

# Pathological patterns of drug induced lesions of the liver

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The liver is a main target of toxicity induced by drugs since it plays a major role in their metabolism. All the liver cell types may be injured, and this explains that drug related lesions may mimic all the patterns observed in hepatic pathology and that a formal etiological diagnosis is not possible on histological grounds in the majority of cases. When a liver biopsy is studied, the possibility of hepatotoxicity should therefore be always kept in mind. In addition, one drug may be responsible for various patterns of liver injury and, conversely, one pattern of liver injury may be induced by various drugs (1-5). A frequent challenge for a hepatologist is, in a patient taking drugs, to try to explain clinical or biochemical abnormalities of the liver by possible hepatotoxicity. Chronological (i.e., delay between beginning of treatment and onset of symptoms, evolution of liver abnormalities after withdrawal of the drugs), clinical (e.g., hypersensitivity manifestations) and biological (e.g., blood eosinophilia, presence of some serum antibodies) criteria are very useful, and liver biopsy is theoretically not mandatory in many cases. However, it is often performed in order to : (a) rule out another cause of liver disease ; (b) demonstrate pathological findings that are sometimes characteristic of a suspected drug ; (c) describe histopathological alterations of so far unreported toxicity of a drug (1).

## **1. Acute and chronic hepatitis**

Acute hepatitis is the most frequent lesion in drug hepatotoxicity. It may be hepatocellular (cytolytic), cholestatic or mixed, hepatocellular and cholestatic. It usually resolves after withdrawal of the incriminated agent, but it may exceptionally have a fulminant course or can evolve towards chronicity with possible progressive constitution of cirrhosis.

A wide variety of iatrogenic agents, including legal and illegal drugs, herbal medicine, industrial and chemical toxics, can cause acute hepatocellular injury. It is estimated that hepatotoxicity accounts for approximately 10 per cent of acute hepatocellular hepatitis and is the most common cause of cholestatic hepatitis.

Usually, hepatitis induced by drugs cannot be differentiated histologically from hepatitis due to another cause. However, three arguments, although not specific, favor hepatotoxicity on a liver biopsy : (a) predominance of the lesions in centrilobular areas, around terminal hepatic veins ; (b) presence of numerous eosinophils in the inflammatory infiltrate ; (c) existence of epithelioid and giant cell granulomas. In addition, eosinophils and epithelioid and giant cell granulomas suggest that injury is explained by an immunoallergic mechanism (3, 5).

In predominantly acute cholestatic hepatitis, clinical symptoms and histological findings may mimic those of biliary obstruction. Liver biopsy shows bile accumulation predominating in centrilobular areas, with minimal necroinflammatory activity, polymorphous portal inflammation and possible cholangitis. Acute cholestatic injury may manifest as centrilobular bland cholestasis, without inflammation or hepatocellular alterations : such pattern is typically observed with anabolic steroids and oral contraceptives. In rare cases, cholestasis may persist, even after cessation of the offending drug. Such chronic cholestasis is responsible for clinical findings and a histological pattern hardly distinguishable from autoimmune cholangitis : indeed, ductopenia, cholangiolar proliferation and portal and periportal fibrosis may be marked whereas hepatocellular necrosis is absent or mild (3, 5).

## **2. Microvesicular steatosis, nonalcoholic fatty liver disease and phospholipidosis**

**Microvesicular steatosis**, in which small lipidic droplets leave the nucleus at the center of the hepatocytes, has been described after intake of sodium valproate, tetracyclins, salicylates or antiretroviral therapy. It strongly resembles steatosis observed in fatty liver of pregnancy or in congenital abnormalities of urea cycle (3, 5).

The whole spectrum of **nonalcoholic fatty liver disease**, which is mainly induced by insulinoreistance, may also be induced by drugs such as amiodarone, calcium channels inhibitors and antineoplastic agents as irinotecan or oxaliplatin (3, 5).

In all patients treated with amphiphilic drugs as amiodarone, electron microscopy shows that all liver cell types contain in their cytoplasm intralysosomal lamellar bodies suggestive of **phospholipidosis**. This lesion could be due to drug inhibition of lysosomal phospholipases activity (3, 5).

### 3. Vascular lesions

All the vessels of the liver can be the target of iatrogenic agents toxicity, but lesions of the efferent hepatic venous system and of sinusoids are the most common (3, 5).

