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Recent Advances in the Histopathology of Drug-Induced Liver Injury

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SYNOPSIS

The field of drug-induced liver injury is constantly changing as new drugs are approved and as new herbals and dietary supplements (HDS) reach the market. The pathologist plays a key role in the evaluation of drug-induced liver injury (DILI) by classifying and interpreting the histological findings considering the patient's medical history and drug exposure. The liver biopsy findings may suggest alternative explanations of the injury and additional testing that should be performed to exclude non-DILI etiologies. Recent reports of iatrogenic liver injury are reviewed with attention to immunomodulatory and anti-neoplastic agents as well as reports of injury associated with HDS use.

Keywords

hepatotoxicity; acute hepatitis; autoimmune hepatitis; hepatic necrosis; cholestasis

Drug-induced liver injury (DILI) is one of the more challenging areas in liver pathology. The complexity of the challenge derives from multiple sources. There are over 350 separate drugs that have been associated with some risk of liver injury in the publicly available reference website LiverTox (livertox.nlm.nih.gov) (1). Each drug may have one or more characteristic clinical presentations and patterns of injury. In well over half of these drugs, the type of injury (clinical and/or histological) has only been the subject of case reports or small series, so that the worldwide published experience is very limited. Overall, the incidence of DILI is low, with population-based incidence rates that vary from 8.1 per 100,000 over a 3-year period in France (2) to 19.1 per 100,000 over a 2-year period in Iceland (3). The incidence of DILI due any individual drug is difficult to estimate, but is

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certainly much lower. Liver biopsies are not performed on all cases of DILI. In the U.S. Drug Induced Liver Injury Network (DILIN), biopsies were performed in only about 50% of cases and were available for central review in only about 33% (4). In a similar clinical network established across Spain to register cases of DILI, biopsy results were only available in about 25% of cases (5). Thus, the potential biopsy material available for review to any one pathologist will be limited, even at busy academic medical centers. The challenge is compounded by co-morbidities that affect the liver and by polypharmacy. Pathologists, as the expert interpreters of tissue findings, must strive to discern the diagnostic possibilities and to offer alternative, non-DILI possibilities for the injury. This review will cover both the basic evaluation of the liver biopsy in cases of suspected DILI as well as some of the recent published information on DILI histology.

Evaluation of the Liver Biopsy

Since a liver biopsy is not a required part of the work-up for a case of suspected DILI, the clinician submitting the biopsy will likely have questions about the etiology of the liver injury. They may be looking for the pathologist to confirm their clinical suspicion of DILI when most of the other possibilities have been excluded, or DILI may be only one of several possible etiological considerations. In some cases, the drug may be providing a clear therapeutic benefit and the clinician may be looking for guidance as to whether the drug may be safely continued, as in the case of methotrexate. Finally, DILI might not be suspected at all but might be suggested by the pathologist.

Figure 1 diagrams an approach to the liver biopsy in cases of suspected DILI (6). It is best to start with an unbiased evaluation of the liver pathology to determine a pattern of injury. The liver, like other organs, shows stereotyped responses to injury that can be organized into particular patterns related to differential diagnosis. Hans Popper was the first to categorize DILI in this fashion, dividing cases into six histologic patterns of injury: zonal necrosis, hepatitis with or without cholestasis, acute hepatitis-like with or without massive necrosis, simple cholestasis, reactive hepatitis and steatosis (7). The U.S. DILIN used a larger classification of 18 categories in its blinded review of cases of suspected DILI. Table 1 organizes the patterns of injury into those that have been most commonly observed in studies of acute DILI and those that are less common. In this DILIN study, necroinflammatory and cholestatic patterns accounted for 86% of the cases(8) while all but one of the cases in Popper's study(7) and 95% of the cases in Andrade's study(5) could be placed into one of these seven patterns. The steatotic patterns are relatively rare. Macrovesicular steatosis and steatohepatitis present with modest elevations of aminotransferases and normal bilirubin and so fail to meet the protocol entry (9), while drug-induced microvesicular steatosis is restricted to a limited list of agents that primarily injure mitochondria (10). The vascular injury patterns are also uncommon in the large cohort studies, which may also relate to case selection bias and a limited number of implicated agents (11). The patterns of glycogenosis (12, 13), ground-glass cell change (14) and inclusions (15, 16) may sometimes be associated with sufficient laboratory abnormalities to result in a biopsy, but are uncommon in the cohort studies.

