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Diagnosis of Liver Disease in Domestic Ferrets (Mustela Putorius)

Minh Huynh, DVM*, Flora Laloi, DVM

INTRODUCTION

Liver diseases have been extensively described in small animal species and are believed common in pet ferrets (Mustela putorius furo). The disease remains often subclinical, which may lead to difficulties in diagnosing those conditions accurately. Blood examination and serum chemistry evaluation are useful tools in screening hepatic pathology and monitoring response to treatment. Diagnostic imaging allows visualization of liver abnormalities, especially gallbladder and bile duct disease. Ultimately, histopathology is often required for definitive diagnosis and staging of the lesions. Various diseases have been reported: inflammatory, infectious and toxic hepatitis, and hepatic lipidosis. Less commonly, neoplasia or other pathology may be seen. After a summary of anatomy and physiology of the ferret liver, hepatic diseases known in ferret species are reviewed with their subsequent diagnostic procedures.

KEYWORDS

- Ferret • Liver • Gallbladder • Hepatopathy • Hepatitis • Lipidosis
- Hepatic neoplasia • Biliary obstruction

KEY POINTS

- Liver disease in ferrets is often subclinical and underdiagnosed.
- Clinical pathology and diagnostic imaging are needed to guide clinicians but definite diagnosis is based on histopathologic lesions.
- Inflammatory digestive conditions can lead to ascending tract infection and hepatobiliary inflammation.
- Ferrets have a specific sensitivity to hepatic lipidosis.
- Incidence of hepatic neoplasia is high in ferrets.
ANATOMY AND PHYSIOLOGY

Anatomy

The liver is the largest visceral organ in all vertebrates. The ferret has a large liver compared with other companion mammals, representing 4.3% of the body weight, compared with 3.4% for a dog.1,2 Normal weight ranges from 35 g to 59 g.1 Anatomy and physiology of biliary tract in ferrets are similar to those of other mammals.2 There are 6 lobes recognized in ferrets: left and right medial, left and right lateral, and quadrate and caudate lobes.

The gallbladder is located in a fossa formed by the quadrate lobe on the left and the right medial lobe. As in the other mammals, it is pear-shaped, is approximately 1 cm × 2 cm, and holds a volume of 0.5 mL to 1 mL.2 Hepatocytes secrete bile that is drained by capillaries between cells. Bile capillaries join to form interlobular ducts, then bile duct. The cystic duct joins the right, central, and left ducts to form the common bile duct. The pancreatic duct usually joins the common bile duct, entering the lumen of the duodenum at the duodenal papilla approximately 2.8 cm caudal to the cranial duodenal flexure. Occasionally, an accessory papilla is present.2 Accessory gallbladder has been reported in 2 ferrets without any concurrent clinical signs.3

Physiology

The liver is a key organ involved in many metabolic processes, including digestion, regulation, and mobilization of carbohydrate, lipid, and protein. Other important roles include detoxification, vitamin storage, and immunoregulation. The liver has a central anatomic topography, receiving a dual blood supply from the hepatic arteries and the portal vein, draining most of the abdominal organs. For those reasons, any systemic disease (infection or neoplasia) has potential detrimental effects on hepatic function.

Bile, which is secreted by the liver, helps digestion of fats in food and is the route of excretion of bilirubin (the product of degradation of red blood cells). It also has some bactericidal activity and helps buffer stomach acid.

SIGNALMENT

History Findings

Because of its unspecific signs, diagnosis of liver disease in ferrets can be challenging. When liver disease is suspected, the clinician has to go through a thorough questionnaire to find history of toxin or medication exposure, diet imbalance, or past episode of viral infection in the household. A high-fat diet can induce lipid hepatic accumulation in ferrets because of their specific liver metabolism.4 Any sign of inflammatory bowel disease, especially Coronavirus infection, must be recorded.5 Ferrets affected by liver disease are usually middle-aged to old ferrets.5

Clinical Signs

Hepatic disease in ferrets is often subclinical.5 If present, clinical signs are usually discrete and unspecific, such as lethargy, anorexia, fever, gastrointestinal disorders, and weight loss.5 Icterus can be a strong sign of liver disease; however, ferrets are rarely icteric because of rapid renal excretion of bilirubin.6,7 Additionally, yellow sebaceous secretions can mask subtle icterus.5 In reports of severe bile duct obstruction, liver cirrhosis, or copper toxicosis, icterus has been observed.5,6–10 The nose, ear, and oral cavity are suggested as sites for searching for icterus (Fig. 1).5 In cases of extrahepatic bile duct obstruction (EHBO) and ruptured gallbladder, acute abdominal pain can be detected on palpation.9,11
In cases of severe liver dysfunction, it is expected that ferrets experience the same clinical signs as dogs, such as hepatic encephalopathy, ascites, and bleeding disorder, but such disorders have not been reported to the authors' knowledge. Several reasons may explain this fact. Because cats rarely have ascites due to chronic liver disease, similar findings can be suggested in ferrets.12 Ascites and hemoperitoneum in ferrets have only been reported with hepatic tumors.13,14 Polyuria-polydipsia is also a clinical sign of liver disease in cats and dogs but has not been reported in ferrets.

