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GUIDELINES

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Diagnostic guide for immune checkpoint inhibitor-induced liver injury

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Abstract

With the widespread use of immune checkpoint inhibitors (ICIs), liver injury (ICI-induced liver injury) as an immune-related adverse event has become a major concern in clinical practice. Because severe cases of liver injury require administration of corticosteroids, a comprehensive evaluation is crucial, including clinical course, blood and imaging tests, and if necessary, pathological examination through liver biopsy. As with liver injury induced by other drugs, classification of injury type by *R*-value is useful in deciding treatment strategies for ICI-induced liver injury. Histologically, the most representative feature is an acute hepatitis-like hepatocellular injury,

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; CMV, cytomegalovirus; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T lymphocyte antigen 4; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; ESMO, European Society for Medical Oncology; GGT, gamma-glutamyltransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; irSC, immune-related sclerosing cholangitis; JDDW, Japan Digestive Disease Week; JSMO, Japanese Society of Medical Oncology; MASLD, metabolic dysfunction-associated steatotic liver disease; MMF, mycophenolate mofetil; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PD-1, programmed cell death 1; PD-L1, programmed cell death-ligand-1; PSC, primary sclerosing cholangitis; PSL, prednisolone; T.Bil, total bilirubin; ULN, upper limit of normal.

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characterized by diffuse lobular inflammation accompanied by CD8-positive T lymphocytes. Another condition that can cause liver injury during ICI treatment is cholangitis accompanied by non-obstructive bile duct dilatation and bile duct wall thickening. Many cases of ICI-induced cholangitis are classified as non-hepatocellular injury type, and they have been reported to respond poorly to corticosteroids. It is essential that gastroenterologists/hepatologists and doctors in various departments work in cooperation to develop a system that achieves early diagnosis and appropriate treatment of ICI-induced liver injury.

KEYWORDS
cholangitis, drug-induced liver injury, immune checkpoint inhibitors, immune-related adverse events, liver injury

INTRODUCTION

In Japan, immune checkpoint inhibitors (ICIs) have been used for the treatment of various cancer types, including digestive cancers, since nivolumab, an anti-programmed cell death-1 (PD-1) antibody drug that serves as an ICI, received pharmaceutical approval and insurance coverage for the treatment of radically unresectable malignant melanoma in 2014. Conversely, the incidence of liver injury, one of ICI-induced immune-related adverse events (irAEs), has been increasing, and many gastroenterologists have difficulty in its diagnosis and treatment. A revised proposal for a new scoring system for predicting the diagnosis of drug-induced liver injury (DILI; RECAM-J 2023) was presented at the workshop "Toward the Revision of Diagnostic Criteria for DILI" (Chairpersons: Nobuyuki Enomoto and Atsushi Tanaka) at the Japan Digestive Disease Week 2023 held in November 2023. However, this scoring system cannot be easily applied to ICI-induced liver injury, unlike those induced by other drugs, leading to the need for developing a new diagnostic guide. Guidelines for irAEs have previously been developed by various academic societies, such as the American Society of Clinical Oncology,[1] the European Society for Medical Oncology,[2] and the Japanese Society of Medical Oncology[3]; however, they were created primarily for doctors who use ICIs in general, with no detailed description of diagnostic criteria. For these reasons, we created the present diagnostic guide to provide more specialized content for gastroenterologists and hepatologists who are consulted by doctors in other fields regarding ICI-induced liver injury. The diagnosis of ICI-induced liver injury, as with other DILIs, is based on the exclusion of other liver diseases that may cause liver injury. With the cooperation of experts in various fields, the present diagnostic guide was created to clarify the test items required for the diagnosis of ICI-induced liver injury, as well as the usefulness and limitations of pathological examination by liver biopsy. This guide also focuses on ICI-induced cholangitis, which has become an issue in recent years. Furthermore, we created the guide by revising the original draft based on public comments solicited on the websites of the Japanese Society of Gastroenterology and the Japan Society of Hepatology. In addition, various names of liver injury as an ICI-induced irAE have been used in previous reports, including irAE liver injury, ICI-associated hepatotoxicity, ICI-induced liver injury, and ICI-induced immune-mediated hepatotoxicity, but we used the term "ICI-induced liver injury," which was used in the cancer immunotherapy guidelines previously published in Japan. We hope that the present diagnostic guide will be useful not only for gastroenterologists and hepatologists who diagnose and treat ICI-induced liver injury, but also for all doctors, including medical oncologists, pathologists, and radiologists, and that the guide will lead to improved prognosis for patients undergoing ICI treatment.

