Chronic Hepatitis and Cirrhosis in Domestic Animals (13-Nov-2004)
T. S.G van den Ingh
Department of Pathobiology, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

Introduction
Chronic hepatitis and cirrhosis refer to a primary lesion of the hepatic parenchyma with hepatocellular death, fibrosis and inflammation. However, inflammation and fibrosis and sometimes hepatocellular death are not restricted to primary parenchymal disorders but also can be seen in primary biliary and circulatory disorders. Differentiation in general is possible through careful histological examination and evaluation of the combination of the parenchymal, vascular and biliary lesions present in the affected liver.

There is an intricate relationship between inflammation in the liver parenchyma and hepatocellular death, the latter often being the initiating event of the inflammation. Knowledge about the various forms of hepatocellular death i.e. apoptosis and necrosis, their morphological substrate and the subsequent response of the liver are essential to understand the development and various morphological aspects of chronic hepatitis and cirrhosis.

Morphological Aspects of Hepatocellular Apoptosis and Necrosis and the Response of the Liver

Apoptosis and necrosis
Hepatocytes may be killed by various insults including hypoxia, toxins, microorganisms, immunological events and severe metabolic disturbances. Classically cell death has been considered to occur through apoptosis or necrosis; however, recent evidence suggests overlap between both processes as moderate exposure to some toxins causes apoptosis whereas greater exposure may result in necrosis [1,2] and that necrosis and apoptosis are morphologic expressions of a shared biochemical network of both caspase dependent mechanisms as well as non-caspase dependent effectors [2]. Apoptosis is a caspase-dependent active process of programmed cell death which results in shrinkage of the cell without loss of integrity of the cell and nuclear membrane, and subsequent fragmentation [3]. Necrosis involves cytoplasmic swelling and loss of integrity of the cell membrane and may result in coagulative necrosis or liquefactive (lytic) necrosis. Coagulative necrosis is the result of sudden and catastrophic denaturation of the cytosolic protein and appears as swollen hepatocytes with acidophilic cytoplasm, preservation of the basic outline of the coagulated cell, and karyopyknosis, karyorrhexis or karyolysis. The acute phase of coagulative necrosis is followed by proliferation of Kupffer cells and infiltration of mononuclear and polymorphonuclear phagocytes and subsequent resorption and lysis of the necrotic cells. Liquefactive or lytic necrosis is the result of osmotic swelling and disintegration of hepatocytes and appears as loss of hepatocytes with subsequent collapse of the residual reticulin network and, or replacement by erythrocytes and eventually the presence of ceroid-laden macrophages. The outcome of a given hepatic insult depends on the nature, extent and duration of the insult, and of course survival of the host.

Morphological Patterns of Apoptosis and Necrosis [4-6]

Apoptotic bodies (acidophil bodies) are shrunken, intensly eosinophilic hepatocytes with condensed nuclei and surrounded by an empty halo. After subsequent fragmentation, the remnants are phagocytosed by adjacent Kupffer cells and hepatocytes, and visible as small cytoplasmic eosinophilic inclusions that are rapidly degraded.

Focal and multifocal necrosis refer to coagulative or liquefactive necrosis of small aggregates of hepatocytes, mostly attended and recognized by the secondary inflammatory reaction of Kupffer cell proliferation and infiltration of mononuclear and, or polymorphonuclear phagocytes.

Confluent and bridging necrosis may be coagulative or liquefactive necrosis and comprises larger areas of hepatocytes, in a
random or zonal distribution. Confluent necrosis linking vascular structures is called bridging necrosis. Bridging at the periphery of acini links terminal hepatic venules to each other and is called central-central bridging. Bridging linking terminal hepatic venules and portal tracts is called central-portal bridging, whereas bridging necrosis with a periportal distribution is called portal-portal bridging. When confluent necrosis is more extensive and involves complete acini or lobules, the process is described as panacinar or panlobular necrosis.