**CLINICAL PATHOLOGY**

*Biochemistry*

Biochemistry testing can reveal hepatocellular change, reflecting damage in the parenchyma or the biliary tract, or used to diagnose hepatic dysfunction, such as abnormal bile elimination and coagulation disorder. Normal ranges are referenced in Table 1.15–17

| Reference Range | Values |
|-----------------|--------|
| ALT (IU/L)      | 110 (49–242.8)15 |
| AST (IU/L)      | 74 (40.1–142.7)15 |
| Bilirubin (mg/dL) | 1.1 (0–3.3)15 |
| GGT (IU/L)      | 4 (0.2–14)15 |
| Cholesterol (mg/dl) | 165 (64–296)16 |
| Protein, total (g/dL) | 6.8 (5.5–7.8)15 |
| Albumin (g/dL)  | 3.6 (2.8–4.4)15 |
| Bile acids (μmol/L) | 5.7 (0–28.9)15 |
| PT (s)          | 10.9 (10.6–11.6)17 |
| PTT (s)         | 20 (18.6–22.1)17 |
| Fibrinogen (mg/dL) | 107.4 (90–163.5)17 |
| Antithrombin (%) | 96 (69.3–115.3)17 |

Fig. 1. Icteric ferret with jaundice observed on the nose and both ears.
Alanine aminotransferase
Alanine aminotransferase (ALT), also known as serum glutamic-pyruvic transaminase, is an enzyme found in the cytoplasm of hepatocytes released in cases of cellular injury in domestic animals. It has been shown valuable in the assessment of hepatic damage in the ferret. The half-life of ALT in dogs is reported as 45 to 60 hours and 5 hours in rabbits. It is likely longer in ferrets. Most ferrets with liver disease present with ALT greater than 275 IU/L. In cases of liver necrosis, however, increases of ALT levels are minimal, whereas increases of biliary enzymes levels as a result of biliary stasis are severe.

Aspartate aminotransferase
Aspartate aminotransferase (AST) is present in similar amounts in liver and muscle and thus is less specific than ALT. The half-life of AST in dogs is longer than ALT. No data about the half-life are available in ferrets. AST has the same properties as ALT.

Alkaline phosphatases
Alkaline phosphatases (ALPs) are isoenzymes that perform the same function (hydrolyzing monophosphates at an alkaline pH) in many if not all body tissues. Cells from liver, bones, kidneys, intestinal mucosa, and placenta have the highest activity. In the ferret liver, membranes bordering the bile canaliculus produce ALPs. Bile stasis, bile duct obstruction, and lipidosis produce increased ALP synthesis.

γ-Glutamyl transpeptidase
γ-Glutamyl transferase (GGT) is an enzyme found mainly in the kidney but also in the liver, spleen, and intestines. In dogs and cats, because of its poor specificity of liver tissue, its main interest is joint interpretation with ALP because ALP is also found in bone and steroid-induced isoenzyme. GGT is supposedly more sensitive than ALP for detection of extrahepatic cholestasis, cholangiohepatitis, and cirrhosis.

Bilirubin
Bilirubin is a product of heme breakdown, produced by the hepatocytes and excreted into the intestines through the biliary tree of the ferret. Thus, serum bilirubin levels are an indication of both hepatocellular and biliary tree function. Ferrets rarely present with hyperbilirubinemia or icterus because of their high renal bilirubin excretion.

Bile acid
Synthesis of bile acid is the primary pathway for catabolism of cholesterol, involving multiple enzymatic reactions in the liver. Additionally, the liver removes bile acid from the hepatic portal vein. Bile acid level assesses the excretory capacity of the liver. Bile acid levels rise in cases of biliary obstruction and in many forms of hepatic disease.

Ammonia
Ammonia is a product of protein catabolism. Elevation is seen when the liver does not remove the ammonia from the portal blood in some pathologic situations, such as a shunt. This test has limited value in ferrets because vascular shunt has never been reported in ferrets.

Cholesterol
Because liver is involved in lipid metabolism, hypercholesterolemia is associated with increased hepatic synthesis, decreased biliary excretion of cholesterol, or both in cats and dogs. High cholesterol values have been reported with cholelithiasis.
Protein
Liver is the main organ involved in protein synthesis. The main categories of serum proteins are albumin, α-globulins (including acute phase protein), β-globulins (including fibrinogen, IgM, and IgA), and γ-globulins (including IgG). The liver is the exclusive site of synthesis of albumin. Albumin levels are typically low in cases of the severe liver disease; however, total protein level may not be affected because globulinemia usually increases. Albumin levels can be affected by various protein-losing conditions but synthesis can be affected by severe liver disease. Decreased albumin and increased globulin levels result in a modification of the albumin/globulin ratio. Liver diseases are usually associated with decreased albumin/globulin ratio.

Serum electrophoresis allows differentiating different protein phases. In the acute inflammatory phase, when IgM are produced, a β peak alone is seen, suggesting an acute hepatitis. Then an increased production of γ-globulin due to the presence of multiple antibodies is seen, and, in severe chronic hepatopathy, an increase of β-globulin and γ-globulin is expected (related to immunoglobulin production). An α2-microglobulin peak is also sometimes observed in cases of chronic hepatitis and cases of lymphoma. In cases of liver cirrhosis, a so-called β-γ bridge can be observed. Aleutian disease (AD) and Coronavirus have been associated with hypergammablobulinemia and polyclonal peaks, and their role has been suggested in chronic hepatopathy.

Coagulation protein
The liver is involved in various clotting pathways and is the exclusive site of synthesis for factors I (fibrinogen), II (prothrombin), V, VII, IX, X, and XI and antithrombin. Prolonged prothrombin time is an indicator of hepatic dysfunction. In some severe cases, elevation of partial thromboplastin time (PTT) is also observed. Dysfibrinogenemia, an interferent with fibrin polymerization, has also been reported in severe liver disease. Moreover, liver disease is known to decrease absorption of fat-soluble substances in the gut, decreasing absorption of vitamin K. Reference ranges for coagulation factors have been determined in ferret species.

