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VCA Clinical Consults

What's Your Diagnosis?

ELEVATED ALT IN AN ASYMPTOMATIC ZUCHON—

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PATIENT HISTORY

SIGNALMENT: "Coz" is a 9.5 year old neutered male Zuchon (Bichon Frise and Shih Tzu mix). Weight 23.5 lb/10.7 kg.

PERTINENT PAST HISTORY: "Coz" has generally been a very healthy dog with no chronic medical issues. He has received all routine health care as recommended by his primary care veterinarian. He is current on vaccinations and monthly preventatives. He eats a commercial adult maintenance dog food.

CURRENT HISTORY: "Coz" was presented to his primary care veterinarian for his annual wellness examination. The owners had complained of marked halitosis. Moderate calculus and gingivitis were noted on exam. A dental cleaning was recommended and pre-anesthetic bloodwork was performed in preparation for the procedure. His ALT was mild to moderately elevated at 326 U/L (reference range 18-121 U/L). The remainder of his liver enzymes as well as the rest of his bloodwork were completely unremarkable.

"Coz" was placed on Denamarin (90 mg PO q day) and his bloodwork was rechecked in one month. He remained clinically asymptomatic. Although slightly improved, his ALT was still elevated at 296 U/L. "Coz" had his dental procedure performed at this time as his veterinarian was concerned the ALT elevation might represent a reactive hepatopathy due to his periodontal disease. ***Clinical Note: Dogs presented with elevations in liver enzymes should always have primary non-hepatic disease ruled out. See* Table 1 *for further information on the condition of reactive hepatopathy.*** After the dental procedure "Coz" was prescribed a four week course of Clavamox and the Denamarin was continued.

A recheck 6 weeks later revealed further, mild improvement in the ALT at 247 U/L but not normalization. "Coz's" veterinarian recommended a recheck in 3 months to determine if the ALT continued to decrease. ***Clinical Note: ALT is a cytoplasmic enzyme present in large quantities within hepatocytes. It is an excellent indicator of active liver damage and since it has such a short half-life (77 minutes in the cat, 2.5 days in the dog); continued elevation is an indicator of ongoing hepatocellular damage. It should not be ignored!*** "Coz's" owner was not comfortable waiting 3 months, however, and requested an internal medicine referral.

ADDITIONAL DIAGNOSTICS

"Coz" had been fasted for his internal medicine evaluation. Paired bile acids were recommended to determine if "Coz" had significant hepatic dysfunction and abdominal ultrasound imaging was also advised.

Abdominal ultrasound revealed a relatively normal sized liver with rounded edges. The hepatic parenchyma, however, was quite abnormal. It was diffusely hyperechoic with a heterochoic mottled echotexture throughout. There were a few hypoechoic nodules present. The remainder of the scan was unremarkable.

The pre-bile acid was mildly elevated at 24.7 umol/L (reference range 0-6.9 umol/L) and the post was moderately elevated at 89.4 umol/L (reference range 0-14.9 umol/L).

TABLE 1.
REACTIVE HEPATOPATHY

This category of hepatopathy is the most common histologic change in dogs and is by far the most common cause of elevated liver enzymes. While any of the enzymes may be elevated (i.e., ALT, AST, ALKP or GGT), there are rarely significant changes in actual liver function tests (i.e., albumin, glucose, BUN, cholesterol, total bilirubin and/or bile acids); indicating this condition causes minimal hepatic dysfunction. This type of hepatopathy generally occurs secondary to non-hepatic diseases such as:

- Gastrointestinal disease (i.e., IBD, infectious or other enteritis, neoplasia, pancreatitis, etc.)
- Renal disease
- Dermatologic disease
- Dental disease
- Infectious disease
- Cardiac disease
- Respiratory disease (i.e., chronic bronchitis, tracheal collapse, chronic hypoxemia, etc.)
- Neoplasia
- Immune-mediated / autoimmune disease

Typically, there are no significant inflammatory infiltrates present in a reactive hepatopathy. The histologic changes are non-specific and characterized by descriptions such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis and hepatic necrosis. These changes occur as a result of the liver's integral role in many metabolic and detoxification functions; it is sensitive to effects by endogenous toxins, anoxia, endogenous stress-related glucocorticoid release and other metabolic and nutritional changes that occur in many disease states. ***These hepatic changes are usually reversible and will resolve once the primary etiology is successfully treated. Hepatosupportive therapy with antioxidants is not absolutely necessary but may be beneficial.***

A liver biopsy was recommended for histopathologic evaluation, aerobic/anaerobic culture and sensitivity as well as samples held for copper or other testing as indicated. The owner was counselled on biopsy options – from ultrasound guidance to open surgical **(see Table 2)** – and opted for a laparoscopic biopsy.

