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Drugs and Toxins Effects on the Liver

Piero Luigi Almasio, Anna Licata and Claudia Randazzo
University of Palermo,
Italy

1. Introduction

Drug induced hepatotoxicity can be defined as a liver injury caused by drug or herbal medicines leading to liver test abnormalities or to a liver dysfunction with a reasonable exclusion of the other competing aetiologies. The liver has a central function in the metabolism of the xenobiotics, and as a result it may be susceptible to its toxic or idiosyncratic effects. While the overall incidence of drug induced liver injury (DILI) is infrequent (1 in 10.000 to 100.000 persons exposed), the impact is significant in the general population, with broad implications for patients, physicians, pharmaceutical industries and governmental regulatory agencies. DILI is the principle reason for the termination in clinical trials and the most frequent adverse event leads to drug non approvals, withdrawals or to a restriction of prescription drug use after an initial approval and post-marketing regulatory decisions. DILI has been shown to have a dose-dependent component. However, most of the cases of DILI are due to idiosyncratic reactions: over 1000 drugs and herbal products have been associated with idiosyncratic hepatotoxicity. It is difficult to establish a diagnosis of DILI. In fact, there is no single pathognomonic test to establish that a given drug in a given subject is the cause of liver injury. Furthermore, the clinical presentation of DILI may considerably vary. It can mimic other known forms of acute and chronic liver diseases and the severity may range from asymptomatic elevations of hepatic enzymes to fulminant hepatic failure. Because of these factors, a diagnosis of DILI is frequently delayed or may be entirely missed. So, the study of DILI is confounded by the heterogeneity of its clinical presentation and by the course of the injury, the delay in establishing diagnosis as it requires exclusion of other causes of liver injury, the lack of standardized criteria or specific 'gold standard' diagnostic tests and underreporting of cases of DILI or their final outcomes. The aim of this chapter is to provide a review and an update of DILI.

2. Epidemiology

Internationally, the data on the true incidence of DILI in the general population remain unknown because of the several methodological limitations of the reporting systems. Most of the epidemiological studies are retrospective and lack standardized diagnostic work-up to exclude other potential causes of the liver injury. Moreover, most studies originate from tertiary referral centres and suffer from selection bias. The underreporting of adverse drug reactions is well known and DILI is not an exception. The number of

included patients in most of the clinical drug trials is less than 10.000 and hepatotoxicity has been mostly detected in the post-marketing phase. According to reporting systems, the incidence in the general population varies between 1.27 per 100.000 person a year in rural England to 2.4 in Spain and Sweden. Among medical inpatients, the incidence is 1.4 %, whereas in an outpatient setting it is 0.014 % for patient a year. In the United States (USA), approximately 2000 the cases of acute liver failure (ALF) occur annually and drugs account for over 50% of them (39% are due to acetaminophen, 13% are idiosyncratic reactions due to other medications). Drugs account for 2-5% of cases of patients hospitalized with jaundice and approximately 10% of all the cases of acute hepatitis. However, these numbers are likely underestimated. The epidemiology of DILI is influenced by geographic and cultural factors. In Western countries, the majority of cases are associated with antibiotics and psychotropic agents. In the USA, for instance, amoxicillin/clavulanate, isoniazid, nitrofurantoin and fluoroquinolones are the most frequent causes of DILI. In Asian countries, herbal and dietary supplements rather than conventional medications are often the most common causes of DILI; herbals/dietary supplements currently represent less than 10% of the cases of DILI in Western countries, although this proportion seems to increase. In the last few years, the USA Food and Drug Administration (FDA) have withdrawn two drugs from the market for causing severe liver injury: bromfenac and troglitazone. Bromfenac, a non-steroidal anti-inflammatory drug (NSAID), was introduced in 1997 as a short-term analgesic for orthopedic patients. Although approved for a dosing period of less than 10 days, patients used it for longer periods. This resulted in more than 50 cases of severe hepatic injury, and the drug had to be withdrawn in 1998. Troglitazone is a thiazolidinedione and was approved in 1997 as an antidiabetic agent. Over 3 years, more than 90 cases of hepatotoxicity were reported, which resulted in a withdrawal of this drug. Kava kava, an herb used for anxiety, was reported as being hepatotoxic and was withdrawn from the German market. The FDA has also issued a warning in this country. This demonstrates the importance of a post-marketing surveillance to identify reactions that are not reported or are underreported in drug trials. Pemoline, used for attention deficit disorder and narcolepsy is no longer available in the USA. The FDA concluded that the overall risk of liver toxicity from pemoline outweighs the benefits. Other drugs having significant use limitations because of their hepatotoxic effects are felbamate, an antiepileptic used for complex partial seizures; zileuton, indicated for asthma; tolcapone, used for Parkinson's disease; trovafloxacin, an antibiotic; benoxaprofen, a NSAID and tienilic acid, a diuretic.

3. Mechanism of hepatotoxicity

The liver is the principal organ for metabolism and elimination of many drugs. The majority of oral drugs and xenobiotics are lipophilic and water-insoluble, enabling easy absorption across cell intestinal membranes. They are rendered hydrophilic via hepatic metabolism and thus more easily excreted. Exogenous products are metabolized in the liver mainly through phase I and II reactions. The products are then excreted on either the canalicular and sinusoidal membranes (phase III reactions). During phase I metabolism, polar groups are added to lipophilic molecules by oxidation, reduction or hydrolysis to increase water-solubility. This group of reactions is catalyzed by a super family of enzymes located in the

smooth endoplasmic reticulum, known as cytochrome P450 (mixed function oxidases). These membrane-bound hemoproteins carry out reactions in concert with nicotinamide adenine dinucleotid phosphate (NADPH) as a source of electrons, so they can generate toxic electrophilic chemicals and free radicals. Following phase I metabolism, most compounds are still insufficiently hydrophilic for excretion and require further processing. Phase II reactions result in the formation of readily excretable, nontoxic substances. The drug or its metabolite are conjugated in cytosol to a large water-soluble polar group, such as glutathione (GSH), glucuronic acid, sulfate, glucuronide. The enzymes responsible for this so-called phase II metabolism are glucuronosyl transferases, sulfotransferases and GSH transferases. Phase III reactions lead to the transport of drugs and metabolites out of hepatocytes. Biliary excretion is mediated by ATP-dependent transporters located in the bile canaliculi. Altered activity of these transporters can lead to hepatotoxicity. Genetic polymorphisms or environmental factors, such as concomitant drugs and alcohol, can account for differences in phase I, II and III drug metabolism among individuals and may be determinants of the susceptibility to DILI by influencing the hepatic exposure to toxic metabolites.

