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Review Article

Immune Checkpoint Inhibitor-Induced Hepatic Injury: A Clinicopathologic Review

Mehran Taherian[1], Deyali Chatterjee[1] and Huamin Wang[1,2*]

[1]*Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA;* [2]*Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA*

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Abstract

Although immune checkpoint inhibitors (ICIs) have been a revolutionary milestone in immuno-oncology, immune-related adverse events (irAEs) may occur due to enhanced T cell activation and immune dysregulation. The irAEs can occur as early as within days to reportedly as late as up to 26 weeks. They may affect any organ system in the body, most commonly the luminal gastrointestinal tract, liver, skin, endocrine system, and lungs. The mechanisms of irAEs are complex and have not been fully understood. A breach of self-tolerance, which leads to autoantigen reactivity due to the enhanced activation and infiltration of T cells or the production of autoantibodies, and a non-specific autoinflammatory mechanism have been proposed. Limited data is available on the clinical and pathologic features of ICI-induced liver injury. This review presents an overview of the clinical and common histopathologic features and patterns of ICI-induced liver injury, the differential diagnoses, and the clinical management. Available data suggest that the histopathologic findings of ICI-induced hepatic injury are often non-specific and overlap with other challenging differential diagnoses. Therefore, a good knowledge of the histopathologic spectrum of ICI-induced hepatic injury and their differential diagnoses combined with the serological test results, clinical correlation, and communication with the clinical team is necessary to make an accurate and timely diagnosis.

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Keywords: Immune checkpoint inhibitor; Immune-related adverse events; Liver; Histopathologic; Hepatitic; Cholangitic.

Abbreviations: ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; FDA, Food and Drug Administration; LFT, liver function tests; DILI, drug-induced liver injury; AIH, autoimmune hepatitis.

***Correspondence to:** Huamin Wang, Department of Anatomic Pathology, Unit 085, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. ORCID: https://orcid.org/0000-0002-2038-5863. Tel: +1 (713) 563-1846, Fax: +1 (713) 563-1848, E-mail: hmwang@mdanderson.org

Introduction

Immune checkpoint inhibitors (ICIs) have become the new standard of care for treating many types of cancers and have been shown to improve survival in some cancer patients.[1] They result in an antitumor immune response by blocking the immune cell checkpoints. Immune checkpoint proteins, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) and protein ligand-1 (PD-L1) receptors, downregulate T cell immunity. CTLA4 is expressed on the surface of T lymphocytes, and CTLA4 signaling is triggered by binding to CD80/86 on antigen-presenting cells, which inactivates lymphocytes.[2,3] Thus, blocking CTLA4 releases the functional suppression of T cells, which enables them to attack tumor cells.[2,3] Blocking the interaction between PD-1 on the surface of T lymphocytes and PD-L1 expressed on cancer cells also enhances the activation of T lymphocytes and enables them to exert their cytotoxic effects against the tumor cells.[4–6] In addition, alternate checkpoint molecules such as lymphocyte activation gene-3 (LAG-3) and T cell immunoglobulin and mucin-domain containing-3 have also been targeted to prevent resistance to common ICIs.[7]

The first clinical studies that reported significant tumor regression after being treated with ICIs were in 2003, using anti-CTLA therapy for metastatic melanoma.[8,9] Clinical benefit of anti-PD-1 was first reported in 2010 in multiple advanced cancers, including colorectal carcinoma.[10] In 2011, the US Food and Drug Administration (FDA) approved the first ICI, the CTLA-4 blocking ipilimumab, to treat unresectable or metastatic melanoma. Since then, the FDA has approved nine more ICIs to treat different types of cancer (Table 1). The first ICI that received FDA approval for gastrointestinal cancers was pembrolizumab, which targets PD-1 for treating patients with recurrent, locally advanced, or metastatic gastric or gastroesophageal junction adenocarcinoma.[11,12] Among the FDA-approved ICIs, ipilimumab, nivolumab, and pembrolizumab are the most widely used drugs.[4]