Once the biopsy has been evaluated for the pattern of injury, and the severity of the lesions has been assessed, the pathologist should establish the non-DILI histological differential diagnosis (Table 1). This process can be analyzed with respect to the clinical history, laboratory and imaging findings. The emphasis should be placed on identifying a non-DILI explanation for the injury, as DILI should always be a diagnosis of exclusion. Depending on the clinical evaluation prior to liver biopsy, additional testing may be suggested by the histologic injury pattern. Checklists of information recommended for publication of DILI cases can be used to identify potentially useful tests (17). If DILI cannot be excluded, the possibility that DILI caused the injury can be entertained. The patient's list of medications can be evaluated for suspects based on several factors, including the temporal exposure to the medication and the likelihood of the medication to cause the pattern of injury observed. Drugs tend to be associated with some injury patterns more than others. For example, minocycline is usually associated with non-cholestatic hepatitis patterns, occasionally with cholestatic hepatitis and not associated with zonal necrosis or acute cholestasis (8, 18).

Recent Reports of Histological Injury Patterns in DILI

The primary literature remains a major reference point for pathologists for information on patterns of liver injury that may be associated with particular agents. However, most of the literature is fragmented, with the primary data scattered across the entire breadth of the medical literature in the form of case reports and small series. Only a portion of the literature describes the results of liver biopsies and fewer still show photomicrographs of the findings. Table 2 summarizes such reports published since 2015 in the English literature along with the pattern(s) of injury extracted from the articles using the written descriptions and photomicrographs according to the classification presented in Table 1.

Herbals and Dietary Supplements

Although a large number of different agents are reported, several themes emerge. First, while most of the reports concern prescription-based pharmaceuticals, the second largest category are herbals and dietary supplements (HDS). HDS encompasses a broad category of agents that includes vitamin and mineral supplements, fish oils, plant extracts, ethnic traditional medicines and proprietary commercial products. In the U.S., HDS are consumed by half or more of the U.S. population(19) and the U.S. Food and Drug Administration may only require limited safety testing of new products prior to marketing(20). Like more conventional medications, there have been numerous case reports and small series implicating HDS with liver injury. In a study drawn from the U.S. DILIN cohort, Navarro et al. identified 136 cases (15%) out of 839 patients who had liver injury due to HDS (21). They divided this group into those with injury due to HDS marketed for bodybuilding (45 cases), HDS marketed for other purposes (85 cases) and patients who were taking both types of HDS at the time of the injury (6 cases). In comparing the bodybuilding HDS cases to the non-bodybuilding HDS cases and DILI due to conventional medications, there was no difference in the rate of hospitalization, but the cases of injury due to non-bodybuilding HDS were much more likely to develop evidence of acute liver failure or undergo liver transplantation than either of the other two groups. The types of non-bodybuilding HDS implicated in cases that led to death or transplantation spanned the full variety of these

agents, from weight loss and energy boosting supplements to Asian herbal remedies to multivitamins. A number of recent studies have focused on acute hepatitis and liver failure associated with proprietary mixtures of HDS such as Herbalife (22, 23) and OxyELITE Pro (24, 25). It is often difficult or impossible to identify the component of the mixture that might be the causal agent, or if two or more of the components are interacting to cause injury. Acute hepatitis and cholestatic hepatitis are the patterns of injury most frequently associated with these compounds (Figure 2A).

On the other hand, while bodybuilding HDS were associated with a high rate of hospitalizations (71%), none of these patients died or required liver transplantation. Bodybuilding agents sometimes contain anabolic steroids, which have been associated with several patterns of injury, most commonly with acute cholestasis or cholestatic hepatitis (26) along with sinusoidal dilation (27) and peliosis hepatis (28) (Figure 2B). They have also been associated with hepatocellular tumors, particularly hepatocellular adenomas (29). The mechanism of cholestasis in these cases is poorly understood, but it is strongly associated with 17-alpha alkylation of the steroid backbone (30), perhaps in individuals with bile salt transporter mutations(31).