Concept

The immune checkpoint is a negative feedback mechanism that suppresses inappropriate and excessive immune responses to self. Cancer cells utilize immune checkpoint molecules (co-inhibitory molecules) expressed on T cells, which play an important role in antitumor immune responses, to evade host immune surveillance and proliferate.[4]

ICIs are the drugs that inhibit the transmission of immunosuppressive signals by binding to inhibitory receptors or their ligands expressed on immune cells, such as effector T cells, reactivating antitumor immune responses mediated by T cells.[5] Although ICIs are expected to have high therapeutic effects, they are sometimes associated with characteristic irAEs that are not observed with conventional cytotoxic anticancer drugs or molecular target agents, and the management of such irAEs has become an important issue.

One of the mechanisms underlying the occurrence of irAEs is thought to be the activation of autoantigen-specific T cells owing to ICI administration, resulting in the destruction of one's own cells and tissues. In particular, an irAE can occur in any part of the body, as major histocompatibility complex class I molecules involved in antigen recognition by CD8-positive T cells, which are central to cancer immune responses, are expressed throughout the body.[6] Although the detailed mechanism of the onset of ICI-induced liver injury remains unclear, it is thought to involve genetic factors, in addition to intrahepatic infiltration of CD8-positive T cells and inflammatory macrophages activated by ICIs.[7] In the *Manual for Handling Disorders*

Due to Adverse Drug Reactions (version revised in 2019) regarding liver injury published by the Ministry of Health, Labor and Welfare, DILIs are classified into general (toxic and idiosyncratic) and specific types, and ICI-induced liver injury falls under the specific type.[8]

The incidence of ICI-induced liver injury has been reported to be 1%–10% for monotherapy with anti-PD-1/programmed cell death-ligand-1 (PD-L1) antibody drugs and 1%–15% for monotherapy with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody drugs. Furthermore, the incidence has been reported to increase to 3%–30% when using combination therapy of anti-PD-1/PD-L1 antibody drugs and anti-CTLA-4 antibody drugs.[9–13] Additionally, the timing of high incidence of liver injury differs depending on the drug; liver injury in monotherapy with anti-PD-1/PD-L1 antibody drugs occurs 6–14 weeks after the start of administration, whereas liver injury is known to occur even earlier and become more severe in combination therapy with anti-CTLA-4 antibody drugs.[14,15] Furthermore, the timing of its onset varies among individuals, with some patients developing liver injury approximately 1 year after the first administration, and thus, strict management is required even after the completion of ICI administration.[16]

Previously reported risk factors for developing ICI-induced liver injury include use of anti-CTLA-4 antibody drugs, development of irAEs in other organs, sex, fever after ICI administration, complications with autoimmune liver diseases, and type of malignant tumors, but further investigation is needed.[16–20]

When diagnosing ICI-induced liver injury, it is important to first exclude diseases that may cause liver injury other than irAEs, as with other drug-induced liver injuries, and to evaluate the pattern and severity of the injury. A liver biopsy is useful in confirming the diagnosis, determining the presence or absence of comorbid liver disease, and evaluating the severity. Lymphocyte infiltration, aggregation of macrophages (focal necrosis), granuloma formation, and vascular endothelial injury have been reported as its histological findings. Additionally, positive immunostaining of CD3/CD8 in infiltrating inflammatory cells can aid in its diagnosis.[21,22]

Meanwhile, when treating liver injury with predominantly elevated biliary enzymes, it is important to consider the possibility of cholangitis caused by ICI administration and to perform imaging tests, such as contrast-enhanced computed tomography and magnetic resonance cholangiopancreatography.