TABLE 2.
LIVER SAMPLING METHODS

	PROS	CONS
Fine needle aspirate	• Less expensive • Easy; usually can be done on a nonsedated patient • Safe; usually not associated with significant bleeding • Reasonably good diagnostic for discrete masses or focal lesions • Valuable if abnormal cells or organisms are present	• Does not adequately reveal hepatic architecture • Easily misses important diseases such as fibrosis and/or infiltrative disease • Very insensitive technique; cannot rule out disease based on negative aspirate results
Needle biopsy	• Relatively easy and safe • Best results obtained with at least 3 samples for histopathology with a 14-gauge needle and gentle tissue handling • If quality samples obtained, can often determine architecture • If quality samples obtained, can often diagnose infiltrative disease	• Very easy to obtain small fragmented samples which are non-diagnostic or too few samples to be diagnostic • Left lateral lobe is often the only accessible lobe; therefore not adequate for many focal lesions. May not be representative of disease in other lobes • Can inadvertently biopsy surrounding organs • Significant hemorrhage can occur • Not as insensitive as FNA but still cannot rule out disease based on negative result
Laparoscopic biopsy	• Provides very good visualization of liver and many other abdominal organs • Relatively large, high quality samples can be obtained from multiple liver lobes and other organs • Less invasive technique when compared to surgery	• Requires special instrumentation and training OR referral • Expensive • May miss deep focal lesions that cannot be seen from the liver surface. This can be minimized by performing hepatic ultrasound prior
Surgical/wedge biopsy	• Readily available; most general practitioners can easily perform • Direct visualization of liver and all other abdominal organs • The largest and most diagnostic samples will be obtained by this method • Easiest procedure to obtain samples from multiple liver lobes and any other organs • Best hemostasis; hemorrhage is easiest to control	• The most invasive procedure with the longest recovery • Typically the most expensive procedure • May miss deep focal lesions that cannot be seen on the liver surface. This can be minimized by performing hepatic ultrasound prior

"Coz's" anesthesia and laparoscopic liver biopsy were uneventful and he recovered without complications. The liver biopsy was submitted as a SUPERLIVER (Antech test code 511039; FBXLSP). ***Clinical Note: Antech's SuperLiver option provides a higher level of analysis for canine (and feline) liver diseases. It offers the expertise of board certified pathologists with hepatopathology specialization, along with a standard set of 3 special stains (rhodanine, Masson's trichrome and reticulum), resulting in more accurate and specific diagnostic and prognostic reports. Additional stains (i.e., iron, glycogen, A1A deficiency, amyloid and fat) may be performed at no additional charge depending on individual biopsy reports. See*** **Table 3** ***for additional information about Antech's SuperLiver service.***

"Coz's" liver biopsy results are outlined in **Table 4.** The results were supportive of significant copper storage disease. Liver tissue had been collected and frozen at the time of surgery and was then submitted for a quantitative copper level. This level was markedly elevated at 2,120 ppm. ***Clinical Note: Normal hepatic copper levels are between 120 and 440 ppm and anything greater than 1,500 ppm is considered hepatotoxic.*** The hepatic cultures were negative.

TABLE 3.
ANTECH'S SUPERLIVER SERVICE

When to order a SuperLiver	• Complex internal medicine cases • Suspected necro-inflammatory hepatopathy, malformations, biliary disease • NOT ideal for intrahepatic tumors or masses, unless survey biopsies are also submitted
How to order a SuperLiver	• Use the regular Antech biopsy form • Request test code 511039 or "Superliver" • Include clinical history and relevant labwork • Include images of the liver, if possible