Immunomodulating Agents and Drug-Induced Autoimmune Hepatitis (DIAIH)

Among the pharmaceutical agents listed in Table 2, there are several agents that stand out. There are several drugs used to control the immune system, including methylprednisolone, the anti-tumor necrosis factor (TNF) agents infliximab and adalimumab, and the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) agent, ipilimumab and the anti-alpha 4 integrin antibody, natalizumab. Methylprednisolone was the subject of three case reports (32–34), two of which showed the same injury pattern: (acute) hepatitis with zonal necrosis. Corticosteroids have been associated with steatosis and may exacerbate underlying chronic hepatitis, but methylprednisolone in particular has been associated with an autoimmune-like hepatitis after several weeks of therapy (35, 36). The mechanism of this paradoxical injury is unknown.

The anti-TNF agents infliximab, adalimumab and etanercept are all potent anti-inflammatory drugs that are used to treat inflammatory bowel disease and various rheumatic conditions. Infliximab and adalimumab are monoclonal antibodies that bind to and block TNF alpha. Etanercept is a soluble form of the TNF alpha receptor that binds to TNF alpha circulating in the serum. All three of these agents have been associated with severe acute liver injury(37) and can cause reactivation of hepatitis B. Two newer members of the class, certolizumab and glumumab, have not yet been reported to cause serious liver injury, but likely or may? have the same potential as the other monoclonal antibodies. Infliximab is the best studied, with most cases reported in the literature. Ghabril et al. summarized the experience in the U.S. DILIN with their report of 6 cases of anti-TNF DILI(37). In their summary of published cases, 26 were due to infliximab while etanercept and adalimumab each accounted for 4 cases. The most common histological pattern of infliximab DILI is acute or chronic hepatitis with features of autoimmune hepatitis (AIH) (Figure 3). These patients frequently have elevated titers of anti-nuclear antibodies and sometime other serological findings as well. Other patterns that have been observed some cases include

hepatocellular necrosis without an associated infiltrate and acute cholestasis(37). Of the 20 cases of anti-TNF agents published in the last two and a half years, 18 showed hepatitis which was usually described as autoimmune-like while there was only one case of acute cholestasis and one mild reactive hepatitis (38–41).

Ipilimumab and tremelimumab are monoclonal antibody agents directed against CTLA-4. CTLA-4 is an immune checkpoint protein that inhibits the activation of cytotoxic T lymphocytes and results in persistent activation of these immune cells. Ipilimumab in particular has been associated with a variety of autoimmune-like reactions with a minority of cases involving the liver(42, 43). The series reported by Johncilla et al. (44) described a panlobular hepatitis with central vein endothelialitis (Figure 4). About half of the cases had a prominent plasma cell infiltrate. Of note, several patients had also received nivolumab, another type of immune-checkpoint inhibitor and combination therapy has been associated with an increased number of immune-related adverse events (45). None of the patients in this series had serological markers of AIH, in contrast to idiopathic AIH and the anti-TNF agents.

Natalizumab interferes with immune responses by blocking migration of lymphocytes to areas of inflammation. It is used in the treatment of multiple sclerosis and inflammatory bowel disease and its use has been associated with an increased risk of central nervous system infection by polyomaviruses. Post-marketing surveillance has resulted in a number of reports of liver injury to regulatory agencies but only a few case reports have been published (46). In the case reported by Antezana et al., there was a lymphoplasmacytic infiltrate in the portal areas with interface hepatitis as well as hepatocyte dropout in zone 3. Serology was positive only for low titers of anti-smooth muscle antibody and anti-F-actin. The hepatitis resolved without corticosteroid treatment as documented by a follow-up liver biopsy. They summarized 11 cases from the literature, 7 of which had liver biopsies. All had autoimmune-like infiltrates and 4 of the 7 also had positive serologies.