Urinalysis
Bilirubinuria
Only the conjugated water-soluble form of bilirubin is excreted in the urine. Traces of bilirubinuria can be detectable in normal ferrets, but true bilirubinuria is present in cases of suppurative hepatitis or biliary obstruction.

Biliverdinuria
Green urine is a common finding in Coronavirus infection. Although the physiologic mechanism of this finding has not been fully elucidated, microhemorrhage into tissues and extravascular destruction of erythrocytes related to vascularitis is hypothesized.

Hematology
Nonspecific modification of hematologic profile can be associated with liver disease. Leukocytosis can be seen in cases of severe cholangiohepatitis, suppurative hepatitis, or Coronavirus infection. Lymphocyte ratio or lymphocytosis can reflect lymphoma. Relative neutrophilia is seen with EHBO. Very severe neutrophilic leukocytosis (>55,000 cells/mm³) has been reported with hemangiosarcoma.

Peritoneal Effusion
Peritoneal effusion is observed when damages are seen in the liver capillaries causing leakage of fluid in the abdominal cavity. The condition worsens because
hypoalbuminemia is often present concomitantly. Abdominocentesis allows diagnostic samples. The fluid is primarily clear but chronic inflammation of the peritoneum can raise the cellularity of a sample, making the fluid serohemorrhagic. Cellularity is usually low. Density is usually between 1.005 and 1.020. As discussed previously, such clinical situations have not been reported in ferrets but can be expected in cases of liver failure. Hemoperitoneum fluid has been observed in case of neoplasia. Bile peritonitis has been reported with a yellow fluid with bile pigment. Serous abdominal effusion has also been reported with Coronavirus infection, as in cats affected by feline infectious peritonitis.

**DIAGNOSTIC IMAGING**

Diagnostic imaging allows direct visualization of the liver and the biliary tree. Ultrasonographic exploration is a noninvasive tool to screen for liver disease. Ultrasound probes with a frequency of 7.5 MHz are suitable but those with 10 MHz to 13 MHz have better resolution.

In ferrets, the structure of the thorax can make visualization with the ultrasound probe difficult. Ultrasonographic appearance is nonspecific in ferrets and similar to cats and dogs.

**Normal Appearance**

Few specific descriptions have been reported in ferrets. The ferret liver parenchyma is usually uniformly hypoechoic, with a coarser echostructure than the spleen, similar to what is visualized in small carnivores (Fig. 2).

The gallbladder appears anechoic with a pear-shaped structure. Size variation is important and volume alone cannot be used as a sign of biliary obstruction. Gallbladder sludge is usually nonsignificant. The afferent vascular flow enters mainly via the portal vein. The efferent flow follows the hepatic vein into the caudal vena cava. The wall of portal veins usually appears hyperechoic compared with hepatic veins.

**Pathologic Findings**

**Liver parenchyma**

There are no specific descriptions of liver parenchyma in ferrets to the authors' knowledge. Diffuse alteration of the echogenicity of the parenchyma can be observed. Abnormalities are listed in Table 2. Hepatomegaly can be demonstrated when the edge of the liver are round shaped. Usually lipidosis is characterized by a diffuse increase of parenchymal echogenicity (Fig. 3). In cats, cholangiohepatitis can be

![Fig. 2. Normal ultrasonographic aspect of the liver of a ferret.](image_url)
observed with a decrease of parenchymal echogenicity and increased visibility of portal vasculature. Chronic hepatitis, fibrosis, and ultimately cirrhosis are characterized with a small or normal sized liver (Fig. 4). Focal lesions, such as nodular hyperplasia, hepatic cyst, neoplasia, and abscess, can be visualized (Fig. 5).

**Biliary tract**
Obstruction of the biliary tract is well observed by ultrasonography. As discussed previously, distension of the gallbladder cannot be the sole criteria for gallbladder obstruction. In ferrets, when the gallbladder is distended, it may separate the 2 lobes but it never extends through the liver to contact the diaphragm as it does in dogs.2 Thickening of the biliary tract and the gallbladder wall can be observed (Figs. 6 and 7).9 In carnivores, usually the cystic duct dilates and becomes more tortuous, which has been reported in ferrets with EHBO and cholelithiasis.9,21

Nodules or neoplasia can arise next to the bile duct. A diffuse thickening of the gallbladder can be observed in cases of cholecystitis. An accumulation of mucus in the lumen of the gallbladder can cause distension, wall necrosis, and obstruction (Fig. 8).

**Neoplasia**
Various types of hepatic tumors and metastasis are described in ferrets (Fig. 9). Focal change can be observed by ultrasound, such as biliary cyst adenomas (Fig. 10).5

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**Table 2**
Diagnostic differentials for diffuse alterations in hepatic parenchymal echogenicity

| Diffuse Hyperechogenicity | Diffuse Hypoechochogenicity | Mixed Echogenicity |
|---------------------------|-----------------------------|-------------------|
| Steroid hepatopathy       | Passive congestion          | Steroid hepatopathy associated with benign hyperplasia |
| Chronic hepatitis         | Acute hepatitis or cholangiohepatitis | Hepatitis         |
| Lymphoma                  | Lymphoma                    | Lymphoma          |
| Fibrosis                  | Lymphoma                    | Neoplasia and metastasis |
| Cirrhosis                 | Lymphoma                    | Necrosis           |
| Vacuolar hepatopathies    |                             |                   |
| Lipidosis                 |                             |                   |

*Data from D’Anjou MA. Liver. In: Penninck D, D’Anjou MA, editors. Atlas of Animal ultrasonography. Ames (IA): Blackwell Publishing Ltd; 2008. p. 226.*