What to submit	• Biopsies from multiple liver lobes
	• Samples from perceived normal and abnormal tissue
	• Label sites of collection
	• Prefer Micromesh cassettes to sponges
	• As much tissue as possible!
	  • Needle biopsy
	  ○ Need 15 portal triads or >2.5 cm of tissue
	  ○ Usually requires 3 to 5 well preserved 14- to 16-gauge core samples
	  ○ Ideal for diffuse diseases (e.g., lymphoma, fatty liver, storage diseases, steroid hepatopathy)
	  ○ May not have enough tissue for copper quantification
	  • Laparoscopic or surgical wedge
	  ○ Offers diagnostic advantages with significantly larger amounts of tissue
	  ○ Ideal for vascular and inflammatory diseases (needle biopsies are NOT recommended in these cases)
	  ○ Additional tissue can easily be saved for copper quantification

What to Expect	• The report includes HE and special stains, which are read out simultaneously by an Antech hepatopathologist
	• Morphologic diagnosis
	• Categorization of the process: inflammation, necrosis, neoplasia
	• Interpretive comments are key and will emphasize the most important element
	• Comment on possible causes or associations
	• Grading / Scoring, when applicable – using WSAVA Liver Diseases and Pathology Standardization Group guidelines
	  • Copper score (1 to 5) [Center, 2013]
	  • Fibrosis score (1 to 4) [Lidbury, 2017]
	• Hepatopathologists will suggest further diagnostics: copper quantification, serology, culture, PCR, toxicology, etc. as indicated
	• Timely results: 3-5 day turnaround time (regular biopsy TAT)
	• Consults (telephone, e-mail, etc.) on difficult or critical cases

Advantages to using the Antech Hepatopathology Service	• Fast turnaround time (3-5 days) • Simultaneous HE and special stain review • Interpretive comments: bottom line, prognosis and additional testing recommendations • Standardization based on WSAVA Liver Diseases and Pathology Standardization Group guidelines • Team oriented review / digipath rounds • Small group of 3 hepatopathologists work as a cohort

TABLE 4.
"COZ'S" SUPERLIVER HISTOPATHOLOGY

Microscopic Diagnoses:
Within the liver are small aggregates of lymphocytes and macrophages randomly dispersed in the hepatic parenchyma. There is a mild infiltrate of lymphocytes, plasma cells and pigment laden macrophages within the portal areas. Hepatocytes are diffusely swollen with rarefied amphophilic to vacuolated cytoplasm. Many hepatocytes contain refractile mahogany colored granules in the cytoplasm. Occasional apoptotic hepatocytes with pyknotic nuclei and dense eosinophilic cytoplasm are seen. There are occasional foci of extramedullary myelopoiesis.

The following special stains have been applied for further evaluation: (rhodanine for copper, trichrome for fibrosis and reticulin for interstitial collapse). Below are my findings:

Morphologic Diagnosis:
Grade 2 (Mild) multifocal lymphohistiocytic hepatitis
Grade 4 Intraphagocytic and intrahepatocellular copper accumulation
Stage 1 Periacinar fibrosis and mild periacinar centrilobular collapse

Comments:
The additional rhodanine stain reveals large numbers of copper granules (Grade 4), indicating significant copper associated hepatitis, either primary or secondary. Excessive copper accumulation in the liver can reflect dietary excess, genetic errors in copper processing, or previous/coexisting hepatic injury that impairs the ability of the liver to maintain a neutral copper balance.

Abundant copper staining indicates that quantitative copper levels are likely above 2,000 ppm. Copper levels greater than 1,500 ppm are considered hepatotoxic. Quantitative copper levels can be performed by contacting Customer Service and requesting Quantitative Copper (test code S16215).

PATHOLOGIST:
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DIAGNOSIS
Periodontal disease
Copper storage disease – severe

DISCUSSION
Detailed discussion of copper storage disease is beyond the scope of this article and the reader is referred to the listed references.

Etiology
Copper storage disease (CSD) occurs when excessive amounts of copper accumulate in the liver. The liver is the main organ that receives absorbed copper from the small intestine. It has the highest stored copper content and delivers copper in protein bound form to other tissues for metabolic processes. The liver is also the main organ to eliminate copper and does this via biliary excretion.

While excess hepatic copper levels can occur from ingestion of markedly elevated levels of copper in the diet, this is not the most common etiology. CSD more commonly occurs as a primary problem due to inborn errors in hepatocellular copper transport proteins. Primary liver diseases (e.g., hepatitis) can also lead to an abnormal accumulation of copper as a secondary problem.