Massive necrosis represents the most severe form of necrosis and generally is used when the liver shows extensive diffuse panlobular and multilobular coagulative and, or, liquefactive necrosis. The sequel of massive necrosis often is collapse of the reticulin and fibrous network so that portal areas and hepatic venules are approximated and the connective tissues subsequently condenses (post-necrotic scarring).

Piecemeal necrosis, recently called interface hepatitis [4], can be defined as death of hepatocytes at the interface of parenchyma and (newly formed) connective tissue. The most likely process involved is apoptosis. The lesion is characterized by a variable degree of mononuclear inflammation and mostly fibrosis of the portal areas with infiltration and destruction of the limiting plate; sometimes apoptotic bodies can be observed in these areas.

Response of the Liver to Hepatocellular Apoptosis and Necrosis -
Following destruction of hepatic parenchyma, regeneration of parenchyma, fibrosis, and ductular proliferation may occur. When hepatocytic destruction is limited and the reticulin network remains intact, regeneration with almost complete restitution of the liver structure can occur. Severe parenchymal destruction with extensive loss of hepatocytes often is followed by ductular proliferation. Many of these structures contain both liver-cell and bile-duct elements and may reflect regenerative proliferation of an hepatic stem cell population analogous to oval cells in the rat, or transformation of proliferating cells. With persistent parenchymal damage or extensive loss of hepatocytes fibrosis and postnecrotic scarring may occur with the formation of intrahepatic portovenous shunts; in these cases prolonged regenerative effort will result in regenerative parenchymal nodules.

Chronic Hepatitis
Chronic hepatitis is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely and it is necessary to include in the diagnosis the activity and stage of the disease as well as the possible etiology. The activity of the disease is determined by the quantity of inflammation and extent of hepatocellular apoptosis and necrosis which may be present as interface hepatitis and in a random focal or confluent pattern within the lobule. The stage of the disease, and thus the possible prognosis, is determined by the extent and pattern of fibrosis and the possible presence of architectural distortion (see cirrhosis). Fibrosis may present as portoportal, porto-central and centro-central fibrosis or lobular dissecting and may occur associated with interface hepatitis, following collapse and condensation of the reticulin network or by direct activation of hepatic stellate cells with perisinusoidal deposition of collagen. Regeneration and regenerative nodules of hepatic parenchyma are often seen as well as proliferation of ductular structures at the periphery of the parenchyma and within fibrous septa. Histochemical stains for connective tissue (reticulin stain according to Gordon and Sweet, Sirius red, Van Gieson’s stain and trichrome stains) may be helpful in detecting the amount and pattern of fibrosis, particularly in early and mild disease.

Cirrhosis
Cirrhosis is the end-stage of chronic hepatitis and is defined as a diffuse process characterized by fibrosis of the liver and the conversion of normal liver architecture into structurally abnormal nodules, and the presence of portal-central vascular anastomosis [7,8]. Like in chronic hepatitis it is essential to include in the diagnosis the extent of the fibrosis, the activity of the disease and the possible etiology. Portal-portal fibrosis without other architectural changes does not constitute cirrhosis, but instead represents biliary-type fibrosis.

In cirrhosis two morphological categories can be distinguished i.e. micronodular cirrhosis with nodules less than 3 mm (the size of a normal lobule) and regular in size and macronodular cirrhosis with nodules greater than 3 mm (up to several centimeters) and irregular in size. Whereas micronodular cirrhosis develops from regular and diffuse alteration and fibrosis of the acini, macronodular cirrhosis develops from irregularly distributed larger areas of necrosis with secondary collapse and scarring and the development of portal-central vascular connections [7,8].

Lobular Dissecting Hepatitis is a form of cirrhosis seen in young or young adult dogs as isolated cases or in groups of dogs from the same litter or kennel with a rapid clinical course [9]. The liver usually has a normal size with a smooth capsular
surface or some small nodules of regeneration. Microscopically bands of fibroblasts and thin strands of extracellular matrix are seen between individual and small groups of hepatocytes which cause dissection of the original lobular architecture. Connective tissue stains (especially for reticulin) are helpful in demonstrating the pattern of connective tissue alterations. Inflammation and hepatocellular apoptosis / necrosis are usually slight to moderate. A similar morphologic pattern is sometimes seen in newborn or aborted calves and foals.