Although ICIs have revolutionized cancer treatment, unfavorable complications may occur due to the enhanced T cell activation and immune dysregulation, referred to as immune-related adverse events (irAEs), with a reported incidence of up to 90%.[13] Ipilimumab and combination regimens have been reported with more irAEs than other approved ICIs.[14] In general, the ICIs targeting PD-1 or PD-L1 are associated with a lower incidence of irAEs than CTLA-4 inhibitors.[15–18] The irAEs may occur as early as within days to reportedly

Table 1. The FDA-approved immune checkpoint inhibitors, their mechanism, and indications

Drug (brand name)	Mechanism	Approved indications
Atezolizumab (Tecentriq®)	PD-L1 inhibitor	Breast cancer, hepatocellular carcinoma, melanoma, non-small cell lung cancer, and urothelial carcinoma
Avelumab (Bavencio®)	PD-L1 inhibitor	Merkel cell carcinoma, renal cell carcinoma, and urothelial carcinoma
Cemiplimab (Libtayo®)	PD-1 inhibitor	Cutaneous squamous cell carcinoma, basal cell carcinoma, and non-small cell lung carcinoma
Dostarlimab (Jemperli)	PD-1 inhibitor	MMR-deficient recurrent or advanced solid tumors
Durvalumab (Imfinzi®)	PD-L1 inhibitor	Non-small cell lung cancer, small cell carcinoma, and urothelial carcinoma
Ipilimumab (Yervoy®)	CTLA-4 inhibitor	Colorectal cancer, hepatocellular carcinoma, melanoma, mesothelioma, renal cell carcinoma, and non-small cell lung carcinoma
Nivolumab (Opdivo®)	PD-1 inhibitor	Colorectal cancer, esophageal squamous cell carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, melanoma, mesothelioma, renal cell carcinoma, urothelial carcinoma, and non-small cell lung carcinoma
Pembrolizumab (Keytruda®)	PD-1 inhibitor	Breast cancer, cervical cancer, colorectal cancer, cutaneous squamous cell carcinoma, endometrial carcinoma, esophageal carcinoma, gastric carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, large B cell lymphoma, head and neck squamous cell carcinoma, melanoma, mesothelioma, Merkel cell carcinoma, MSI-high/MMR-deficient/TMB-high cancers, renal cell carcinoma, urothelial carcinoma, and non-small cell lung carcinoma
Relatlimab	LAG-3 inhibitor	In combination with Nivolumab (together known as Opdualag™) for subsets of patients with melanoma
Tremelimumab	CTLA-4 inhibitor	Mesothelioma

FDA, the Food and Drug Administration; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; PD-1, programmed death-1; PD-L1, programmed death ligand-1; LAG-3, lymphocyte activation gene-3, MMR, mismatch repair; MSI, microsatellite instability; TMB, tumor mutational burden.

as late as up to 26 weeks after the initiation of ICI therapy, with a median onset of approximately 40 days.[16] The irAEs can affect any organ system in the body, most commonly the luminal gastrointestinal (GI) tract, liver, skin, endocrine system, and lungs.[19,20] Hepatic and GI involvements can be expected four to seven weeks after initiation of therapy, presenting as elevated liver enzymes, hepatitis, vomiting, diarrhea, and colitis.[21–23]

The precise immunologic mechanisms of irAEs are complex and have not been fully understood. The breach of self-tolerance, which leads to the autoantigen reactivity due to the enhanced activation and infiltration of T cells or the production of autoantibodies, and a non-specific autoinflammatory mechanism have been proposed.[24] Autoantibodies, autoactivation of T cells, interleukins, and other inflammatory cytokines contribute to the pathophysiology of irAEs.[25] It is unclear why some patients have immune-related severe adverse events and others do not.[6] The composition of the gut microbiome has also been linked to both irAEs and tumor response to ICIs.[26]

This review will focus on the clinical and common histopathologic patterns and features of ICI-induced liver injury, the differential diagnoses, and the management of the hepatic toxicity associated with ICI treatment.

