Inflammatory Disorders of the Canine and Feline Liver - The Known and the Unknowns

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Acute Hepatitis

- Inflammation
- Hepatocellular apoptosis
- Hepatocellular necrosis
- +/- Regeneration
Specific Causes of Acute Hepatitis

Dog
- Infectious canine hepatitis (adenovirus)
- Herpes virus
- *Clostridium piliformis*
- *Leptospirosis* spp.
- Septicemic bacteria
- *Toxoplasma gondii*

Cat
- Herpes virus
- Feline Infectious Peritonitis (corona virus mutant)
- *Clostridium piliformis*
- Septicemic bacteria
- *Toxoplasma gondii*
Quiz

Dog
Neonate

Cat
Lives outdoor
Enlarged multinodular spleen
Giant cell Hepatitis
Chronic Hepatitis:

- Hepatocellular apoptosis or necrosis
- Variable inflammatory infiltrate
- Fibrosis
- Regeneration
Fibrosis and Nodular Regeneration

- May disrupt the lobular architecture and be accompanied by:
  - nodules of regeneration in dogs only
Ductular Proliferation
Chronic Hepatitis

- **Dogs**
  - Not common
  - diagnosed in < 0.5% of dogs
- Chronic hepatitis more common than acute hepatitis
  - About half of acute hepatitis chronic

- **Cats**
  - Rare

Poldervaart JH et al. JVIM 2009
Chronic Hepatitis

- Activity
  - Inflammation
- Stage
  - Fibrosis

- We need a standardized grading scheme for both
Grading Inflammation: Options

Interface Hepatitis

Parenchymal activity

Dr. Z. Goodwin
Stage 1

Stage 2

Stage 3

Stage 4

Batt K et al., 1995
Simple grading and staging systems for chronic viral or autoimmune hepatitis

<table>
<thead>
<tr>
<th>IASL</th>
<th>Battts–Ludwig</th>
<th>Metavir</th>
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<tbody>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
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<tr>
<td>Chronic hepatitis with minimal activity</td>
<td>Grade 1</td>
<td>A1</td>
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<tr>
<td>Chronic hepatitis with mild activity</td>
<td>Grade 2</td>
<td>A1</td>
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<tr>
<td>Chronic hepatitis with moderate activity</td>
<td>Grade 3</td>
<td>A2</td>
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<tr>
<td>Chronic hepatitis with marked activity</td>
<td>Grade 4</td>
<td>A3</td>
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<tr>
<td>Chronic hepatitis with marked activity</td>
<td>Grade 4</td>
<td>A3</td>
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<tr>
<td>and bridging or multiacinar necrosis</td>
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<tr>
<td><strong>Stage</strong></td>
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<tr>
<td>No fibrosis</td>
<td>No fibrosis</td>
<td>Stage 0 F0</td>
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<tr>
<td>Fibrous portal expansion</td>
<td>Mild fibrosis</td>
<td>Stage 1 F1</td>
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<tr>
<td>Few bridges or septa</td>
<td>Moderate fibrosis</td>
<td>Stage 2 F2</td>
</tr>
<tr>
<td>Numerous bridges or septa</td>
<td>Severe fibrosis</td>
<td>Stage 3 F3</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Cirrhosis</td>
<td>Stage 4 F4</td>
</tr>
</tbody>
</table>

Corresponding terms in the IASL [17], Batts–Ludwig [18] and Metavir [14] scores.
Assessing fibrosis: Sirius red

Lobular dissecting hepatitis:
Chronic Hepatitis

- Sampling errors can be a serious problem in evaluating livers with chronic hepatitis as there may be considerable variation in severity between and within liver lobes.
Causes of Chronic Hepatitis

- **Known**
  - Copper retention
    - 36% of 47 dogs with CH
      - (Poldervaart, JVIM, 23:2009)
  - Drug toxicity
    - Anticonvulsants
    - NSAIDS

- **Unknowns**
  - Most are idiopathic

- **Speculations**
  - Infectious disease
    - Bacterial
    - Viral
  - Immune-Mediated?
Copper-associated hepatitis affects dogs primarily

- Hepatitis associated with accumulation of copper in hepatocytes
- **Starting in the centrilobular regions**
- Progressive accumulation results in hepatocellular necrosis and inflammation with copper-laden macrophage aggregates
- Acute and chronic hepatitis and cirrhosis
Canine copper metabolism

- Absorbed in proximal GI tract
- Intestinal dose cleared in bile
- In 80 min hepatic copper normal or reduced following dose in normal dogs-High in bile
- In 80 min affected Bedlingtons hepatic copper increased ~50%-low in bile
  - In lysosomes
  - Kaneko et al.
Mechanism of Toxicity