CSD is becoming increasingly prevalent in dogs and many breeds have been documented or suspected to have metabolic errors **(see Table 5)** – although "Coz's" case supports the understanding that CSD can occur in any breed.

Clinical Signs
Clinical signs of CSD are extremely variable and run the gamut from asymptomatic to vague chronic maladies such as lethargy, inappetence, polyuria/polydipsia and weight loss all the way to peracute presentation with a patient in fulminant liver failure. ***Clinical Note: CSD is commonly diagnosed in asymptomatic dogs having wellness bloodwork performed with a serendipitous finding of ALT elevation. Although the elevations are often mild, a full workup should be pursued as prognosis is best when CSD (or chronic hepatitis) is detected early.***

Diagnosis
The minimum database findings in dogs affected by CSD can be variable depending on the severity of their underlying disease. The CBC changes are usually non-specific and may include anemia, thrombocytopenia and/or leukocytosis. ***Clinical Note: Although rare, excess copper may cause oxidative injury to red blood cells resulting in a Coombs negative anemia and methemoglobinemia.*** The chemistry panel changes reflect hepatocellular damage and cholestatic disease with elevations in ALT,

TABLE 5.
CSD – BREED INFORMATION

Bedlington terrier • Only breed with an identified genetic cause of CSD. Mutation in the COMMD1 gene leads to the absence of the MURR1 protein which is involved in biliary copper excretion • Autosomal recessive mode of inheritance • 50% of Bedlington terriers are affected
Labrador retriever • A complex genetic trait involving the ATB7B gene has been postulated • Copper accumulation secondary to chronic hepatitis also occurs commonly in the breed
Doberman pinscher • A genetic defect in copper metabolism is suspected but not completely identified • Generally occurs in middle-aged females
Other breeds with excess hepatic copper accumulation and suspected to have a familial primary metabolic defect in copper metabolism include: • Dalmation • West Highland White terrier • Anatolian Shepherd • Skye terrier

AST, GGT and ALKP being common. The elevations in ALT are generally greater than the ALKP elevations as the primary disease is more hepatocellular in nature. Other findings include mild (to severe) changes in liver function parameters and may include one or multiple of the following: hyperbilirubinemia, hypoalbuminemia, decreased BUN, hyper- or hypocholesterolemia, and hyper- or hypoglycemia. Urinalysis findings are non-specific but may include bilirubinuria and/or bilirubin crystals. ***Clinical Note: Copper can induce proximal renal tubular injury in some dogs resulting in glucosuria in the absence of hyperglycemia – a form of acquired Fanconi's syndrome. Affected dogs may also have granular casts present on urinalysis.***

Dogs with documented persistent ALT elevations should have pre- and post-prandial bile acids performed. ***Clinical Note: Paired bile acids should be performed EARLY in the diagnostic evaluation. They are relatively inexpensive, easy to perform and give valuable information about the presence of significant hepatic disease and guidance in the decision process on when to biopsy.*** If bile acids are significantly elevated, an abdominal ultrasound +/- biopsy should be the next diagnostic procedure. Even if bile acids are within normal limits, a dog with a persistently elevated ALT should have a liver biopsy performed.

Ultrasound imaging may be normal in dogs with CSD or may reveal homogenous or coarse hyperechoic hepatic parenchyma. ***Clinical Note: As CSD is often associated with glycogen or lipid vacuolation and inflammation, a mottled hyperechoic echotexture is common in affected dogs.*** Fine needle aspirates are not recommended in most cases of chronic ALT workup. Most chronic hepatopathies require assessment of zonal lesion distribution and architectural hepatic features – which will be missed with FNA. ***Clinical Note: There is very poor correlation between fine needle aspirates and even small needle biopsy specimens compared with histopathology from large hepatic wedge biopsies.***

