Common liver diseases in the dog

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Abnormal liver enzymes are a common encounter in the dog and can be due to a number of etiologies. The following discussion includes some common conditions. Another common histological diagnosis is chronic hepatitis but this will be discussed elsewhere as there are important implications of specific diagnostic testing, therapy, and prognosis.

**Reactive hepatopathies**
These occur secondary to non-hepatic disease with increased serum biochemical hepatic tests (ALT, AST, GGT, ALP) and histomorphologic abnormalities. In most cases there are little if any changes in tests that evaluate hepatic function (bilirubin, albumin, glucose, BUN and bile acids). Histological findings associated with secondary reactive changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis and periportal or variable hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis. The reason the liver often undergoes these changes revolves from the fact that the liver is involved in many metabolic and detoxification functions.

Endogenous toxins, anoxia, metabolic changes, nutritional changes and endogenous stress related glucocorticoid release are examples of conditions responsible for the majority of these changes. Even non-specific mild liver changes routinely also occur following general anesthesia. In a review of liver biopsies at Colorado State University reactive hepatopathies made up the largest category of abnormalities (approximately 25%).

Mild portal hepatitis is a common histology thought to be secondary to uptake of enteric bacteria, toxins, irritating food substances or inflammatory cytokines. Mild ALT and ALP increases can occur. I always look for underlying GI disease and anecdotally have had some resolve feeding a hypoallergenic diet (such as hydrolyzed proteins), enteric antibiotic therapy or ursodiol. Although chronic in nature I avoid putting patients on immunosuppressive therapy as the disease does not tend to progress.

**Abnormal ALP in the asymptomatic dog**
A very common and often frustrating clinical problem encountered by many veterinarians is the identification of elevations in only the serum ALP in dogs completely asymptomatic. In these cases, a number of clinical conditions could be responsible. (Refer to Abnormal ALP Workup Algorithm figure). One must remember the three major isoenzymes of ALP are bone, liver, steroid or drug induction. Bone source is relative easily eliminated if the patient is not a young dog with open growth plates that returns to normal when the dog matures. Siberian Husky puppies are reported to have a benign familial hyperalkalinephosphatasemia from bone origin. Osteoblastic bone tumors can also be associated with elevations in bone source ALP. Most all dogs with bone tumors present with clinical signs relative to the tumor.
Osteogenic sarcomas having concurrent ALP increases generally have a very guarded prognosis.

A drug history is important including administration of herbal medications, phenobarbital or glucocorticoids causing steroid ALP induction. It is important to remember that topical steroids (otic, ophthalmic and cutaneous) will also cause ALP elevations and it could take up to two months to return to normal levels following a course of corticosteroid administration. Although hyperadrenocorticism (HAC) can cause marked increases in ALP (and sometimes mild ALT increases), dogs generally have clinical signs referable to Cushing’s disease. Dogs with HAC and without systemic signs would be quite uncommon. Specific testing with an ACTH stimulation test, dexamethasone suppression test and/or urine cortisol to creatinine ratio usually will rule out HAC as the cause of ALP elevations.

At this point in the work up the next diagnostic test I perform is an abdominal ultrasound carefully examining the liver and biliary system. The main differentials for asymptomatic ALP increases include gallbladder mucocele, hepatic nodular hyperplasia, hepatic neoplasia or an idiopathic vacuolar hepatopathy. Gallbladder mucocles have a characteristic ultrasound appearance and early mucocele formation could cause cholestasis without clinical signs. Other cholestatic conditions such as cholecystitis, cholangitis or cholelithiasis are also possible etiologies.

Vacular hepatopathy
Hepatic vacuolar change is a common histological diagnosis in dogs but not cats. When we reviewed 150 consecutive liver biopsies performed at Colorado State University approximately 12% of the cases had predominately a vacuolar hepatopathy (VH) as the major histological finding. By definition according to the WSAVA Liver Standardization Group VH refers to a reversible parenchymal change that is characterized by swollen hepatocytes with clear cytoplasm due to glycogen without displacement of the nucleus from the center. The distribution and the extent of the lesion can vary being either diffuse, zonal, or involve individual cells. VH is a relatively easy histological diagnosis to make however Periodic acid Schiff (PAS) staining with or without diastase can be used to demonstrate glycogen accumulation. Vaculated hepatocytes can also result from fat accumulation secondary to abnormal fat metabolism and is referred to as hepatic steatosis or lipidosis. Hepatic steatosis is a distinct histological vacuolar classification associated with abnormal fat metabolism and is uncommon often associated with hypothyroidism, hyperlipidemia (Schnauzers) and obesity.

