Copper Hepatopathy in Dogs: A case series

Lenny

Patient: **Lenny, 9-year-old, intact male Labrador retriever**

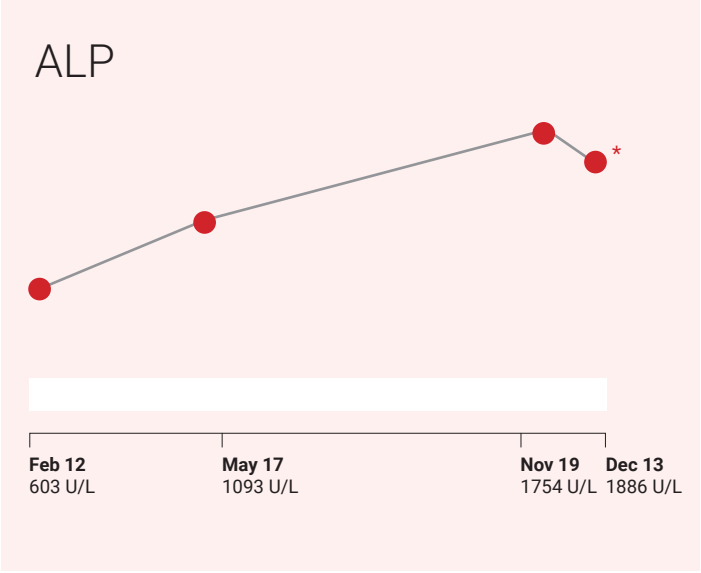
Reason for presentation: **Lenny underwent a liver biopsy due to a progressively elevating ALP over a 10-month period. Initially, Lenny received nonsteroidal anti-inflammatory medication for coxofemoral joint osteoarthritis. When his ALP was found to be elevated, NSAIDs were discontinued but elevation persisted (see below).**

Abdominal ultrasound had recently revealed hepatomegaly with rounded margins and heterogenous echogenicity; no liver mass was observed. The adrenal glands were within normal limits for this patient.

Testing for hyperadrenocorticism was not supportive of this condition.

Physical examination

Lenny was bright, alert, and responsive. The balance of Lenny's exam was unremarkable.



**The trend line goes down for the fourth value even though the numeric value is increased compared to the third value. This is because the ALP reference ranges at the IDEXX Reference Laboratories and on the Catalyst One® Chemistry Analyzer are different. The percentage of increase above the reference range for the fourth value is decreased compared to the third value. This example demonstrates another benefit of using the trending feature in VetConnect® PLUS.*

Diagnostic testing

Due to the progressive ALP increase, surgical liver biopsy via exploratory laparotomy was performed with samples submitted for histopathology (test code HISTOLIV1 Liver Biopsy with Staining Panel) and copper quantification (test code 843 Copper Quantification of Tissue)

Diagnostic results

Copper level is 311 ppm (120–400 ppm) and considerably below the level considered to be toxic (>1500 ppm).

