SOME NEW EMERGING LIVER DISEASES
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Several hepatobiliary disorders have in the last few years come under increased recognition and interest in dogs. Understanding these specific conditions is essential in the diagnosis and management of canine liver disease.

VACUOLAR HEPATOPATHIES

The histological report of diffuse vacuolar hepatopathy is a common and frustrating diagnosis often without an underlying etiology. When hepatocytes become injured one response is for them to swell and become vacuolated. Hepatocellular vacuoles distending the cytosolic compartment may contain, fat, glycogen, intracellular water (edema) or other metabolic wastes or intermediates. Vacuolar hepatopathies may occur in conjunction with hydropic degeneration in which there is cytosolic swelling but devoid of distinct vacuoles. A number of conditions causing non-specific reactive hepatopathies (NSRH) can be responsible for vacuolar hepatopathies or lesions may develop as a result of secondary chronic stress (presumed to be endogenous steroid induced) resulting from concurrent disease.

Glucocorticoid (steroid) hepatopathies occur in the dog secondary to exogenous or endogenous glucocorticoids. On histology the vacuolar lesions contain glycogen that is not easily differentiated from other vacuolar contents without specialized histopathology processing. The development of steroid hepatopathies is linked with marked increases in ALP. The glucocorticoid associated ALP (G-ALP) is unique to the dog and dogs having steroid hepatopathies are associated with a large component of G-ALP. Experimentally when steroids are administered to dogs there is initially an increase in liver ALP but latter G-ALP increases and may comprise the majority of ALP concentration. Determining the G-ALP portion of ALP has been suggested as a screening test for hyperadrenocorticism but unfortunately many other conditions are also associated with increased G-ALP which is most likely secondary to chronic stress of the disease. Hence, the diagnostic usefulness of G-ALP is limited.

Dogs having hyperadrenocorticism or those given corticosteroids have considerable individual sensitivity or variation in liver lesions and ALP concentrations. Dogs given 4 mg/kg prednisone will have liver lesions in 2 to 4 days and marked increases in ALP to follow. Rarely if ever total bilirubin increases but bile acid concentrations may become slightly abnormal and possibly as high as 40-50 µmol/L. Topical steroid administration can also cause steroid hepatopathies and may take a month or longer for values to return to normal once medication is discontinued. A single dose of long acting methylprednisolone acetate can alter adrenocortical function for five weeks or longer.

A subset of dogs have an idiopathic vacuolar hepatopathy (IVH). They generally have no clinical signs and usually are only identified during investigation of unexplained elevations in serum ALP found on routine health screens. Several theories have been proposed regarding the cause of IVH. Some believe adrenal steroids are the cause and suggest increases in 17-hydroxyprogesterone and
progesterone are responsible for these abnormalities however, critical evaluation and validation of adrenal steroid panels (measuring 17- hydroxyprogesterone, progesterone, estradiol, testosterone, and androstenedione) are still lacking, and a direct association to IVH has not be made. IVH dogs by definition have normal serum cortisol concentrations and the VH changes are typical of glucocorticoid excess. Obviously future research is necessary to delineate this syndrome and the relationship to adrenal steroids.

Scottish terriers also are reported to have a breed-specific syndrome associated with a VH containing glycogen and elevated serum ALP. These affected dogs generally have no clinical signs. The authors of this study found that the elevated ALP was predominantly the corticosteroid isoform and following ACTH stimulation test in conjunction with an adrenal steroid panel found increases in one or more non-cortisol steroid hormones. The authors concluded that affected Scottish terriers have a type of HAC on the basis of exaggerated adrenal hormone response.