3.1 Mechanisms of injury

The drugs can directly have an effect on the cellular biochemistry or elicit an immune reaction. In most of the instances, the bioactivation of drug to chemically reactive metabolites or free radicals promote some chemical reactions (i.e. depletion of reduced glutathione and/or covalent bind intracellular macromolecules) leading to their changes. The reactive metabolites may induce the mitochondrial dysfunction resulting in a decrease in ATP levels; the consequential disassembly of the actin fibrils on the surface of the hepatocyte causes blebs and rupture of the membrane. Furthermore, toxic metabolites influence the transport of proteins through the canalicular membrane with the interruption of the bile flow. The stoppage of the transport pumps such as a multidrug resistance (MDR)-associated protein 3 prevents the excretion of bilirubin, causing cholestasis. Alternatively, the drugs/metabolites have the capacity to initiate immunological reactions, including both innate and adaptive immune responses. Hepatocyte stress and/or damage could result in the activation of the innate immune system. Natural killer (NK)-NKT cells in the liver modulate the innate immune response by secreting interferon (IFN)-gamma, interleukin (IL)-4, and so directly killing the cells by FasL expression. Kupffer cells, NK and NKT cells contribute to the progression of liver injury by producing pro-inflammatory mediators such as cytokines, chemokines, reactive oxygen intermediates and reactive nitrogen intermediates. These pro-inflammatory mediators can be directly cytotoxic (e.g., hydrogen peroxide, nitric oxide, peroxynitrite) and degrade the extracellular matrix (e.g., collagenase, elastase); furthermore they promote a cell adhesion and infiltration (e.g., IL-1, tumor necrosis factor-alpha, chemokines). In addition, the adaptive immune system is activated and involved in the pathogenesis of the liver injury. The reactive metabolite may covalently bind to or alter the liver proteins, such as cytochrome P450 enzymes, activating cytotoxic T cells and cytokines (immune-mediated injury). The mechanism of the immune-mediated drug reaction is not clear, but it may involve a hapten-like action. Generally, the low-molecular-weight organic chemicals are not immunogenic, but may become such when they are

bound to a macromolecule, such as a protein. If a drug metabolite produced by cytochrome P450 is able to act as a hapten, it covalently binds to a liver protein, so it will perceive as foreign by the immune system, resulting in an autoimmune attack on the normal hepatocellular constituents. This hypothesis, however, does not explain many aspects of immune-mediated DILI. For instance, covalent binding (haptenation) is a regular occurrence with drugs, such as halothane, that rarely cause an immune-mediated toxicity. It is possible that a reactive metabolite also has to injure or stress the liver cells, in addition to a modification of a protein, and may cause an immune response. The outcome of the events initiated by toxic metabolites either directly affecting the cellular biochemistry or inducing immune-mediated response is the cell death. The mode of the cell death may be apoptosis or necrosis. Apoptosis involves shrinkage, organelles compaction, nuclear condensation and fragmentation of the cell into smaller bodies with the intact plasma membranes. The apoptotic cells are then rapidly removed by phagocytosis. Necrosis is characterized by a cell swelling and a membrane lysis with a release of the cytoplasmic contents. Apoptosis generally represents the activation of an enzyme-mediated autolytic cell disposal system, whereas necrosis represents a loss of osmotic regulation. Apoptosis results from the activation of a family of highly conserved proteases (caspases) through a membrane-associated death receptor. The drugs that alter the expression and function of the death receptors disrupt the mitochondrial functions and can be expected to activate apoptosis. If apoptosis occurs at a rate that exceeds the capacity of the phagocytic cells to remove the apoptotic cells, large fields of contiguous cells will swell and lyze. The selection between apoptosis versus necrosis depends on several factors, involving the ATP status. A more severe injury to mitochondria leads to a cellular energetic impaired; as a consequence the osmotic regulation is lost and the cell undergoes to swelling and lysis (necrosis), whereas a less severe injury to mitochondria without a profound ATP depletion can maintain the osmotic regulation and undergo to apoptosis. Hepatocyte death is the main event that leads to a liver injury, although the sinusoidal endothelial cells or the bile duct epithelium may also be targets.

4. Classification

DILI can be classified according to the clinical presentation and the laboratory features, the mechanism of toxicity and/or the histological findings (see section 5).

4.1 Clinical pattern

A consensus defined the liver injury as an increase of more than twice the upper limit of the normal range (ULN) in the levels of serum alanina aminotransferase (ALT) or alkaline phosphatase (Alk P) and total bilirubin, providing that one of these was more than twice the ULN. The Council for International Organizations of Medical Sciences (CIOMS) developed a series of standard designations of DILI and a classification of the injuries. According to these, the pattern distinction is based on the ratio of serum ALT results to Alk P with respect to their ULN. A ratio > 5 denotes an hepatocellular injury and a ratio < 2 denotes a cholestatic injury. Ratios between 2 and 5 are categorized as mixed. In the case in which ALT or Alk P are elevated before the medicine is started, the baseline values can be taken into account instead of the ULN.

Type of injury			
	Hepatocellular	**Cholestatic**	**Mixed**
ALT	> twice normal	normal	> twice normal
Alk P	normal	> twice normal	> twice normal
ALT/Alk P	≥ 5	≤ 2	2 – 5
	Acetaminophen Allopurinol Amiodarone Amoxicillin– clavulanic acid Baclofen Herbals: kava kava and germander Isoniazid Ketoconazole Lisinopril Losartan Methotrexate NSAIDs Omeprazole Paroxetine Rifampin Risperidone Sertraline Statins Tetracyclines Trazodone Trovafloxacin Valproic acid	Amoxicillin–clavulanic acid Anabolic steroids Chlorpromazine Clopidogrel Oral contraceptives Erythromycins Estrogens Irbesartan Mirtazapine Phenothiazines Terbinafine Tricyclics	Amitriptyline Azathioprine Captopril Carbamazepine Clindamycin Cyproheptadine Enalapril Flutamide Nitrofurantoin Phenobarbital Phenytoin Sulfonamides Trazodone Trimethoprim– sulfamethoxazole Verapamil

Table 1. Pattern of drug-induced liver Injury

4.1.1 Hepatocellular (hepatitis) injury

The majority of drugs produce a hepatocellular pattern of injury. Most of these instances are asymptomatic and mild. When they are severe, patients on average have symptoms similar to those expected in the ones with an acute viral hepatitis. The laboratory features typically included a normal complete blood count, although a mild increase in white count may occur, and a minority of patients with immunoallergic-type reactions will show a peripheral eosinophilia. Given the fact that the underlying pathogenesis involves primarily an apoptosis and/or a necrosis of the hepatocytes, the serum aminotransferases levels are elevated. For most of the drugs producing an idiosyncratic DILI, the degree of elevation of serum aminotransferases is generally less marked than in the cases of intrinsic hepatotoxicity caused by acetaminophen, carbon tetrachloride or other halogenated hydrocarbons. The serum Alk P is generally normal or mildly elevated (less than twice the ULN). Serum total and direct bilirubin are variable. The hepatobiliary imaging shows a normal liver or a diffuse homogeneous hepatomegaly. It is very important the lack of evidence of the dilatation of the biliary tree or cholecystitis especially when patients are

jaundiced. The typical findings on liver biopsy, during an acute injury, are variable and greatly dependent upon the causative drug. In most of the instances of a hepatocellular injury a rapid improvement in symptoms, signs and laboratory features can occur when the medication is discontinued.