The cases of DILI described above raise the difficult issue of distinguishing idiopathic AIH from drug-induced autoimmune hepatitis (DIAIH). Both conditions are diagnoses of exclusion and often require a liver biopsy for confirmation. The incidence of AIH is low—about 1.9 per 100,000 (47), in the range of the overall incidence of DILI. There are a number of drugs that have been associated with either clinical or histological presentation mimicking AIH. These include nitrofurantoin, minocycline, hydralazine, methyldopa and the statins. In a large retrospective study, Bjornsson et al. examined 261 patients with AIH and identified 24 (9%) that appearance to be medication-related (48). In most of these cases, the implicated drug was nitrofurantoin or minocycline. There were few differences between the histology of the DIAIH cases and the rest of the AIH cases except that none of the DIAIH cases were cirrhotic. A study from the U.S. DILIN cohort examined cases of nitrofurantoin, minocycline, hydralazine and methyldopa since these are drugs most commonly associated with DIAIH(18). Although most of the minocycline and nitrofurantoin cases presented with serological finding of AIH, only half of the hydralazine and methyldopa cases had positive serologies. Not all the cases had typical AIH pathology either; 29% of the cases showed cholestatic hepatitis. Hisamochi et al. investigated a cohort of 16 DILI cases with AIH-like findings on biopsy and divided them into two groups based on whether they relapsed after an

initial treatment period (49), a finding that was suggested by Bjornsson's study as a differentiation factor between idiopathic AIH and DIAIH (48). They identified no clinical or histological differences between these two groups, but the sample size was small. Nevertheless, liver biopsy remains a useful tool, particularly in cases in which either the clinical presentation or the histological findings do not fit with idiopathic AIH. Cholestasis in a suspected DIAIH case has been suggested as a finding in favor of a drug etiology (50).

Temozolomide and Vanishing Bile Duct Syndrome (VBDS)

Three of the recent case reports concern temozolomide, an anti-neoplastic alkylating agent mainly used in the treatment of gliomas (51–53). Temozolomide mainly causes cholestatic patterns of injury, spanning from acute cholestasis to cholestatic hepatitis to chronic cholestasis with ductopenia. Bile duct injury with a high incidence of significant bile duct loss characterizes most of the cases. In a study of four cases by Grant et al., three demonstrated at least mild ductopenia and the fourth showed bile duct injury (54). Because the drug is used to treat a highly lethal malignancy it is difficult to understand the long-term hepatic implications of the duct loss, but at the very least the patient is deprived of a potentially effective medication if they recover from the hepatic injury. In general, vanishing bile duct syndrome (VBDS) is a diagnosis associated with poor prognosis. In a recent series of 26 patients with VBDS due to DILI, 7 patients either underwent liver transplant or died in follow-up, despite treatment with corticosteroids and ursodiol (55). Even if the liver survives, recovery is likely to be delayed. Patient with liver enzyme abnormalities persisting more than a year after onset are more likely to show chronic cholestatic changes with or without ductopenia than any other pattern of injury (56).

The Pathologist's Role in the Evaluation of Suspected DILI

The first job of the pathologist is always the careful evaluation of histological changes. When a liver biopsy is performed in a case of suspected DILI, determination of drug involvement becomes a collaborative effort between the pathologist and the patient's physician. With expert interpretation of histological findings, the liver biopsy can identify alternate etiologies and raise or lower the likelihood of a particular drug injury based on reported patterns. As Table 2 suggests, the histological landscape of findings is constantly changing as new drugs are approved and cases are published. The histological findings may influence clinical decision-making. Additional testing may be indicated. Both the histological pattern of injury and the severity of injury (inflammation, necrosis, fibrosis, cholestasis, vascular) should be clearly communicated in the written report and the pathologist may consider supplementing the interpretation as new clinical information is generated in follow-up. Although DILI may be one of the more challenging areas of hepatic pathology, the potential clinical benefit of a carefully interpreted biopsy is incalculable and is well worth the extra time investment that the case may require.