Dogs with IVH generally have no clinical signs. They usually are identified serendipitously on a biochemical profile identifying elevations in serum ALP concentrations, which subsequently initiates a diagnostic workup. Most affected dogs are middle-aged or older at the time of diagnosis. No breed or sex predisposition is apparent other than the syndrome described above in the Scottish terrier. A small percentage of dog owners may have reported polyuria and polydipsia (PU/PD) in their dogs, but the other signs typical of HAC generally are absent. The workup of the asymptomatic dog with an IVH usually begins after the identification of an elevation in serum ALP. The ALP increases are often 5 to 10 times normal concentrations; the other liver enzymes are usually normal, or occasional mild elevations in alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) occur. Marked elevations in liver enzymes other than ALP are not typical of this syndrome, and if present other types of liver disease should be investigated. Proteinuria and hypertension occasionally are identified in cases of IVH, and the affected dose should be monitored periodically for these complications and, if identified, managed appropriately. Dogs with IVH also are thought to have an increased risk for developing biliary mucoceles. Some anecdotal evidence suggests that some Scottish terriers with VH are at an increased risk of development of hepatic neoplasia (hepatocellular adenoma or carcinoma). Consequently it would be prudent to monitor IVH dogs every 6 to 12 months with an ultrasound of the liver and biliary system. Some have suggested melatonin 3 mg bid (<15 kg bw) for antigonatropic hormone effect or flaxseed hull products with lignans which competes with estradiol production or lysodren (mitotane, given at low doses) has been suggested. Triostane or lysodren is not recommended for the treatment of this syndrome.

HEPATIC NODULAR HYPERPLASIA

This is a benign process causing an increase in liver enzymes and histological changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains normal. Grossly, the appearance may be suggestive of chronic hepatitis or neoplasia. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater than 10 years of age. Laboratory findings generally include an ALP
increase, but some may have mild increases in ALT and AST concentrations as well. Ultrasound may be normal (microscopic nodules and not observed) or as hyper or hypoechoic nodules. Biopsy confirms the diagnosis, however a wedge section may be required, as a needle biopsy may not demonstrate the nodules. There is no specific therapy.

HEPATIC NEOPLASIA
In the dog liver tumors can be either metastatic or primary. Metastatic tumors are more common and would include the carcinomas and sarcomas. Hepatocellular adenoma is common in dogs and generally restricted to a single liver lobe. Previous terminology calls these tumors hepatomas using human terminology that is incorrect. These tumors are very slow growing and often are found as an incidental finding on ultrasound or during a work up for abnormal liver enzymes. Some oncologists may monitor them in old dogs or those with poor anesthetic risk using ultrasound every several months. Only if they grow in size then surgery is suggested. However, if they become large they may not lend to resection or may become necrotic and rupture causing abdominal bleeding making some believe a more aggressive surgical approach is indicated. Hepatocellular carcinomas are malignant neoplasms that can be either solitary (more slowly growing) or diffuse having a poor prognosis. Sometimes telling the difference from adenoma and carcinoma is difficult on a needle aspirate or biopsy. Sometimes large liver masses may be associated with hypoglycemia due to production of an insulin like factor. The more diffuse cholangiocellular and hepatic carcinomas have poorer prognosis and do not respond well to chemotherapy.

COPPER ASSOCIATED HEPATITIS
When we reviewed liver biopsies of 130 dogs having histological evidence of inflammatory liver disease we found 49% of those dogs also had abnormal hepatic copper (>400 ppm) with a mean copper content of 984 ppm. The mechanism of copper accumulation for most dogs is yet unknown. Abnormal hepatic copper accumulation may result from increased dietary copper intake, from defects in copper metabolism (copper located in zone 3 location) or secondary to cholestasis (zone 1 location). The Bedlington terrier has an inherited disorder of copper homeostasis as the result of a deletion of the COMMD1 gene involved in abnormal hepatic copper excretion. Some other breeds associated with abnormal copper accumulation include the Doberman pinscher, Dalmatian, West Highland white terrier and the Labrador retriever. The mechanism of copper accumulation in these and other breeds is yet to be elucidated.

We now speculate that a number of other dogs may have the inability to handle dietary copper resulting in hepatic copper accumulation. This theory comes about because the normal hepatic copper concentration for dogs has been increasing over the years and the fact that canine commercial diets are over supplementation with copper (if you compare that to copper requirements for humans). Further, in a study investigating feral dogs that were unlikely to have ever eaten commercial dog food were found to have significantly lower hepatic copper concentrations compared with normal control dogs eating a commercial diet. Consequently, we believe some dogs taking in excessive copper may have the inability to handle the high copper will develop copper associated hepatitis. The
definitive diagnosis of abnormal hepatic copper requires a quantitative analysis of liver tissue Cu. A semi-quantitative estimation involves histochemical staining for hepatic Cu. Reliable tissue bound copper stains include used rhodanine and rubeanic acid. A grading system estimating the quantity of Cu granules correlates roughly with quantitative determination of hepatic Cu.