Clinical features

Immune-mediated hepatic injury has been reported in 3–10% of patients who received ICI monotherapy and up to 30% of patients treated with combination therapy.[23,27,28] ICI-induced liver injury is even higher in patients with other irAEs, most commonly colitis.[29] The most common manifestation is an asymptomatic increase in liver function tests (LFTs), particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[23,30,31] Other clinical symptoms reported are fever, fatigue, myalgia, jaundice, ascites, nausea, vomiting, confusion, and abdominal pain.[27,32] Since the clinical presentations and elevated LFTs of ICI-induced liver injury are non-specific and overlap with viral hepatitis, autoimmune hepatitis, other drug-induced liver injuries (DILI), and hepatitis of other non-ICI-related etiology, it is essential to rule out non-ICI-related hepatitis before making the clinical diagnosis of ICI-induced liver injury. The baseline LFTs and clinical history before initiating ICI treatment are essential in differentiating the pre-existing liver disease/injury from the ICI-induced liver injury. Once the diagnosis is made, the clinical grading of the ICI-induced liver injury is according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (Table 2).[23,33]

Radiological features

ICI-induced liver injury may demonstrate variable imaging findings according to its severity. Mild cases mostly appear unremarkable, while more severe cases may show non-specific findings in various imaging modalities (CT scan, MR, and ultrasonography) such as mild hepatomegaly, attenuated hepatic parenchyma, steatosis, periportal edema and periportal lymphadenopathy, and conspicuous periportal echogenicity.[34,35]

Histopathological characteristics

Because ICIs are relatively new, limited data is available on the microscopic features of ICI-induced liver injury, especially when the liver biopsy is not routinely performed for all cases. Few studies reported the histopathologic changes of liver specimens in patients with ICI-induced liver injury.[36–44] The reported histopathologic patterns/features and their differential diagnoses are summarized in Table 3. The

Table 2. The CTCAE grading system for the ICI-induced hepatic injury[33]

Grade	Definition
Grade 1	AST or ALT 1–3× ULN or Total bilirubin ≤ 1.5× ULN
Grade 2	AST or ALT > 3–5× ULN or Total bilirubin > 1.5–3× ULN
Grade 3	AST or ALT > 5–20× ULN or Total bilirubin > 3–10× ULN
Grade 4	AST or ALT > 20× ULN or Total bilirubin > 10× ULN
Grade 5	Death

CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

Table 3. The histopathological patterns/features of ICI-induced hepatic injury and major differential diagnoses

Microscopic pattern	Major differential diagnoses
Hepatitic pattern	Viral infections, DILI by other concurrent drugs, autoimmune hepatitis, granulomatous hepatitis, Wilson disease, malignancy
Cholangitic pattern	DILI, extrahepatic biliary obstruction, primary biliary cholangitis, primary sclerosing cholangitis, IgG4-related cholangitis, acute cellular rejection, graft versus host disease
Mixed hepatitic and cholangitic pattern	DILI
Steatotic/steatohepatitic pattern	Alcoholic or non-alcoholic fatty liver disease
Granulomatous inflammation	Bacterial and fungal infections, sarcoidosis, primary biliary cholangitis, DILI
Mild non-specific inflammatory changes	DILI, systemic conditions such as celiac and thyroid disease, vascular disorders, metabolic conditions

ICI, immune checkpoint inhibitor; DILI, drug-induced liver injury; Ig, immunoglobulin.

frequencies of different histopathologic patterns/features of ICI-induced hepatic injury in the published studies are summarized in Table 4. The available data suggest that the histopathologic findings associated with ICI-induced hepatic injury are often non-specific. Therefore, the diagnosis of the ICI-induced hepatic injury on liver biopsies is often very challenging and requires careful correlations of the histopathologic findings with the clinical and radiological data and the laboratory testing results, including the LFTs, the viral hepatitis panel, and the autoantibodies to exclude autoimmune hepatitis, *etc.*

Hepatitic pattern

The most common pattern of ICI-induced liver injury is the hepatitic pattern, which has been reported in 47% in an extensive study of 60 patients by Cohen *et al.*[36] and up to 100% in smaller studies.[41] This pattern is characterized by panlobular or centrilobular (zone 3) inflammation composed of predominantly lymphocyte and histiocyte aggre-

