The Avian Liver in Health and Disease

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Embryology

A. Ventral outgrowth of gut entoderm

1. Hepatic diverticulum arises from the future duodenum

   a. Cranial portion-glandular tissue and bile ducts
   b. Caudal portion-gall bladder and common bile duct

2. Grows into septum transversum [primitive diaphragm]

   a. Cranial portions buds off epithelial cords that invade septum and proliferate into expanding cellular network
   b. Diverticulum is close to vitelline veins which send branches into the proliferating cell mass-leads to formation of sinusoids
   c. Wings of the liver enclose and interrupt vitelline veins and then only sinusoids connect supplying [portal] and draining [hepatic] vessels - as liver expands the vascular systems branch and grow steadily toward each other-create characteristic hepatic lobules

B. Fetal blood cells differentiate between hepatic cells and endothelium. Some hematopoietic activity remains for varying times post-hatching.

C. Caudal portion of diverticulum differentiates into the common bile duct, hepatic duct and gall bladder. The latter arises from a separate region of the original diverticulum.

D. The septum transversum gives rise to the ventral mesentery and as the liver grows the mesentery becomes the liver capsule. As the liver descends into the mid-peritoneal cavity it produces a ventral mesentery which encloses the liver and gives rise to the hepatic ligaments [supporting mesentery].

1. the mesentery between the stomach and duodenum and the liver is the lesser omentum.

   a. Cranial portion is hepato-gastric ligament and caudal is the hepato-duodenal. Connection of liver to body wall is the falciform ligament.

E. As liver expands it comes into contact with the umbilical veins-blood goes directly to the heart via the hepatic sinusoids.

1. After hatching the umbilical vessels contract and become umbilical ligaments. the vein becomes the ligamentum teres of the liver-from umbilicus to liver in the falciform ligament.

Anatomy

A. Gross structure

1. Comprised of right and left lobes that are joined cranially at the midline.

    a. The right lobe is usually larger, but not in all avian species.

2. Either right or left lobes may be subdivided into dorsal and ventral sections.

3. Cranioventral portion surrounds the heart apex.

4. Gall bladder on the visceral surface of the right lobe.

    a. Is not present in most pigeons. psittacine birds and the ostrich.
    b. May extend caudally to the level of the cloaca in some species.

5. Each lobe is drained by a bile duct.

6. Blood supplied by the coeliac artery which gives rise to the right and left hepatic arteries. Blood also comes via portal veins from the gastrointestinal tract. Blood from the liver goes via hepatic veins to the caudal vena cava.

    a. Within the liver blood from the portal veins goes to sinusoids and then to the hepatic veins.

7. In precocial species the liver is yellow at hatching and for 8-14 days post-hatch. It then becomes red-purple.

    a. color due to pigment carried with lipids that arrive from the yolk sac in the late stages of incubation.

8. In altrichial species the liver is usually red-purple from the time of hatching.

Histology

1. Capsule of liver is comprised of collagen and elastic fibers. It is continuous with the interstitial connective tissue.

    a. Loose connective tissue most prominent in portal areas.

2. The morphologic unit of the liver is the lobule.

    a. Polygonal mass that has plates of hepatocytes between anastomotic sinusoids.
    b. Central vein at the center of the unit.

3. Hepatocytes

   a. Polyhedral cells with vesicular nuclei that is centrally located.
   b. After eating hepatocytes are larger and contain glycogen and lipid-foamy appearance.
   c. Hepatocytes contain many mitochondria and an extensive RER and SER.
   d. Adjacent cell membranes have indentations that contain small microvilli. The indentations ramify between cells as the system of bile canaliculi.
   e. Hepatocytes form a continuous branching sheet-1-2 cells thick. The canaliculi lie within the sheets of hepatocytes.