Diets low in copper are recommended for the dogs that have copper associated liver disease based on liver biopsy. However the restriction of dietary copper may do little to lower hepatic copper concentrations in diseased dogs having already large amounts of hepatic copper but diet will lessen further absorption of the metal. It is difficult to limit dietary copper because most commercial dog foods contain supplemental copper that likely exceeds the dog’s actual dietary requirements. Most formulated “liver diets” have lower copper concentrations and are recommended. Homemade diets can also be prepared so that they do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron. The company www.BalanceIt.com makes a copper free dietary vitamin mineral supplement that can be used with homemade diets. They also have formulations for a homemade diet.

If the liver biopsy of a dog with chronic hepatitis indicates significant abnormal hepatic copper accumulation, a low copper diet and copper chelation or zinc therapy should be started. I believe hepatic copper levels of greater than 750 µcg/g dry weight (dw) liver (normal <400 µg/g dw) requires therapy to reduce copper concentrations. Animals having greater than 1,500 µcg/g dw should all have chelator therapy because that is a concentration considered to definitely be toxic to hepatocytes.

Zinc given orally as the acetate, sulfate, gluconate or other salt has been shown to be effective in preventing hepatic copper absorption from the GI tract in Wilson’s disease patients that have been previously decoppered with penicillamine. Oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cell dies and is sloughed, the metallothionein bound copper becomes excreted through the stool. I will sometimes use zinc after a course of chelation therapy or as a primary therapy in a dog having modest hepatic copper accumulation or when the client can not afford penicillamine therapy. An initial induction dose of 5-10 mg/kg body weight divided BID of elemental zinc. Following one to 3 months of induction period the dose can be reduced in approximately half. The goal is to get serum zinc concentrations greater than 200µg/dl but less than 500 so I will often check serum zinc concentrations several times during a course of therapy. The zinc must be administered on an empty stomach and has the frequent side effect of vomiting. Zinc also has anti-fibrotic and hepatoprotective properties as well.

Chelator treatment using penicillamine is the primary therapy for copper associated liver disease. Penicillamine binds with copper and then promotes copper removal through the kidneys. Penicillamine is the most frequent copper chelator recommended for use in dogs. The dose is 10-15 mg/kg bid given on an empty stomach. Side effects include anorexia and vomiting but can be managed by starting at a lower dose and then increasing the dose over time or by giving a small amount of food with the drug. Therapy using penicillamine is a slow and prolonged
process taking months to cause a substantial reduction in hepatic copper concentrations. Penicillamine also has been shown to have a protective effect in the liver beyond chelation therapy. It is believed penicillamine induces a hepatic copper binding protein, metallothionein, thus binding and sequestering copper in a nontoxic form in the liver. The length of chelation therapy is variable but based on past experience some general recommendations can be made. Ideally repeat liver biopsies should be obtained to determine success of the chelation and to direct duration of therapy. The following is only a general recommendation; if copper is less than 1000 I will generally treat for 3-4 months, if 1000-2000 I treat for 4-6 months and if greater than 2000 6-8 months. I monitor ALT levels and if they become normal I often discontinue therapy, maintain on a low copper diet and will in some cases consider zinc supplementation as well. Ideally repeat liver biopsies with copper quantitation is the gold standard to direct therapy. Recently Cupramine has gone up in significant cost and therefore compounding formulations or DePen out of Canada is an option.

**GALLBLADDER MUCOCELE**

To date greater than 130 cases of gallbladder mucocoele have been documented in the literature. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile stellate or finely striated patterns of mucoid material within the gallbladder lumen detected with ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the ABCB4 hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocoele cases include endocrine disease (hypothyroidism, Cushing’s disease) and idiopathic vacuolar hepatopathy, hyperlipidemia and dogs on high fat diets.

Gallbladder mucoceles appear ultrasonographically as an immobile accumulation of anechoic-to-hypoechoic material characterized by the appearance of stellate or finely striated bile patterns (wagon wheel or kiwi fruit appearance). This should be differentiated from biliary sludge (bile sludge can be found in normal animals), by the absence of gravity dependent bile movement while the mucocele is non-movable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic or common bile duct may be normal size or dilated suggesting biliary obstruction. Gallbladder wall discontinuity on ultrasound indicates rupture whereas neither of the bile patterns predicted the likelihood of gallbladder rupture.

