Drug-induced Liver Injury: Pathology Patterns and Common Culprits

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Abstract: Drug-induced liver injury (DILI) has an incredible range of morphologic presentations, from acute extensive necrosis to resolving injury with ceroid-laden macrophages. The diversity in presentation on biopsy is diagnostically challenging, but DILI is becoming more widely recognized, especially with the aid of resources like LiverTox. Some medications, such as acetaminophen, have well-established patterns of injury. However, newer medications, such as immune checkpoint inhibitors, are continually being developed, and our understanding of their effects on the liver are evolving. In this chapter, we will focus on the DILI patterns and frequently encountered DILI culprits. Ultimately, DILI is a diagnosis of exclusion, and close clinical correlation is essential when navigating the differential.

Key Words: drug-induced injury, liver, checkpoint inhibitors, hepatitis, cholangiopathy, ductitis, sclerosing cholangitis, cholestatic hepatitis, peliosis, portosinusoidal vascular disease

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The review begins with a systematic approach to evaluating liver biopsies concerning drug-induced liver injury (DILI), including a brief discussion of general clinical management for DILI, which leads into how to produce the most informative pathology report. The remainder of the review focuses on a more detailed discussion of common culprits as reported by the DILI network around the world.[1–3]

A general approach to drug-induced liver injury from a pathology point of view centers around the exclusion of alternative causes and the identification of the culprit(s). It should start with a detailed review of the clinical history, including baseline liver disease (such as alcohol use, viral hepatitis, metabolic dysfunction, and hemochromatosis) and autoimmune conditions. Next, there should be a thorough review of the medication list, which includes prescription drugs, over-the-counter medications, dietary/herbal supplements, and recreational drugs. After excluding competing causes, the key to diagnosis is often the temporal relationship between the medication and the change in liver enzyme levels. The onset of liver enzyme elevation typically occurs 2 to 24 weeks after the initiation of the offending agent, with the exception of hypersensitivity reactions, which often occur within 24 to 72 hours.[4] However, delayed liver injury is not uncommon and can occur weeks or even months after cessation of the offending agent. This injury is not dose-dependent, and the latency period can vary. Possible reasons for this include one or more of these factors: a long half-life of the drug, the production of a toxic metabolite, mitochondrial dysfunction, or an immune-mediated process that may or may not be accompanied by autoantibodies.

Liver enzyme patterns also aid in the pathology diagnosis, confirming the pathologic pattern seen on biopsy. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation indicate hepatocellular injury, often with an ALT/AST ratio >1. However, the ratio can flip, and this is often related to toxin/drug-induced acute liver failure in addition to the better known cause of alcohol-induced liver damage or end-stage cirrhosis. Elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) indicate cholestatic or biliary injury.

Liver toxic agents can produce a frustrating variety of histologic changes in the liver. While direct/intrinsic hepatotoxicity is considered more common in DILI, due to its dose-dependent nature and predictability, these cases are often diagnosed clinically without tissue sampling. Idiosyncratic or indirect toxicity is more frequently encountered by pathologists, as these mechanisms involve unpredictable effects in individuals, with varying lengths of latency as discussed previously.

Histologic findings of DILI consist of one or a combination of these mechanisms: hepatocyte necrosis or apoptosis, bile duct injury (cholangiopathy), canalicular and hepatocellular cholestasis, steatosis, ballooning or swelling of hepatocytes, vascular remodeling with associated hepatocyte regeneration, inflammation (including granulomas), and fibrosis if the injury targets the fibrogenesis pathway in the liver. Diagnosis often seems intimidating at first and it can be difficult to know where to start. A practical approach is to begin with a microscopic description, systematically recording all the findings in the biopsy. Then, assign a pathologic pattern (Table 1)[4–6] based on the most significant findings; examples of each pathologic pattern are demonstrated in Figures 1–14. From there, first rule out competing causes (Table 1), and then check the suspected drugs/toxins on the LiverTox website.[7] If the culprit is identified, in addition to immediate cessation of the agent and supportive care, drug-specific interventions may be available.

However, even after an extensive literature search, it is possible that the culprits cannot be identified. This could be due to agents that patients are not willing to disclose, or too many potential candidates simultaneously, or synergic effect of certain drugs that have not been characterized. Without a clear culprit drug/toxin, the next major question is whether immunosuppression should be administered if liver enzymes continue to rise. This question is easier to answer when patients also have autoimmune serologic markers, in which case a diagnosis of autoimmune hepatitis can be made with

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TABLE 1. Common Patterns in DILI With Examples of Culprit Agents and Potential Diagnostic Pitfalls Due to Non-DILI Causes

	Morphologic components			
Pathologic injury pattern	**Key features**	**Other possible findings**	**Selected examples of culprit agents**	**Pitfalls/non-DILI causes**
Zonal or extensive necrosis	Necrosis	Steatosis or vacuolization of remaining viable hepatocytes	Zone 3 predominant Acetaminophen Halothane *Amanita phalloides* toxin Cocaine Zone 1 predominant Ferrous sulfate Cocaine	Ischemia Heatstroke HSV Adenovirus Varicella AIH (zone 3 predominant)
Acute hepatitis	Lobular inflammation Variable degree of necrosis Apoptosis Lobular disarray	Mild portal inflammation Mild bile duct injury Significant, submassive or massive necrosis Cholestasis (if there is significant cholestasis, refer to "cholestatic hepatitis")	Many medications, Recreational drugs, dietary supplements	Viral hepatitis (A, B, C, E) AIH (acute phase) Exotic infections GVHD
Lobular/sinusoidal hepatitis (mononucleosis pattern)	Inflammatory cells (predominantly in sinusoids)	Mild portal inflammation	Dapsone Antiepileptics (dilantin, phenytoin) Troglitazone Antibiotics (sulfonamides, para-aminosalicylic acid)	EBV hepatitis Toxoplasmosis Lymphoma or leukemia (such as hepatosplenic T-cell lymphoma, hairy cell leukemia)
Chronic hepatitis	Portal inflammation Interface activity	Mild bile duct injury Autoimmune serology (ANA and ASMA) Cholestasis (if there is significant cholestasis, refer to "cholestatic hepatitis")	Statins Antibiotics (isoniazid, nitrofurantoin, minocycline) Antihypertensives (methyldopa, hydralazine) Diclofenac TNF-alpha antagonists Interferons Herbal (black cohosh, turmeric)	Chronic viral hepatitis (HBV, HCV) De novo AIH CVID Celiac disease Biliary diseases (such as PBC) with portal inflammation
Cholestatic hepatitis	Cholestasis (zone 3) Acute or chronic hepatitis	Mild bile duct injury	Antibiotics (erythromycin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole) ACE inhibitors Phenothiazine neuroleptics Statins	Acute viral hepatitis Exotic infections Acute LDO PFIC GVHD
Granulomatous hepatitis	Granulomas	Acute or chronic hepatitis Fibrin-ring granulomas	Allopurinol Sulfonamides Sulfonylurea Antiepileptics (phenytoin, carbamazepine) Quinidine Hydralazine Interferon alpha ICI	Sarcoidosis PBC Fungal or mycobacterial infection Atypical bacterial infection Foreign body
Bland cholestasis	Canicular cholestasis without significant inflammation, without hepatocellular or bile duct injury	Mild hepatocyte swelling (zone 3)	Anabolic steroid Oral contraceptives Antibiotics (such as erythromycin)	Sepsis BRIC Acute LDO TPN use
Bile duct injury/cholangiopathy (including acute and chronic injury, vanishing bile duct syndrome, and sclerosing cholangiopathy)	Bile duct injury Portal inflammation	Bile ductular reaction Cholestasis Periductal concentric fibrosis Periportal fibrosis	Antibiotics (such as amoxicillin-clavulanate, flucloxacillin) ACE inhibitors Antifungals (such as terbinafine,	PSC PBC LDO PFIC