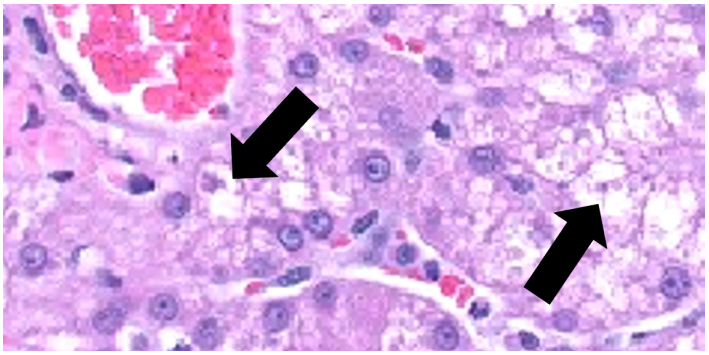
Summary of pathologist's report

Interpretation

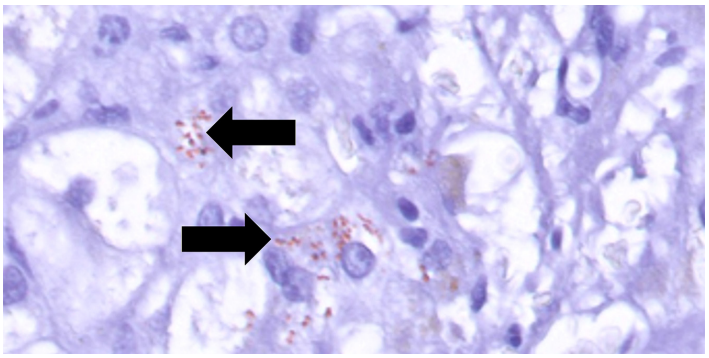
Liver: Moderate chronic diffuse glycogen vacuolar hepatopathy with parenchymal collapse, nodular regeneration, and cholestasis.

Comments

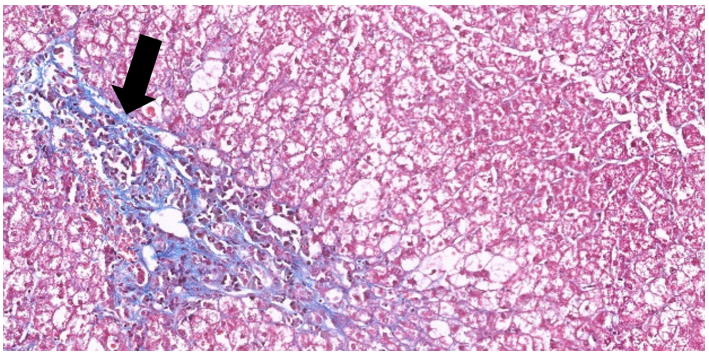
Degenerative glycogen vacuolar hepatopathy is the predominant feature within the liver biopsy. In addition, there is mild copper accumulation in the liver. The degree of copper accumulation is not indicative of a primary copper associated hepatopathy. However, there is enough copper-accumulation present to drive oxidative hepatocellular injury. Therefore, there may be benefit from a copper-reduced diet and/or a combination of chelation therapy.



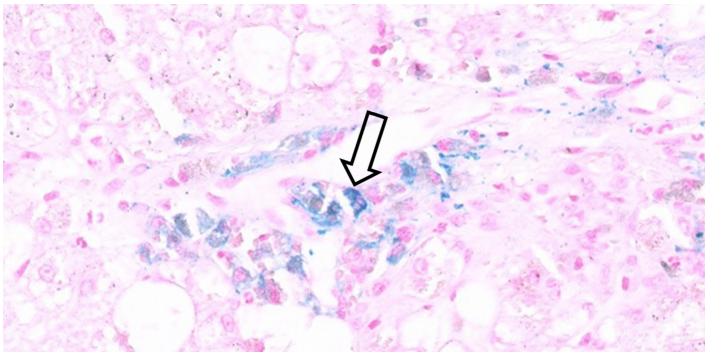
Portal triad with vacuolated hepatocytes (arrows).



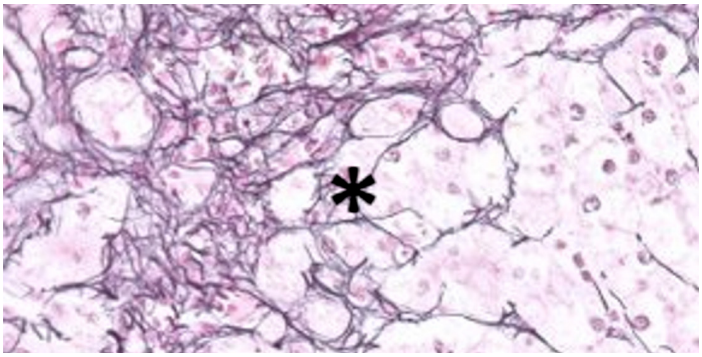
Rhodanine stain positive for copper indicated by red granules (arrows).