Table 4. Summary of the published studies on the histologic patterns and features of ICI-induced hepatic injury

Study	Number of cases	Histologic Patterns and Features					
		Hepatitic	Cholangitic	Mixed hepatitic/cholangitic	Granulomas including fibrin ring type	Steatosis	Other features
Kleiner *et al*,[41] 2012	5	4	n/a	n/a	1	1	n/a
Johncilla *et al*,[40] 2015	11	9	1	n/a	n/a	1	Central vein endotheliitis (8/11)
Everett *et al*,[39] 2017	2	2	n/a	n/a	2	2	Endotheliitis
Doherty *et al*,[38] 2017	3	n/a	2	n/a	n/a	1	Vanishing bile duct syndrome (1/3)
De Martin *et al*,[37] 2018	16	12	n/a	4	9	n/a	Central vein Endotheliitis (7/16)
Zen *et al*,[43] 2018	7	5	n/a	2	n/a	2	n/a
Zhang *et al*,[44] 2020	8	6	1	n/a	1	3	n/a
Zen *et al*,[42] 2020	10	6	1	2	2	1	Cholestasis with multiple bile casts (1/10)
Cohen *et al*,[36] 2021	60	28	16	8	18	3	Central vein endotheliitis (20/60)

ICI, immune checkpoint inhibitor; n/a, not applicable

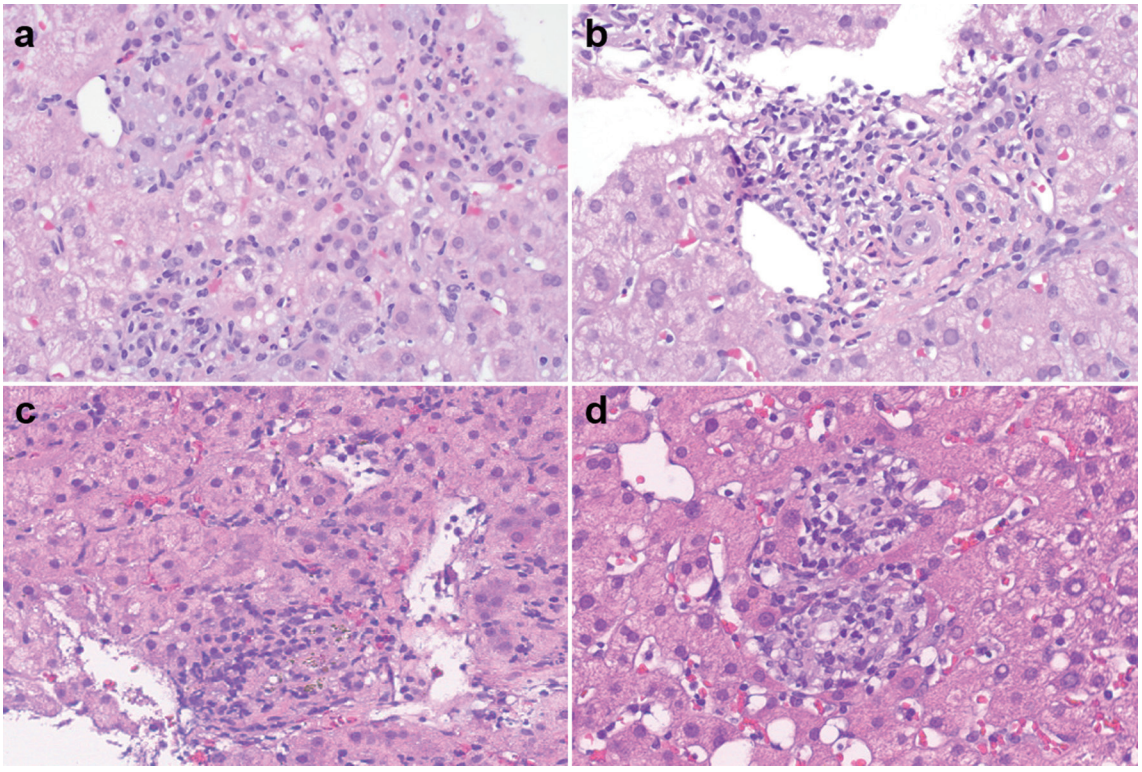

Fig. 1. Immune checkpoint inhibitor-induced liver injury, hepatitic pattern. (a) Lobular inflammatory infiltrate consisting of predominantly lymphocytes, histiocytes, scattered neutrophils and eosinophils, and ballooning degeneration (hematoxylin and eosin ×100); (b) Portal vein endotheliitis, characterized by lymphocytes underneath endothelial cells (hematoxylin and eosin ×100); (c) Central perivenulitis (hematoxylin and eosin ×100); (d) Early fibrin ring granuloma represented by a cluster of macrophages containing a small central lipid droplet (hematoxylin and eosin ×200).

gates with scattered neutrophils, eosinophils, and only a few plasma cells.[42] The liver parenchyma shows foci of spotty/focal necrosis, and sometimes multifocal hepatocyte apoptosis, ballooning degeneration, and acidophil bodies. Portal inflammation is usually mild to moderate,[45,46] and steatosis has also been reported.[36] Granulomas, including fibrin ring granulomas (a central fat globule surrounded by a circumferential rim of fibrin and histiocytes), have been reported in the hepatitic pattern of ICI-induced liver injury, primarily located in the lobules.[36,39] Central vein endotheliitis with centrilobular necrosis and lymphocytic infiltrate has been reported in many cases and can be a somewhat specific finding in this type of liver injury.[36,40,41,43] Only minimal bile duct injury and/or ductular reaction in the hepatitic pattern may be observed (Fig. 1).[36]