TABLE 1. (*continued*)

Pathologic injury pattern	Morphologic components: Key features	Morphologic components: Other possible findings	Selected examples of culprit agents	Pitfalls/non-DILI causes
		Bile duct loss	itraconazole, thiabendazole)	IgG4 cholangitis
		Cholate stasis (feathery degeneration)	Floxuridine (PSC-like) (prodrug of 5FU)	LCH
		Fibrosis	ICI (can be PSC-like)	TPN use
				Ischemic cholangiopathy
				GVHD
				Chronic rejection
				A1AT deficiency
Pure microvesicular steatosis	Diffuse microvesicular steatosis		Valproic acid	Cholesterol storage disease
			Tetracycline	Alcohol foamy degeneration
			Acetylsalicylic acid (Reye syndrome)	Fatty liver of pregnancy
			Cocaine	
Steatosis and steatohepatitis	Steatosis (predominantly macrovesicular)	Steatohepatitis	Glucocorticoids	MASLD
			Methotrexate	Alcohol
			Irinotecan	
			Tamoxifen	
			Amiodarone	
			Asparaginase	
			ICI	
Budd-Chiari syndrome	Sinusoid dilatation		Oral contraceptives	Polycythemia vera
	Hepatocyte atrophy			Factor V Leiden mutation
	Extensive zone 3 necrosis and dropout			Myeloproliferative disorders
SOS/VOD	Sinusoid dilatation		Busulfan	Venous outflow obstruction
	Hepatocyte atrophy		Cyclophosphamide	
	Fibrous obliteration of terminal hepatic venules		Oxaliplatin	
	Proliferation of reticulin fibers in sinusoids and terminal hepatic venules		Gemtuzumab ozogamicin	
			Adriamycin	
			Total body irradiation	
PSVD-spectrum	Portal vein stenosis or other signs of portal vein anomaly		Azathioprine	Collagen vascular disease
			Oxaliplatin	CVID
	Hepatocyte regenerative changes		Thioguanine	Lymphoproliferative disorders or autoimmune conditions associated with increased risk of PSVD
			Didanosine	
			Arsenic trioxide	
			Tamoxifen	
Peliosis	Sinusoidal dilation that is often midzonal or periportal, without abnormal portal vessels		Oral contraceptives	Venous outflow obstruction
			Anabolic steroids	PSVD
				SOS/VOD

A1AT indicates alpha-1 antitrypsin deficiency; AIH, autoimmune hepatitis; BRIC, benign recurrent intrahepatic cholestasis; CVID, common variable immune deficiency; GVHD, graft versus host disease; ICI, immune checkpoint inhibitor; LCH, Langerhans cell histiocytosis; LDO, large duct obstruction; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; PSVD, porto-sinusoidal vascular disorder.

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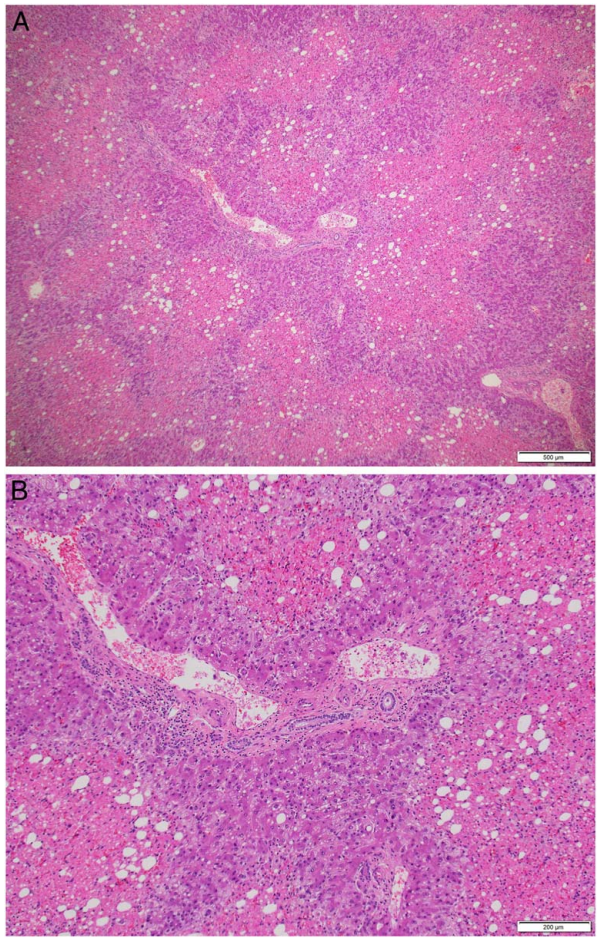

FIGURE 1. A and B, Zonal necrosis without significant inflammation due to acetaminophen toxicity (low and high power). Extensive necrosis, involving zone 3 and expanding to zone 1 with only macrophages and scattered mononuclear cells within the areas of necrosis. Noticeable macrovascular and microvesicular steatosis in the area of necrosis.

compatible histology. The distinction between drug-induced autoimmune hepatitis (AIH) and de novo AIH is difficult[8–13] (Box 1) and ultimately, successful treatment by identification and cessation of the offending agent with a short period of corticosteroid treatment without the need of long-term immunosuppression often points to a secondary cause (drug-induced) of autoantibodies. It becomes more challenging when the patient is seronegative, which accounts for a significant number of cases of immune-mediated drug-induced hepatitis. The pathologic pattern could be acute or chronic hepatitis, or cholestatic hepatitis. It is crucial to rule out competing causes, especially infectious ones, before administering immunosuppression. Fortunately, most patients respond to corticosteroid treatment within a short period, which supports the diagnosis of immune-mediated DILI. Ursodeoxycholic acid may provide symptomatic relief to patients with pruritis and a cholangiopathy pattern of injury, but the benefit and optimal treatment plans are still under clinical investigation. In cases that the injury is extensive and severe, liver transplant may be the only option.