The severity of adverse events is graded using the Common Terminology Criteria for Adverse Events version 5.0 (Table 1), and measures are taken according to the grade. Administration of corticosteroids is considered for grade 2 with persistent liver injury, as well as grade 3 or higher. However, it is necessary to evaluate the hepatic reserve capacity with reference to serum bilirubin levels and prothrombin time, and to administer corticosteroids at an appropriate time, especially in cases of hepatocellular injury type. Additionally, combined use of mycophenolate mofetil (not covered by insurance) is considered for patients showing resistance to steroid treatment.

Diagnosis

As many patients with ICI-induced liver injury do not present with characteristic clinical symptoms, hepatobiliary enzymes need to be regularly monitored when administering ICIs. Upon observation of abnormal values in hepatobiliary enzymes, liver diseases other than ICI-induced liver injury are excluded by performing tests including the following: hepatitis virus-related markers, autoantibodies (such as antinuclear antibodies and antimitochondrial antibodies), thyroid function, muscle-related enzymes, cardiac function, and abdominal imaging tests. Furthermore, there have been reports of the risk of hepatitis B virus reactivation, which requires attention (See Hepatitis B Treatment Guidelines, edited by the Japan Society of Hepatology[23]) Figure 1.

【Conditions for suspecting ICI-induced liver injury】

1. The patient has a history of ICI administration.
2. Liver injury from other causes has been ruled out through blood and imaging tests.
3. Histological findings consistent with ICI-induced liver injury are observed.

TABLE 1 Severity classification of immune checkpoint inhibitor-induced liver injury.

	Baseline	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AST	Within standard range	>1.0–3.0 × ULN	>3.0–5.0 × ULN	>5.0–20 × ULN	>20 × ULN	-
ALT	Abnormal value	1.5–3 × baseline	>3.0–5.0 × baseline	>5.0–20 × baseline	>20 × baseline	
T.Bil	Within standard range	>1.0–1.5 × ULN	>1.5–3.0 × ULN	>3.0–10 × ULN	>10 × ULN	
	Abnormal value	1.0–1.5 × baseline	>1.5–3.0 × baseline	>3.0–10 × baseline	>10 × baseline	
ALP	Within standard range	>1.0–2.5 × ULN	>2.5–5.0 × ULN	>5.0–20 × ULN	>20 × ULN	
	Abnormal value	2.0–2.5 × baseline	>2.5–5.0 × baseline	>5.0–20 × baseline	>20 × baseline	
GGT	Within standard range	>1.0–2.5 × ULN	>2.5–5.0 × ULN	>5.0–20 × ULN	>20 × ULN	
	Abnormal value	2.0–2.5 × baseline	>2.5–5.0 × baseline	>5.0–20 × baseline	>20 × baseline	

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; T.Bil, total bilirubin; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