4. Adjacent lobules are connected by sinusoids.

   a. Lined by endothelial cells-Kupffer's cells present in sinusoids [phagocytes].
   b. Are the intralobular vascular supply. Receive blood from interlobular vessels.
   c. Have no basement membrane-permit free movement of materials between plasma and hepatocytes.
   d. There is a small perisinusoidal space [of Disse}

5. Biliary system

   a. Bile canaliculi are smallest component.-Between hepatocytes.
   b. Canaliculi continue as ductules that become interlobular biliary ducts.
      - **S** interlobular ducts associate with hepatic artery and portal vein branches and form the portal triad.
      - **S** ducts lined by simple cuboidal or columnar epithelium and surrounded by loose collagenous tissue. May be elastic fibers or smooth muscle around larger ducts.
   c. Interlobular ducts become lobar ducts that in turn become right and left hepatic ducts. These extend to the small intestine, but may unite to form a common bile duct
   d. The gall bladder has the same layers as the extraheptic bile duct-it is a diverticulum of the duct and not present in all birds.

Structure/function relationships

A. **Digestive function.**

1. Produces and secretes bile.

   a. emulsifies fats
   b. activates pancreatic lipase
   c. contains amylase and is involved in carbohydrate digestion

2. Primary constituents of of bile are Na+ and K+ salts of glycocholic and taurocholic acid.

   a. deoxycholic acid may not be present in birds
   b. cholic acid is formed from cholesterol and conjugated to glycine or taurine

c. biliverdin is the primary bile pigment-birds have low levels of glucuronyl transferase and very little or no biliverdin reductase in their livers.
d. bile salts are readily absorbed in the small intestine, particularly the lower portion.

B. Biotransformation

1. Many biologically active substances are altered by the liver a.change toxicity [less or more] reduce activity, or facilitate elimination

    a. change toxicity (less or more) reduce activity, or fascilitate elimination.
    b. occurs within the smooth endoplasmic reticulum, mitochondria and cytosol.
    c. synthetic/conjugation reactions in the cytosol couple substances to endogenous reactive compounds such as sulfates or amino acids.
    d. nonsynthetic reactions can occur anywhere in the cell and include oxidation, reduction and hydrolysis
        - Example: ethylene glycol oxidized to oxalic acid-can chelate calcium and becomes toxic to kidney

2. biotransformation essentially increase compounds water solubility and polarity

    a. if less lipid soluble, compound cannot penetrate cell membranes-it is inactivated and eliminated.

C. Metabolic functions

1. **Carbohydrate metabolism.**

    a. gluconeogenesis-key enzymes are the same as in mammals. ex. glucose-6-phosphatase - gluconeogenic reactions important prior to hatching as avian embryo is highly dependent on yolk lipid for energy to support morphogenesis. Yolk is low in CHO.

        i. after hatching, the diet is high in CHO and low in lipid and demand on gluconeogenic pathways decreases.
        ii. greatest gluconeogenic activity from lactate, pyruvate dihydroxyacetone, glyceraldehyde and fructose.
        iii. differences in gluconeogenic activity between birds and mammals is probably due to localization of rate-limiting enzymes within mitochondria of bird hepatocytes, rather than within the cytosol.
        iv. gluconeogenesis responsible for making CHO available to carnivorous birds during fasting periods-blood glucose levels are more stable than in granivorous species.

            - glycogen synthesized primarily from D-glucuronic acid
            - vitamin c also synthesized.
            - photoperiod affects the amount of glycogen in hepatocytes, and therefore liver fat and weight.
            - decrease with onset of darkness.
            - ambient temperature may also alter plasma glucose and hepatic glycogen-levels decrease with cold.

2. **Protein metabolism**

a. In the avian liver the ornithine cycle is not well developed and not very effective-no carbamyl phosphate available.
b. In birds there is an antagonism between arginine and lysine. Excess lysine decreases arginine efficacy-partially due to depression of hepatic transamidinase activity.
c. Transamination and deamination are important reactions in metabolic transformations involved in amino nitrogen metabolism.
d. Formation of nitrogenous waste products [uric acid].

- increased protein in the diet can lead to elevation of plasma uric acid due to changes in levels of hepatic xanthine dehydrogenase-an enzyme responsible for uric acid formation

e. Plasma proteins synthesized in liver.