Fine tendrils of collagen stained blue with Masson's trichrome indicating Grade 2 fibrosis (arrow).



Iron in Kupffer cells revealed with Prussian blue stain (open arrow). Minimal iron accumulation is noted here. Iron accumulation in Kupffer cells generally indicates increased red blood cell turnover, anemia of chronic disease, or oversupplementation rather than hepatocellular injury.



Gordon and Sweets' reticulin highlights type III collagen, the fiber meshwork supporting hepatocytes. Moderate parenchymal collapse with early nodular remodeling is noted by the asterisk.

Treatment and outcome

A low-copper therapeutic diet was prescribed. Multimodal pain management was continued, including supplements for support of joint and liver health.

Lenny's findings indicate diffuse vacuolar hepatopathy with parenchymal collapse and moderate fibrosis. Canine vacuolar hepatopathy is a nonspecific finding associated with both clinical and subclinical disease and caused by a broad range of factors including corticosteroid administration, endocrinopathies, gastrointestinal disease, neoplasia, and other systemic diseases.[1]

Continued monitoring for copper-associated chronic hepatitis is recommended for this patient. Quantitative copper analysis can be repeated in the future on subsequent biopsies to monitor responsiveness to therapy. A repeat biopsy (test code HISTOLIV1 Liver Biopsy with Staining Panel) at a later date may also provide additional diagnostic information and evaluation for copper-associated disease.

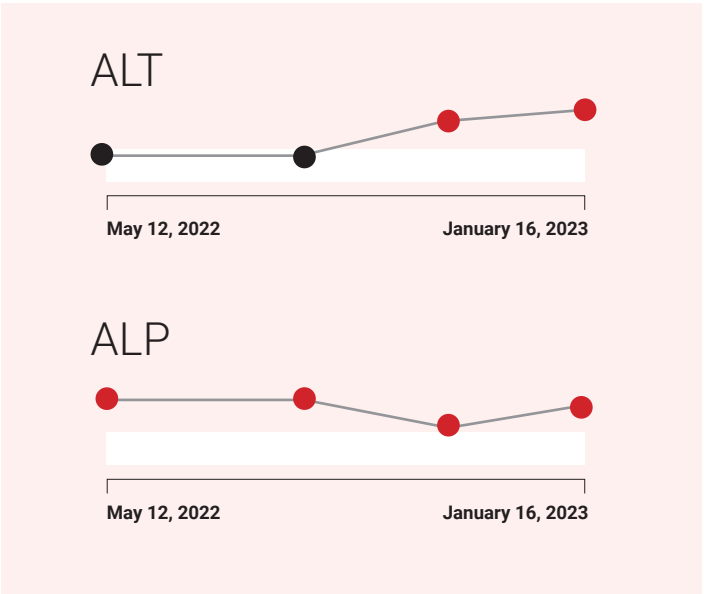
Copper Hepatopathy in Dogs: A case series

Honey

Patient:	**Honey, 7-year-old, spayed female terrier mixed-breed dog**
Reason for presentation:	**Honey presented for annual preventive care exam and vaccines.**
Physical examination:	**Physical examination was unremarkable.**
Diagnostic plan:	**As part of the preventive care visit, IDEXX CBC™, serum chemistry including IDEXX SDMA®, complete urinalysis, Lab 4Dx® Plus Test, and Fecal Dx® Profile were performed.**
Diagnostic review:	**Honey's ALP was increased at 278 U/L (5–160 U/L). There was mild reticulocytosis 129 K/µL (10.0–110.0 K/µL). The other diagnostic results were unremarkable.**

Plan

Vaccines were administered, and a follow-up exam was scheduled in 3 months for monitoring of the increased ALP. The ALP was found to be persistently elevated over the next 8 months and was accompanied by elevated levels of ALT. Using the graphing feature in VetConnect® PLUS, the trend was easily demonstrated to the client.