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Photomicrographs in Figure 2 and 3 courtesy of the U.S. Drug-induced Liver Injury Network.

Abbreviations

DILI	Drug-induced liver injury
DILIN	Drug-induced liver injury network
VBDS	Vanishing bile duct syndrome
AIH	Autoimmune hepatitis
PBC	Primary biliary cholangitis
CVID	Common variable immunodeficiency
LDO	Large duct obstruction
PFIC	Progressive familial intrahepatic cholestasis
HDS	Herbal and dietary supplements
DIAIH	Drug-induced autoimmune hepatitis
TNF	Tumor necrosis factor
CTLA-4	cytotoxic T-lymphocyte antigen-4

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KEY POINTS

- Liver biopsy provides clinically useful information on differential diagnosis and character of injury in drug-induced liver injury (DILI)
- The pattern of injury on biopsy relates to the etiological differential diagnosis, including both drug and non-drug etiologies
- Recent reports of DILI show several themes, including injury from herbals and dietary supplements and from traditional pharmaceuticals
- A variety of immunomodulatory agents have been associated with DILI in recent years, most associated with an autoimmune hepatitis-like injury.

¹Unusual patterns include cholestatic hepatitis, combination patterns (e.g. cholestasis with steatohepatitis), and patterns with eosinophils, granulomas and necrosis

Figure 1. Algorithm for Biopsy Evaluation in Suspected Drug-Induced Liver Injury. From Kleiner (6).

Figure 2.

Examples of HDS injury. A. Acute hepatitis associated with a green tea containing supplement. There is diffuse parenchymal injury with inflammation, hepatocyte swelling and rosette formation. (H&E, 100x). B. Acute cholestasis associated with anabolic steroids. Numerous bile plugs are present in canaliculi. (H&E, 600x).

Figure 3.

Autoimmune hepatitis-like injury from Infliximab. A. Dense portal inflammation with zone 3 inflammation is evident from low power (H&E, 100x). B. Interface hepatitis with plasma cells (H&E, 600x). C. Perivenular inflammation with hepatocyte dropout (H&E, 400x).

Figure 4.

Injury associated with ipilimumab. A. Diffuse parenchyma and portal inflammation without necrosis. (H&E, 100x). B. Portal inflammation with bile duct injury and increased numbers of eosinophils (H&E, 400x). C. Perivenular inflammation with focal endothelialitis (H&E, 600x).