Cholecystectomy is the treatment of choice for biliary mucocoeles. Following cholecystectomy and recovery of postoperative period the prognosis is excellent especially when the liver enzymes are normal. Mortality rates have been reported
to be in the 20% range and some may persist in having liver disease with elevated liver enzymes. There are reports of resolution of some mucoceles using ursodeoxycholic acid (ursodiol) and a low fat diet but this should only be attempted in the healthy patient and with careful monitoring. Ursodeoxycholic acid is thought to up-regulate biliary excretion of phospholipids and increase bile salt dependent flow.

On histopathology the gallbladder demonstrates cystic mucinous hyperplasia. The pathophysiology of this condition is unknown. It is possible biliary stasis and abnormal bile composition or lack of solubility results in gallbladder mucosal irritation and subsequent mucinous hyperplasia. Infection does not appear to be a factor in this condition. A mucocele is reported the most common cause of a gallbladder perforation.

PORTAL VEIN HYPOPLASIA

Portal vein hypoplasia (PVH), also referred to as microvascular dysplasia (MVD), is a common syndrome in the dog associated with abnormal microscopic hepatic portal circulation. It is thought that PVH is 15 to 30 times more common that a congenital portosystemic shunt (PSS). Hepatic PVH has been suggested as the terminology by the WSAVA Liver Standardization Group that may better reflect the etiology of this condition although MVD is ingrained in the veterinary literature. It is believed that the primary defect in affected dogs is the result of hypoplastic small intrahepatic portal veins. This condition is thought to be a defect in embryologic development of the portal veins. With paucity in size or number of portal veins there is a resultant increased arterial blood flow in attempt to maintain hepatic sinusoidal blood flow. The hepatic arteries become torturous and abundant in the triad. Sinusoidal hypertension occurs under this high pressure system. Lymphatic dilation results and it is thought that this opens up of embryologic sinusoidal vessels to reduce pressure and thus acquired shunts develop to transport some (but not all) of the blood to the central vein thus by-passing the sinusoidal hepatocytes. This results in abnormal hepatic parenchymal perfusion and lack of normal trophic factors bathing the sinusoids causing hepatic atrophy. With portal shunting of blood increased iron uptake also occurs that results in hepatic iron granuloma formation. Ascites or portal hypertension generally do not occur in this condition.

Because similar histological changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary.

The condition that was first described in Cairn terriers and now is felt to occur in other breeds of dogs. Yorkshire Terriers and Maltese may be over represented. Animals show no outward clinical signs and are usually identified because of elevated liver enzymes (ALT). All patients have abnormal serum bile acid concentrations (usually moderate elevations) but generally they are less than 100 µmole/L. It is reported PVH dogs have normal protein c concentrations while PSS dogs have concentrations less than 70% normal. There is no specific therapy.
Some suggest antioxidants (i.e., SAMe, milk thistle etc.). The long-term prognosis is uncertain because of lack of experience with this relative new disease. There may be a small number of dogs developing portal hypertension over time.

**PORTAL VEIN HYPOPLASIA AND SECONDARY PORTAL HYPERTENSION**

Portal vein hypoplasia with portal hypertension and ascites occurs as a fibrosis variant of portal vein hypoplasia. It has also been called congenital hepatic fibrosis and idiopathic noncirrhotic portal hypertension but may in fact could be a congenital ductal plate abnormality. The ductal plate is the embryological precursor to development of bile ducts in the portal region. Some ductal plate abnormalities result in proliferation of small bile ducts and fibrosis with secondary portal hypertension. This subgroup of dogs with portal vein hypoplasia that have moderate to marked fibrosis of the portal tracts, a varying proliferation of arterioles and bile ductules, particularly at the periphery of the portal area. Ascites, portal hypertension and secondary acquired portosystemic shunts occur.

The hepatic histology demonstrates portal tracts associated with multiple arterioles, small or absent portal veins with variable portal fibrosis, lymphatic distention and variable bile duct proliferation. The pathology is void of inflammatory infiltrates. There are also increased amounts of hepatic iron deposited in the liver.