- help preserve blood volume
- specialized proteins that contribute to hemostasis [prothrombin and fibrinogen]
- antibody formation
- structural protein formation
- hormones and neuropeptides

3. **Fat metabolism**

a. The liver is the major site of fatty acid synthesis.

- two major enzyme systems-acetyl-CoA carboxylase [biotin dependent] and fatty acid synthetase.
  i. the system requires presence of NADPH+ and H+
  ii. mitochondrial and extramitochondrial systems

  iii. the extramitochondrial systems can be affected by nutritional factors including biotin, dietary fat level, degree of unsaturation of dietary fat, starvation and dietary levels of mercury and selenium- high CHO will increase lipogenesis and high fat will decrease

4. **The liver is the major site of cholesterol synthesis**

a. affected by heredity, nutrition, age, sex, and environmental conditions.
b. hypercholesterolemia can be induced by; complex CHO, vit. A, plant sterols, and some drugs.
c. hepatic cholesterol is in free form but esterified form is primary type in the blood.

5. **Blood lipids derived from absorption, synthesis and mobilization.**

a. high levels seen in females during egg formation. The lipids are synthesized in the liver and are transported by lipoprotein complexes to the ovary.

6. **Other functions**

a. Vitamin D metabolism

Clinical/Laboratory assessment of hepatic function

A. **Metabolic functions**

1. **Plasma proteins.**

a. albumin is produced by the liver. A decrease can occur with a variety of hepatic diseases. It is not specific for a particular type of disease.
b. Globulin increase can be secondary to disease involving the liver, as well as other conditions, and must be assessed in conjunction with clinical signs and other laboratory analyses.
c. Age, hormonal status and environmental conditions [temperature, stress, etc.] can affect the total protein.

2. **Carbohydrates**

a. Glucose levels are maintained primarily by converting liver glycogen. Decreases may be due to hepatic disease.

3. **Lipids**

a. Are synthesized in the liver.

i. Cholesterol-precursor of steroid hormones, bile acids and cell membranes.
- both elevated and decreased cholesterol can result from a variety of conditions, including liver disease, particularly hepatic lipidosis.

ii. Triglycerides-partially synthesized in the liver. Are the primary storage form of lipids.
- elevations may indicate liver disease but are not specific and can be caused by a variety of problems.

4. **Bile acids.**

a. The concentration is a reflection of the clearing capacity of the liver. Extraction [uptake], conjugation [storage], and excretion involved.

b. Not elevated in muscle disease.
c. With hepatic function impairment, there is a problem with bile acid resorption from the blood, and the blood level increases.
d. Chronic hepatic disease leading to fibrosis, and hepatic atrophy/hypoplasia may lead to a decrease in bile acids .

5. **Uric acid.**

   a. Synthesis occurs in the liver as well as the kidney. Reduced synthesis may lead to hypouricemia.

   b. Hyperuricemia may be associated with lipemia and therefore may occur secondarily to hepatic disease, particularly lipidosis.

B. **Enzymology**

1. Enzymes can be unique to certain cells or may occur in a variety of cells. When all or portions of a cell is disrupted enzymes may leak into tissue fluid and blood and can be measured.

   a. The amount of increase depends on the rate of leakage and/or production of the enzyme.
      - cytoplasmic enzymes can leak following membrane damage-may not be irreversible.
      - for release of organelle [mitochondria] enzymes, necrosis is necessary.
      - the longer the elevation half-life the more beneficial for testing purposes

2. Aspartate aminotransferase [AST/SGOT]

   a. Widely distributed in tissues - variable with the species.
   b. Elevation often indicates liver or striated muscle disease
   c. Least affected by sampling artifacts
   d. Not of benefit in chronic/end stage liver disease. It may be low due to loss of hepatocytes.

3. Alanine aminotransferase [ALT/SGPT]

   a. Low levels in avian liver, and minimal serum elevations. Can increase with damage to many tissues.