- CU initially stored in MT in cytoplasm, then lysosomes
- CU can participate in the Fenton Reaction (like iron) and produces oxygen radicals
- Oxygen radicals damage cell membranes
- Lipofuscin typically seen with chronic copper toxicosis
Hepatic pigment

Copper

Iron

Hall’s stain for bile

Lipofuscin

Copper
Inflamed livers should be stained for copper

- **Histology**
  - Initial centrilobular accumulation of copper
  - Primarily mononuclear infiltrate
    - Histiocytic infiltrates to aggregate formation
  - Individual cell necrosis

[Image with histological sections showing copper staining in livers]
Liver Copper Determination

- Beware
  - Needle biopsies are often inaccurate

- Can use tissue from paraffin block
How Much Copper is Too Much?

- < 400 ppm d.w. in normal dogs
- >1200-1500 ppm d.w. cause for concern
- > 2000 ppm d.w. likely associated with disease
- Effect of antioxidant status?
- Accuracy of measurement?
Causes for Copper Accumulation

- Genetic
  - Bedlington Terriers
- Cholestasis?
  - Cu in bile
- Inflammation?
- Cirrhosis?
Bedlington Terriers

- Murr1 gene-exon 2 deletion (variants)
- Copper increases with age in affected dogs
- Copper accumulates in lysosomes
- Liver disease -> end stage liver likely
- Liver copper and liver disease do not correlate precisely
Copper Excess

- Bedlington Terriers
  - Only breed with age-related Cu increases
  - Homozygous > 10,000 ppm
  - Gene Comm1 (Murr1) possible chaperone
    - Not ATP7B or ATOX1
Doberman Pinchers-Thornburg

- Middle aged female dogs
- Lesion starts in C.L.
  - Copper accumulation in same site as inflammation
  - 30 with increased copper
    - 10 > 2,000 ppm up to 4,700 ppm
    - 7 ~ 650-1,900 ppm
    - 5 < 250 ppm

- Inflammation/disease not driven by copper levels as histology similar with or without copper elevation (Thornburg L. Vet Pathol, 35:1998)
Doberman Hepatitis: Utrecht

- ~30% 3 yo dogs with enzyme elevations have hepatitis
  - 6:1 F:M
- Liver copper increases with time
- Hepatitis increases with time in ~ 30% (Mandigers, JVIM, 2004)
- Copper metabolism gene expression
  - Reduced mRNA for chaperones and membrane pumps-ATP7A
  - Reduced antioxidant levels
- Chelation improves histology of subclinical liver disease
  - Cu vs. anti-inflammatory action
Doberman Hepatitis

- Some form likely related to copper
- Other types of hepatitis in this breed may occur
  - Autoimmune?
- Some dogs have impaired copper metabolism
Labrador Retrievers

- Clinically affected (N=15)
- 3:1 M:F
- Copper 400-2,600 ppm in affected
  - 100-300 ppm in normals
- Hereditary?
- Typical lesions
- Not all chronic hepatitis in Labs is copper-related

Hoffman et al. JVIM 2006
Other Breeds with Copper Issues

- Skye Terriers
- Dalmatians
- West Highland White
Post chelation
2700 ppm
It’s not all Copper

Labrador Retriever
Chronic Hepatitis
Copper/no copper
American and English Cocker Spaniels

- Chronic hepatitis
- Copper not always an issue
Characterization of a canine homolog of hepatitis C virus

Amit Kapoora,1, Peter Simmondsb, Gisa Geroldc, Natasha Qaisar, Komal Jain, Jose A. Henriqueza, Cadhla Firtha, David L. Hirschberga, Charles M. Ricec, Shelly Shieldsd, and W. Ian Lipkina

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Edited by Robert H. Purcell, national institutes of health, Bethesda, MD, and approved April 28, 2011 (received for review February 1, 2011)
Virus?