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*Fig. 3.* Diffuse hyperechogenicity in the liver parenchyma of a ferret consistent with hepatic lipidosis.
Hepatic congestion
Hepatic congestion is usually seen with right-sided cardiopathy, with increased pressure of the cranial vena cava and thus increased pressure in the hepatic vein. The liver is typically enlarged and appears diffusely hypoechoic.\(^{28}\) In cases of severe congestion, some investigators report that the liver can appear almost cystic.\(^{27}\)

**CYTOLOGY**

Smears prepared from liver aspirates include blood and hepatocytes distributed singly and in clusters. Hepatocytes are polyhedral cells that have an oval nucleus, granular chromatin, a single small nucleolus, and a moderate amount of blue-gray cytoplasm. Macrophages are frequently present in small numbers.\(^{30}\) Liver cytology is not the gold standard for accurate diagnosis.\(^{31}\) Because cytology does not reflect hepatic architecture, its major indications are fine-needle aspirate of a focal lesion, such as neoplasia and hepatic lipidosis.\(^{5}\) Increased numbers of lymphocytes in liver fine-needle aspirate can indicate lymphosarcoma.\(^{30}\) It is not recommended in diffuse parenchymal disease, such as lymphocytic hepatitis.\(^{5}\) Cytologic criteria have been developed in dogs and the same criteria can be extrapolated in ferrets (Box 1).\(^{32}\)

**HISTOPATHOLOGY**

Most diagnosis of liver disease relies on histologic descriptions. Every effort should be made to approach a standardized description, as described in canine medicine.\(^{33}\) Biopsy sample can be obtained preferably by surgery or with true-cut needles.

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**Fig. 4.** Diffuse hyperechogenicity and increase visibility of hepatic vein consistent with chronic hepatitis.

**Fig. 5.** Hypoechoic nodule consistent with a hepatic cyst in an asymptomatic ferret. Hepatic cysts are common findings.
LIVER DISEASE

Inflammatory Liver Disease

Pathogenesis of hepatitis is poorly understood and causes of most cases remain unknown in dogs and cats. Ferrets have been studied as a model of hepatitis, with speculation of a close liver metabolism to dogs. \(^\text{34}\)

In case of hepatitis, inflammation is characterized by infiltration of inflammatory cells with edema and congestion around hepatocytes, bile ducts, or blood vessels defining hepatitis, cholangitis or vasculitis, respectively.

In the first acute inflammation phase, cellular change occurs, including apoptosis, necrosis, and possibly regeneration. \(^\text{34}\) Regeneration can take place at this stage if the supportive reticulum is intact and fills the gap integrally. Portal inflammation may involve all or some portal fields. Cells involved are mostly lymphocytes (Fig. 11). This portal inflammation may be accompanied by bile extravasation, granulomas, purulent exudate, destruction of bile duct, ductular reaction, or fibrosis (Fig. 12).

Secondly, an influx of inflammatory cells can be observed leading to chronic hepatitis. In areas where the reticulum is changed, healing can only occur by scarring and the process leads to fibrosis. The severity of the disease is determined by the quantity of inflammation, the extent of hepatocellular apoptosis and necrosis, and the pattern

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Fig. 6. Hyperechogenicity and thickening of the biliary tract in a ferret with severe cholecystitis.

Fig. 7. Hyperechogenicity and thickening of the gallbladder with a biliary sludge in the lumen observed in a ferret with EHBO.
of fibrosis. If scarring tissue is produced extensively, vascular changes and structure distortion occur, leading to cirrhosis.

Cirrhosis is defined as a diffuse process characterized by fibrosis of the liver and conversion of normal liver architecture into abnormal nodules and portal-central vascular anastomosis. This end result of chronic damage to the liver seems uncommon in ferrets. Serum chemistries are compatible with liver damage (elevation of ALT and GGT) and loss of function (elevation of bilirubin). Ultrasound may detect changes in size and consistency of the liver suggestive of cirrhosis. A definitive diagnosis is made via biopsy. Histopathology shows bridging fibrosis with areas of regeneration but overall loss of healthy hepatocytes.

**Lymphocytic hepatitis**

Lymphocytic hepatitis is common in pet ferrets and potentially underdiagnosed because it is subclinical. Moreover, clinical signs are difficult to distinguish from gastrointestinal disease because both are usually present. Most patients are over 1.5 years old when diagnosed. This disease can be discovered incidentally during routine blood panel. Some investigators state that mild lymphocytic portal infiltrate is normal in this species. Lymphocytic hepatitis is usually associated with digestive conditions (inflammatory bowel disease or chronic inflammation caused by...
Fig. 10. Multiple hypoechoic nodule consistent with a biliary cystadenoma in a ferret.

| Box 1 | Cytologic findings consistent with liver disease |
|-------|-------------------------------------------------|
| **Acute and nonspecific reactive hepatitis** | - Presence of moderate reactive nuclear patterns (more pronounced chromatin, prominent nucleoli)  
- Increased numbers of inflammatory cells, excluding lymphocytes  
- Absence of increased numbers of bile duct cell clusters  
- Increased numbers of mast cells also indicative of nonspecific reactive hepatitis |
| **Cirrhosis** | - Chronic hepatitis criteria  
- Intracellular bile accumulation  
- Increased numbers of bile duct cell clusters |
| **Lymphoma** | - Presence of large numbers of lymphoblasts with a minimum of 5% of all cells found |
| **Carcinoma (primary or metastatic)** | - Clusters of epithelial cells with several cytologic characteristics of malignancy intermixed with normal hepatocytes  
- Liver cells presenting a high nucleus/cytoplasm ratio, large cell diameters, increased numbers of nucleoli per nuclei, small numbers of cytoplasmic vacuoles  
- Frequently, small numbers of lymphocytes |
| **Extrahepatic cholestasis** | - Excessive extracellular bile pigment in the form of biliary casts  
- Increased numbers of nucleoli within hepatocytes  
- Decreased hepatic cell size  
- Low numbers of lymphocytes. |