4. Lactate dehydrogenase [LDH]

   a. Not specific for hepatic damage unless isoenzymes determined-rarely done.
   b. Can be elevated in liver disease and may be of more value in conjunction with CPK determination to rule out striated muscle damage.
   c. LDH has a shorter half-life than CPK and if elevated when CPK is normal it probable indicates hepatic disease.

5. Alkaline phosphatase [SAP/AP]

   a. May elevate in hepatic disease but not specific unless isoenzymes determined.

6. Gamma glutamyl transferase [GGT]

   a. Mitochondrial enzyme found in many tissues, and localization may vary by species.

b. Indicates cell necrosis and probable severe disease.
c. Significance for diagnosis of hepatic disease in birds is questionable.

7. Glutamate dehydrogenase [GLDH]

a. Mitochondrial enzyme.
b. Present in a variety of tissues.
c. Considered one of most sensitive indicators of hepatic disease in pigeons.

Hepatic disease

A. **Infectious disease**

1. **Viral**

a. **Herpes virus**

- Causes disease in a variety of avian species. Pacheco's disease in psittacines.
- DNA virus-several serotypes affect birds.
- When infected orally, viral antigens usually first found in cloacal mucosa. Lesions are usually first seen in the liver prior to dissemination of the virus.
- in some birds there may be latent infection. Virus in these birds can be activated by stress with resultant acute affects on the liver [these may be superimposed upon chronic liver disease].
- Pertinent clinical tests would include enzyme measurement and biopsy, but the disease is usually acute or peracute and tests are of no value.
- Grossly the liver is enlarged and friable. There is variable mottling [yellow-grey] and hemorrhage.

- Histologically the virus causes acute necrosis with variable inflammation, syncytial cell formation and intranuclear inclusion bodies.

  i. inclusions can usually be differentiated histologically, but can be confirmed by DNA in-situ hybridization and electron microscopy.

b. **Polyoma virus**

- Most commonly reported in psittacines, but also causes disease in small passerines and ramphastids.

  i. exact relationship between the viruses is not known.

- DNA virus-identical in budgerigars and nonbudgerigar parrots.

  i. virus shed in droppings, oral secretions and feather and skin dander in budgerigars. Vertical infection is also possible in budgerigars.

ii. there is widespread viral dissemination following infection.

iii. in nonbudgerigar parrots, virus is shed in the droppings. The exact pathogenesis is not clear, but viral inclusion bodies are found in mononuclear phagocytes such as the Kupffer's cells of the liver.

iv. infection of adults is unusual.

- Clinical tests

  i. Serologic assays and PCR available. There is hepatic necrosis and tests to measure enzyme leakage possible in subacute disease.

- Grossly the liver is enlarged and friable. There is variable mottling depending on severity. Liver lesions vary with the species.

  i. lesions most severe in eclectus parrots and macaws and least severe in African grey parrots and cockatoos.

- Histologic lesions in the liver include variable necrosis [multifocal or midzonal] and hemorrhage. Characteristic inclusion bodies seen in Kupffer's cells.

- the amount/severity of necrosis and hemorrhage and the occurrence of inclusion bodies is variable depending on species.

- affected nuclei usually enlarged

- can be confirmed in sections by DNA in-situ hybridization.

c. **Adenovirus**

- DNA virus that can cause disease in psittacine birds.

  i. literature mentions lovebirds and budgerigars. in my experience cockatiels and budgerigars have subclinical [possibly immunosuppressive] disease with minimal or no liver lesions at necropsy.

  ii. clinical disease-either sporadic or in outbreak form-occurs most commonly in senegal parrots and relatives.

- Young senegal parrots affected and usually present as acutely ill or found dead.

- Virus acquired by ingestion or inhalation and replicate in the GI or respiratory tracts. Viremia results in spread of virus to most organs.

- may be opportunistic pathogens in some birds-more virulent in non-host adapted species.

- in some avian species there may be latent infections with virus shedding occurring during stress.

- Diagnostic tests include assays for antibodies [FA, ELISA, etc]. Tests for hepatic enzyme elevations can be used in birds that do not die acutely. DNA probes are available.