Therefore, it is generally helpful if the pathology report includes the following components (Box 2 and Box 3): the pathologic injury pattern, degree of injury, degree of inflammation, consideration of potential competing etiologies that need to be evaluated clinically, and identification of candidate offending agent(s) if possible.

BOX 1. Features that are reportedly more common but not pathognomonic for DILI when compared with de novo AIH.

Features that are reportedly more common but not pathognomonic for DIli when compared with de novo AIH.

Well-defined zone 3 necrosis/drop out without significant inflammation, especially plasma cells.

Canalicular cholestasis.

Abundant neutrophils.

Abundant eosinophils.

Granulomatous inflammation.

Less likely to have abundant plasma cells.

Less likely to present with significant fibrosis /cirrhosis.

BOX 2. Components of a DILI pathology report

Pathologic injury pattern (Table 1).

Degree of injury (percentage of hepatocyte necrosis; percentage of bile duct loss).

Degree of inflammation.

Competing etiologies (Table 1 and Box 3).

Candidate offending agent(s).

BOX 3. Competing causes of DILI that should be considered before finalizing the case.

Viral hepatitis (HAV, HBV, HCV, HEV)—including reactivation of latent diseases.

HSV, varicella, CMV, or adenovirus infection.

EBV infection.

Wilson disease.

Biliary obstruction due to inflammatory causes or tumors.

TPN use.

ANTIBIOTICS

In 2022, over 236 million outpatient antibiotics were prescribed in the United States.[14] One prospective study found that antimicrobials account for 45% of DILI with the top 5 agents being amoxicillin-clavulanate, isoniazid, nitrofurantoin, sulfamethoxazole/trimethoprim (SMZ/TMP), and minocycline.[15] A cholestatic pattern of injury; zone 3 canalicular and hepatocellular cholestasis has been identified in the majority of cases with variable rates of duct injury[16] (Figs. 7 and 8A). Less frequently reported histologic features include duct paucity, granulomatous inflammation, acute hepatitis, and zone 3 to submassive necrosis.[16,17] Sulfamethoxazole/trimethoprim (SMZ/TMP) also presents as cholestatic hepatitis. Liver biopsies show parenchymal lymphohistiocytic inflammation, canalicular cholestasis, variable portal inflammation, and granulomas.[18]

Nitrofurantoin and minocycline primarily present with elevated hepatocellular LFTs and a hepatitis with autoimmune-like features.[19] Cases of nitrofurantoin-induced injury show portal inflammation with lymphocytic portal infiltrate, interface hepatitis, bile ductular proliferation, and variable eosinophil inflammation.[20] Biopsies from patients with minocycline injury had variable lymphoplasmacytic inflammation within the portal tracts, ballooned

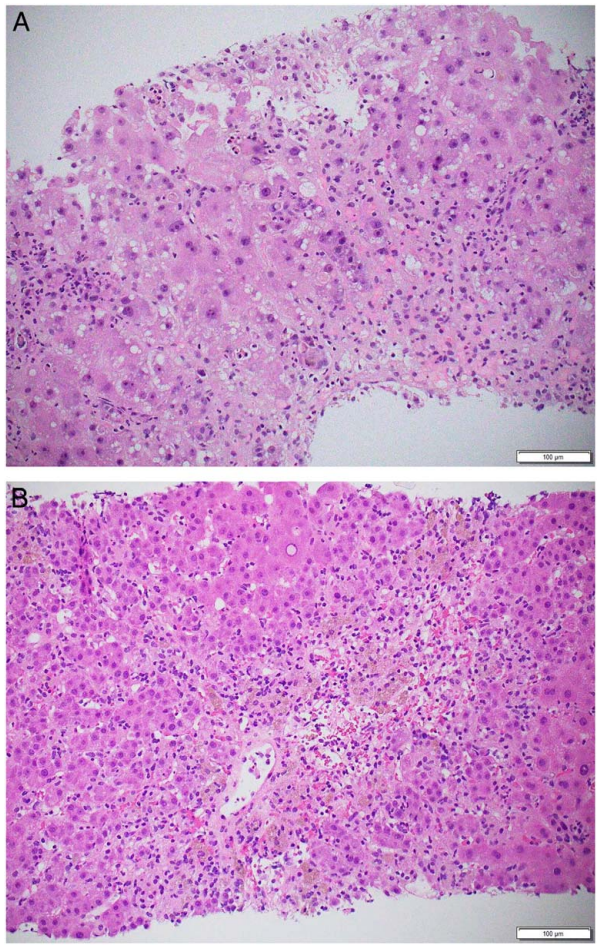

FIGURE 2. A, Acute hepatitis due to topiramate toxicity. Significant hepatocyte necrosis and lobular disarray with a noticeable neutrophilic infiltrate. B, Acute hepatitis due to bicalutamide toxicity. Well-demarcated zone 3 dropout with more pronounced inflammation compared with Figure 1. Please see this image in color online.

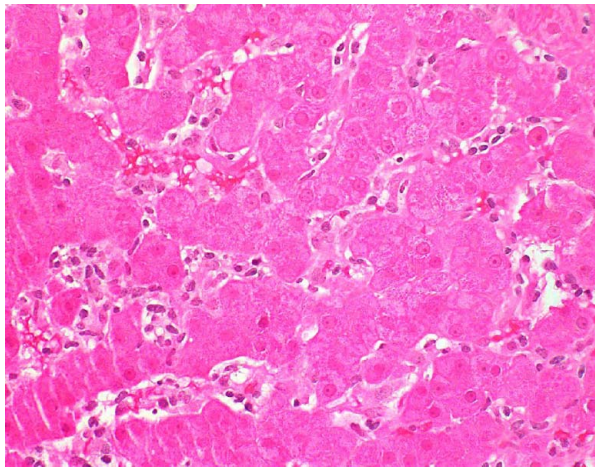

FIGURE 3. Lobular hepatitis (mononucleosis pattern). Sinusoidal lymphocytosis due to phenytoin toxicity (Image courtesy of Dr Hanlin Wang, UCLA). Please see this image in color online.

