ( $n = 9$ ) and bevacizumab ( $n = 3$ ) before or after the use of ICIs. It is not clear whether paclitaxel and bevacizumab had participated in the injuries of bile ducts.

Furthermore, we need to keep in mind that sepsis, a common complication of immunosuppression therapy, is another cause of intrahepatic cholestasis [45]. If ALP or bilirubin rebounds in the process of steroids therapy for IMC, we need to exclude sepsis carefully, rather than increasing the dosage of steroids or initiate additional immunosuppressants immediately. In this review, one patient died due to sepsis [27].

### Management

According to the guidelines of management of irAEs published by multiple scientific societies, GC is recommended for the treatment of high-grade irAEs [2,55]. Most cases of IMH are sensitive to GCs and resolve within 6–12 weeks [3]. However, GC seems to be less effective for the treatment of IMC, in contrast to that of IMH. In this review, the treatment response of IMC has two characteristics: (1) biliary enzymes can decrease to varying degrees in the majority of patients by GC therapy, but are hard to drop to normal; (2) biliary enzymes need an extended time to recover. In this study, the biliary enzymes were not normalized even after 18 months of followed-up in a patient [34]. This situation was consistent with bile duct injury caused by other drugs. In Wang's research on DILI, the recuperation time of LFTs in groups with bile duct damage was 3–4 months, regardless of the severity of hepatocyte injury [56]. Gudnason's research indicated that patients with SSC induced by the drug had a longer time to resolution of the raise of LFTs [31]. The abnormal LFTs of SCC resolved within 3–6 months in five patients and more than 6 months in three patients. The longest time to resolution was 820 days [31]. Unfortunately, patients with IMC usually have limited survival time because of advanced cancer. Persistent abnormal LFTs probably lead to the loss of the opportunity for further antitumor therapy, which promotes the progression of cancer. Five patients died from progressive primary diseases in this study, rather than irAEs [7,16,36,57].

The results of the second liver biopsy might give us some enlightenment about the therapeutic strategy of IMC. The amounts of inflammatory cells in portal tracts reduced in all four cases that underwent repeated liver biopsy. It suggested that GC was beneficial for reducing inflammatory infiltration, thereby preventing further immune injury mediated by inflammatory cells. Nevertheless, the bile duct injury was still in progress in two cases after 2–4 weeks of GC therapy. We hypothesized that the bile duct lesions of IMC need to be repaired by regeneration for a long time, on the basis of the previous experience of bile duct injury in patients with DILI mentioned above [31,56]. On the basis of real-world experience of IMH from the UK, prednisolone higher than 60 mg/day has not demonstrated any

additional benefit regarding time to hepatitis resolution [28]. Therefore, if no inflammation remains in a repeated biopsy, tapering of GC is recommended [58].

UDCA may be a potential choice for the treatment of IMC. UDCA is increasingly used for the treatment of cholestatic liver diseases, for its cytoprotective, antiapoptotic and immunomodulatory effects. It can reduce bile toxicity by removing hydrophobic biliary acids and stimulate biliary secretion of bile acids and other organic anions [19,59]. It also has immunomodulatory properties by inhibiting the release of cytokines and suppressing the overexpression of MHC antigens [19,60]. Twenty patients receiving the treatment of UDCA in this review. After the withdrawal of GCs in some patients, UDCA was continued to use for a long term, the decline of ALP was still going on [15,61]. Unlike GC, UDCA is safe, well-tolerated and appropriate for long-term application. Hence, GC combined with UDCA is possibly a reasonable therapeutic strategy for IMC. The application of GC in the early stage is to control the inflammation induced by ICIs. UDCA is used for the long term to foster the recuperation of bile ducts. More clinical trials are needed to verify this strategy.

### Limitations

The limitations of this study were as follows: (1) this study was on the basis of case reports and case series, which were retrospective observational studies with relatively low quality of evidence. Basic researches and prospective controlled clinical studies are required to delineate the molecular mechanisms of IMC and evaluate the efficacy of GC and UDCA for the treatment of IMC. (2) Some cases did not provide complete medical records, such as the values of LFTs, imaging information, dosage and course of GCs, the degree of improvement of LFTs and the time to resolution of abnormal LFTs.

In conclusion, ICIs-associated IMC can involve the entire biliary system. The patients with the large-ducts type of IMC have a later onset time and higher ALP level than the patients with the small-ducts type of IMC. Most IMC cases respond partially to immunosuppression. It takes a long time for IMC to resolution. Awareness of the clinical features and management of IMC is crucial for oncologists and hepatologists, as the use of ICIs is rapidly increasing.

### Acknowledgements

This work is supported by the Zhejiang Provincial Natural Science Foundation of China under Grant No.LY21H030011.

### Conflicts of interest

There are no conflicts of interest.

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