Source: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

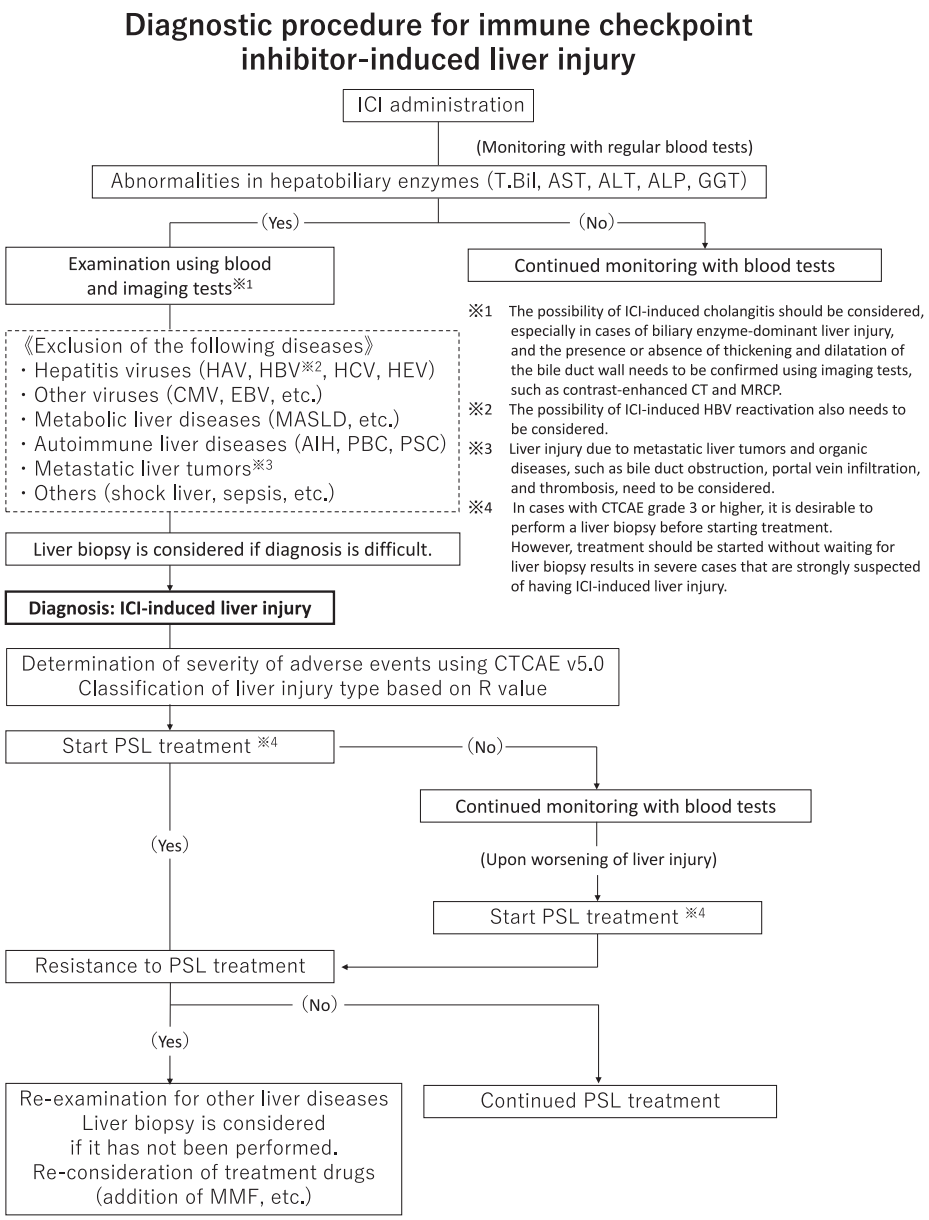

FIGURE 1 Diagnostic procedure for liver injury induced by immune checkpoint inhibitors. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EBV, Epstein–Barr virus; GGT, gamma-glutamyltransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; ICI, immune checkpoint inhibitor; MASLD, metabolic dysfunction-associated steatotic liver disease; MMF, mycophenolate mofetil; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PSL, prednisolone; T.Bil, total bilirubin.

(Reference findings)

a. A preceding or concurrent irAE in other organs is present.
b. Corticosteroid administration shows a therapeutic effect.

【Differential diagnosis】

- Conditions including the following are excluded through the clinical course, and blood and imaging tests: hepatitis viruses (hepatitis A virus, hepatitis B virus, hepatitis C virus, and hepatitis E virus), cytomegalovirus, Epstein–Barr virus, alcohol, drugs other than ICIs that may cause liver injury (including supplements and health foods), fatty liver, autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis), and shock liver.
- Liver injury due to the appearance of metastatic liver tumors or enlargement of existing lesions, as well as organic diseases, such as bile duct obstruction and the presence of infiltration/thrombosis

of the portal vein, are excluded using imaging tests. It is important to be aware that metastatic liver tumors may diffusely infiltrate in the form of small tumor masses within the sinusoids, and present with hepatomegaly and liver injury without forming a mass in image diagnosis.

Notes:

1. Because the response rate of corticosteroids for ICI-induced liver injury differs depending on the type of liver injury,[24] the *R*-value should be used to classify liver injury at the time of diagnosis. Briefly, corticosteroids respond well to the hepatocellular injury type; however, some of the non-hepatocellular types (i.e., cholestasis and mixed) are corticosteroid-resistant.

   R-value = (ALT / ULN) / (ALP / ULN)[25]
   $R \geq 5$: Hepatocellular
   $2 < R < 5$: Mixed
   $R \leq 2$: Cholestatic (ULN: upper limit of normal in each facility)

2. If patients with a severe case of liver injury with poor general conditions are strongly suspected of having ICI-induced liver injury based on the disease course, it is desirable to proceed with the differential diagnosis and simultaneously consider early initiation of corticosteroid treatment. Even if a liver biopsy has been performed, especially in severe cases, it is important to start treatment at an appropriate time without waiting for the results of the pathological diagnosis.
3. If no clinical improvement is observed after starting corticosteroid treatment without a liver biopsy, it is desirable to again conduct a thorough examination for other liver diseases and, if possible, to perform a liver biopsy.