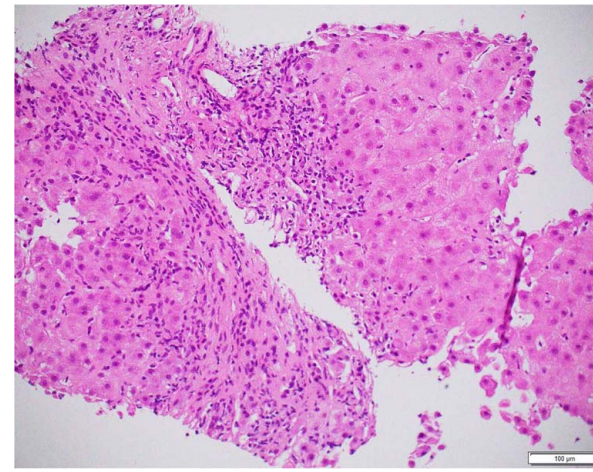

FIGURE 4. Chronic hepatitis due to atorvastatin. Portal inflammation consisting of lymphocytes and plasma cells with interface activity. Please see this image in color online.

hepatocytes, acidophil bodies, and zone 3 hepatocellular collapse.[21,22] Rare case reports of nitrofurantoin and minocycline demonstrate massive necrosis.[19,23] Isoniazid has been estimated to cause liver function test (LFT) elevations in 10% of patients, and severe effects occur rarely (~1% of patients).[24] Isoniazid-induced DILI can be monitored with LFTs, and liver biopsies are not often encountered in pathologic practice. Histologic patterns include acute hepatitis with a prominent interface component and chronic hepatitis with lobular inflammation and hepatocyte dropout.[18] Cases from the 1960s to 1970s describe a primary finding of necrosis that ranges from bridging to massive in extent.[25,26]

HERBAL AND DIETARY SUPPLEMENTS

Herbal and dietary supplements are a diverse category comprised of vitamins, minerals and elements, herbal components, and steroids. They are estimated to cause up

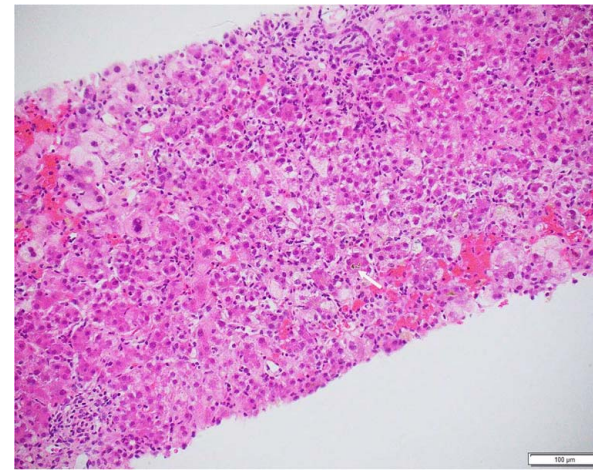

FIGURE 5. Cholestatic hepatitis due to unknown drug/toxin. Prominent lobular inflammation, lobular disarray, hepatocyte swelling, and rare foci of cholestasis (arrow). Please see this image in color online.

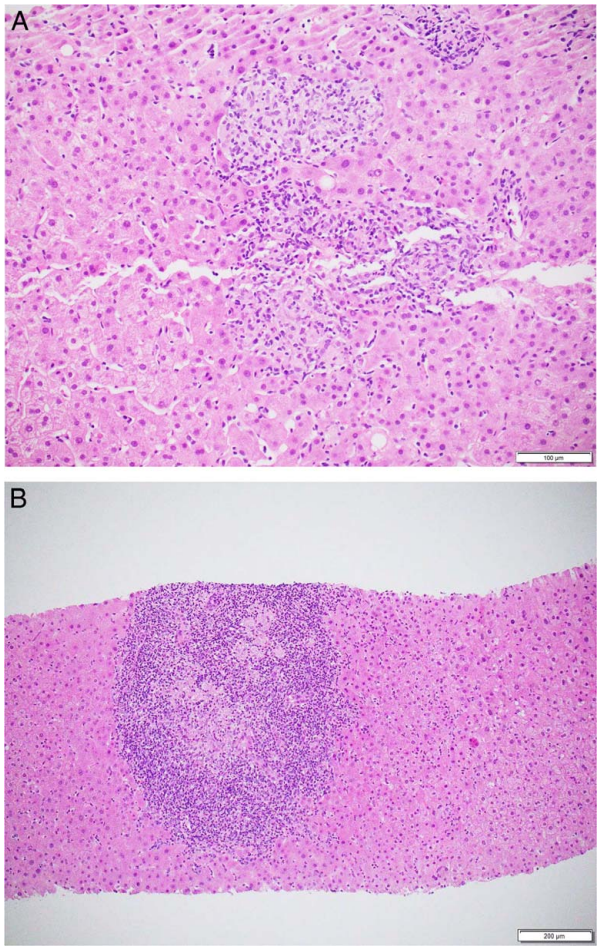

FIGURE 6. A, Granulomatous inflammation due to immunotherapy (ipilimumab). Non-necrotizing epithelioid granulomas in a background lobular lymphohistiocytic infiltrates. B, Granulomas in a patient with chronic use of allopurinol and recent diagnosis of autoimmune hepatitis. Epithelioid granulomatous inflammation present within dense lymphocytic infiltrate involving some of the portal tracts in a patient with chronic use of allopurinol and recent elevation of liver enzymes with positive ANA 1:320 and elevated total IgG. It is unclear whether the AIH is de novo or drug-related. Allopurinol is known to cause granulomas in liver but there is no report of allopurinol-induced autoimmune hepatitis in the literature. Please see this image in color online.

to 20% of drug-related liver injury.[27] Well-documented causes of liver injury include anabolic steroids and green tea extract but other supplements, such as turmeric, have been newly described as a source of DILI. Worldwide prevalence of anabolic-androgenic steroids has been approximated to be 3.3%.[28] Liver injury typically presents clinically as significant jaundice with a primary histologic finding on biopsy of prominent canalicular cholestasis.[29,30] Mild non-specific portal and lobular inflammation have also been identified in a cohort of cases, and infrequently, patients can develop vascular injury in the form of peliosis hepatis.[31,32] Very rarely, the development of hepatic adenomas has been reported after long-term androgenic steroid use.[33] Various preparations of green tea, including extract used in herbal weight-loss supplements, can cause hepatotoxicity with a