Virons ~30-35 nm
Most Chronic Hepatitis in Dogs is Idiopathic
Lobular Dissecting Hepatitis

Affects young dogs
High mortality rate
Portal hypertension
Ascites
Idiopathic Hepatitis: Possible Pathogenesis

- Possible Autoimmune hepatitis
  - Lymphocyte stimulation in response to hepatocyte membrane preps (primary or secondary)
  - CD3+ lymphs most common in chronic hepatitis
  - MHC II upregulation in chronic hepatitis
Chronic Hepatitis: Immune Issues

- Breed Specific — various breeds
  - Labrador Retrievers, Dobermans, Cocker Spaniels, Terriers and others
  - Some copper and some are not
- CD 4/CD 8 ratio high during chronic hepatitis (2.96 vs ref 0.33 +/- 0.12)
- Dobermans have upregulated MCH II antigens on hepatocytes (Speeti M et al. Vet Immunol Immunopathol 103, 2003)
Drug-induced Immune-mediated hepatitis

Immune recognition of neoantigen or native protein

Humoral response: Ab

Cell-mediated Response: CTL

Protein

Covalently bound adduct

B. Fromenty
Human (and Veterinary) drugs associated with autoimmune hepatitis

- Diclofenac/carprofen
- Anti-convulsants
- Halothane hepatitis
- Sulfonamide hepatitis
Trimethoprim Sulfa drugs

Massive Hepatic Necrosis

Destructive Cholangitis
Granulomatous/pyogranulomatous hepatitis

- **Histochemical**
  - Silver stains
  - Acid-fast
    - Fite’s
  - PAS
  - Giemsa
  - Tissue Gram
- **Bacterial Culture**

- **PCR**
  - Bartonella canis
  - B. henslae
  - B. vinsoniae
  - Ehrlichia canis
  - Rock Mountain Spotted Fever

- **FISH**
  - Bacterial probes
Granulomatous hepatitis

HE

Acid-fast

*Mycobacterium avium*
Granulomatous Hepatitis *Histoplasma capsulatum*
Phlebitis and portal inflammation

Schistosomiasis (*Heterobilharzia americana*)

Pyogranulomas around ova in portal veins and portal tracts

Ova lack spine, hook or knob, may have miracidium

Typical life cycle:
Snails to raccoons via cercariae
Granulomatous or Histiocytic Disease

- Infectious agents difficult to detect
- Neoplastic (histiocytic, Langerhans cells) variants?
Middle Aged Dog
08-2879

Dramatic recovery following Doxycyline therapy

Negative for all serologic and histochemical evaluations
Middle-aged Mixed Breed Dog

- Ehrlichia canis +
- >1:64
- Transaminases, Alk Phos elevated
- Bilirubin mildly elevated
- Clinically in poor condition
- No evidence of other organ involvement
Middle-aged Mixed Breed Dog 09-508

Euthanized 1 week post-biopsy
Middle Aged Dog
08-2102
Middle Aged Dog  
08-2102  
Birch Garth

Elevated transaminases, ALK Phos, bilirubin

Recurrent fevers

Negative for all serology and histochemical staining

Dramatic recovery on corticosteroids
Nonspecific Reactive Hepatitis

- A hepatic response to systemic or gastrointestinal disease
- Resolution of primary hepatic disease
- Mild enzyme elevations
- Modest inflammatory infiltrate without hepatocellular necrosis
- NOT-cholangiohepatitis, minimal to mild
Eosinophilic hepatitis

- Unusual variant
- Hypersensitivity?
- Parasitic?
Conclusion

- Chronic Hepatitis remains an enigma in veterinary pathology
- High proportion of idiopathic cases
- Possible etiologies
  - Viruses
  - Other infectious agents
  - Chemical/Drug toxicity
- Alpha1-antitrypsin?
  - Primary or secondary
Biliary Inflammatory Disorders
Neutrophilic Cholangitis

- Risk Factors
  - Acute Pancreatitis
  - Chronic Pancreatitis
  - Trauma to sphincter of Oddi
  - Malfunction of sphincter of Oddi
  - Septacemia?
Neutrophilic Cholangitis

Acute

Chronic
Lymphocytic Cholangitis: Cats

- Diagnostic Features
  - Small lymphocytes
  - Variable plasma cells
  - Centered around portal tracts and bile ducts
  - Biliary response
    - Hyperplasia
Lymphocytic Cholangitis

Variants
- Destructive forms
- Ductopenia
- Prognosis?

Differentials
- Lymphoma
  - PAAR
- Immunophenotype
  - Most lymphs CD3+
  - Not really helpful
- Nonspecific reactive hepatitis
Destructive cholangitis: Drug Hypersensitivity

- Hypersensitivity likely
  - Trimethoprim sulfa

- Different sized ducts affected
Large ducts spared
Destructive cholangitis

Biopsy
Postmortem
Biliary Flukes
Conclusions

- Many forms of acute hepatitis have a cause that can be diagnosed.
- Chronic hepatitis has one main etiology - copper, but this accounts for less than half of the cases.
- Most chronic hepatitis remains idiopathic.
- Lymphocytic Cholangitis in cats is idiopathic.