Table 1

Common and Uncommon Patterns of Injury in DILI

Pattern	Characteristic Features	Caveats	Non-DILI Etiologies	
			Common	Uncommon
Common Patterns				
Zonal Coagulative Necrosis	Zone 3 or 1 coagulative necrosis, usually without significant inflammation	Steatosis may be seen in the non-necrotic parenchyma; veins should be examined for changes of veno-occlusive disease	Hypoxic-ischemic injury	
Submassive to Massive Necrosis	Extensive pan-acinar necrosis, variable inflammation	Often a consequence of severe acute hepatitis	Fulminant viral or autoimmune hepatitis	Herpetic or adenoviral hepatitis
Acute (Lobular) Hepatitis	Lobular-dominant inflammation with/without confluent or bridging necrosis; no cholestasis	Mild presentations will overlap with nonspecific reactive hepatitis	Acute viral or autoimmune hepatitis	Graft-vs-host disease
Chronic (Portal) Hepatitis	Portal-dominant inflammation, interface hepatitis (also includes mononucleosis pattern), with or without portal-based fibrosis; no cholestasis	Mild presentations will overlap with nonspecific reactive hepatitis	Chronic viral or autoimmune hepatitis	Early PBC, EBV hepatitis, CVID, Hepatitis A
Cholestatic Hepatitis	Acute or chronic hepatitis pattern plus zone 3 cholestasis	Often an inverse relationship between the severity of inflammation and severity of cholestasis	Acute viral hepatitis (acute form), acute LDO	Graft-vs-host disease, PFIC
Acute Cholestasis (Intrahepatic, Canalicular)	Hepatocellular and/or canalicular cholestasis in zone 3; may show duct injury, but little inflammation	Hepatocytes may be complete normal or may be ballooned in areas of cholestasis.	Sepsis, acute large duct obstruction (LDO), post-surgical cholestasis,	Benign recurrent intrahepatic cholestasis
Chronic Cholestasis	Periportal cholate stasis, periportal fibrosis, copper accumulation, duct sclerosis or injury, duct loss	Zone 3 cholestasis may also be seen	PBC, sclerosing cholangitis, chronic LDO	Ischemic cholangitis, idiopathic ductopenia, PFIC
Uncommon Patterns				
Granulomatous Hepatitis	Inflammation dominated by granulomas (usually non-necrotizing), portal or lobular	Granulomas are usually non-fibrogenic and may be mixed with lymphocytes or eosinophils	Sarcoidosis, PBC, fungal or mycobacterial infection	Atypical bacterial or rickettsial infection
Steatosis, microvesicular	Predominantly microvesicular steatosis, inflammation variable	Small groups of hepatocytes with microvesicular steatosis may be seen in the context of other injury patterns		Cholesterol ester storage disease and variants, alcoholic foamy degeneration, fatty liver of pregnancy
Steatosis, macrovesicular	Predominantly macrovesicular steatosis without significant portal or lobular inflammation, no cholestasis	Vacuoles may be variably-sized but cells should not have a foamy appearance	Obesity, diabetes, alcohol	Lipodystrophy
Steatohepatitis	Zone 3 ballooning injury, sinusoidal fibrosis, Mallory bodies, variable inflammation and steatosis, no cholestasis	Ballooning should not be the cell swelling sometime seen with cholestasis	Obesity, diabetes, alcohol	Lipodystrophy

Pattern	Characteristic Features	Caveats	Non-DILI Etiologies	
			Common	Uncommon
Sinusoidal Obstruction syndrome/ Veno-occlusive disease	Occlusion or loss of central veins, thrombosis, with or without central hemorrhage and necrosis	Masson trichrome stains useful to identify occluded central veins		Environmental toxins
Hepato-portal sclerosis	Disappearance of portal veins	Often a subtle finding unless there are clear occlusive changes in the portal veins		Environmental toxins
Nodular regenerative hyperplasia	Diffuse nodular transformation, with or without mild inflammation and sinusoidal fibrosis	Should always be in the differential when minimal changes are apparent on the routine stain	Collagen vascular diseases, CVID, lymphoproliferative diseases	
Sinusoidal Dilation/Peliosis	Sinusoidal alterations with/without mild lobular inflammation, sinusoidal fibrosis	Sinusoidal dilation may be associated with atrophic hepatocyte plates	Central venous hypertension	
Glycogenosis	Diffuse hepatocyte swelling with very pale bluish-gray cytoplasm		Type 1 diabetes	
Ground-glass change	Diffuse homogenization of cell cytoplasm due to induction of smooth endoplasmic reticulum			
Hepatocellular inclusions (poly-glucosan like bodies)	Discrete cytoplasmic inclusions that stain variably with periodic-acid Schiff			

Abbreviations: PBC: Primary biliary cholangitis; CVID: Common variable immunodeficiency; LDO: Large duct obstruction; PFIC: Progressive familial intrahepatic cholestasis

Table 2

Case reports and small series reporting iatrogenic hepatic injury findings, 2015–2017