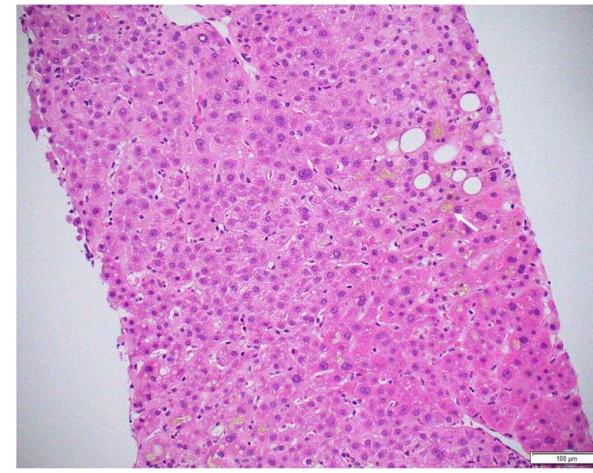

FIGURE 7. Bland cholestasis (arrow) due to amoxicillin-clavulanate. Other than hepatocellular and canalicular cholestasis, there is no significant inflammation or epithelial injury. Please see this image in color online.

hepatocellular pattern of elevated LFTs. A common finding on biopsies is necrosis, ranging from focal to massive; other reported features include portal inflammation, cholestasis, and slight fibrosis.[34,35] Of note, patients with HLA-B*35:01 have a higher prevalence of hepatotoxicity from green tea extract compared with patients with other HLA genotypes.[36] Finally, a developing cause of liver injury, turmeric, is a plant within the ginger family. Turmeric is a spice frequently used in cooking and a supplement marketed for treating arthritis and other inflammatory conditions. Recent studies showed variable patterns of injury including acute hepatitis (pan-lobular and zone 3 inflammatory patterns), cholestatic hepatitis, lobular histiocytic aggregates, chronic hepatitis, and autoimmune-like hepatitis with interface activity.[27,37–39]

LIPID-RELATED MEDICATIONS

Statins are one of the most frequently prescribed medications in the United States. The US Preventive Services Task Force recommends that statins be prescribed for prevention of cardiovascular disease (CVD) in patients between 40 and 75 years old with CVD risk factors and a 10-year CVD risk of 10%; in the United States, Medicaid was estimated to have covered 28.6 million statin prescription claims in 2022.[40,41] Statins are a well-established etiology of DILI with mixed hepatocellular and cholestatic LFTs. One histologic pattern is cholestatic hepatitis with bile duct injury, canalicular cholestasis, and hepatocellular cholestasis; in addition to cholestasis, one case found steatohepatitis with Mallory-Denk bodies and perisinusoidal fibrosis.[42] The second histologic pattern shows features of autoimmune hepatitis: portal and lobular hepatitis with interface activity comprised of lymphocytes and plasma cells.[43]

Other antilipemic agents, such as niacin and fibrates, are less frequently prescribed but also carry a low risk of hepatotoxicity. Niacin (vitamin B3) is prescribed to increase high-density lipoprotein (HDL) cholesterol. Hepatotoxicity occurs primarily with the sustained-release preparation of niacin, and biopsies have shown centrilobular cholestasis, ballooning degeneration, and variable necrosis.[44,45] Of the

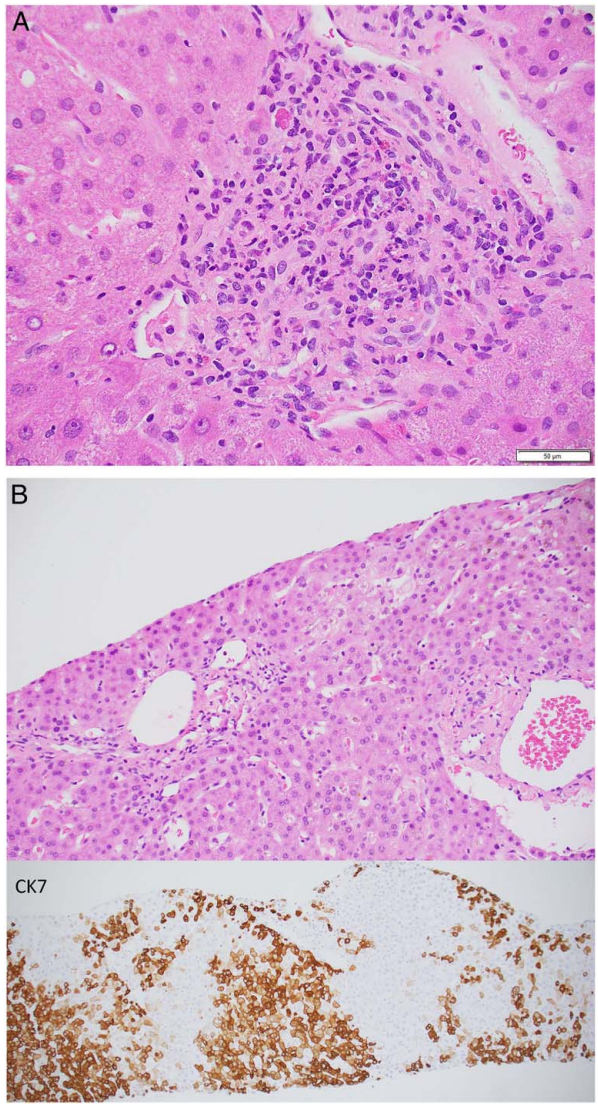

FIGURE 8. A, Biliary injury/cholangiopathy (acute) due to amoxicillin-clavulanate. Mild bile duct injury without significant evidence of chronic cholestasis (cholate stasis). B, Vanishing bile duct syndrome due to immunotherapy (pembrolizumab). Virtually no bile duct remains on H&E and CK7 immunostain. Please see this image in color online.

fibrates, fenofibrate most frequently causes DILI, but significant injury is rare (<0.3% of patients).[46] Ahmad and colleagues described 4 patients with diverse histologic features. Several patients presented with zone 3 cholestasis and mild portal inflammation, and one patient developed an autoimmune hepatitis pattern with bridging necrosis.[46]

