Pathology of the Liver and Biliary Tract – 4
Toxic and Idiopathic diseases

Shannon Martinson, March 2017
http://people.upei.ca/smartinson/
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Protozoa

- Histomoniasis in turkeys*
- Coccidiosis (rabbits)*
- Leishmaniasis
- Toxoplasmosis
- Neosporosis
- Amoebiasis

*INFECTIOUS DISEASES OF THE LIVER – PARASITIC INFECTIONS

Entamoeba invadens in a reticulated python
Protozoa

Histomoniasis
“Black head”

Histomonas meleagridis

- Turkeys > Chickens
- Typhlitis
- Target-like areas of Hepatic necrosis
- Transmitted in the ova of Heterakis gallinarum
Hepatic Coccidiosis

*Protozoa*

**Eimeria stiedae**

- Disease of rabbits
- Coccidia live in biliary epithelial cells
- Proliferative cholangitis
Liver is the most common site of toxic injury because:
- Ingested toxins $\rightarrow$ GIT $\rightarrow$ Liver
- Biotransformation of endogenous / exogenous substances for excretion
  - Bioactivation $\rightarrow$ more toxic
- Predictable or idiosyncratic
- Common Lesions:
  - **Acute**: Hydropic degeneration, lipidosis & necrosis, often **centrilobular**
  - **Chronic**: Fibrosis, biliary hyperplasia and nodular regeneration (= cirrhosis)
Classification of hepatotoxic liver injury

Biotransformation (most common)
- Cytochrome p450 system (in centrilocular area)
- Phase I: Bioactivation – reactive intermediates
- Phase II: Conjugation
- Phase III: Excretion (via bile)

Stimulation of autoimmunity

Stimulation of apoptosis

Disruption of calcium homeostasis

Canalicular injury causing cholestasis

Mitochondrial injury

Hepatoxic Agents
- Toxic plants
- Mycotoxins
- Cyanobacteria
- Chemicals
- Therapeutic agents
TOXIN INDUCED LIVER DISEASE – TOXIC PLANTS

- Pyrrolizidine Alkaloid Poisoning
- Alsike Clover
- Cycad palms
Pyrrolizidine Alkaloid Poisoning

- Occur worldwide
- Pigs > cattle > horses > goats and sheep
- Alkaloids → cytochrome p450 system → Toxic pyrrolic esters
  - Alkylating agents – react with nuclear and cytosolic proteins and nucleic acid: antimitotic
  - Prevent cell division but not DNA synthesis*
- Toxic compound in milk → transferred to neonates
- Acute
- Chronic*

Common genera:
- Senecio, Crotalaria, Heliotropium, etc
Pyrrolizidine Alkaloid Poisoning

Lesions

Acute: (rare)
- Centrilobular necrosis

Chronic (common)*

Gross
- Small firm finely nodular liver

Histology
- Megalocytosis (antimitotic effect)
- Fibrosis
- Biliary Hyperplasia
- Minimal nodular hepatocyte regeneration

Horse Noah's Arkive

Liver, Chronic PA toxicity

www.askjpc.org/wscco/wsc/images/2014/142302-1.jpg
• Palm like plants (sago palms)
  • Ornamental
  • Kept as yard plants
• Contain nontoxic glycoside (cycasin)
  • Deconjugated by intestinal bacteria
    • Creates a toxin (*methylazoxymethanol*)
  • Bioactivated in liver
    • *Alkylating agent*
  • Also contain neurotoxins – ataxia / paralysis
• Lesions
  • Similar to pyrrolizidine alkaloid poisoning
  • Cattle, sheep and goats
  • Dogs are also susceptible

[Image of cycad plant]
TOXIN INDUCED LIVER DISEASE – TOXIC PLANTS

Alsike Clover

- Horses
  - Chronic liver disease
  - Photosensitization (2°)
- Histo
  - Portal hepatitis and fibrosis
  - Biliary hyperplasia
- Toxic principle unknown
  - Possibly a mycotoxin
  - “Sooty blotch”

Trifolium hybridum

Noah’s Arkive

http://extension.psu.edu

www.omafra.gov.on.ca/english/.../info_alsike_clover.htm
TOXIN INDUCED LIVER DISEASE - MYCOTOXINS

- Aflatoxins
- Sporidesmin
- Phomopsin
- Poisonous mushrooms
• Aspergillus flavus and A. parasiticus
• 4 major aflatoxins: B1, B2, G1, G2
  • Aflatoxin B1*
• Occur in mouldy feed
  • Corn, peanuts, cottonseed
  • Pig, poultry/ducks, calves
  • Commercial dog food
  • Dogs
• Most common in stored feed when temperatures are warm and humid
• Bioactivated (cytochrome p450) in liver
  • Toxic intermediates bind to DNA, RNA, protein
  • Toxic
  • Carcinogenic
TOXIN INDUCED LIVER DISEASE - MYCOTOXINS

Aflatoxins

Acute intoxication
• Dogs
  – Centrilobular to massive necrosis, hemorrhage and lipidosis

Diagnosis: Submit food / stomach content / vomit for aflatoxin testing

**Chronic intoxication**
- Pigs, horses > cattle
- Lipidosis
- Fibrosis
- Biliary hyperplasia
- Mild megalocytosis

Sporidesmin

• **Pithomyces chartarum**
  
  • Occurs in dead ryegrass in warm climates (NZ/Australia)
  • Unconjugated sporidesmin excreted in bile → toxic to biliary epithelium → cholestasis → photosensitization
  • Facial eczema