The differential diagnoses for hepatitic patterns include viral hepatitis, other DILI, autoimmune hepatitis (AIH), and Wilson disease. Viral hepatitis can be further assessed by clinical history, serological viral testing, and *in situ* hybridization. The DILI, secondary to other drugs, does not have specific microscopic features. However, it may show prominent eosinophils and fewer histiocytes.[46] The DILI manifesting as confluent necrosis and bile plugs are not common in ICI-induced hepatitis.[43,47] Unlike AIH, ICI-induced hepatitis lacks a prominent plasma cell infiltrate, and the interface activity is often present in AIH. Also, features like hepatocyte rosettes and confluent necrosis are frequently noted in AIH but not reported in ICI-induced hepatic injury.[43] The serological markers of AIH, such as immunoglobulin G, antinuclear antibody, and smooth muscle antibody, are usually normal in ICI-induced hepatic injury. Some studies have suggested that prominent sinusoidal histiocytes and central vein endotheliitis may help differentiate the hepatitic patterns of the ICI-induced liver injury from AIH and DILI.[37,40] Fibrin ring granulomas are rare, but if seen, the differentials that need to be excluded are infections like Q fever, Epstein Barr virus (EBV), cytomegalovirus (CMV), toxoplasmosis, and systemic diseases like lupus.[48,49] Wilson disease shows a spectrum of histologic features depending on the disease stage and varies from non-alcoholic steatohepatitis to features similar to AIH, and finally, the cirrhotic stage.[50]

Cholangitic pattern

The second most common pattern is the cholangitic pattern which has been observed in 27% of the cases in a study involving 60 liver biopsies,[36] and is associated with elevated alkaline phosphatase and serum bilirubin.[30] This pattern is characterized by varying degrees of bile duct injury in the form of lymphocytic cholangitis, ductular reaction, or even ductopenia. Lobular inflammation, including granulomas, is minimal or absent. The accompanying portal inflammation is composed of a mixed inflammatory infiltrate, predominated by lymphocytes (Fig. 2).[37,38,42–44] Endotheliitis has not been identified in the cholangitic pattern of the liver.[36,37,40]

The primary differential diagnoses for the cholangitic pattern of the ICI-induced hepatic injury include other DILI, distal biliary obstruction, primary biliary cholangitis, acute cellular rejection in the liver transplant setting, and graft versus host disease (GVHD).[45] Classic features of acute cellular rejection are the triad of mixed portal inflammation, bile duct damage with intraepithelial lymphocytes, and endotheliitis, a