ANTIHYPERTENSIVE MEDICATIONS

Between 2015 and 2020, an estimated 34.1 million patients in the United States utilized antihypertensive medications.[47] The treatment regimens and antihypertensive medication class are broad–our focus will be to address the most prevalent monotherapies, angiotensin-converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARBs),[48] as well as the medications with a high incidence of drug-induced liver injury: methyldopa and hydralazine. Both hydralazine and methyldopa are strongly associated with drug-induced autoimmune-like hepatitis, and rare cases of granulomatous hepatitis have been reported with both medications.[9,49,50] With methyldopa, additional histologic findings include patchy to massive necrosis, bile duct proliferation, cholestasis, and fibrosis ranging from periportal to end-stage cirrhosis.[51] Hydralazine-related injury can also have a variable pattern with acute hepatitis, cholestasis, and centrilobular necrosis.[52] Liver injury has been reported for a subset of angiotensin-converting enzyme inhibitors, including captopril, enalapril, fosinopril, lisinopril, and ramipril with biopsies showing prominent intrahepatic cholestasis.[53] Small case series and reports describe bile duct necrosis and centrilobular necrosis with ramipril and lisinopril, respectively.[53,54] ARB-associated DILI is uncommon; there have been rare cases of injury associated with candesartan, which presented histologically with ductopenia and portal inflammation with lymphocytes, plasma cells, and eosinophils.[55]

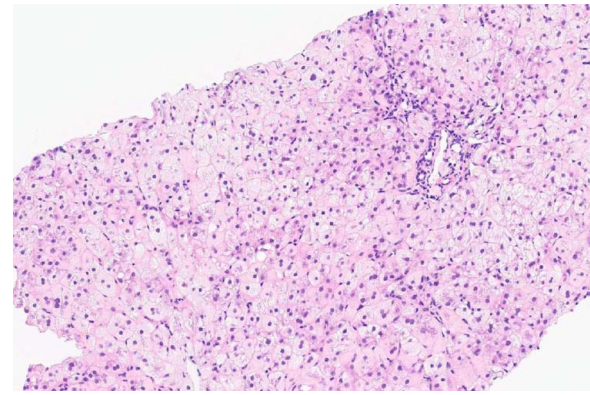

FIGURE 9. Pure microvesicular steatosis due to valproic acid. Diffuse microvesicular steatosis due to valproic acid (Image courtesy of Dr John Hart, University of Chicago). Please see this image in color online.

PAIN RELIEF MEDICATIONS

Acetaminophen is one of the most well-known culprits of drug-related liver injury; 48% of acute liver failure cases are estimated to be related to acetaminophen toxicity.[56] The primary histologic finding is extensive centrilobular necrosis (Fig. 1A, B), and of note, inflammation is usually minimal-to-mild.[57,58] DILI has also been reported in nonsteroidal anti-inflammatory medications (NSAIDs), most often with diclofenac, followed by ibuprofen, sulindac, acetylsalicylic acid, naproxen, piroxicam, and nimesulide.[59] However, the overall frequency in the United States is rare (about 1 to 10 cases per 100,000 prescriptions).[60] Liver biopsies are not usually required for diagnosis, so histologic descriptions of NSAID-associated hepatotoxicity are limited. A case series showed a nonspecific injury pattern with cholestatic hepatitis, plasma cells, eosinophils, and zone 3 necrosis.[61]