Additional testing

Abdominal ultrasound was performed. Findings for the liver and other abdominal organs were unremarkable.
Honey was scheduled for surgical liver biopsy via exploratory laparotomy. Tissue was submitted for histopathology (test code HISTOLIV1 Liver Biopsy with Staining Panel).

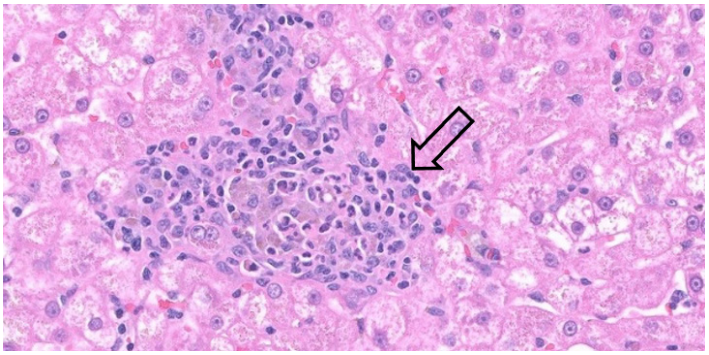
Summary of pathologist's report

Interpretation

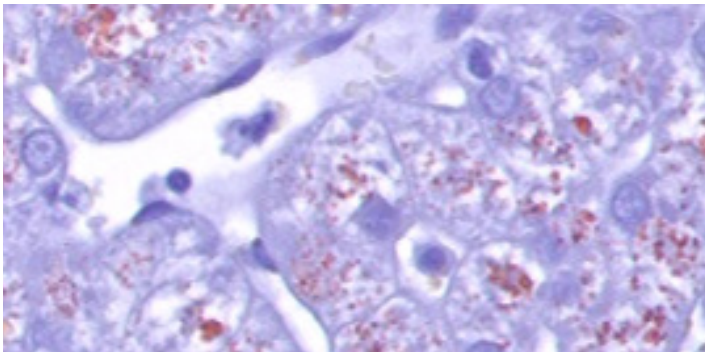
Liver: Vacuolar hepatopathy, mild, with prominent extramedullary hematopoiesis, hepatocellular pigment, and rare lipogranulomas.

Comments

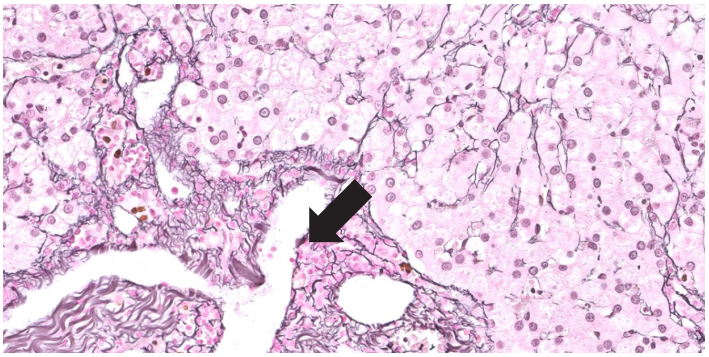
Histopathology of the liver reveals evidence of a mild vacuolar hepatopathy that could result from a number of underlying causes. Common causes include endogenous or exogenous hyperadrenocorticism, adrenal hyperplasia syndrome with abnormal sex hormone production, diabetes mellitus, lipid metabolic disorders, toxin exposure, and biliary disease. There is no evidence of lipid-type vacuolation; hepatocellular degeneration or depth; or biliary lesions to suggest diabetes mellitus, hepatic lipidosis, toxin exposure, or biliary disease as causes of the vacuolation in these samples. Additionally, any condition associated with chronic stress (greater than



Portal hepatocytes are mildly to markedly vacuolated (solid arrows). Portal regions exhibit varying levels of extramedullary hematopoeisis (open arrow).



Rhodanine-positive red granules are noted throughout most zones of the hepatic lobules.