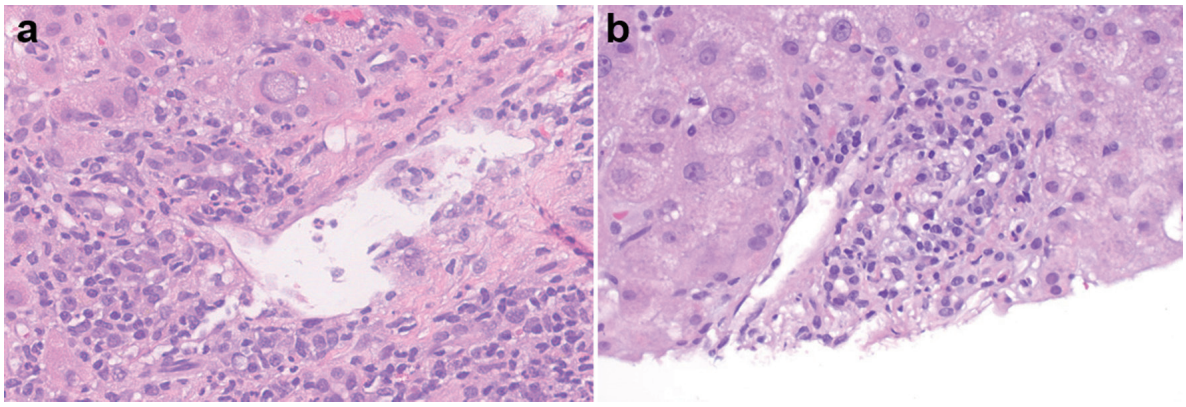

Fig. 2. Immune checkpoint inhibitor-induced liver injury, cholangitic pattern. (a) Portal tract with mixed inflammatory infiltrate and (b) bile duct injury showing inflammatory cells within the duct epithelium (hematoxylin and eosin ×200).

finding uncommonly reported in the cholangitic pattern. The ICI-induced liver injury with a cholangitic pattern is a diagnosis of exclusion. It requires reviewing the imaging, clinical history, and serological tests. The ICI-induced injury to the extrahepatic and intrahepatic bile ducts can mimic primary sclerosing cholangitis and is histologically characterized by lymphocyte infiltration of bile duct epithelium and periductal fibrosis.[51] This pattern of sclerosing cholangitis should be differentiated from immunoglobulin (Ig) G4-related cholangitis by histologic features, serum IgG4, and immunohistochemistry.[52] IgG4-related cholangitis presents with plasma cell infiltrate in the portal tracts and increased $IgG4^+/IgG^+$ ratio of plasma cells. It may or may not show features of obliterative phlebitis or storiform fibrosis.[47] GVHD occurs after stem cell transplant and is characterized by bile duct epithelial damage, as seen in the ICI-mediated liver damage. However, portal inflammation is typically mild in GVHD, and endotheliitis may be observed.[53]

Mixed hepatitic and cholangitic pattern

To qualify as a mixed hepatitic/cholangitic pattern, the liver biopsy has to show both significant lobular injury as well as portal inflammation with more than minimal bile duct injury and/or ductular reaction (Fig. 3). This mixed pattern has been seen in 13% of patients treated by ICIs in the study by Cohen *et al*.[36] The granulomas in this group are reportedly more portal-based compared to lobular-based in the hepatitic pattern.[36] The major differential diagnosis for the mixed hepatitic and cholangitic patterns of ICI-induced hepatic injury is the drug induced-hepatitis caused by other drugs(s). A careful review of patient treatment history and clinical correlation are required for making the correct diagnosis.

Other patterns

Another less common histologic pattern that could develop in 5% of the cases is primarily granulomatous hepatitis.[40] For cases with granulomatous hepatitis, bacterial/fungal/mycobacterial infections should be ruled out by special stains, culture, or polymerase chain reactions. Other etiology and drug-induced granulomatous hepatitis should also be considered in the differential diagnosis.