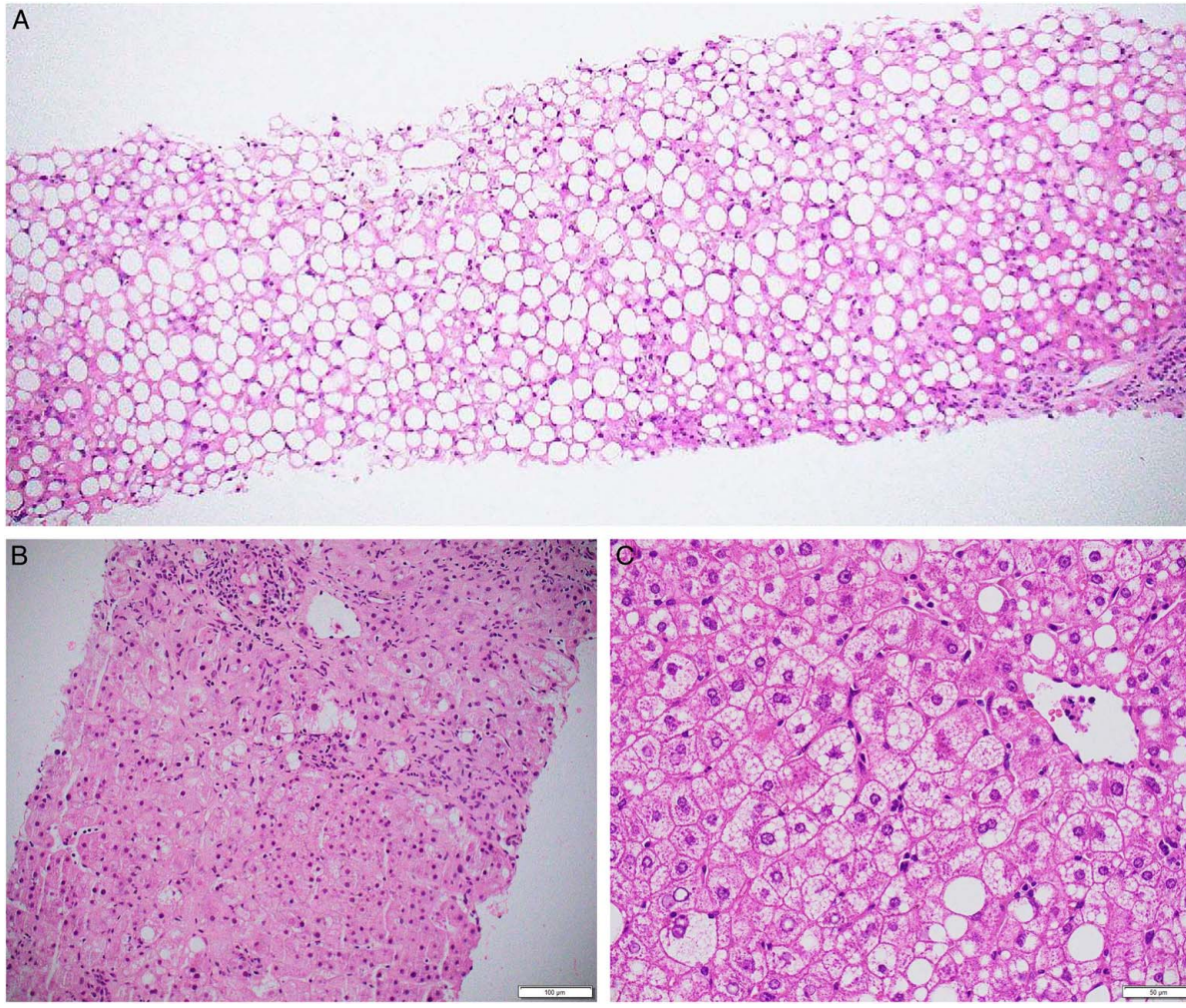

FIGURE 10. A, Diffuse steatosis due to asparaginase toxicity. Diffuse macrovesicular steatosis involving the entire liver lobule without any zonal variance. B, Prominent ballooning degeneration due to amiodarone toxicity. Prominent ballooning degeneration and Mallory hyaline without significant steatosis and clinical history of metabolic dysfunction should raise a red flag and prompt an investigation for drug-induced injury. C, Mixed macrovesicular and microvesicular steatosis due to irinotecan. Please see this image in color online.

BIOLOGICS FOR INFLAMMATORY BOWEL DISEASE

In moderate-to-severe active inflammatory bowel disease, biologics may be indicated if patients are nonresponsive to first-line therapies or have extraintestinal manifestations.[62] With tumor necrosis factor-α (TNF-α) antagonists, the most commonly reported culprit is infliximab, although DILI associated with etanercept and adalimumab has also been documented.[63] An autoimmune pattern of injury has been frequently identified on biopsy with interface hepatitis, plasma cell inflammation, eosinophilic inflammation, and variable necrosis; clinically these patients have also developed positive titers for ANA and ASMA.[63] Less frequently identified patterns of injury include acute hepatitis with lymphocyte predominant inflammation, nonspecific chronic hepatitis, and canalicular cholestasis.[64] One case report with infliximab-associated injury identified severe lobular cholestasis, necrosis, and bile duct loss, consistent with vanishing bile duct syndrome.[65] Of note, hepatitis B reactivation is a risk factor associated with TNF-α antagonist therapy.[66]

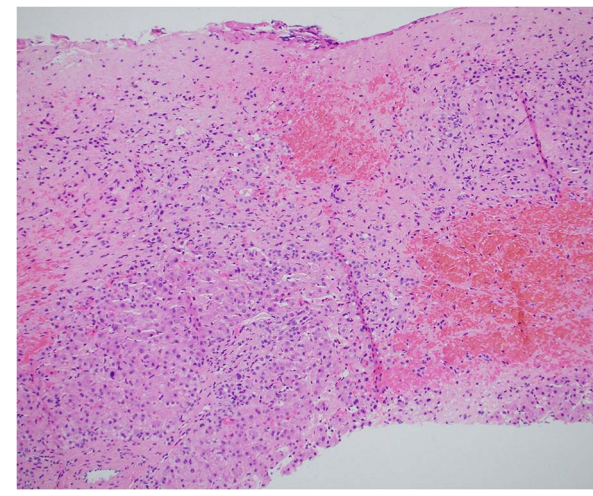

FIGURE 11. Budd-Chiari due to oral contraceptive. Extensive hemorrhage, hepatocyte dropout, and stromal hyalinization expanding from zone 3 to zone 1. Please see this image in color online.

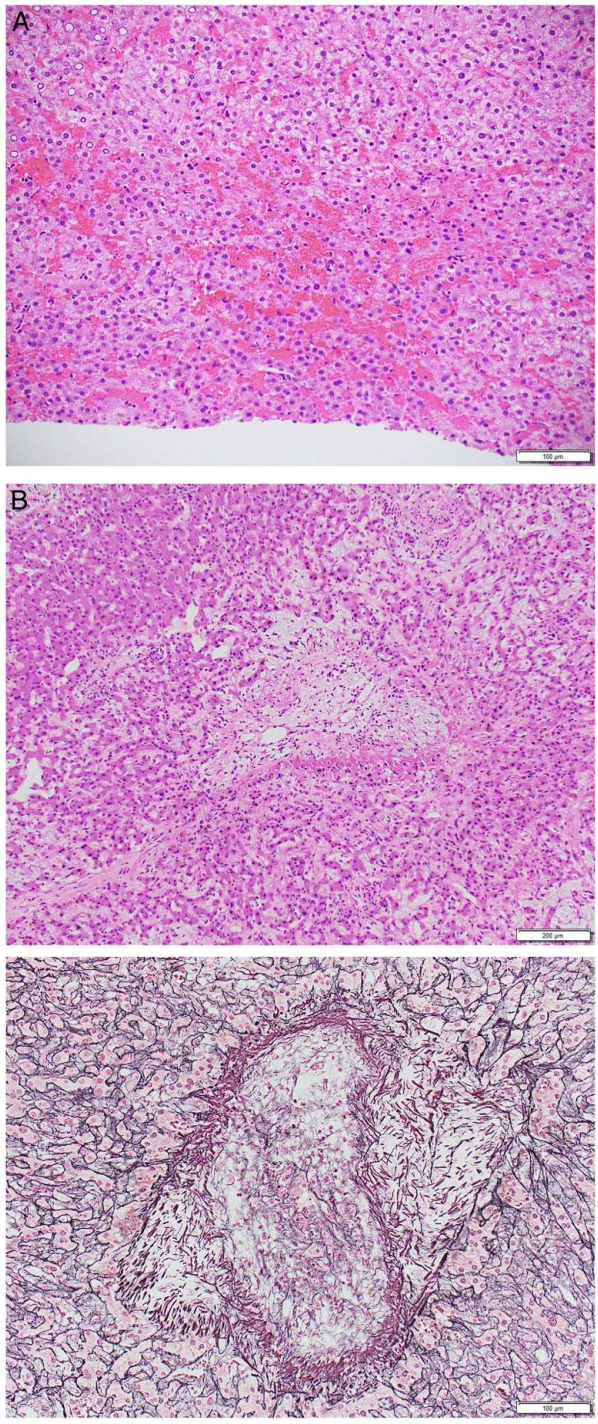

FIGURE 12. A, Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) due to Inotuzumab ozogamicin. Diffuse sinusoidal congestion with hepatocytes atrophy. B, SOS/VOD likely relate to carboplatin. Endothelial proliferation within central veins and vein wall fibrosis highlighted by reticulin stain.