Histopathology is required to make a definitive diagnosis of CSD. ***Clinical Note: Plasma copper levels cannot be used to determine tissue copper concentrations.*** Copper granules can be identified on staining with copper specific stains (i.e., rhodanine, rubeanic, etc.) and this provides a QUALITATIVE estimate of copper accumulation. Qualitative scores range from 0 to 5 with 5 reflecting the most severe accumulation. The distribution of copper granules also helps determine if copper accumulation is a primary or secondary problem. With primary disease, copper accumulates in Zone 3 (centrilobular) hepatocytes as well as other areas. With secondary disease, copper accumulation is found only in areas adjacent to cellular injury and inflammation. Histologic assessments and qualitative copper assessments should be confirmed with measured QUANTITATIVE copper concentrations. Copper quantification guides the need for and duration of copper chelation therapy. Frozen tissue, formalin-fixed tissue or paraffin-embedded tissue can be used for copper quantification. ***Clinical Note: Variation in copper distribution within biopsy specimens can lead to erroneously low measurements when separate biopsy samples are submitted for histopathology (which the qualitative copper is estimated from) and quantitative copper analysis. A digital scanning technique has been developed at Cornell to quantitate hepatic copper concentrations using the entire histologic biopsy specimen (stained with rhodanine). A recent study showed high correlation between this digital scanning and measured concentrations in the same biopsy samples. This can even accommodate fragmented needle core biopsies.***

Treatment

Normal canine hepatic copper concentrations are < 400 ug/gm dry weight liver tissue. Liver copper concentrations > 600 ug/gm dry weight are common in dogs with hepatitis and concentrations > 1,000 ug/gm are considered severe.

Dogs with quantitative copper levels > 1,000 ug/gm dry liver weight should be treated with chelation to remove copper from tissues. Therapy is usually administered for 2 to 6 months depending on the severity of the CSD and histologic changes. ***Clinical Note: Liver copper concentrations between 600 and 1000 ug/gm fall into a grey zone. Copper chelation may benefit some dogs in this range and the decision to chelate should be based on evidence of histologic hepatic damage and knowledge of the individual case.*** As d-penicillamine may induce a B6 (pyridoxine) deficiency with long term usage, consideration should be given to pyridoxine supplementation in dogs requiring long term chelation.

D-penicillamine is the most commonly used copper chelator. It binds copper in blood and tissues and promotes its excretion in the urine. D-penicillamine also has anti-fibrotic and anti-inflammatory effects.
D-penicillamine is dosed at 10-15 mg/kg PO BID 30 minutes before feeding or 2 hours after feeding for best absorption. The drug may be best tolerated if started at one-third of the calculated dose per day and increasing the dose to desired levels every week. The most common side effects are inappetence, nausea and vomiting. ***Clinical Note: Although administration with food may help ameliorate adverse gastrointestinal signs, a recent pharmacokinetic study revealed co-administration of d-penicillamine with food significantly decreased (up to 70%) plasma concentrations of the drug.*** If gastrointestinal signs are persistent, d-penicillamine should be stopped for approximately one week and re-started at a lower dosage; titrating upward over several weeks. Administration of a long-acting antiemetic (e.g., Cerenio) one hour before dosing d-penicillamine often helps curb nausea. Co-administration with glucocorticoids may help alleviate gastrointestinal side effects.

Other possible, but less common side effects, include hypersensitivity reactions (lethargy, fever, pruritus and/or lymphadenopathy), proteinuria and a lupus-like syndrome. Consideration should be given to the concurrent administration of glucocorticoids to help alleviate these side effects. D-penicillamine is capable of chelating zinc, iron and other metals as well. Long term dosing at initial therapeutic levels has rarely been reported to lead to iron deficiency anemia.

In some dogs, side effects can only be controlled by using a 50% dose reduction of d-penicillamine which will dramatically increase time for systemic copper chelation. While d-penicillamine is the preferred copper chelator, there is another option (i.e., trientine) if a patient experiences significant side effects which cannot be controlled by other means. The reader is referred to the references for additional information.

All dogs with CSD should have LIFELONG dietary restriction of copper. ***Clinical Note: Dietary restriction of copper is an important part of therapy but does not replace copper chelation if excessive copper storage is already present. Reducing copper intake by feeding a low copper diet and starting zinc therapy may be beneficial in asymptomatic dogs and in dogs without high enough hepatic copper concentrations to require chelation therapy.*** Dietary copper should be restricted to <5 mg/kg (ppm) dry matter basis. Most canine adult maintenance foods are far too high in copper for dogs with CSD with concentrations of 15-25 mg/kg (ppm) dry matter basis. Prescription diets such as Royal Canin Hepatic® and Hill's® prescription diet® l/d® have much lower copper levels (4.9 mg/kg or ppm) and are recommended for dogs affected by CSD. The diet should not provide protein restriction unless hepatic encephalopathy is present. If feeding prescription hepatic diets to dogs who do not require protein restriction, consideration should be given to the addition of protein to their diets. The USDA food tables can be used to determine copper concentrations in meat as well as other foods and can be shared with clients who enjoy feeding treats to ensure they are only providing low copper options.