#### 3.1. Lesions of the hepatic veins

They concern either the main branches of the hepatic veins or only small intrahepatic centrilobular or sublobular veins.

Thrombosis of large hepatic veins is responsible for **Budd-Chiari syndrome**, which is a rare complication of oral contraceptives intake in patients having a latent or a patent myeloproliferative disorder or another risk factor for thrombosis.

**Sinusoidal obstruction syndrome, previously termed venoocclusive disease**, consists of fibrous non thrombotic obliteration of terminal hepatic veins, without obstruction of the main hepatic veins. Clinical symptomatology is similar to that of Budd-Chiari syndrome. Histologically, outflow block leads to centrilobular sinusoidal dilatation and hemorrhagic necrosis. This disease has nearly always an iatrogenic cause. It is particularly a remarkable adverse effect of the association of radiotherapy and chemotherapy used as a conditioning regimen to prepare patients for bone marrow transplantation. The disease can be acute and may have a fulminant fatal outcome ; it may regress after withdrawal of the responsible agent, but can also chronically evolve towards fibrosis of terminal hepatic veins and centrilobular areas, with possible progression to cirrhosis.

#### 3.2. Sinusoidal lesions

**Periportal sinusoidal dilatation** has been reported after oral contraceptives treatment.

**Peliosis hepatis** consists of sinusoidal dilatation without zonal predominance, that may form large blood filled cavities. Electron microscopy shows sinusoidal

endothelial abnormalities with an abnormal passage of red blood cells from the sinusoidal lumen into the perisinusoidal space of Disse. Peliosis is most often due to drugs (e.g., anabolic steroids, immunosuppressive agents) that could be directly toxic towards sinusoidal endothelial cells.

**Perisinusoidal fibrosis** is frequently associated with portal and periportal fibrosis. It is observed in hypervitaminosis A, in which hepatic stellate cells, implicated in collagen synthesis, are loaded with autofluorescent lipidic vacuoles made of vitamin A. As in peliosis, electron microscopy demonstrates sinusoidal endothelial lesions similar to those observed in peliosis hepatitis. It is of interest that iatrogenic agents that are responsible for perisinusoidal fibrosis are the same as those inducing peliosis hepatitis, thus suggesting a pathophysiological relationship between these two lesions.

#### 4. Biliary tract lesions

In addition to aforementioned lesions of interlobular bile ducts, drugs may be the cause of large bile ducts injury (3, 5). Indeed, extrahepatic as well as intrahepatic **sclerosing cholangitis** has been reported either after direct exposure of biliary tract to toxic agents (e.g., sodium chloride or formaldehyde used for sterilization of hydatid cysts) or in relation with biliary sclerosis secondary to ischemic injury provoked by toxic alterations of the hepatic arteries (e.g., after intraarterial infusion of 5-fluorodeoxyuridine administered for treatment of hepatic metastasis of colorectal carcinoma), which vascularize the biliary tract.

#### 5. Tumors

Iatrogenic agents may be at the origin of benign or malignant tumors of the liver (3, 5).

##### 5.1. Benign tumors

Whereas the association of oral contraceptives and hepatocellular adenoma has been well recognized, such a relation probably does not exist between this drug and the occurrence of focal nodular hyperplasia or angioma of the liver.

## 5.2. Malignant tumors

Hepatic angiosarcoma is secondary, sometimes after several years, to exposure to various toxic agents (e.g., vinyl chloride, thorium dioxide), which are the same as those responsible for peliosis hepatis and perisinusoidal fibrosis. These agents may also induce hepatocellular carcinoma or cholangiocarcinoma. Rare cases of well differentiated hepatocellular carcinoma difficult to distinguish from hepatocellular adenoma have been described in patients receiving anabolic steroids.

## 6. Miscellaneous lesions

Endoplasmic reticulum hypertrophy, giving to the hepatocytes a ground glass appearance resembling that observed in hepatitis B infected patients, is observed after intake of enzymatic inducers such as phenobarbital. Similar changes can also be seen with cyanamide used in alcohol withdrawal programs (3, 5).

Some agents such as gold and titanium can be deposited as pigments in the liver (3, 5).

Accumulation of lipofuscins, corresponding to hypertrophied lysosomes, may be noted in the cytoplasm of centrilobular hepatocytes in patients treated with chlorpromazine or phénacétine (3, 5).

## Références

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