4.1.2 Cholestatic pattern of injury

The typical manifestations of a cholestatic drug-induced hepatitis are jaundice and itching. The classic laboratory features are the elevations in serum Alk P, which is more than twice the ULN, and in the serum total and direct bilirubin. Serum aminotransferases are normal or only mildly elevated. In general, the hepatobiliary-pancreatic imaging findings show no evidence of the biliary dilatation and of the pancreatic abnormalities. The liver is usually normal or nearly normal. The typical iter of the cholestatic hepatitis is more protracted than in the hepatocellular DILI. In fact, it is not uncommon for signs and laboratory worsening to continue after the drug has been stopped, sometimes for a period of 30-60 days. There is a gradual improvement thereafter, unless the categories of the drugs are re-administered. There are rare instances in which the injury does not resolve but rather goes on to produce chronic liver diseases.

4.1.3 "Mixed" pattern of injury

The 'mixed' pattern, as the name implies, involves hepatocellular and cholestatic manifestations. The usual clinical ones are nausea, anorexia, and vomiting when severe; also jaundice and itching are present. The typical laboratory findings may include serum aminotransferase levels higher than three times the ULN and serum Alk P, total and direct bilirubin being more than twice the ULN. The biopsy features for the two types of injury are also a mixture of characteristics described above. The general course is longer than in the hepatocellular injury, but shorter than in the pure cholestatic DILI.

4.2 Mechanism of toxicity

The toxic hepatocellular injury may be classified into two groups: predictable (intrinsic) and unpredictable (idiosyncratic) reactions. The predictable drug reaction accounts for 80% of all toxicities. Intrinsic hepatotoxins cause predictably a dose-dependent hepatocellular necrosis (higher concentrations cause more liver damage) and which can be reproducible in the animal models. The latent period between the exposure and the onset of the reaction is brief (i.e. hours/days) and varies from person to person. Most cases of DILI hepatotoxicity are related to idiosyncratic reactions. The main characteristic of this type of reaction is the apparent unpredictability of the liver injury in human beings. The effects tend to be species-specific and often cannot be reproduced experimentally on the laboratory animals. There is no a constant relationship between the dose and the occurrence or severity of the drug reaction, and the latent period between the exposure to it and the sensitivity reaction is quite variable. Idiosyncrasy may be either metabolic or immunologic/allergic. In the first case, a covalent binding of drug metabolites to the cellular structures can damage the cellular functions causing the cell death. The immunologic reactions are the hypersensitivity reactions to a specific drug. The immunologic response depends upon the interaction of the drug and its metabolites with the immune system, with a resultant hepatocyte necrosis and apoptosis; this can cause the release of cytokines that can lead to the secondary cell damage

or can have immune modulating effects. There is a prompt recurrence of symptoms in response to the drug re-challenge of one or two doses.

5. Histology

Specific histological patterns of liver injury caused by a drug-induced damage are discussed below.

5.1 Acute hepatocellular injury

The landmarks of an acute hepatocellular injury are the portal and the parenchyma inflammation and/or necrosis. By definition, fibrosis is absent. Regenerative features such as binucleate hepatocytes and thick cell plates are common. Prominent Kupffer cells are often present in the sinusoids. The acute hepatocellular injury can result in necrosis affecting single (spotty necrosis) or groups of hepatocytes (confluent necrosis). Hepatocellular necrosis consists of a ballooning degeneration or apoptosis associated with an infiltration of the inflammatory cells and can be zonal or nonzonal, depending upon the offending drug. Zonal necrosis is characteristic of compounds with a dose-dependent toxicity, such as carbon tetrachloride and acetaminophen (zone 3). Isolated necrosis affecting zones 1 and 2 is rare; toxins such as cocaine and ferrous sulfate or phosphorus poisoning typically affect zone 1 (periportal), while beryllium has been implicated in zone 2 necrosis. Nonzonal necrosis is more often seen with compounds that produce an idiosyncratic injury (i.e. phenytoin, methyldopa, isoniazid, and diclofenac).
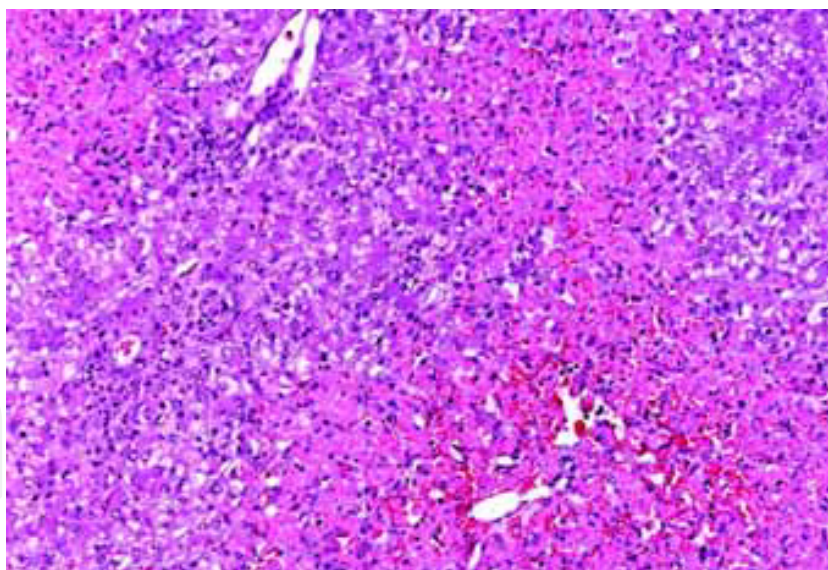

Fig. 1. Acetaminophen toxicity. Hepatocellular necrosis present in a zonal, centrilobular pattern; the inflammatory infiltration is minimal

5.1.1 Fulminant hepatitis

There are three morphological categories related to ALF. Extensive microvesicular steatosis (rare) has been observed with tetracycline and nucleoside analogues such as zidovudine. Necrosis with a marked inflammatory activity is the most common pattern seen in the idiosyncratic reactions. The confluent necrosis involves most of the liver parenchyma

(massive/submassive hepatic necrosis) and the mainly implicated drugs are isoniazid, others are antimicrobial agents (sulfonamides, cotrimoxazole, ketoconazole), monoamine oxidase inhibitors and anticonvulsants (phenytoin, valproate). Necrosis with little or no inflammation is seen with acetaminophen, recreational drugs such as cocaine and 3,4-methylenedioxymethylamphetamine (MDMA; ecstasy), industrial organic compounds such as carbon tetrachloride, and some herbal preparations.