Pathological findings

The most representative pathological feature of ICI-induced liver injury is acute hepatitis-like hepatocellular damage, characterized by necroinflammation and lymphocytic infiltration (Figure 2). Unlike autoimmune hepatitis, ICI-induced liver injury often shows inconspicuous plasma cells.[26] Because eosinophils are also prominent in approximately 20% of the cases, it is important to differentiate ICI-induced liver injury from normal DILIs. The sinusoids show prominent granulomatous inflammation due to infiltration and aggregation of histiocytes, in addition to Kupffer cell enlargement. Cases with portal inflammation also show vascular endotheliitis similar to acute cellular rejection after transplantation, and often present with findings of bile duct injury. The image of cholangiopathy is that of bile duct injury associated with hepatitis changes (hepatitis-associated bile duct injury).

The histological patterns of lobulitis are further classified into panlobular hepatitis type, isolated central zonal necrosis type, and granulomatous hepatitis type.[27,28] The panlobular hepatitis type is the most common pattern of ICI-induced liver injury, but it needs to be differentiated from classical DILIs. Moreover, some patients show only a non-specific lobular necroinflammatory reaction. In contrast, the isolated central zonal necrosis type raises an issue in its differentiation from acute-onset autoimmune hepatitis, in addition to classical DILIs. The granulomatous hepatitis type presents with a characteristic histological image, but it needs to be differentiated from the granulomatous hepatitis that occurs after bacillus Calmette–Guérin therapy for bladder cancer. Additionally, because limited lobulitis can also be found in cases where only portal region inflammation is prominent or cases that show only fatty degeneration, a comprehensive judgment that includes not only pathological findings, but also physical findings, such as blood test data and body mass index, is ultimately important in confirming the diagnosis.

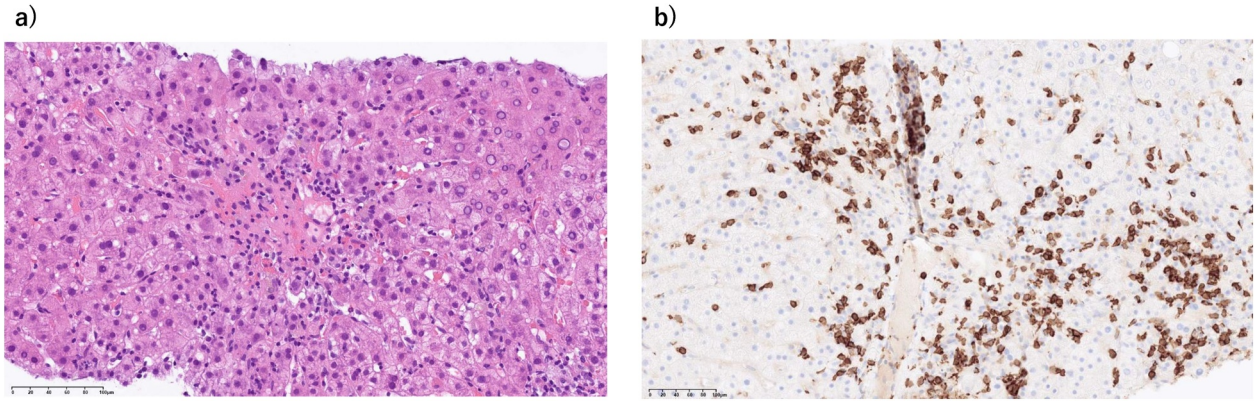

FIGURE 2 Typical hepatic pathological findings in liver injury induced by immune checkpoint inhibitors. (a) Hematoxylin–eosin staining. (b) CD8 immunostaining. Liver tissue collected through liver biopsy on occurrence of liver injury 1 month after the administration of an anti-programmed cell death 1 antibody drug for gastric cancer. It showed liver injury mainly consisting of hemorrhagic necrosis around the central vein, and inflammatory cell infiltration consisting mainly of CD8-positive lymphocytes was observed.