Data from Stockhaus C, Van Den Ingh T, Rothuizen J, et al. A multistep approach in the cytologic evaluation of liver biopsy samples of dogs with hepatic diseases. Vet Pathol 2004;41:461–70.
Coronavirus infection), suggesting an ascending inflammatory process from the lower digestive tract, and biliary inflammation is often noted.\textsuperscript{5} Biochemistry change include elevation of ALT (200–500 IU/L) and GGT.\textsuperscript{5} An index of ALT values between 200 IU/L and 700 IU/L has been reported as suggesting mild to severe lymphocytic hepatitis.\textsuperscript{5} Definite diagnosis is confirmed with liver biopsy sampling intestinal tract and lymph node in the same procedure are recommended. Other diagnostic procedures include ultrasound-guided biopsy.\textsuperscript{5}

**Suppurative hepatitis**

In suppurative hepatitis, clinical signs are usually more obvious and ferrets affected show more profound lethargy than in case of lymphocytic hepatitis. Fever, anorexia, vomition or diarrhea, icterus are usually present. Suppurative hepatitis shares the same cause as lymphocytic hepatitis; thus, underlying disease must be investigated.\textsuperscript{5}
There is probably underlying lymphocytic gastroenteritis present in most cases, leading to intestinal bacterial overgrowth, ascending biliary inflammation, and lymphocytic hepatitis, all of which predispose patients to bacterial cholangiohepatitis. Suppurative hepatitis has been associated with disseminated idiopathic myofasciitis. Granulomatous hepatitis has been seen in Coronavirus infection and Mycobacterium infection. Severe elevation of ALT of more than 1000 IU/L, with lesser elevations of GGT, AST, and ALP, are described. Bilirubin is also elevated.

Infectious and toxic hepatitis

Several etiologic agents have been identified in cases of liver disease, causing liver inflammation.

Bacterial disease

Helicobacter The ferret is an animal model for Helicobacter infection because H mustelae shares several characteristics with the human H pylori. Some species of Helicobacter are so-called enterohepatic species but, although H mustelae is well known in gastric disease, its pathogenicity in liver disease remains undescribed. One retrospective study of hepatobiliary disease in a ferret colony showed presence of bacteria related to H cholecystus in hepatic biopsy, suggesting a potential cause of cholangiohepatitis. Isolation of Helicobacter DNA in affected tissue and relationship with liver disease are controversial. In dogs, Helicobacter DNA has been detected in liver tissue affected with primary biliary cirrhosis and primary sclerosing cholangitis. In the same study, however, Helicobacter DNA was also detected in the control group; thus, statistical evidence of pathogenicity was not proved. Equally in humans, incidence of Helicobacter spp is slightly raising the risk of cholelithiasis and benign liver disease but pathogenicity remains difficult to establish.

Campylobacter Campylobacter jejuni is a pathogen that is associated with diarrhea and enterocolitis in several species. Experimental infection of young ferrets with C jejuni caused diarrhea and severe inflammatory response. During the acute phase, the bacteria were isolated in the liver but did not trigger any inflammatory response or histologic change. A similar case reported an intracellular campylobacter-like organism related to Desulvibrio spp, which was isolated in liver tissue of a ferret affected with proliferative colitis. Liver changes included inflammatory infiltrate.

Mycobacterium Ferrets may be naturally or experimentally infected by bovine, avian, and human mycobacteria. Sporadic cases are described in pet ferrets and are common in the wild population of ferrets in New Zealand. M avium and M celatum have been isolated in liver tissue in ferrets affected with disseminated mycobacteriosis. Experimental infections with M bovis occasionally involve liver. Characteristic granulomatous lesions have been observed in affected liver tissue. Mycobacteriosis remains a major differential to consider with hepatic abscess in ferrets.

Sepsis Septicemia and hematogenous spread of bacteria can affect liver secondarily. Escherichia coli hepatitis and enteritis have been associated with in a colony of black-footed ferrets. A Corynebacterium mustelae sp Nov has been isolated from liver, lung, and kidney in a 3-year-old ferret with lethal sepsis.

Parasitic disease

Toxoplasma Toxoplasma gondii is a protozoal parasite that infects ferrets, but there is only a single report of toxoplasma-like infection in ferrets. Areas of necrosis in the liver and toxoplasma-like organisms were isolated. The black-footed ferret, a related
species, has demonstrated clinical toxoplasmosis. Lesions include pneumonia, encephalitis, myocarditis, myositis, and acute to chronic hepatitis.53

**Fungal disease**

*Cryptococcus* There are several reports of disseminated *Cryptococcosis* in ferrets.54–56 When they developed generalized *Cryptococcosis*, clinical signs and findings are limited to lower respiratory tract disease with pneumonia, pleurisy, and mediastinal lymph node involvement or infection in a segment of intestine with subsequent spread to mesenteric lymph nodes. *C bacillisporus* (formerly *C neoformans* var *grubii*) accounted for the infections in ferrets. Liver involvement is rare and has only been reported once; respiratory and neurologic signs were predominant.54