Steatosis and steatohepatitis have also been described in 5% of patients with ICI -induced hepatic injury and are indistinguishable from non-alcoholic steatosis or steatohepatitis.[36,40,44] It is unclear whether this finding represents the pre-existing fatty liver disease or is genuinely related to ICI therapy. Some authors propose that fibrin ring granulomas and steatosis may be pathogenically related.[48] Furthermore, the ICIs may induce only mild and non-specific changes with no or focal lobular inflammation and absent or focal mild portal inflammation;[36,44] these non-specific mild changes can also be seen in systemic conditions such as celiac and thyroid disease.[54] ICI-induced nodular regenerative hyperplasia has rarely been reported as well (Fig. 4).[55]

Treatment

Systemic glucocorticoids represent the primary treatment for patients with ICI-induced hepatic injury whose liver enzymes do not resolve spontaneously. More frequent liver monitoring is recommended for patients with the CTCAE grade 1 ICI-induced hepatic injury. The ICI therapy should be withheld for patients with grade 2 ICI-induced hepatic injury until resolution to grade 1. For symptomatic patients, prednisone may be administered. For patients with grades 3–4 ICI-induced hepatic injury, ICI treatment should be discontinued, and consultation with a hepatologist and liver biopsy may be needed. A high dose of steroids should be initiated. Second-line immunomodulators, such as azathioprine or mycophenolate, may be considered if there is no improvement in clinical hepatitis after being treated with steroids for 3–5 days. This treatment usually leads to near or complete resolution of liver function tests in nearly all cases, confirming the diagnosis of an ICI-induced liver injury.[56,57] Some studies showed that ICI-related cholangitis was more resistant to steroid therapy.[38]

Conclusions

With an exponential increase in the use of ICIs in cancer immunotherapy, the incidence of ICI-induced hepatic injury is also expected to rise. Pathologists play a significant role in the multidisciplinary clinical team in the early diagnosis of these hepatic irAEs to provide optimal management of cancer patients and to avoid significant morbidity and mortality. However, the histopathologic features of ICI-induced hepatic injury are not specific and overlap with other challenging differential diagnoses. Hence, a good knowledge of the histopathologic spectrum of ICI-induced hepatic injury and their differential diagnoses combined with the serological test results, clinicopathologic correlation, and communication with the clinical team is necessary to make an accurate and timely