5.2 Chronic hepatocellular injury

A progression to chronicity has been reported in 5-10% of DILI and it is higher for the cholestatic/mixed injury pattern and can reveal with many forms. A chronic hepatitis with negative autoimmune markers presents histological features indistinguishable from the chronic viral hepatitis, and a progression to fibrosis can occur. Drugs associated to it include lisinopril, sulfonamide, trazodone and chemotherapeutic agents such as uracil, 5-fluorouracil pro-drug tegafur and tamoxifen. Isolated case reports implicate numerous other drugs including phenytoin and the Chinese herb Jin bu huan. Several drugs and herbs (i.e. minocycline, nitrofurantoin, diclofenac, fenofibrate, phenytoin, germander, statins, ecstasy) can cause a chronic hepatitis that is serologically and morphologically indistinguishable from de novo type I of the autoimmune hepatitis (AIH).
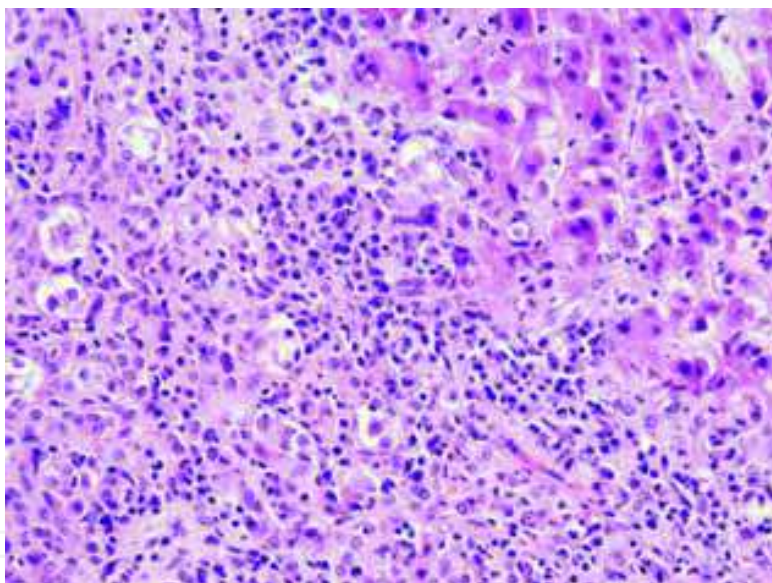

Fig. 2. Minocycline-induced autoimmune hepatitis. Necroinflammatory activity with several plasma cells

The lipofuscin pigment storage in the hepatocytes has been reported with phenothiazines, phenacetin, aminopyrine, and cascara sagrada. An hemosiderin accumulation in the liver cells may result from the excessive iron ingestion or the parenteral iron. Phospholipidosis is rare. It may develop acutely, but it is more commonly seen after a prolonged administration of the offending agent. This condition has been described in the patients taking amiodarone, amitriptyline, trimethoprim-sulfamethoxazole, chloroquine. The hepatocytes can be seen as foamy as a consequence of phospholipid accumulation in the lysosomes. These abnormal, lamellated lysosomes are visible through the electron microscopy (Figure 3).
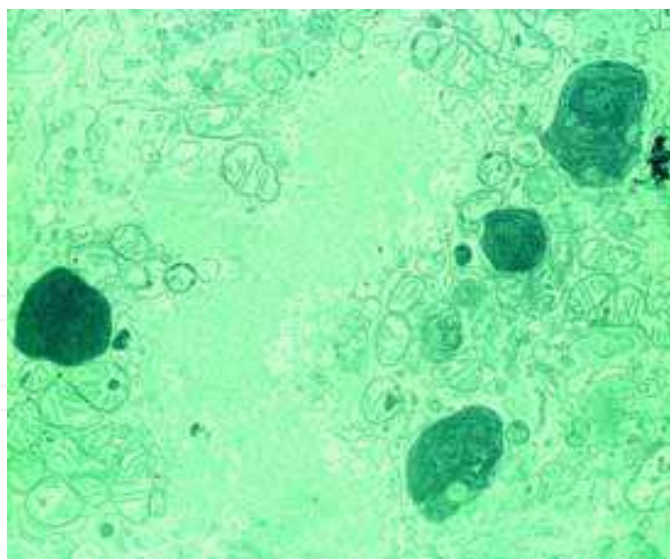
Fig. 3. Histological pattern of hepatic phospholipidosis. Presence of lysosomal inclusion bodies due to an accumulation of amiodarone

5.3 Acute cholestasis

Two forms of this histological pattern of injury can be observed. Canalicular (bland or non-inflammatory) cholestasis is characterized by bile plugs in the hepatocytes or canaliculi and it is more prominent in zone 3. Inflammation and hepatocellular injuries are not detected. Drugs causing this type of injury interfere with the hepatocyte secretion of the bile components through the bile salt excretory protein (BSEP). The degree of cholestasis is characteristic for each drug; typical examples are the anabolic steroids (Figure 4) and the oral contraceptives. Hepatocanalicular (cholangiolitic or inflammatory) cholestasis is accompanied by a portal inflammation and by only a slight hepatocytes injury, usually localized in the zones of the cholestasis. Cholestatic hepatitis is the classic pattern seen with macrolide antibiotics such as erythromycin (figure 5) and the antipsychotic agent chlorpromazine. This pattern manifests as a mixed-type injury on the liver biochemical tests.
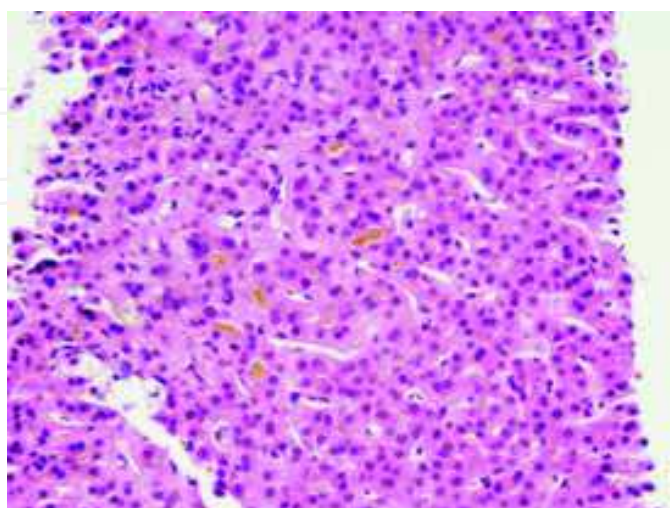

Fig. 4. Anabolic-steroid-induced cholestasis. Bile plugs present in the hepatocytes and canaliculi without inflammation or hepatocellular damage
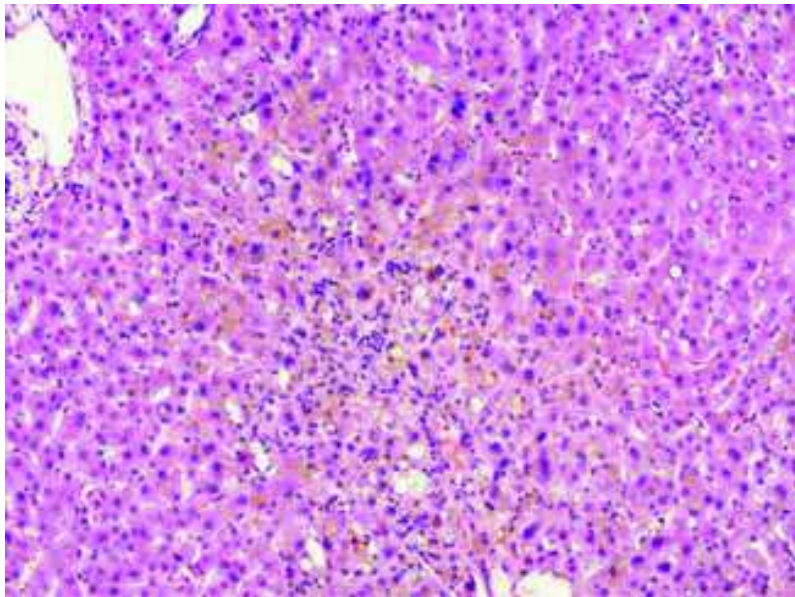
Fig. 5. Erythromycin-induced cholestatic hepatitis. Features similar to an acute hepatitis, as well as bile plugs in the hepatocytes and canaliculi