- Grossly the affected liver is discolored and mottled with scattered yellow-gray areas present. Histologically, there is multifocal necrosis and hemorrhage, nonsuppurative cholangitis and large basophilic intranuclear inclusion bodies within hepatocytes.

- inclusion bodies are characteristic, but can be conclusively identified by DNA in-situ hybridization on paraffin-embedded tissues.

d. **Paramyxovirus**

- RNA virus that has a variety of serotypes that affect a wide variety of avian species. PMV-3 most common in pet species.

- Variable presentation clinically-liver is usually an incidental/secondary organ affected.

- Primary infections in respiratory or GI tracts-may be dependent on strain of virus. Viraemia results in spread to numerous organs.

- Serologic tests and virus isolation are primary methods of antemortem diagnosis

- Gross lesions may include hepatomegaly in some cases.Histologic change is primarily a lymphoplasmacytic infiltrate within portal areas.

e. **Circovirus [PBFD]**

- Small DNA virus that affects psittacine birds and other avian species.

- Virus can be ingested or inhaled, with resultant viremia.

- Primary presentation is feather and/or beak damage in older birds, but in young it may present as poorly-defined chronic disease or sudden death.

- DNA probe used for diagnosis if disease suspected.

- Liver lesions usually present only in young birds with systemic disease, but can be seen in some older birds that die with severe feather damage.

    i. gross changes minimal-may be scattered discolored foci

ii. histologic lesions can include mild necrosis and a lymphohistiocytic inflammatory reaction in portal areas. Inclusion bodies have been reported in Kupffer's cells. There can also be secondary lesions due to immunosuppression and infection by bacteria or fungi.

f. **Reovirus**

- RNA virus that has been reported in a variety of psittacine birds, particularly imported birds.

- Ingestion the most common means of spread, but inhalation also possible. Recovered birds may carry the virus-long term shedding has not been documented in psittacines.

- Usually presents as an acute systemic disease.

- LDH and AST elevations have been documented.

- Grossly the liver is enlarged and mottled with scattered gray-white or yellow foci. Histologic lesions are hepatocellular necrosis with minimal inflammation.

  i. no inclusion bodies seen on light microscopy. Intracytoplasmic viral particles can be seen by EM.

g. **Hepadnavirus**

- DNA virus [duck hepatitis B] that is one of several viral agents causing hepatitis in ducks. The disease is often subclinical, but there can be persistant infections and vertical transmission.

  i. host range limited to primary species [pekin ducks] and close taxonomic relatives-has been experimentally transmitted to geese.

- Can cause hepatic necrosis and periportal inflammatory infiltrates.

  i. virus receptors [gp180] concentrated in the Golgi apparatus of hepatocytes.

2. **Bacterial**

a. ***Gram Positive Bacteria***

- Usually become a hepatic problem secondary to septicemia or possible extension from lung/air sac. Initial problem in some birds may be chronic necrotizing dermatitis.

- Staphylococci or streptococci most common aerobic organisms.

- Clostridial hepatitis reported in some avian species.

- May be elevated hepatic enzymes. If active septicemia blood culture can identify organisms.

- Lesions.

    i. gross changes include variable hepatic swelling and multifocal to confluent yellow-white foci within parenchyma. Can be abscess formation in chronic cases. Anerobic infections may lead to variable hemorrhage.

    ii. histologically there is multifocal to confluent necrosis with an inflammatory reaction that is primarily heterophils and macrophages. Lesion specificity is due to finding the organisms.

b. ***Gram negative bacteria***

- Infections by a variety of gram negative bacteria cause similar signs and lesions when the liver is involved.

- Salmonella, E. coli, Pseudomonas and Yersinia some of the common gram negative pathogens. They can affect a variety of avian species. Campylobacter has been reported as a cause of hepatitis in ostriches.

- Birds usually present as systemically ill, although signs of gastrointestinal disease may be the first signs seen. Enzyme elevations may occur but are not specific for bacterial disease. Blood culture may be of value in determining the cause of a possible septicemia.

    i. the gastrointestinal tract is the portal of entry, with bacteria reaching the liver via the general circulation or by ascending infection of the extrahepatic bile duct.