VH in dogs is most often associated with hyperadrenocorticism (HAC). The dog is particularly sensitive the effects of glucocorticoids that both induce serum alkaline phosphatase (ALP) steroid isoenzyme activity and causes hepatic glycogen accumulation. Congenital glycogen storage disorders, breed specific disorders, hepatic nodular hyperplasia and a variety of stress-associated secondary diseases are conditions that can cause typical hepatic vacuolar changes. In a large study of 336 histological liver specimens having VH (defined as making up greater than 25% of the
hepatocytes) were retrospectively reviewed for an underlying etiology. The authors report 55% of the cases were associated with either endogenous or exogenous glucocorticoids with the remaining 45% having no known glucocorticoid exposure. Most all of the dogs with no glucocorticoid exposure had other identifiable concurrent illness. Conditions such as renal, immune-mediated, cardiac, hepatic, gastrointestinal disease, or neoplasia accounted for many cases. The author’s hypothesis was that stress-induced hypercortisolemia associated with acute or chronic illness likely contributed to the development of the VH. A second in vivo study showed that by experimentally inducing a chronic four to five-fold elevations in plasma cortisol concentrations to simulate a stress-like state in normal dogs inhibited non-hepatic glucose utilization and increased hepatic gluconeogenesis and glycogen formation through enhanced substrate delivery to the liver.

**Idiopathic vacuolar hepatopathy.** There is a subset of dogs having elevations in serum alkaline phosphatase and excessive hepatic glycogen accumulation that do not have evidence of either a stress induced illness, evidence of HAC based on cortisol testing, a history of recent glucocorticoid administration or have a specific hepatic disease. These dogs are referred to as having an idiopathic vacuolar hepatopathy (IVH). They generally have no clinical signs and are usually identified during investigation of unexplained elevations in serum alkaline phosphatase (ALP) found on a routine health screen. Several theories have been put forward as to the cause of IVH. Some believe adrenal progestogens; most likely increases in 17-hydroxyprogesterone and progesterone are responsible as these changes as they are frequently identified to be abnormal when a commercial adrenal steroid panel is performed. However, critical evaluation and validation of the adrenal steroid panel (17-hydroxyprogesterone, progesterone, estradiol, testosterone and androstenedione) is as yet still lacking and a direct association has not be made. Because the VH changes are typical of glucocorticoid excess it is entirely possible that a yet to be identified adrenal steroid could be responsible for the VH. Obviously future research is necessary to delineate this syndrome and the relationship to adrenal steroids.

Scottish terriers are also reported to have a breed-specific syndrome associated with a VH and elevated serum ALP. These affected dogs generally have no clinical signs. The authors found that the elevated ALP was predominately the corticosteroid isof orm and following ACTH stimulation test in conjunction with an adrenal steroid panel found increases in one or more non-cortisol steroid hormones. The authors conclude that affected Scottish terriers have a type of hyperadrenocorticism on the basis of exaggerated adrenal hormone response. We have also observed similar non-cortisol steroid hormone increases in Scottish terriers but also in Scottish terriers without VH or increases in ALP adding more confusion to this syndrome.

Most affected dogs with IVH are middle-aged or older at the time of diagnosis. There does not appear to be a breed or sex predisposition other than the syndrome described above in the Scottish terrier. A small percent of dogs may have reported polyuria and polydipsia (PU/PD) but the other signs typical of HAC are generally absent (this differentiates from the syndrome referred to as atypical Cushings disease having signs but normal cortisol testing. The work up of the asymptomatic dog having 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 there are occasional mild elevations in alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT). Marked elevations in liver enzymes other than ALP is not typical of this syndrome and if present other types of liver disease should be investigated. The work-up should first rule out common causes for an elevated ALP such as drug administration (including topical or systemic steroids, phenobarbital, or herbal medications), cholestatic liver disease, or bone disorders. Next adrenal testing...
ACTH stimulation or low dose dexamethasone suppression) would be prudent to perform to eliminate possibility of HAC. Determining the percent of ALP steroid isoenzyme is generally not helpful. Dogs with IVH will have predominately a steroid-induced ALP isoenzyme but this is neither specific for HAC or IVH and other non-adrenal illness may also have similar increases in the steroid-induced ALP isoenzyme. Basic tests of liver function tend to be normal however the author has seen a few cases having very mild elevations in serum bile acids (30 to 50 µm/L range). Abdominal ultrasound of the liver is helpful to rule out hepatic nodular hyperplasia, occult hepatic neoplasia or cholestatic disorders that all could be differentials for an elevated ALP. Affected IVH dogs generally have an enlarged uniformly hyperechoic liver with rounded borders. Adrenal glands are generally normal. Fine needle aspiration of the liver with cytology supports a diffuse vacuolar change. A PAS stain of the cytology sample can help confirm the presence of hepatic glycogen. A liver biopsy confirms diffuse vacuolar change but is rarely necessary. I generally make the diagnosis of IVH based on the above diagnostic findings and after exclusion of HAC, drugs, hepatic nodular hyperplasia, hepatic neoplasia or cholestatic liver disease.