4 weeks duration) can also result in vacuolar change within hepatocytes. Chronic infections and neoplasia fall into the latter category. Other conditions that can be associated with vacuolar hepatopathy include pancreatitis, gastroenteritis, and bacterial septicemias with or without endotoxemia.

Most of the other described changes are largely incidental and/or nonspecific for a particular cause of increased hepatic enzyme values. Many hepatocytes contained intracytoplasmic pigment which is primarily interpreted as age-related lipofuscin pigment.

Liver staining panel results

1. Copper—qualitative copper grade: 5

Copper grade comments: This qualitative grade is considered abnormal and supports prominent copper accumulation in hepatocytes in most zones of the hepatic lobule. These rhodamine copper stain results could support a copper-associated chronic hepatitis (CuCH) in this case. This assessment should be correlated to additional clinical information, clinicopathologic data, diagnostic imaging results, and copper quantification on a liver biopsy sample.

2. Reticulin—qualitative assessment

There are multifocal sites of mild reticulin framework collapse that are associated with the aforementioned foci of extramedullary hematopoiesis (solid arrow).

Additional stains (trichrome for fibrosis, Prussian blue for iron) were unremarkable.

Summary of staining panel findings

The special stain results on this liver sample overall suggest that the abnormally high levels of copper are being stored within hepatocytes. It is possible that low-grade copper-mediated hepatocyte injury is contributing to the chronically increased liver enzyme levels. That being said, histological levels of copper storage do not always correlate to the overall hepatic load of copper. For this reason, correlation of these results to copper quantification performed on these liver biopsy samples should be considered.

As suggested by the pathologist, copper quantification (test code 843 Copper Quantification of Tissue) was requested. Copper level in the liver tissue was 4,020 ppm (120–400 ppm), which is considered to be toxic (greater than 1,500 ppm).

Diagnosis:
Copper-associated chronic hepatitis.

Treatment and outcome
A low-copper therapeutic diet was prescribed along with a copper chelating agent. Three months after diagnosis, liver enzymes had decreased. Continued monitoring for copper-associated chronic hepatitis is recommended for this patient. Quantitative copper analysis can be repeated in the future on subsequent biopsies to monitor responsiveness to therapy. A repeat biopsy (test code HISTOLIV1 Liver Biopsy with Staining Panel) at a later date may also provide additional diagnostic information and evaluation for copper-associated disease.

Discussion

Copper accumulation in the liver is the most common toxic injury cause of chronic hepatitis in dogs. Copper-associated hepatitis may be a result of abnormal copper accumulation from a genetic alteration in hepatic copper transport or from acquired causes of chronic cholestasis. Diagnosis of copper-associated hepatitis requires histologic evidence of chronic hepatitis associated with hepatic copper accumulation, histochemical copper staining showing hepatocyte copper accumulation, and hepatic copper quantification with concentrations usually greater than 1,000 µg/G dry weight liver.[2] Lenny's case illustrates an example of acquired copper hepatopathy, whereas Honey has primary copper-associated chronic hepatitis.

Additional information regarding the diagnosis and treatment of copper-associated chronic hepatitis is available online in the American College of Veterinary Internal Medicine (ACVIM) consensus statement.[2]

The IDEXX liver biopsy code automatically includes liver stains that evaluate for fibrosis, copper accumulation, and other heavy metal accumulation.

Quantitative copper analysis can be performed on formalin-fixed or fresh tissue samples from the liver at the same time as evaluation of formalin-fixed liver biopsy samples for histology.

The clinical signs and diagnosis of the case presented here are specific to this patient. Diagnostic and treatment decisions are the responsibility of the attending veterinarian.

References
1. Sepesy LM, Center SA, Randolph JF, Warner KL, Erb HN. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). *J Am Vet Med Assoc.* 2006;229(2):246–252 doi:10.2460/javma.229.2.246 PMID: 16842046.
2. Webster CRL, Center SA, Cullen JM, et al. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med.* 2019;33:1173–1200 doi:10.1111/jvim.15467