5.4 Chronic cholestasis and ductopenia

Drugs causing long-lasting cholestasis (longer than 3 months) and ductopenia include antibiotics (amoxicillin-clavulanic acid, flucloxacillin), antifungals (terbinafine), amiodarone (Figure 6). If the disease persists for a few months or further, it can occur a loss of bile ducts and an overt ductopenia termed ''vanishing bile duct syndrome''. A persistent inflammation and a bile ductular reaction may also be present. A vanishing bile duct syndrome can be triggered by anticonvulsants (carbamazepine, zonisamide), antipsychotics (chlorpromazine, sulpiride), NSAIDs (ibuprofen, tenoxicam) and antibiotics (amoxicillin, flucloxacillin, clindamycin, trimethoprim-sulfamethoxazole).
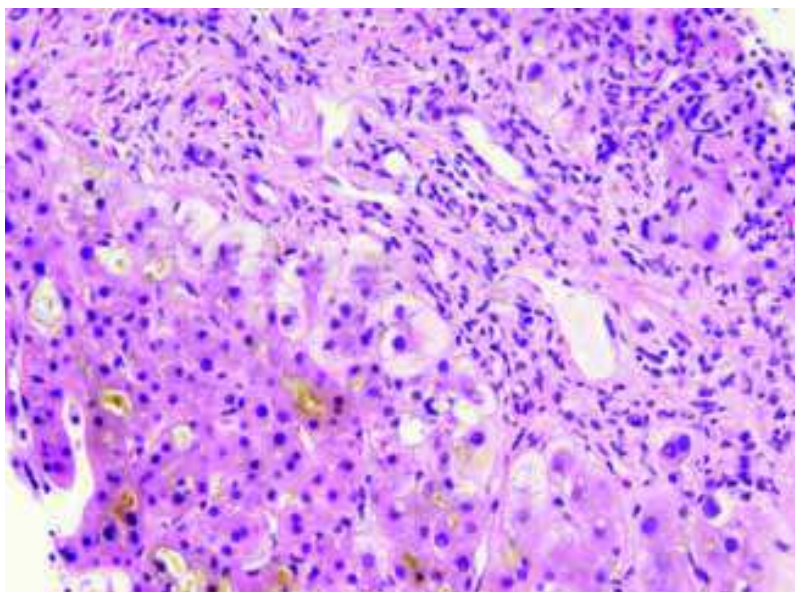

Fig. 6. Prolonged cholestasis. Persistence of canalicular bile plugs associated with a feathery degeneration of the periportal hepatocytes

5.5 Granulomatous hepatitis

At least 60 drugs have been selected to cause hepatic non-caseating granulomas, for instance allopurinol, amiodarone, diazepam, diltiazem, isoniazid, sulfonamides and sulfonylureas. Unlike in the primary biliary cirrhosis, the granulomas are habitually located in the periportal and portal tracts. They can be associated with a hepatocellular injury (granulomatous hepatitis) or cholestasis, but are more often silent and it is usually transient. The term fibrin-ring granuloma has been used for small granulomas characterized by a ring of fibrin around a central fat vacuole. Epithelioid histiocytes are present around the ring of fibrin. Fibrin-ring granulomas have been described with allopurinol, BCG vaccination and intravescical therapy for carcinoma. Gold salts may lead to the formation of lipogranulomas with black pigments.
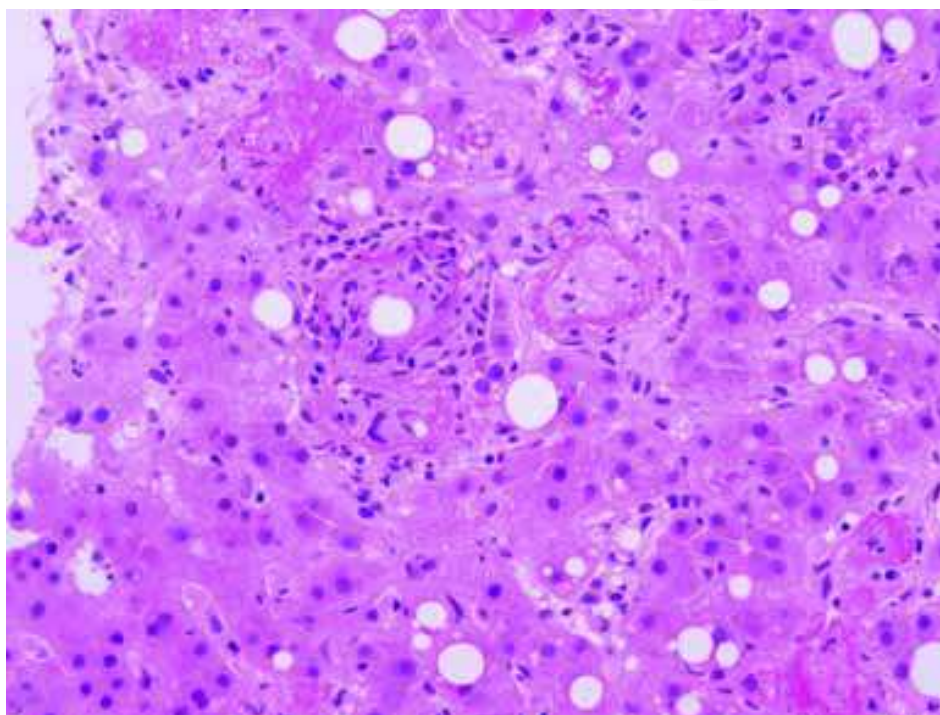

Fig. 7. Fibrin-ring granulomas. Fat vacuole surrounded by a ring of fibrin and epithelioid cells

5.6 Steatosis and steatohepatitis

Steatosis secondary to drug toxicity may be in the form of medium-sized and large droplets (macrovesicular) or small droplets (microvesicular). The term ''large droplet fat'' is used when at least half of the hepatocyte cytoplasm is full of a single lipid vacuole, while multiple lipid vacuoles are seen in the small droplet fat. Drugs that can cause macrovesicular steatosis include corticosteroids, methotrexate, nifedipine, parenteral nutrition, gold, NSAIDs (ibuprofen, indomethacin, sulindac), antihypertensives (metoprolol) and chemotherapeutic agents (5-fluorouracil, cisplatin, tamoxifen). An exclusive or predominant microvesicular steatosis is the result of mitochondrial injury and is observed with aspirin (Reye's syndrome), cocaine, high doses of tetracycline, valproic acid and zidovudine. By definition, steatohepatitis is characterized by steatosis, lobular inflammation and hepatocellular ballooning (with or without the acidophil bodies

or Mallory hyaline) or pericellular fibrosis. A few drugs (particularly amiodarone and irinotecan) play a direct aetiological role in the steatohepatitis. Many other drugs exacerbate or precipitate steatohepatitis in the presence of other risk factors such as obesity and diabetes.