I believe adrenal sex steroid panel testing for most cases is not necessary for two reasons; first, our inability to adequately interpret the tests results and second, most all IVH dogs are generally asymptomatic and information obtained from the testing offers little important diagnostic or therapeutic information. Several labs offer adrenal hormone analysis and currently the most extensive adrenal steroid hormone profile is offered by the Clinical Endocrinology Laboratory at the University of Tennessee. The protocol for running the test is identical to that for a standard ACTH stimulation test.

Both proteinuria or hypertension are occasionally identified in cases of IVH and the affected dos should be periodically monitored for these complications and if identified, managed appropriately. Dogs with IVH are also thought to have an increased risk for developing biliary mucoceles and there is also some anecdotal evidence to suggest 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 from time with an ultrasound of the liver and biliary system.

The management of IVH is controversial at best and there are no studies critically evaluating therapy for this syndrome. I believe that specific therapy is unnecessary unless complicating factors such as hypertension, proteinuria or significant PU/PD exist. Problem associated with therapy arise from the fact we do not know what the endpoint of therapy should be; is it normalization of adrenal hormones, return of ALP into the normal range or histological resolution of the VH? There are anecdotal reports of dogs with IVH being successfully treated using low doses of mitotane (lysodren) and monitoring clinical parameters and measuring adrenal steroid concentrations including cortisol to assure hypoadrenocorticism does not result. Trilostane often shows a similar clinical response however concentrations of 17-hydroxyprogesterone and progesterone are frequently higher following this therapy. Anecdotal reports of clinical improvement in dogs having IVH using either therapy suggests abnormal adrenal steroid production may be involved in the pathogenesis of this syndrome. However, these treatments beg the question if therapy is warranted due to the expense of medication and difficulty in monitoring as well as the potential complications associated with the therapy alone. Until more is known about this syndrome this author can’t recommend specific adrenal therapy unless significant clinical findings would warrant a trial therapy.

Alternative therapies suggested includes melatonin and flax seed products. Melatonin has been shown to decrease sex hormone concentrations in normal dogs. It is reported to be beneficial in some dogs with alopecia X syndrome, and has also been suggested
for IVH. Doses of 3 mg/15 kg q 24h PO has been recommended however here is no published data showing effectiveness for dogs with IVH. Flaxseed hull products with lignans have also been suggested because they compete with estrogens production but again there is no reported evidence of benefit for IVH syndrome.
Liver support therapy using products such as s-adenosylmethionine (SAMe), the milk thistle products, or other antioxidants may have some beneficial effects. One study showed dogs given glucocorticoids and treated with SAMe failed to show a decrease in serum ALP or amount of VH but did have improvement in hepatocyte oxidative status through increased glutathione concentrations. The above products are generally safe for liver support but will unlikely have any effect in the resolution of IVH.

**Hepatic nodular hyperplasia**
This is a benign process causing an increase in hepatic values and histomorphologic changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. 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 include an ALP increase (mean ALP ~ 600 IU/L), but some may have mild increases in ALT and AST concentrations as well. Ultrasound may be normal or may demonstrate larger nodules (many can be only microscopic and not observed on ultrasound). Biopsy confirms the diagnosis, however a wedge section is preferred. A needle aspirate or needle biopsy may only demonstrate a vacuolar hepatopathy. There is no specific therapy and it does not progress to a neoplastic process.

**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 as hepatomas human terminology that is incorrect. These tumors are very slow growing and often are found as an incidental finding on ultrasound as a work up for abnormal liver enzymes. There is no spread to this tumor. Sometimes we will just watch them using ultrasound every several months and if they grow in size rapidly then surgery can be suggested. If they become large they may not lend to resection or may become necrotic and rupture causing abdominal bleeding. 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. FNA or a biopsy sample. It has also been reported that 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.

**Selected references**