Notes:

1) A liver biopsy can aid in making a definite diagnosis of ICI-induced liver injury, including exclusion diagnosis, and evaluate the severity of the disease, as well as the presence or absence of background liver disease. A liver biopsy is performed when deemed necessary based on clinical symptoms and blood test data. It is desirable to perform a liver biopsy prior to corticosteroid administration. In particular, liver biopsy is considered whenever possible in cases that require the exclusion of other diseases or cases with severe liver injury, such as those with grade 3 or higher. If pathological diagnosis is difficult, it is recommended to actively consult a hepatopathologist with extensive experience in diagnosing ICI-induced liver injury.
2) The histological image of ICI-induced liver injury is basically acute hepatitis consisting of diffuse lobulitis, but it has many histological similarities with acute hepatitis caused by other factors. Additionally, acute hepatitis-like diffuse lobulitis is observed even in patients with preceding chronic liver disease. In addition, the appearance of acute hepatitis changes over time, which requires attention.
3) Most of the infiltrating lymphocytes seen in immunostaining are CD3-positive T cells and CD20-positive B cells are few. In addition, CD8-positive T cells are known to be more dominant than CD4-positive cells. However, it is important to note that these findings are common to various hepatobiliary diseases and are not specific to ICI-induced liver injury.

ICI-induced cholangitis

Cholangitis induced by anti-PD-1/PD-L1 antibody drugs or CTLA-4 antibody drugs has also been reported as a type of irAE (Figure 3), many cases of which are classified as non-hepatocellular injury type.[24] Although this is sometimes described as immune-related sclerosing cholangitis, the present guide describes it as ICI-induced cholangitis, as its clinical presentation differs from that of primary sclerosing cholangitis. Its symptoms include abdominal pain and fever; however, some patients are asymptomatic and discovered incidentally through blood tests.[29] The following have been reported as clinical and pathological features of ICI-induced cholangitis: (1) extrahepatic bile duct dilatation or multiple intrahepatic bile duct stenosis with no cause of obstruction, (2) diffuse thickening of the extrahepatic bile duct wall, (3) biliary enzyme-dominant liver injury, (4) negative for autoantibodies (such as antinuclear antibodies and antimitochondrial antibodies), (5) normal range of serum immunoglobulin G4 levels, (6) bile duct infiltration of CD8-positive T cells (Figure 4), and (7) moderate to poor therapeutic effect of corticosteroids.[30,31] However, no conclusion has been reached regarding the appropriateness of endoscopic retrograde cholangiopancreatography. Although ICI-induced cholangitis is a rare pathological condition, its early detection is important, as it greatly impacts the patients' prognosis once it develops. If biliary system-dominant liver injury is observed while using ICIs, the presence or absence of thickening and dilatation of the bile duct wall needs to be confirmed using contrast-enhanced computed tomography and magnetic resonance cholangiopancreatography.

CONCLUSION

This publication comprises the first diagnostic guide specific to ICI-induced liver injury in Japan. Because ICI-induced liver injury requires the introduction of treatment centered on corticosteroids at an appropriate time, it is hoped that treatment guide will be developed in the future. Moreover, it is necessary to discuss the safety and