- Grossly the liver is usually congested and swollen. Gray-white-yellow foci are seen throughout the parenchyma. Their size and number are variable.

- Histologic changes are characterized by multifocal necrosis with an inflammatory response that includes primarily heterophils and macrophages. Rod-shaped, gram-negative bacteria can be found free in the lesions, as well as in the cytoplasm of Kuppfer's cells and macrophages.

    i. there is usually no specificity to the appearance of the lesion, except for a characteristic appearance of colonies of Yersinia.

c. ***Mycobacteria***

- Avian mycobacteriosis has a wide geographic distribution and incidence in exotic birds in captivity.

- Waterfowl, psittacine birds and passerine birds are particularly affected.

- Mycobacterial infection in birds is usually chronic and the gastrointestinal tract the usual primary site, although cutaneous nodules may be the first sign in some birds. If there is liver damage some enzyme elevation may be noted.

    i. elevations usually mild due to less acute necrosis than other infections.

    ii. bile acids may be elevated.

- there may be a polyclonal gammopathy early in the disease, and in chronic cases the albumin may be decreased due to decreased production in the liver as well as intestinal loss.

- the source of infection is usually not determined, and the transmissibility of some organisms [*M genavense*] is supposed to be low.

    i. ingestion of contaminated environmental material probable in most birds.

- the infection usually begins in the intestinal tract with subsequent spread to the liver and other parenchymal organs

- Affected livers are usually enlarged and contain multifocal to confluent areas of necrosis/caseation that are yellow-white.

- Histologically early hepatic lesions are comprised of heterophils and macrophages. Few microorganisms may be seen.

    i. as the condition advances, the primary cell is a large epithelioid macrophage that contains organisms in it's cytoplasm. The organisms can be difficult to see without acid-fast staining. The amount of necrosis and caseation varies. It may be more severe in waterfowl than in psittacine birds.

d. ***Obligate intracellular bacteria***

- Chlamydiosis

    i. chlamydia are obligate intracellular parasites whose exact taxonomic classification is still not settled. There are different serovars of organisms from birds.

    ii. there is a wide host range of susceptible avian species.

iii a wide variety of clinical signs are seen. The “lime-green”faeces are nonspecific indicators of hepatic disease.

iv. numerous clinical laboratory tests available

*nonspecific increase in liver enzymes
*leukocytosis and monocytosis
*numerous serologic tests
*PCR testing
*immunoassays

v. infection usually via the respiratory or gastrointestinal tracts. Organisms propagate in epithelial cells of the respiratory tract and then generalize to other organs. Oral infection may result in a latent infection rather than clinical disease.

vi. affected livers are enlarged, discolored and may contain numerous grey-yellow foci of necrosis.

vii. histologically there is multifocal to confluent necrosis, and an inflammatory reaction that is primarily mononuclear. Some heterophils may be present as a response to necrosis. In some cases organisms can be found in macrophages and/or hepatocytes/

- ***Bacillus piliformis***

i. rod-shaped bacteria that cannot be grown in cell-free media.

ii. affects a wide variety of mammals, and has been reported in a cockatiel.

iii. exists in the environment and may spread via the fecal-oral route, as well as transplacentally in some mammals. Stress probably plays a part in the activation of clinical disease.

iv. there may be hepatic enzyme elevations.

v. grossly the liver is enlarged and contains numerous foci of necrosis.

vi. histologically there is multifocal necrosis, a variable pleocellular inflammatory reaction, and intracytoplasmic bacilli in hepatocytes. These may be difficult to see without special stains.

3. Mycotic disease

a. The liver is usually involved as a result of extension from the lung/air sacs, or as a result of septicemia.

b. Aspergillus the most common organism, but other genera can cause disease, including systemic candidiasis.

c. No specific tests, but with necrosis there may be enzyme elevation.

d. Gross lesions similar to any other infection that leads to hepatic enlargement and multifocal grey-white areas of necrosis.

e. Histologic lesions similar to bacterial infections-finding fungal organisms necessary for specific diagnosis.