5.7 Vascular lesions

The drug-induced hepatic vascular disease is uncommon but can have several manifestations. Vascular lesions result from the injury of the endothelium. The hepatic sinusoidal obstruction syndrome (veno-occlusive disease) is due to the occlusion of the terminal hepatic venules and sinusoids rather than the hepatic veins and inferior vena cava that manifests histologically as an endothelial swelling and thrombosis. The resultant venous outflow obstruction leads to a sinusoidal dilatation, congestion, hepatocellular necrosis, resulting in centrilobular fibrosis. Cytotoxic/chemotherapeutic drugs (i.e. oxaliplatin) can cause injury to the sinusoidal endothelial and hepatic stellate cells. Other drugs associated with veno-occlusive diseases include pyrrolizidine alkaloids (found in herbal remedies), azathioprine, mercaptopurine, vitamin A, tetracycline.
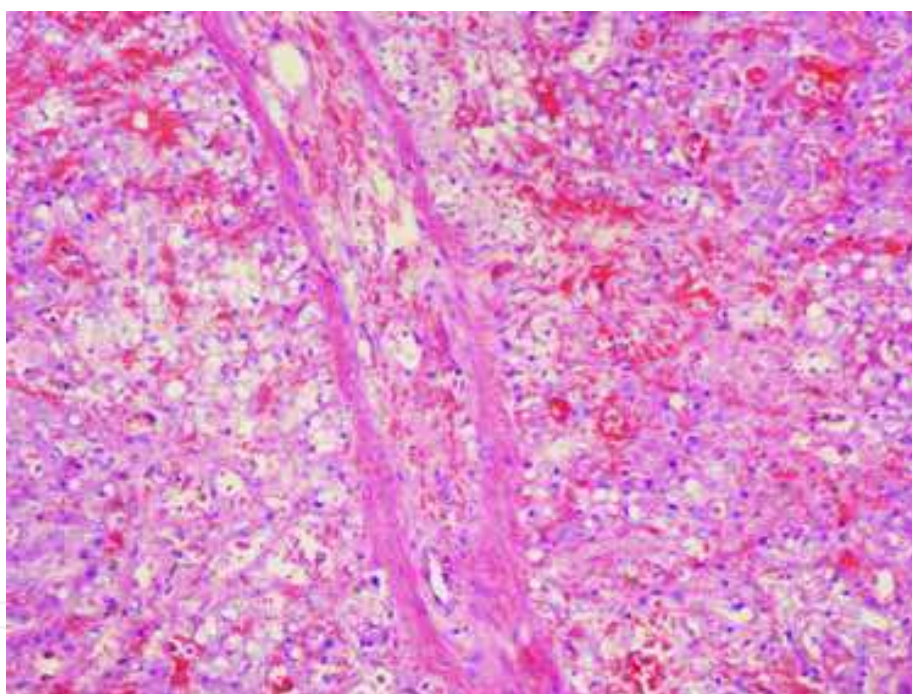

Fig. 8. Veno-occlusive disease. Endothelial injury in small hepatic venules leading to sinusoidal dilatation and congestion.

Peliosis is rare and is characterized by multiple, small, dilated blood-filled cavities without an endothelial coating in the hepatic parenchyma. It can be caused by several drugs including anabolic steroids, arsenic, azathioprine, mercaptopurine, danazol, tamoxifen, vitamin A and hydroxyurea. Lesions may resolve with a discontinuation of the offending agent. The hepatic venous outflow obstruction is a rare complication that may arise from a drug-induced thrombosis of the hepatic veins or of the inferior vena cava. The most well-known drugs associated with this syndrome are the oral contraceptives and dacarbazine. Clinically it manifests as the Budd-Chiari syndrome.
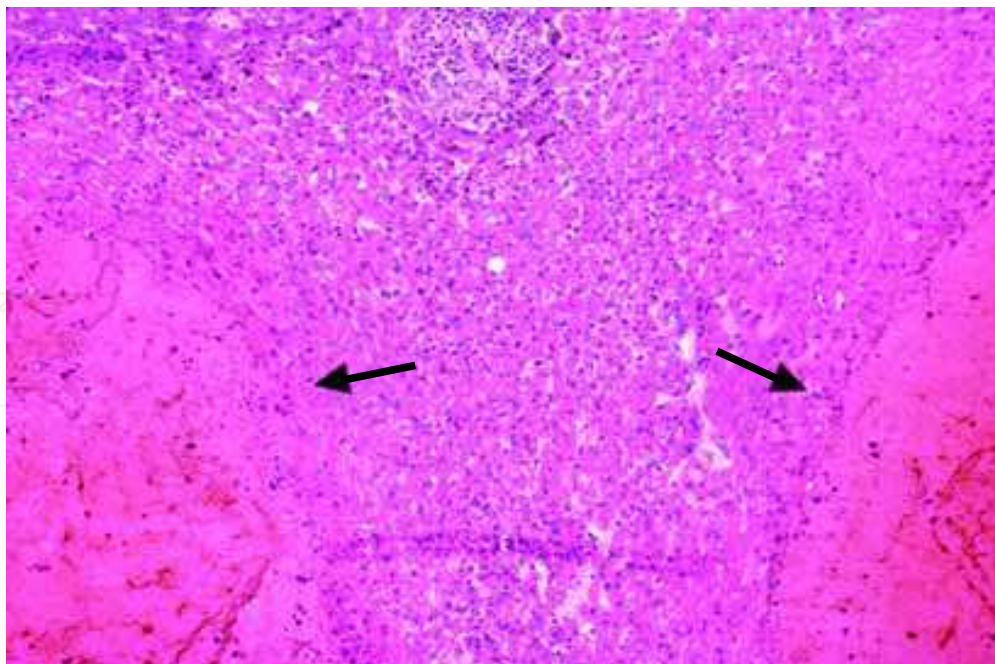
Fig. 9. Peliosis. Hepatic parenchyma containing blood-filled cavities without an endothelial lining

6. Diagnostic elements

DILI is a diagnosis of exclusion that relies on multiple elements in the medical history, presentation, laboratory results.

6.1 Time to onset

The time to onset (latency) is evaluated from the first day on which the suspected drug(s) was taken to the day on which the symptoms or the laboratory test abnormalities are manifested. A definition of the exposure to the drug and the hepatic toxicity is not always clear because the initial symptoms can be vague and are poorly remembered; the onset of the symptoms can occur days or weeks after the medication is stopped; laboratory tests are obtained at an arbitrary time. Furthermore, the drug can be stopped and started or given in several courses or in different doses and patients may take multiple medications making the identification of a single offending agent difficult.