Cirrhosis associated with Superficial Necrolytic Dermatitis - The latter is a cutaneous disease in dogs usually associated with chronic hepatic disorders and rarely glucagon-producing endocrine pancreatic tumours [10-12]. The livers in this disease are strikingly similar and are a peculiar form of macronodular cirrhosis. They are divided into regenerative hyperplastic nodules by fibrous septa containing ductular structures and pigment-laden macrophages, and show minimal or no inflammation and hepatocellular necrosis. The nodules are characteristically bordered by areas of clear swollen hepatocytes similar to steroid induced hepatopathy.

In ruminants, horses and pigs cirrhosis often has limited non-specific clinical signs; hepatocerebral sequelae and hepatogeneous photosensitivity being the most frequent signs. In dogs cirrhosis is a rather common condition often associated with portal hypertension and the presence of multiple portosystemic collateral veins. Some animals may have compensated cirrhotic disease and show no or minor clinical signs, while other animals show manifestations of liver failure, e.g. hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatocerebral sequelae. Cirrhosis is rarely seen in cats, but in such cases the animals will also show hyperbilirubinemia, hypoalbuminemia, ascites and hepatocerebral sequelae.

Causes of Chronic Hepatitis and Cirrhosis in Domestic Animals

In contrast to man where the hepatitis viruses are an important cause for chronic hepatitis and cirrhosis, the role of viruses or other (micro-)organisms in the pathogenesis of chronic hepatitis and cirrhosis seems to be very limited in domestic animals. In herbivores the main cause for chronic hepatitis and cirrhosis seems to be the ingestion of mycotoxins, particularly aflatoxin, and toxic plants products, particularly pyrrolizidine alkaloids from plants as Senecio, Crotalaria and Heliotropum. Also in pigs mycotoxins and other environmental toxins are the main cause for chronic hepatitis and cirrhosis. The cause of most spontaneous cases of canine chronic hepatitis is undetermined although some cases have been associated with leptospirosis [13], and experimental and spontaneous infectious canine hepatitis virus infection [14,15]. Chronic hepatitis has also been reported in dogs treated with drugs for instance the anticonvulsants primidone, phenytoin and phenobarbital [16-18]. Chronic hepatitis and cirrhosis are rarely seen in cats; hepatic fibrosis in cats usually represents porto-portal bridging fibrosis associated with chronic biliary disease.

Copper-Associated Chronic Hepatitis and Cirrhosis -

In the Bedlington terrier a genetic mutation in copper transport proteins causes accumulation of copper in hepatocytes resulting in inflammation or necrosis [19,20]. Copper accumulation leading to inflammation and necrosis appears to be familial in the West Highland white terrier [21], Skye terrier [22], and Dalmatian [23]. In these animals copper accumulates in hepatocytes, starting in the centrolobular regions, and with progressive accumulation results in hepatocellular necrosis, inflammation with copper-laden macrophages and finally chronic hepatitis and cirrhosis. Other breeds (Doberman pinschers, Labrador retrievers, and American and English cocker spaniels) have been reported to have elevated copper concentrations in association with chronic hepatitis but it remains to be determined whether this copper accumulation is primary or secondary to chronic inflammation, fibrosis, and cholestasis. Copper-induced chronic hepatitis and cirrhosis was recently observed in a cat [24] and was characterized by severe copper deposition in hepatocytes and macrophages in the fibrotic areas and slight to moderate copper deposition in the regenerative nodules.

Copper-induced chronic hepatitis and, sometimes, cirrhosis is well known in sheep breeds, who have their origin in regions with very low natural copper levels in the soil, such as the Texelaar in the Netherlands. When copper is ingested over a longer period in higher quantities, this causes progressive copper accumulation in the hepatocytes with subsequent hepatocellular necrosis finally resulting in chronic hepatitis and cirrhosis.

References


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