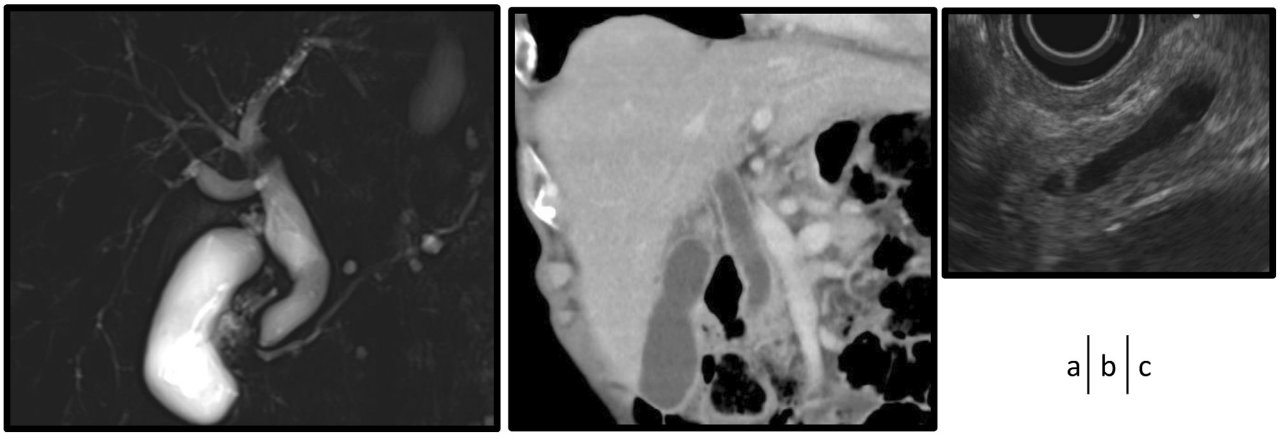

FIGURE 3 (a) Typical imaging findings in cholangitis induced by immune checkpoint inhibitors magnetic resonance cholangiopancreatography. (b) Contrast-enhanced computed tomography. (c) Endoscopic ultrasonography. The patient was a man aged in his 90s. Cholestatic liver injury with Common Terminology Criteria for Adverse Events grade 3 appeared 442 days after the initial administration of an anti-programmed cell death 1 antibody drug for bladder cancer. Aspartate aminotransferase 249 (U/L), alanine aminotransferase 215 (U/L), alkaline phosphatase (IFCC) 1572 (U/L), and gamma-glutamyltransferase 1010 (U/L). Extrahepatic bile duct dilatation and diffuse thickening of the bile duct wall with no cause of obstruction were observed.

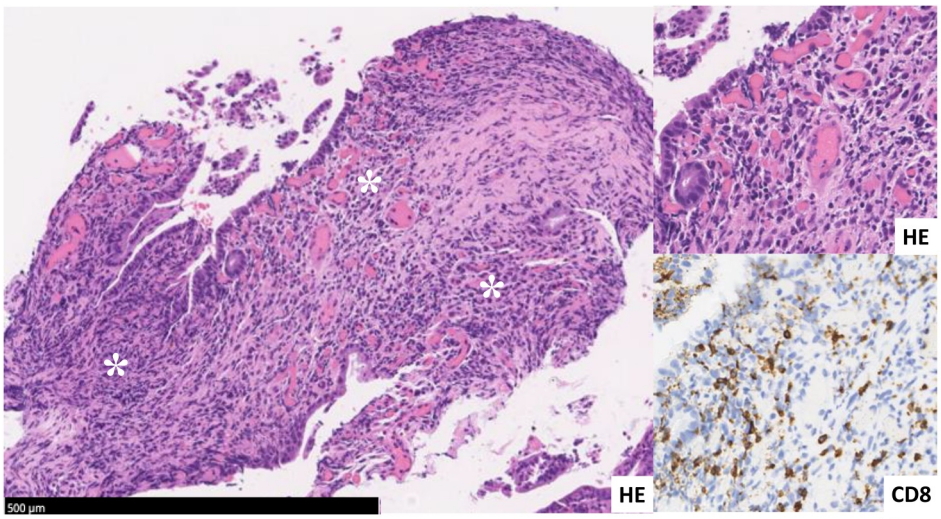

Figure 4

FIGURE 4 Typical bile duct pathological findings in cholangitis induced by immune checkpoint inhibitors. Inflammatory cell infiltration, consisting mainly of lymphocytes, was prominent in the lamina propria (*) and was shown to be CD8-positive. HE, hematoxylin–eosin.

efficacy of re-administration of ICIs after the onset of ICI-induced liver injury, treatment strategies for cases of complications with irAEs in other organs, and establishment of biomarkers for predicting the onset of ICI-induced liver injury. As the number of patients using ICIs increases year by year, the incidence of ICI-induced liver injury is expected to increase, and its evidence is expected to accumulate. The present diagnostic guide will continue to be revised periodically in the future.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article, as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Approval of the research protocol: N/A.

Informed consent: N/A.

Permission to reproduce material from other sources: N/A.

Clinical trial registration: N/A.

Animal studies: N/A.

Research involving recombiant DNA: N/A.

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