6.2 Clinical and laboratory features

The clinical presentation varies from the asymptomatic mild liver test abnormalities to a symptomatic acute liver disease. Many drugs can induce asymptomatic high levels of the liver enzymes without producing an overt clinical disease. DILI is generally considered subclinical if the serum ALT is < 3 times the ULN; it has been described with antibiotics, antidepressants, lipid-lowering drugs, sulfonamides, salicylates, sulfonylureas and quinidine, generally in fewer than 5-10% of individuals. About 50% of patients receiving tacrine for Alzheimer's disease have shown high ALT levels. This tolerance is also observed in 25-50% of the patients taking methyldopa or phenytoin, and it is especially well described with isoniazid. When symptomatic, DILI shows a high variability and symptoms as fatigue,

nausea, abdominal pain, fever, dark urine, jaundice and itching can be present. Rash, facial edema and lymphadenopathy, along with eosinophilia or atypical lymphocytosis, are important early features that, when present, point to a hypersensitivity and are typical for aromatic anticonvulsants, sulfonamides and allopurinol. Laboratory tests for patients to be made include a complete blood cell count, an hepatic and renal function, a total protein and an electrophoresis, coagulative parameters and urinalysis. Hepatitis B surface antigen, hepatitis C and hepatitis A serology should be performed to exclude an infectious aetiology. Anti nuclear antibodies (ANA) and anti smooth muscle antibodies (SMA) tests may help in the cases of a possible AIH.

6.3 De- challenge

The course of the liver injury after the ending of the suspected drug(s) is considered the de-challenge. If a medication causes DILI, its withdrawal should be followed by a clinical improvement; however, the liver injury may continue to worsen a few weeks after the causative toxic agent is stopped.

6.4 Risk factors

- Age: the adults are generally more susceptible to hepatotoxicity than children. Elderly people are at a higher risk of a hepatic injury because of the decreased clearance, the drug-to-drug interactions, the reduced hepatic blood flow, the variation of the drug binding and of the lower hepatic volume. Older age appears to be an important risk factor for the development of the hepatic injury in response to isoniazid, but younger age appears significant for the valproate-induced liver injury and for the aspirin-induced Reye's syndrome.
- Sex: the women may be more likely to develop the hepatic injury from medications, but they are also more likely to take them.
- Race: the Blacks or African American subjects appear to be more susceptible to develop anticonvulsant hypersensitivities and liver injuries, whereas Caucasian whites appear to be at an increased risk for developing a flucloxacillin-related liver injury.
- Genetic: the most important susceptibility factor for hepatotoxicity is a genetic variability. Genetic polymorphisms have a strong influence on drug metabolism, however, are largely medication-specific. For example, polymorphism of the *N*-acetyltransferase 2 (NAT-2) gene differentiates fast from slow acetylators; the latter have increased their susceptibility to isoniazid toxicity. The human leukocyte antigen (HLA)-B*5701 genotype is the major determinant of abacavir and flucloxacillin hypersensitivity reactions. Estrogen-induced cholestasis is closely linked to variants in adenosine triphosphate–binding cassette B11 (bile salt export pump), and valproate toxicity is closely linked to the variants of mitochondrial polymerase gamma (POLG1). None of these factors is, however, absolute, and hepatotoxicity can occur in patients without these specific markers.
- Alcohol: it causes depletion of glutathione (hepatoprotective) stores that make the person more susceptible to toxicity caused by drugs.
- Obesity and malnutrition: they are susceptibility factors, particularly in the case of acetaminophen, which, when used in malnourished patients, may deplete glutathione.

- Others: pregnancy, concomitantly administered medications and an history of drug reactions also increase susceptibility. Long-acting drugs may cause more injury than shorter-acting drugs. Pre-existing liver diseases and coexisting illnesses may have a greater effect on the ability of the patient to recover from the liver injury than on the likelihood that it will develop.

6.5 Exclusion of other causes of a liver injury

Most of the causality instruments for assessing DILI include results of virological, serological and radiological tests. A number of scales to codify causality of drug toxicity into objective criteria have been developed. Examples include the CIOMS Roussel-Uclaf causality assessment method (RUCAM) scale and the Maria & Victorino (M & V) clinical scale. However, they do not address all risk factors in all patients and none of these scales are used routinely in the clinical practice. A checklist of minimal required elements in the diagnosis of DILI is shown in the table 2.

Patient age (at the time of injury onset) and sex
Implicated drug, herbal or dietary supplement with generic name, dose and regimen of administration
Date on which the agent was started and stopped (or the duration of therapy)
If symptoms are present, the pattern and date of onset (or the time from the beginning of therapy), the types of symptoms
Date of the first abnormal laboratory results indicative of injury (or the time from the beginning of therapy)
Previous history or risk factors of the liver disease
Alcohol use history
Other medical conditions of importance (pertinent negatives being heart failure, shock, sepsis, and parenteral nutrition shortly before the onset of liver injury)
Other medications taken in the 2 months before the onset of the injury
Initial ALT, AST, Alk P, GGT, serum bilirubin value
Prothrombin time or INR
Eosinophils (number/mcL or %) at the onset of the injury or early in the course of the injury
Selected serial ALT (or AST) values (peak values and values demonstrating recovery)
Selected serial Alk P (or GGT) values (peak values and values demonstrating recovery)
Selected serial bilirubin values (peak values and values demonstrating recovery)
Blood test results to exclude other causes of an acute liver disease
a. IgM anti-HAV (or negative anti-HAV)
b. HBsAg and IgM anti-HBc (or negative anti-HBc)
c. Anti-HCV and HCV RNA
d. ANA and SMA (and titer if positive)
Imaging of the liver (type and results)
Abbreviations: ANA, antinuclear antibody; anti-HBc, antibody to hepatitis B core antigen; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M; SMA, smooth muscle antibody.

Table 2. Elements necessary for reporting cases of DILI

History of previous DILI, exposure to the drug or similar agents

Results of serum ALT, Alk P and total bilirubin before the exposure to the agent or onset of DILI

Weight and height expressed as the body mass index

LDH level at the onset of the injury or early in the course of the injury

CPK level at the onset of the injury or early in the course of the injury

Serum albumin and globulin levels at the onset of the injury or early in the course of the injury

IgG level at the onset of the injury or early in the course of the injury

Anti-HEV or HEV RNA

Anti-HIV

IgM anti-CMV or CMV-DNA by PCR

Heterophil antibody or EBV-DNA by PCR

If HBsAg is present, anti-HDV and serial HBV DNA levels

Other autoantibody results such as AMA and anti-LKM

Date of resolution of the symptoms or duration of the symptoms

Liver biopsy results

Results of the re-exposure or challenge

Abbreviations: AMA, antimitochondrial antibody; CMV, cytomegalovirus; CPK, creatinine phosphokinase; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; LKM, liver-kidney microsomal; MRCP, magnetic resonance cholangiopancreatography; PCR, polymerase chain reaction

Table 3. Elements not always necessary but supportive of the assessment and helpful in reporting some cases of DILI

6.6 Previous reports of DILI

An important aspect in assessing DILI is whether the drug, herbal/dietary supplement have been previously reported as a causative agent of hepatotoxicity. Except for the most common medication with a characteristic pattern of injury, this information is largely unknown. A proposal was made to classify drugs with respect to their likelihood of causing a liver injury. Thus, agents were placed in five categories based on the number of published cases and case series in the literature: (A, known) > 50 cases, (B, rare) 11 to 50 cases, (C, very rare) 3 to 10 cases, (D, unproven) < 3 cases and (E, not implicated) not convincingly linked to cases of hepatotoxicity; a final category (X, insufficient information) is necessary for those agents that have not been adequately assessed (i.e. new drugs) or are too rarely used to judge their potential for hepatotoxicity.