[Image of sheep affected by facial eczema]

**Photosensitization**

[Image of mycotoxins]

http://luirig.altervista.org/schedeit/fo/lolium_perenne.htm

www.mycology.adelaide.edu.au/images/pitho1.gif
Lesions

- Cholangiohepatitis and cholestasis
  - Portal fibrosis and biliary hyperplasia
- Atrophy of the left hepatic lobe
- Photosensitization
• **Diaporthe toxica** (*Phomopsis leptostromiformis*)
  - Grows on lupins
  - Chronic damage in cattle, sheep, and horses:
    - Small livers, finely nodular
    - Mitotic abnormalities and fibrosis
    - Photosensitization
Poisonous Mushrooms

- *Amanita phalloides* (Death Cap)
  - Produce toxic cyclopeptides:
    - *Amatoxin*
      - *Inhibits of RNA polymerase II function*
    - One mushroom is sufficient to kill
  - Acute damage:
    - Shrunken hemorrhagic liver
    - Centrilobular to massive lipidosis, necrosis and hemorrhage

Phase I – latent: 6-12 hrs
Phase II – GI signs: 6-24 hrs
Phase III – false recovery: 12 – 24 hrs
Phase IV – hepatic failure: 36-48 hrs

Diagnosis: Test for α-amanitin in serum, urine, gastric content, liver
Cyanobacteria – more like bacteria than fungi
- Grows as blooms on lakes and ponds
- Late summer or early fall
- Microcystin (pre-formed toxin)
  - Inhibits protein phosphatase and causes cytoskeletal damage and cell death
- Livestock, dogs, and cats
- Signs develop rapidly
  - Diarrhea, Prostration and Death

Blue-green algae

- Microcystis
- Anabaena
- Aphanizomenon
- Nodularia

TOXIN INDUCED LIVER DISEASE – CYANOBACTERIAL TOXINS

http://dogtrekker.com/userfiles//GreenDogCCJillSiegrist.gif
TOXIN INDUCED LIVER DISEASE – CYANOBACTERIAL TOXINS

Lesions
- Acute hemorrhagic gastro-enteritis
- Red swollen liver:
  - Centrilobular to massive necrosis
- Often die within a few hours
- Chronic liver disease in survivors

Diagnosis: Test gastrointestinal content /vomit or liver for Microcystin

Blue-green algae

• Xylitol
• White Phosphorus
• CCl₄
• Metals
  – Iron
    • Iron dextran in pigs
    • Ferrous fumarate in foals
  – Copper (already covered)

TOXIN INDUCED LIVER DISEASE – HEPATOXIC CHEMICALS

• Vomiting
• Weakness
• Incoordination
• Tremors
• Depression or lethargy
• Seizures /Coma

Xylitol
• Artificial sweetener
• Acute toxicity in dogs – 0.5 mg/kg
• Hyperinsulinemia and marked hypoglycemia
• Centrilobular to massive hepatic necrosis
TOXIN INDUCED LIVER DISEASE – HEPATOXIC THERAPEUTIC DRUGS

- Some are predictable
  - Acetaminophen – cats (↓ glucuronyltransferase activity)
- Idiosyncratic reactions – rare individuals affected
  - Usually centrilobular hepatocytes; often via unknown mechanisms
  - Species and individual variation
    - Trimethoprim-sulfonamide - Doberman pinschers
    - Carprofen - Labrador retrievers
    - Anticonvulsants (primidone, phenytoin and phenobarbital) → end stage liver in some dogs
    - Diazepam – acute hepatic failure in some cats
DISEASES OF UNCERTAIN ORIGIN

- Equine serum hepatitis
- Canine chronic hepatitis
Equine Serum Hepatitis (Theiler’s Disease)

- Typically occurs 1-2 months after injection with a biological of equine serum
- Etiology has long been unknown
  - Now thought to be a Flavivirus
- Clinical signs - Jaundice and encephalopathy

Gross
- Small, flabby and pale liver
Equine Serum Hepatitis (Theiler’s Disease)

Histology:
- Centrilobular to massive necrosis
- Fatty degeneration
- Cholestasis
- Mononuclear infiltration
- Slight fibrosis and regeneration

www.askjpc.org/vspo/show_page.php?id=134
Chronic-active hepatitis

- Descriptive term

Etiology:

- **Idiopathic**
  - Copper associated (36%)
  - Leptospirosis
  - Infectious Canine Hepatitis
  - Progression from acute hepatitis
  - Therapeutic drugs
  - Immune-mediated
  - Toxic injury
Canine Chronic Hepatitis

- **Clinical features**
  - Anorexia, lethargy, weakness, vomiting, diarrhea, weight loss
  - Icterus, coagulopathies, ascites, hepatic encephalopathy
  - ↑ALT ↑AST ↑ALP ↑GGT, ↓albumin

- **Gross**
  - Small liver, coarsely nodular
Diseases of Uncertain Origin

- Histology
  - Portal + periportal mononuclear inflammatory cells
  - Piecemeal necrosis ("interface hepatitis")
  - Intrahepatic cholestasis
  - Bridging fibrosis
  - Regenerative nodules

Canine Chronic Hepatitis

Limiting plate

Questions?