*Pneumocystis carinii* *Pneumocystis carinii* is a fungal organism causing pneumonia in ferrets and in immunocompromised humans. Research has been focusing on studying experimental infection with *P carinii* in immunosuppressed ferrets. In experimental conditions, inducing extrapulmonary *P carinii* infection in the liver was successful in a minority of individuals, however this finding has not been reported in pet ferret.57

**Viral disease**

*Distemper* Ferret distemper, due to the same morbillivirus that causes distemper in dogs, is one of the most important diseases of the species. Clinical signs are similar to those seen in dogs: weight loss, anorexia, hyperkeratosis of the nasal planum and footpads, and oculonasal discharge. The diagnosis may be confirmed by microscopic examination of necropsy tissues; numerous viral inclusions and syncitia are seen in a wide range of tissues, including the liver and gallbladder.58 Fluorescent antibody tests can be run on peripheral blood, mucous membrane scrapings, or conjunctival swabs, and vaccines do not interfere with these tests. Biopsy samples of footpad skin can be examined microscopically for the characteristic viral inclusions.

*Influenza* Influenza viruses are part of the family of orthomyxovirus and ferrets are highly susceptible. Ferrets are an experimental model in influenza research, especially because of their susceptibility to influenza A and B from human strains. Experimental infection of different strains of influenza induced severe pneumonia and fever, and some strains have a degree of liver involvement, including severe portal hepatitis.59–61

*Coronavirus* Infectious hepatitis and enteritis of ferrets have been reported under the names, *epizootic catarrhal enteritis* and *green slime disease*. A type 1 coronavirus has been identified as a causative agent.37 It is highly contagious with transmission from direct contact. Outbreaks of the disease have been reported anecdotally at ferret shows, in pet shops, and in multiferret homes.7 Young ferrets seem to experience a milder form of the disease; older ferrets are severely affected. A significant hepatitis and enteritis cause the signs of the disease: profuse, green, mucoid diarrhea, depression, dehydration, anorexia, weight loss, and death.7

AST levels greater than 700 U/L in ferrets are suggestive of this disease. Polyclonal gammopathy is also observed. Ultrasound features include peritonitis, abdominal adenomegaly, splenomegaly, and nephromegaly. No change in the liver ultrasound structure was seen in a study of 11 ferrets.62 Diagnosis is confirmed with biopsy of the liver showing varying degrees of hepatic destruction and the gastrointestinal tract showing pyogranulomatous inflammation.7 White foci and white nodules can be seen on affected tissue.22,25 Postmortem, pyogranulomatous lesions are seen in the parenchyma of various tissues: spleen, kidney, liver, and lymph nodes.22,25 Reverse transcription–polymerase chain reaction assays were developed to screen for ferret coronavirus. Fecal swabs or sample are
Coronavirus serology is also available and demonstrates past exposure to the virus. These tests alone cannot confirm a systemic Coronavirus infection.\textsuperscript{22}

**Aleutian disease** AD is a parvovirus associated with neurologic dysfunction in ferrets.\textsuperscript{23,63} Pathogenesis of AD in ferrets is controversial; many individuals remain asymptomatic.\textsuperscript{23,64} A case report of AD in a ferret with liver involvement was described.\textsuperscript{53} Histologic findings included plasmocytic infiltrates in various organs, mainly kidney but also in the liver. Lymphocytic and plasmocytic infiltrates in periportal areas and proliferations of the bile ducts were seen.\textsuperscript{63} Experimental infection by mink AD and ferret AD showed a high prevalence of periportal lymphoid cell infiltration.\textsuperscript{65} Some investigators report that AD may cause mild periportal lymphocytic infiltrate in asymptomatic ferrets.\textsuperscript{1}

AD is typically difficult to investigate because asymptomatic carriage is common.\textsuperscript{64} Hyperproteinemia and hypergammaglobulinemia can be present but are inconsistent.\textsuperscript{63,66} Serology testing demonstrates past exposure but positive titer is frequent in asymptomatic ferrets.\textsuperscript{23}

**Hepatitis E** Hepatitis E can cause liver inflammation in humans, potentially causing death in pregnant women. The role of pet animals has been investigated, suggesting a potential relationship and a carriage of the virus.\textsuperscript{67} Fecal testing and polymerase chain reaction screening in pet ferrets in the Netherlands have shown evidence of a ferret hepatitis E virus.\textsuperscript{68} Clinical importance has not been reported but should be kept in mind in cases of hepatitis due to the potential zoonotic threat.

**Toxic hepatitis** Few reports of toxic hepatitis have been reported in ferrets. Acetaminophen toxicity has been reported in ferrets.\textsuperscript{69} Overdose potentially causes acute hepatic necrosis, methemoglobinemia, and renal failure. Toxicity of aflatoxin remains to be proved in ferrets. In one study, ferrets fed with a toxic ration of groundnut meal did not show any significant histopathologic change.\textsuperscript{70}

**Copper Toxicosis** Copper toxicosis was diagnosed in 2 sibling ferrets on the basis of high hepatic copper concentrations and histologic changes in hepatic tissue. Clinical signs in these 2 ferrets were mostly nonspecific and included severe central nervous system depression, icterus in 1 ferret, hypothermia, and lethargia. A genetic copper toxicosis in these 2 ferrets was suggested because they were siblings with the same phenotypic coat color and because no environmental source of copper was identified.\textsuperscript{8}