6.7 Re-challenge

Re-challenge is defined as the intentional or inadvertent re-exposure to a drug believed to have caused either a current or a past hepatotoxicity. A positive re-challenge consists of the recurrence of the DILI, usually with a shorter latency and a greater severity. While it remains the gold standard for the diagnosis of a DILI, the re-challenge is not advised. However, a careful re-challenge might be appropriate for some cancer chemotherapeutic agents, antiretroviral or antitubercular medications.

6.8 Liver biopsy

The role of a liver biopsy in the diagnostic work-up of DILI is controversial. Although some histological features may increase the index of suspicion of DILI, there are none which can unequivocally confirm the diagnosis. If the patient demonstrates a rapid improvement in the liver tests following the ending of the drug, a routine liver biopsy is not indicated. If the patient has an underlying liver disease and /or if AIH is suspected despite negative serologies, a liver biopsy can be valuable. A liver biopsy can be helpful when the drug has not been previously implicated causing a liver injury, or when the drug reaction has a very slow regression. However, the impact of identifying some of these unusual histological patterns on management is uncertain and the indication of a liver biopsy depends on the course of the liver injury as mentioned above.

7. Grading severity in DILI

Severity in DILI can be graded as mild, moderate or severe. Most of the severity scales are based on the presence and on the number of symptoms, the height of the liver biochemistry, the presence of signs of a hepatic failure and the ultimate outcome, such as recovery, chronicity or death. In developing a prospective database of cases, Drug-Induced Liver Injury Network (DILIN) established a five-point system for grading severity.

Score	Grade	Definition
1	Mild	Elevations in serum ALT and/or Alk P levels, but the total serum bilirubin level is < 2.5 mg/dL, and INR is < 1.5
2	Moderate	Elevations in serum ALT and/or Alk P levels, and the serum bilirubin level is ≥ 2.5 mg/dL, or INR is ≥ 1.5
3	Moderate-severe	Elevations in serum ALT, Alk P, and bilirubin or INR levels, and hospitalization or ongoing hospitalization is prolonged because of a DILI episode
4	Severe	Elevations in serum ALT and/or Alk P levels, and the total serum bilirubin level is ≥ 2.5 mg/dL, and there is at least one of the following: Hepatic failure (INR ≥ 1.5, ascites, or encephalopathy) Other organ failure believed to be due to a DILI event (i.e., renal or pulmonary)
5	Fatal	Death or liver transplantation from a DILI event

Table 4. Disease severity scales used in the DILIN prospective study

8. Prognosis

The majority of the patients with a symptomatic acute DILI recover completely after the discontinuation of the drug(s). First described by Hy Zimmerman (Zimmerman, 1999), the drug-induced jaundice (total bilirubin > 2.5 mg/dL) was associated with a poor prognosis. This observation called Hy's Law is used by regulatory agencies in the evaluation of the

investigational drugs showing potential hepatotoxicity during clinical trials. The outcome is obviously dependent on the severity of the liver impairment at presentation. For example, the prognosis of idiosyncratic DILI patients with ALF, coagulopathy (INR > 1.5) and encephalopathy is usually poor without a liver transplantation. Also patients with a cholestatic DILI have a significant mortality. The prognosis is also dependent on the specific compound involved. For instance, in one series, mortality ranged from 40% with a halothane-induced liver injury, whereas all patients with an erythromycin-induced liver injury survived. A longer duration of the therapy before the recognition of DILI and a continuation of the therapy despite a liver dysfunction seems to increase the risk of developing a chronic liver disease. Drugs most frequently associated with chronicity were amoxicillin/clavulanate, bentazepam and atorvastatin. Patients with a cholestatic liver injury develop more frequently a chronic liver injury. Peripheral eosinophilia has been shown to have a prognostic importance, in fact it was extremely rare in fatal DILI cases. Limited data exist on the impact of histology on the clinical outcome. Recently, in a study of patients with a disulfiram-induced liver injury, the hepatic eosinophilic infiltration is associated with a good short-term prognosis, whereas hepatocytes dropout or necrosis with a poor prognosis.

9. Treatment of DILI

Once DILI is suspected, a prompt cessation of drug(s) implicated is obviously the first step in the management. At the onset of the reaction, patients with jaundice and who also have coagulopathy and/or encephalopathy should be hospitalized. It is important to recognize the severity of the liver injury in a patient with jaundice and coagulopathy before the development of the encephalopathy. Encephalopathy is a very late sign and after its development, a rapid deterioration is often observed. Few specific therapies have been shown to be beneficial in clinical trials. Two exceptions are the use of N-acetylcysteine for acetaminophen toxicity and L-carnitine for cases of valproic acid overdose. Corticosteroids are of unproven benefit for most forms of drug hepatotoxicity, although they may have a role in the case of a hypersensitivity syndrome, in the AIH (if it is considered to be induced by drugs) and in patients with a severe or progressive liver injury, but data supporting their safety and efficacy are lacking. Patients should be followed by serial biochemical measurements.

10. Conclusion

DILI is a rare but important complication that will continue to be problematic with the new drugs coming onto the market. Recent data highlight antibiotics, central nervous system agents, herbal/dietary supplements and immunomodulatory drugs as the most common causes of DILI in the USA. The limitations of the available instruments to measure causality in DILI may be minimized by the use of expert panel opinions, while biomarkers of DILI have not been discovered yet. It is the health care system, including the physician's responsibility to monitor and report drug-induced hepatotoxicity. A systematic approach should be taken to determine the aetiology of hepatotoxicity and to remove the offending agent. New therapies for the drug-induced acute liver failure are needed.

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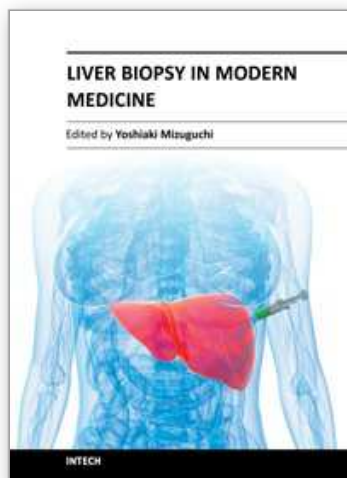
Liver Biopsy in Modern Medicine

Edited by Dr. Yoshiaki Mizuguchi

Liver biopsy, first performed by Paul Ehrlich in 1883, remains an important diagnostic procedure for the management of hepatobiliary disorders and the candidate/donated organ for transplantation. The book "Liver biopsy in Modern Medicine" comprises 21 chapters covering the various aspects of the biopsy procedure in detail and provides an up-to-date insightful coverage to the recent advances in the management of the various disorders with liver biospy. This book will keep up with cutting edge understanding of liver biopsy to many clinicians, physicians, scientists, pharmaceutics, engineers and other experts in a wide variety of different disciplines.

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