Zinc supplementation should be instituted as a maintenance therapy AFTER copper chelation is completed. Zinc decreases intestinal absorption of copper by inducing synthesis of the protein metallothionein. Copper binds to metallothionein which increases excretion in the feces. ***Clinical Note: Zinc should never be used concurrently with chelator therapy as the chelator will bind zinc and become less effective at removing copper.*** Zinc should be administered on an empty stomach and gastrointestinal side effects are the most common problem encountered with zinc therapy. Plasma zinc levels should be monitored at baseline as well as one month into therapy to achieve at least doubled plasma zinc concentrations. If no increase is observed the zinc dosage should be increased. Zinc levels should periodically be measured (q 3-4 months) to ensure excessive zinc concentrations (800-1,000 ug/dL) do not occur as this can result in hemolytic anemia.

Other supportive therapies for dogs affected by CSD include ursodeoxycholic acid, S-adenosylmethionine (SAMe), vitamin E, and sometimes immunotherapy. Immunotherapy with medication like glucocorticoids, cyclosporine, mycophenolate or azathioprine is not routinely used or recommended in copper storage disease. These are reserved for more severe cases of chronic hepatitis in which there may be an element of copper accumulation. Histopathology should reveal a significant necro-inflammatory disease process prior to instituting immunotherapy.

Monitoring

Dogs receiving copper chelation therapy should be regularly monitored with examination and bloodwork to monitor for side effects. In dogs receiving zinc therapy, periodic plasma zinc levels should be evaluated to ensure zinc toxicity does not occur.

Only repeat liver biopsy with quantitative copper measurement confirms the extent of tissue copper removal after chelation, however, ALT functions as a marker of successful de-coppering. ALT notably declines after the first month of chelation and usually normalizes by 3 to 6 months.

Prognosis

The prognosis for CSD is variable and depends on how early the disease is diagnosed and how effective therapy is. If detected and treated early, prognosis can be good. In one study, dogs with CSD experienced a median survival time of 16.9 months while in another study was closer to one year. Dogs with advanced hepatitis, cirrhosis and liver failure have a poorer prognosis.

"COZ'S" TREATMENT

Due to the severity of his copper accumulation and the lack of significant hepatic inflammation, "Coz's" condition was felt to be a primary copper storage disorder and immunotherapy was not indicated. "Coz" was transitioned to a hepatic diet to help minimize his dietary copper exposure. White meat chicken breast was added as a low copper source of protein as he did not require protein restriction for hepatic encephalopathy. Once his dietary transition was complete (approximately 10 days) and he experienced no gastrointestinal distress, he was started on d-penicillamine (125 mg PO BID; 11.7 mg/kg PO BID) for active copper chelation. A 6 month course was planned due to his very high levels of copper (qualitative Grade 4, quantitative 2,120 ppm).

"Coz" experienced inappetence, nausea and vomiting within 36 hours of starting the d-penicillamine. These signs resolved within 24 hours after stopping the d-penicillamine. It was restarted at 125 mg PO once daily and he did well for one week. An attempt to increase to BID dosing was made again and he promptly developed inappetence and vomiting. Once his signs resolved and he was back on once daily penicillamine doing well, a long-acting antiemetic was given and again BID dosing was attempted. His owner felt he became very lethargic and inappetent, although he did not experience vomiting. The decision was made to keep him on chronic once daily d-penicillamine dosing and increase the overall length of chelation time; likely closer to 12 months. B6 supplementation and ursodiol were started at this time and the previously prescribed Denamarin was continued.

"Coz's" ALT normalized after 2 months and he continues to do very well. A repeat laparoscopic liver biopsy will be performed after 10 to 12 months on therapy to determine success of his once daily copper chelation and the need for ongoing chelation therapy.