This latter condition is observed in dogs are under 2.5 years of age and there is no breed prevalence however Doberman Pinschers, Cocker Spaniels and Rottweilers may be over represented. The clinical presentation is similar to dogs having either congenital intra or extrahepatic shunts except most dogs have ascites. The liver enzymes are generally increased with a hypoalbuminemia and very high bile acid concentrations. Work up of these patients fails to identify a single shunting vessel, but rather these cases have marked portal hypertension associated with multiple acquired portosystemic shunts. These dogs will generally present with ascites and signs of hepatic encephalopathy. Ultrasound is often helpful showing microhepatia, hepatofugal portal blood flow and multiple abnormal extrahepatic collateral shunts. Portal contrast studies demonstrate acquired portal shunts and pressure measurements document portal hypertension. The prognosis for this condition is generally guarded but some dogs are reported to have a prolonged survival using anti-fibrotic agents and hepatic encephalopathy therapy.

**HEPATOCUTANEOUS SYNDROME**

Hepatocutaneous syndrome, also known as superficial necrolytic dermatitis or metabolic dermatosis, is an uncommon disease observed in middle aged to older dogs. The skin lesions have characteristic histological changes (superficial necrolytic dermatitis or necrolytic migratory erythema) and when combined with the hepatic changes typify this syndrome. The liver has mistakenly been described by some as cirrhotic because of the nodular appearance of the liver. The hepatic changes are best described as an idiopathic hepatocellular collapse with nodular regeneration. Changes are generally devoid of major inflammation. The hepatic nodular regeneration consists of vacuolated hepatocytes. To date the pathogenesis of the hepatic disease is still controversial. In humans other types of liver disease have been noted to produce the similar cutaneous lesions however the hepatocellular collapse described in the canine hepatocutaneous syndrome has not been reported. It is not known if the liver dysfunction is the major mediator of the
necrolytic skin lesions or whether another metabolic disease produced both the skin and hepatic lesions. Affected dogs almost all have pronounced reductions in amino acid and albumin concentrations. Some authors believe this condition to be the result of exaggerated amino acid catabolism. Uncommonly some dogs and humans have hyperglucagonemia secondary to a glucagon-secreting tumor. Diabetes mellitus occurs in some dogs. Recently hepatocutaneous syndrome has also been associated with chronic long-term phenobarbital therapy.

Most dogs are presented because of the skin disease. Abnormal liver enzymes are identified and in most, ALP and bile acids are increased. The albumin is typically below normal and almost every affected dog has hypoaminoacidemia if measured. The liver has a characteristic ultrasound appearance looking like “Swiss cheese” due to the hypoechoic nodules. It is thought that the necrolytic skin lesions are directly related to the hypoaminoacidemia. The hypoaminoacidemia may be responsible for the hepatic changes as well. This is supported in part by observations that dogs fed a protein deficient diet for prolonged periods develop hypoalbumenemia and hepatic changes that resemble hepatic changes described in the hepatocutaneous syndrome, however skin lesions were not observed. The importance of hypoaminoacidemia in this disease is further supported in that administration of intravenous amino acid solutions transiently improved the lesions in many but not all dogs. The cause of the amino acid deficiency is unknown. The affected dogs appear to have been feed adequate protein content diets. The reported prognosis for this disease is grave and invariably most succumb either due to liver dysfunction or to the severity of the skin lesions, or both.

Our current therapy includes administration of intravenous amino acid solution. We give approximately 500 ml of Aminosyn™ (10% solution, Abbott) over 8-12 hours. If given too fast, hepatic encephalopathy can occur. Repeated infusions are given weekly or more frequently. If after four weekly amino acid infusions and if there is no improvement it is unlikely the patient will respond to therapy. Some dermatologists suggest that daily infusion of amino acids for the first week results in a quicker response. With a positive response repeated the amino acid infusions are given as needed. In addition, we generally treat the patient with a dietary protein supplement of egg yolks (as an amino acid source) and other protein supplements. Additional support includes antibiotics if a secondary skin infection exists, omega 3 fatty acids, ursodeoxycholic acid, vitamin E and/or zinc.