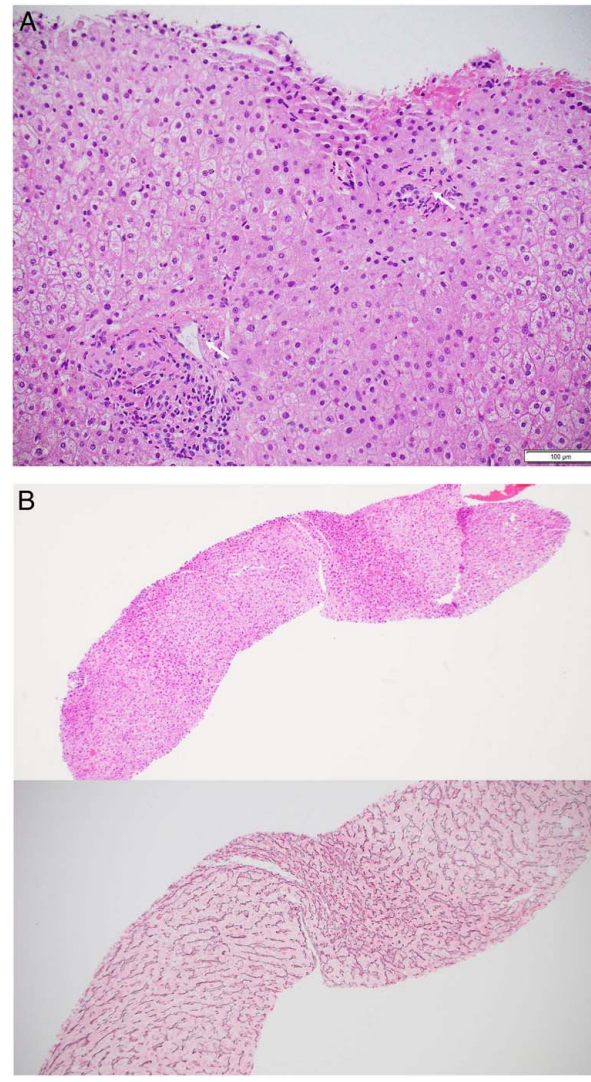

FIGURE 13. A, Porto-sinusoidal vascular disorder (PSVD)-like changes in a patient with breast cancer and oxaliplatin treatment. Hepatocyte regenerative changes and stenotic portal veins (arrows) in some portal tracts. Clinically, the patient had evidence of portal hypertension without cirrhosis. B, PSVD/nodular regenerative hyperplasia (NRH) due to T-DM1 (trastuzumab emtansine). Marked zonal hepatocyte hypertrophy alternating with atrophy, highlighted by reticulin stain, produces a nodular appearance without fibrosis. Please see this image in color online.

Anti-integrin therapies and interleukin blockers have been approved as treatment lines in inflammatory bowel disease. Although DILI is uncommon with anti-integrin medications, liver injury has been more frequently seen with natalizumab than vedolizumab. Of the limited biopsies that have been performed, natalizumab-associated injury has presented with autoimmune-like hepatitis.[67,68] In a small case cohort, vedolizumab-related injury presented with variable features of chronic cholangiopathy, portal inflammation, concentric periductal fibrosis, and nodular parenchymal degeneration.[69] Ustekinumab is a monoclonal antibody targeting interleukin-12 and interleukin-23 that has a markedly low risk of liver injury—only 0.5% of patients within one trial developed ALT elevations.[70] Rare case reports show liver biopsies with mild active lobular hepatitis and a chronic inflammatory infiltrate predominantly in zone 3, consistent

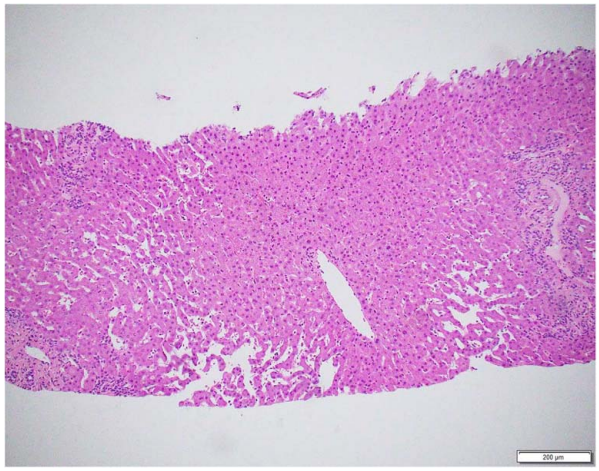

FIGURE 14. Sinusoidal dilatation due to oral contraceptive in a patient who developed peliosis hepatis. Notice the sinusoidal dilatation is more pronounced in zone 1 with intact zone 3, different from venous outflow obstruction. Please see this image in color online.

with drug-induced liver injury, as well as an autoimmune-like hepatitis pattern with portal lymphoplasmacytic infiltrate and patchy necrosis.[71,72] Similar to other immunomodulators, ustekinumab carries a risk of reactivation of HBV and HCV in a subset of patients.[73]

IMMUNE CHECKPOINT INHIBITORS

The role of immune checkpoint inhibitors in chemotherapy regimens has rapidly grown since 2011, when ipilimumab, an antibody that targets cytotoxic T-lymphocyte antigen 4 (CTLA-4), was first introduced.[74] In addition to CTLA-4, targets for ICIs include PD-1, PD-L1, and more recently LAG3. ICIs are utilized to treat a wide variety of solid tumors, including but not limited to melanoma, cervical cancer, non-small cell lung carcinoma, and mesothelioma.[75] With the expansion of ICIs, there has also been an increase in the recognized immune-related adverse effects (irAEs).

Hepatotoxic irAEs are screened for by monitoring aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase—elevations above the upper limit of normal are graded using the Common Terminology Criteria for Adverse Events (CTCAE). Grades 3 and 4 (LFTs $>$ 5x ULN and $>$ 20x ULN, respectively) are considered severe and require treatment with steroids or additional immunosuppressive agents.[76] Severe hepatotoxicity is generally uncommon and is dependent upon the ICI prescribed. The highest incidence of grade 3 to 4 hepatic injury is 11% with high-dose ipilimumab, and the lowest incidence is 0.14% with pembrolizumab monotherapy.[76]

Most frequently ICI-associated injury presents with a pan-lobular lymphohistiocytic inflammation with variable sinusoidal histiocytic aggregates, granulomatous inflammation, and necrosis (Fig. 6A). The second most common pattern of injury is cholangiopathic with portal-based inflammation, biliary injury, duct loss, or ductular reaction. Further classification and histologic details for ICI-induced hepatitis have been previously described.[77]

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