Author, Year	Implicated Agent	Histological Pattern(s) *
Pharmaceutical Agents		
Slim, 2015(57)	Acetaminophen	Cholestatic hepatitis
Eder, 2015(58)	Agomelatine	Chronic hepatitis
Taylor, 2016(59)	Anakinra	Acute hepatitis
Kumar, 2015(60)	Artemisinin	Cholestatic hepatitis
Carrascosa, 2015(61)	Atorvastatin	Chronic hepatitis
Yun, 2016(62)	Bicalutamide	Cholestatic hepatitis
Chintamaneni, 2016(63)	Bupivacaine	Cholestatic hepatitis (2)
Kumagai, 2016(64)	Camostat mesilate and/or benzbromarone	Chronic hepatitis (AIH-like)
Pisapia, 2015(65)	Clopidogrel	Acute hepatitis with cholestasis
Bessone, 2016(66)	Cyproterone acetate	Submassive to massive necrosis (3); acute hepatitis with cholestasis (2); AIH-like chronic hepatitis (1); Cirrhosis (1)
Miyashima, 2016(67)	Daclatasvir/Asunaprevir	Acute on chronic hepatitis with eosinophilia
Bohm, 2016(68)	Febuxostat	Acute cholestasis
Harati, 2016(69)	Hydralazine	Acute hepatitis with zone 3 necrosis
Bjornsson, 2015(38)	Infliximab	Acute hepatitis (3); mild reactive hepatitis (1); acute cholestasis (1)
Parra, 2015(39)	Infliximab	Acute hepatitis with necrosis
Shelton, 2015(41)	Infliximab	AIH-like hepatitis (6)
Rodrigues, 2015(40)	Infliximab (7), Adalimumab (1)	AIH-like chronic hepatitis (8)
Villamil, 2015(70)	Interferon beta 1a	AIH-like acute hepatitis
Kim, 2016(71)	Iodine-131	Acute hepatitis
Johncilla, 2015(44)	Ipilimumab	Acute hepatitis (9), Acute cholangitis (1)
Jung, 2016(72)	Levocetirizine	Chronic hepatitis
Salvado, 2015(73)	Masitinib	AIH-like acute hepatitis
Stelzer, 2015(74)	Mesalazine	Granulomatous hepatitis
Davidov, 2016(32)	Methylprednisolone	Acute hepatitis with zone 3 necrosis
Grilli, 2015(33)	Methylprednisolone	Chronic hepatitis with incomplete cirrhosis
Oliveira, 2015(34)	Methylprednisolone	Hepatitis with zone 3 necrosis
Sakamura, 2017(75)	Multi-agent chemotherapy	Veno-occlusive disease
Antezana, 2015(46)	Natalizumab	Acute hepatitis with zone 3 necrosis
Bernardes, 2015(76)	Nimesulide	Acute hepatitis with extensive necrosis
Kumar, 2015(77)	Oral contraceptives	Sinusoidal dilation
Conrad, 2016(78)	Sertraline	Ductal paucity
Dyson, 2016(79)	Sofosbuvir	Cholestatic acute hepatitis (superimposed on underlying cirrhosis) (2)
Aygun, 2016(51)	Temozolomide	Cholestatic hepatitis
Balakrishnan, 2016(52)	Temozolomide	Cholestatic hepatitis with ductopenia
Grieco, 2015(53)	Temozolomide	Acute cholestasis

Author, Year	Implicated Agent	Histological Pattern(s) *
Herbals and Dietary Supplements		
Brazeau, 2015(27)	Anabolic steroid supplement	Sinusoidal dilation
Yokomori, 2016(80)	Freshwater clam extract supplement	Acute cholestasis
Corey, 2016(81)	Garcinia cambogia	Acute hepatitis with massive necrosis
Jin, 2015(82)	Herbal medication (not specified)	Nodular regenerative hyperplasia
Rios, 2016(22)	Herbalife products	Hepatoportal sclerosis (2)
Alhaddad, 2016(83)	Khat	Cholestatic hepatitis (1); Chronic hepatitis (1); Possible confounding prior liver disease
Mahamoud, 2016(84)	Khat	Chronic hepatitis, bridging fibrosis
Gedela, 2016(85)	Kombucha tea	Chronic hepatitis
Hayashi, 2016(86)	Multiple dietary supplements	Acute hepatitis with zone 3 necrosis
Heidemann, 2016(24)	OxyELITE Pro	Massive necrosis (2); Severe hepatitis with necrosis (1); Cholestatic hepatitis (1)
Occupational and Recreational Agents		
Atayan, 2015(87)	Ecstasy	Zonal necrosis
Ito, 2016(88)	Organic solvents	Acute hepatitis

* Numbers in parentheses indicate case numbers when multiple cases are reported.