**Hepatic Lipidosis and Vacuolar Hepatopathy**

**Hepatic lipidosis** Liver has a key role in metabolizing fatty acid in exporting lipids and lipoproteins. Lipid accumulation in the liver occurs because the intake of fatty acid rises in the diet. But mustelids, including ferrets, have a metabolic ability to mobilize rapidly visceral fat and polyunsaturated fatty acid, predisposing them to liver steatosis.\textsuperscript{71} For those reasons, ferrets are an experimental model of fatty liver syndrome.\textsuperscript{71,72} In experimental conditions, 5 days of food deprivation after being fed a high-fat diet induced liver steatosis.\textsuperscript{71} Obese ferrets and ferrets fed an inappropriate high-fat diet are predisposed to this condition, although healthy ferrets in general do not seem sensitive to lipidosis, according to some investigators.\textsuperscript{5}

Any cause of sudden weight loss, anorexia, or any debilitating disease can be related to hepatic lipidosis. Hepatic lipidosis has been associated with various causes
of dysorexia: chronic gastric disease, megaesophagus, \(^{73}\) diabetes mellitus, \(^{74,75}\) pregnancy toxemia, \(^{76}\) and Coronavirus infection. \(^{5,77}\)

Many cases of lipidosis are subclinical. \(^{5}\) Serum chemistries may be normal or may show mild elevation of ALT, ALP, and GGT. \(^{5}\) The liver looks generally brown to yellow and swollen. Definite diagnosis can be achieved by ultrasound-guided or surgical biopsies of liver and histologic analysis. Screening for concurrent disease is recommended because this is usually a secondary condition. Steroid usage or endocrine conditions may predispose to this disease. \(^{5}\) Histolopathology shows diffuse lipid vacuolation of the hepatocytes (Fig. 13).

**Vacuolar hepatitis**

Most cases of vacuolar hepatitis are subclinical. Clinical signs are vague: lethargy, malaise, and dysorexia. It is a common histopathologic finding with increased vacuolization of hepatocytes. \(^{5}\) Hormone impregnation is a potential cause, with high estradiol level secondary to adrenal gland disease. \(^{5}\) Corticosteroid administration can also be incriminated although steroid hepatopathy is reported as rare in ferrets by some investigators. \(^{5,6}\)

**Biliary Tract Disease**

**Cholecystitis**

Cholecystitis is an inflammation of gallbladder, most often due to lithiasis or biliary sludge. In a case report, a ferret presented for acute abdominal pain was diagnosed with a severe cholangiohepatitis and a cholecystitis leading to a ruptured gallbladder (Fig. 14). Visualization of gas bubbles in ultrasound was diagnostic of emphysematous cholecystitis due to presence of gas-producing bacteria. *Pseudomonas aeruginosa* was isolated from bile culture. *Escherichia coli* and *Clostridium perfringens*, frequently isolated bacteria in dogs, have been seen in ferrets (Minh HUYNH, DVM, 2012, personal communication). Ultrasound-guided cholecystocentesis can be recommended in order to submit a bile sample for bacteriology. Chemical bile peritonitis was seen and cytologic examination of the abdominal effusion showed biliary yellowish pigments or a basophile acellular characteristic substance. \(^{11}\)

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**Fig. 13.** Photomicrograph of moderate hepatic lipidosis showing a diffuse vacuolation of the hepatocytes. Hematoxylin-eosin staining (original magnification ×10). (Courtesy of Vet-Diagnostics, A. Nicollier.)
Extrahepatic bile duct obstruction

EHBO associated with cholangiohepatitis has been reported in 2 ferrets (Fig. 15).\textsuperscript{9} Severe elevation of ALT (>1000 IU/L) and bilirubin (>60 $\mu$mol/L) was observed in both ferrets with EHBO with mild elevation of AST and ALP. Bilirubinuria were seen in both cases. A protein plug was detected and removed in both cases. Gallbladder has not been removed in both ferrets, so histologic confirmation of gallbladder mucocele has not been established. Cultures of the biliary tract contents were negative for bacteria. Another report of EHBO was seen postmortem in a cystic mucinous hyperplasia of the gallbladder mucosa.\textsuperscript{10}

Cholelithiasis has been reported associated with cholestasis.\textsuperscript{21} Total obstruction was not observed but sediment accumulation had a role in cholestasis. Severe elevation apply to 5 measurements were also observed in ALT (>1000IU/L), GGT (97IU/L), bilirubin (6.2 mg/dL), ALP (361 IU/L), and cholesterol (458 mg/dL). Flocculent material was seen in the bile. Marked hyperplasia of the epithelium of the common bile duct was observed. Neutrophilic inflammation and hepatic necrosis was seen. No bacterial growth was seen.
The obstruction of biliary tract may be functional (altered gall bladder wall contractility or thickening of the biliary tract) or structural (result of a cholelith or mucous plug). Pancreatic disease is one of the most common causes of canine EHBO, whereas tumors and inflammatory disease of the biliary tract, pancreas, or both are the most common causes in cats. Pancreatitis is a rare condition in ferrets even if it is common to find hypoechoic appearance of pancreas during ultrasound, but individuals with this condition usually show no symptoms.

**Coccidiosis**
Probably the most common parasites seen in young ferrets are coccidia. They are protozoal parasites that multiply inside the cells. Infections may be subclinical or associated with moderate to severe diarrhea. *Isospora* spp are common species reported in pets, but *Eimeria* spp have been found in free-ranging black-footed ferrets. A case of biliary coccidiosis was reported in a 9-week-old male ferret in a research colony. Hepatic coccidiosis should be considered in young ferrets showing signs of decreased hepatic function and blockage of bile ducts. At necropsy, the liver appears enlarged with nodular abcesses and distended bile ducts. The gallbladder may also be distended. Developing stages are observed on histopathologic examination of tissues. Characteristic oocysts may be seen in fresh bile.