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CLINICAL ASSESSMENT

1 Which of the following hepatic copper concentrations (in ug/gm dry liver weight) is considered normal?

- **a.** 300
- **b.** 800
- **c.** 1,000
- **d.** 2,000

2 Which of the following is a liver function parameter found on the chemistry panel?

- **a.** ALT
- **b.** AKLP
- **c.** Cholesterol
- **d.** AST

3 ALT has a very long half-life and may stay elevated for weeks after the inciting hepatocellular injury. **True or False?**

4 In CSD, the elevations in ALT are generally greater than the ALKP elevations as the primary disease in more hepatocellular in nature. **True or False?**

5 Fine need aspirates of the liver are the recommended first step in a dog with an asymptomatic elevation of ALT +/- bile acid abnormalities. **True or False?**

6 Plasma copper levels are very helpful indicators of tissue copper concentrations and can be used to indicate copper storage disease. **True or False?**

7 A diagnosis of copper storage disease requires special stains applied to routine histopathology as well as measurement of quantitative hepatic copper level. **True or False?**

8 Reducing copper intake by feeding a low copper diet and starting zinc therapy may be beneficial in asymptomatic dogs and in dogs without high enough hepatic copper concentrations to require chelation therapy. **True or False?**

9 Common side effects of d-penicillamine include nausea and vomiting. If a patient experiences these side effects, administering d-penicillamine with food is advised. **True or False?**

10 If d-penicillamine cannot be dosed at 10-15 mg/kg PO BID due to side effects it will be ineffective at chelating copper. **True or False?**

11 Dietary copper restriction is only necessary during the chelation time for a dog affected by copper storage disease. **True or False?**

CLINICAL ASSESSMENT ANSWERS:

1. **A. 300 ug/gm.** Normal canine hepatic copper concentrations are < 400 ug/gm dry weight liver tissue. Liver copper concentrations > 600 ug/gm dry weight are common in dogs with hepatitis and concentrations > 1,000 ug/gm are considered severely elevated.
2. **C. Cholesterol.** There are 5 liver function parameters found on a routine chemistry panel – albumin, cholesterol, BUN, glucose and bilirubin. Alterations of one or more of these function parameters gives clues to the presence of liver dysfunction.
3. **False.** ALT has a very short half-life (77 minutes in the cat and 2.5 days in the dog) so ongoing changes in ALT indicate ongoing hepatocellular damage and should be worked up aggressively.
4. **True.** Often only minor ALT elevations are the only indicator of CSD in asymptomatic dogs. If the ALT stays persistently elevated – even mildly – pre and post bile acid assay and ongoing workup should commence.
5. **False.** Fine needle aspirates are NOT recommended in most cases of chronic ALT workup. Most chronic hepatopathies require assessment of zonal lesion distribution and architectural hepatic features – which will be missed with FNA. There is actually very poor correlation between fine needle aspirates and even small needle biopsy specimens compared with histopathology from large hepatic wedge biopsies in dogs with chronic hepatopathies.
6. **False.** Plasma copper levels cannot be used to determine tissue copper concentrations. Histopathology is required to make a definitive diagnosis of CSD.
7. **True.** Copper granules can be identified on staining with copper specific stains (i.e., rhodanine, rubeanic, etc.) and this provides a qualitative estimate of copper accumulation. Histologic assessments and qualitative copper assessments should be confirmed with measured quantitative hepatic copper concentrations.
8. **True.** Dietary restriction of copper is an important part of therapy but does not replace copper chelation if excessive copper storage is already present. Generally copper chelation should be prescribed in dogs with quantitative copper levels > 1000 ug/gm dry liver weight – even if they are asymptomatic. If a dog has greater than normal copper levels (> 400 ug/gm) but < 1000 ug/gm consideration can be given to a low copper diet and zinc therapy as the sole treatment.
9. **False.** Although administration with food may help ameliorate adverse gastrointestinal signs associated with d-penicillamine, a recent pharmacokinetic study revealed co-administration of d-penicillamine with food significantly decreased (up to 70%) plasma concentrations of the drug.
10. **False.** Many dogs are intolerant of d-penicillamine and even a 50% dose reduction can be effective at chelating copper in the liver. These dogs will simply require a much longer duration of chelation therapy.
11. **False.** Lifelong copper restriction is required in dogs affected by CSD unless there was a known copper ingestion/exposure which caused the condition.