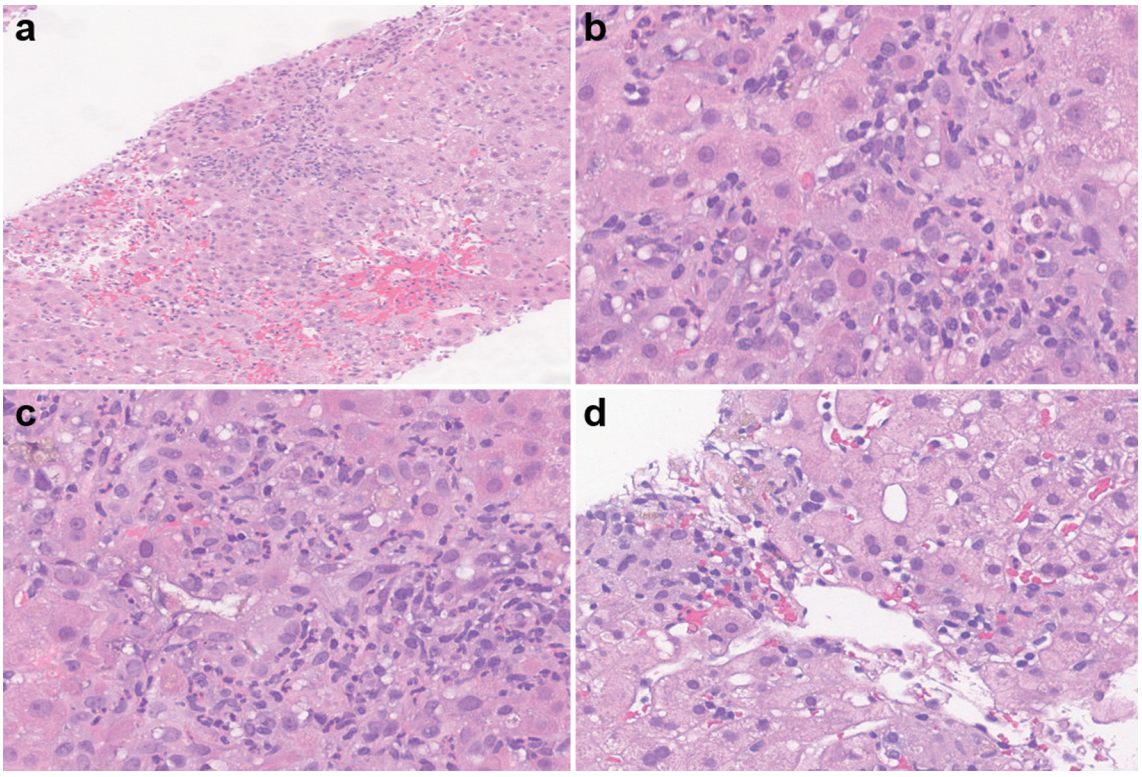

Fig. 3. Immune checkpoint inhibitor-induced liver injury, mixed hepatitic and cholangitic pattern. (a) The liver biopsy shows bile duct injury, portal and lobular inflammation, prominent ductular reaction, and foci of hepatocellular necrosis (hematoxylin and eosin ×100); (b, c) Bile duct injury, prominent ductular reaction, portal and lobular inflammation composed of lymphocyte and histiocyte aggregates, neutrophils, and eosinophils with rare apoptotic bodies (hematoxylin and eosin ×200); (d) Perivenulitis (hematoxylin and eosin ×200).

diagnosis.

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Conflict of interest

HW has been an editorial board member of the *Journal of Clinical and Translational Pathology* since May 2021. The authors have no other conflicts of interest related to this publication.

Author contributions

Study concept and design (HW, MT), provision and collection of study materials (HW, DC, MT), drafting of the manuscript (HW, DC, MT), and critical revision of the manuscript

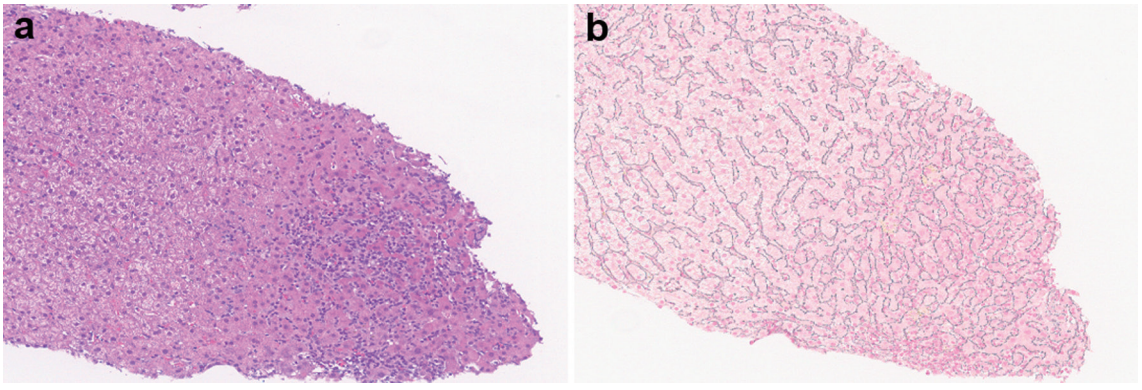

Fig. 4. Immune checkpoint inhibitor-induced liver injury showing (a) nodular regenerative hyperplasia-like change, which is characterized by ill-defined parenchymal nodules with atrophic hepatocytes; no fibrous septa around nodules are seen (hematoxylin and eosin ×40); (b) The reticulin stain shows the alternating areas of nodularity and compression of the reticulin network between nodules.

for important intellectual content (DC, HW). All authors have contributed significantly to this study and approved the final manuscript.

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