**Neoplasia**
The liver is a common site for primary and metastatic neoplasia in the ferret. In a review of 1525 neoplasms, 25 primary neoplasms and 71 metastatic neoplasms were seen. It is the most affected gastrointestinal organ. In a survey of 155 tumors, 17 were hepatic tumors. Lymphoma, adenocarcinoma, hepatobiliary adenomas, and biliary adenocarcinomas are reported most frequently. Susceptibility of mustelids to hepatotoxins and hepatocarcinogens has been incriminated to explain the high incidence of hepatic tumors.

**Hepatic cysts and cystadenomas**
Hepatic cysts can be incidentally found in one or more hepatic lobes and are reported as common in pet ferrets. They are variable, from small and focal to large and numerous. Hepatic cysts have to be distinguished from the biliary cystadenoma. Ultrasound monitoring for mass growth and evidence of biochemistry modification is strongly recommended. Biliary cystadenomas are the most common primary liver tumors in ferrets. They are reported as one of the most common tumors, with an incidence of 20% in captive black-footed ferrets. Although they are histologically benign, they can have an aggressive behavior. They may grow and replace large portions of hepatic parenchyma in multiple lobes and could result in loss of hepatic function, leading to hepatic failure. Mild to moderate increases in ALT and GGT can be seen in some cases.

**Hepatoma**
Hepatomas are benign hepatocellular neoplasms, which can produce clinical disease, either by damaging the hepatic tissue or by altering the hepatic function. In humans they are reported to cause hypoglycemia. Clinical signs may include weight loss and lethargy. A report indicated a severe elevation of ALT of 1050 IU/L without elevation of AST or GGT with hypoglycemia.

**Hepatic carcinoma**
One case of peliod hepatocellular carcinoma was diagnosed in a ferret. The left medial liver lobe was affected with a 12-cm diameter mass. The mass had rubbery-to-soft
consistency and had completely effaced normal hepatic parenchyma. Immunohistochemical analysis was necessary to differentiate hepatocellular neoplasia from vascular neoplasm, such as hemangiosarcoma. Concurrent adrenocortical hyperplasia was observed in this case and the investigator speculated about a possible association. Hepatic carcinoma generally results in increased concentration of hepatic enzyme.

Hepatocellular and biliary adenocarcinomas are malignant aggressive tumors that may involve one or more lobes and have metastatic potential. Serum chemistry in a report included elevated ALT (>4000 IU/L) with mildly elevated AST (>500 IU/l) and GGT (>100 IU/L), normal ALP, and hypoglycemia. Cholangiocarcinoma was seen in a ferret colony with Helicobacter involvement.

Hemangiosarcoma
Incidence of hepatic hemangiosarcoma is variable, according to the literature. Hepatic hemangiosarcoma seems rare in ferrets in a retrospective study. Cases from a ferret colony were reported, however, with up to 22% incidence of hepatic hemangiosarcoma. Its macroscopic appearance can be a mass involving several lobes or a bleeding mass. Few case reports of hepatic hemangiosarcoma in ferrets exist and may have a similar biologic behavior to hemangiosarcoma in other species. Its behavior is highly malignant, and metastasis to other lobes is common.

Lymphoma
Lymphoma is considered the most common malignant neoplasm of ferrets, and the disease spectrum involves peripheral and visceral lymph nodes, including hepatic nodes. Clinically, hepatomegaly is often seen with other typical signs of lymphoma (weight loss, anorexia, lethargy, adenomegaly without fever, lymphocytosis, dyspnea, and pleural effusion in cases of concurrent mediastinal lymphoma). Juvenile ferrets more often acutely have a lymphoblastic form, whereas, from 5 years, older ferrets often suffer from multicenter or isolated lymphoma but are typically affected with a chronic lymphocytic form of lymphoma. Lymphoblastic lymphoma has been reported with hepatic involvement. Lymphoma has been associated with mycobacterial infection and granulomatous lesion in a ferret. Concurrent liver

Fig. 16. Photomicrograph of hepatic lymphoma. Portal areas are diffusely severely infiltrated by large round blastic cells showing nuclear atypia. Numerous mitoses are observed. Hematoxylin-eosin staining (original magnification ×20). (Courtesy of VetDiagnostics, A. Nicollier.)
eosinophilic infiltrate and granulomas have been seen with a Hodgkin-like lymphoma in ferrets, suggesting that T-cell lymphoma can induce hypereosinophilic syndrome. The diagnosis may not be possible by cytologic examination of aspirates unless infiltration of neoplastic cells is diffuse enough. Hepatic biopsy and histopathology are the gold standard for diagnosing lymphoma in ferrets (Fig. 16).

**Hepatic metastasis**

The most common neoplastic processes seen in ferret livers are metastatic masses from other sites, mainly adrenal cortical adenocarcinomas and lymphomas. Both of these neoplasms tend to produce pale multiple masses when they involve the liver; some right adrenal neoplasias invade the caudate liver lobe locally without general metastasis.

In one retrospective study, among 71 metastatic neoplasms recorded, there were 48 malignant lymphomas, 11 cases of metastatic adrenocortical carcinoma, 10 cases of adenocarcinoma of unspecified origin, 1 malignant mast cell tumor, and 1 metastatic pancreatic exocrine adenocarcinoma.

**SUMMARY**

Hepatic diseases in ferrets are common but symptoms are often subclinical. Concurrent digestive disease and systemic signs are often observed. Clinical pathology and diagnostic imaging are useful tools to screen such conditions. Histopathology is necessary to have an accurate diagnosis. Inflammatory hepatitis, hepatic lipidosis, and hepatic neoplasia are the most common diseases encountered in this species. Because liver disease can be part of a systemic disease, screening for concurrent disease and additional examination must be interpreted accordingly.

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