4. Protozoal infections

a. Apicomplexa [coccidia]

- cause a variety of diseases in numerous avian species. Birds can be final or intermediate hosts.

- hepatic disease can be caused by *Cryptosporidium*, *Atoxoplasma*, *Sarcocystis* and *Toxoplasma.*

- with some infections there may be hepatic necrosis and hepatic enzyme elevation.

- birds infected by *Sarcocystis* and *Toxoplasma* are usually intermediate hosts.

    i. infection acquired by ingestion of oocysts-direct or via mechanical insect vectors.

    ii. after ingestion sporozoites released. Schizonts form and may migrate to the liver

- *Cryptosporidium* affects birds following ingestion of oocysts. sporozoites released and infect epithelial cells, including those of the biliary tract.

- *Atoxoplasma* is transmitted via infected oocysts in faeces. sporozoites form in the small intestine and penetrate lymphocytes and macrophages with subsequent spread to parenchymal organs via the blood. schizogony
occurs in the liver.

- Gross lesions

    i. birds with toxoplasma, sarcocystis and atoxoplasma infections are usually enlarged, reddened and have multifocal yellow-white lesions.

    ii. birds affected by hepatic cryptosporidiosis often have no gross change.

- Histologic lesions

    i. the liver of birds with toxoplasma, sarcocystis and atoxoplasma have a generalized inflammatory reaction that is comprised primarily of macrophages plasma cells and lymphocytes. Heterophils may be seen in cases of toxoplasmosis, associated with multifocal areas of necrosis. Necrosis is variable in sarcocystis and atoxoplasmosis. Organisms are usually not seen in sarcocystis and are difficult to find in atoxoplasmosis. They are in macrophages or Kupffer's cells. In toxoplasma infections organisms are usually more plentiful and may be in macrophages or free.

    ii. cryptosporidia attach to the surface of bile duct epithelial cells. There may be some proliferation of bile duct epithelium and a mild chronic mononuclear inflammatory response is sometimes seen.

b. *Hemoprotozoa*

- Plasmodium

    i. cause avian malaria. Wide distribution with mosquitos as the intermediate hosts. Organisms injected into avian host by mosquito. schizogony begins in reticuloendothelial cells of many organs. Merozoites produced and enter the blood to infect erythrocytes.

    ii. passerine birds, penguins and falcons commonly affected, and infections have been reported in other avian species including psittacine birds.

    iii. clinical signs may include hemolytic anemia and haemoglobinuria.

    iv. organisms may be present in peripheral blood smears. Organisms may be seen in erythrocytes, thrombocytes, leukocytes and endothelial cells.

    v. grossly the liver enlarged, and particularly in falcons, may be diffusely grey-black.

    vi. histologically affected livers are infiltrated by numerous macrophages. plasma cells and lymphocytes. Organisms may be found in some of the inflammatory cells.

- *Hemoproteus*

    i. usually considered nonpathogenic

    ii. no gross lesion seen, but schizonts can be found in endothelial cells of the liver.

- *Leukocytozoon*

    i. wide distribution a variety of species including passerines, and psittacine birds. Simuliid flies are the vectors for the organism.

    ii. often subclinical but in some birds it causes acute, severe hepatic necrosis and hemorrhage leading to death. A variety of nonspecific clinical signs can also be seen in some cases.

    iii. gametocytes may appear in the peripheral blood. When there is hepatic damage is it usually acute and severe and there is no time to use hepatic function/enzyme tests

    iv. sporogony occurs in the insect vector and sporozoites are passed to the avian host when the insect feeds. Initial development is in the liver and spleen with schizogony occurring in endothelial cells macrophages and hepatocytes.

    v. grossly affected livers are variably enlarged and contain numerous dark foci.

    vi. histologically the dark foci are areas of hemorrhage surrounding megaloschizonts and necrotic hepatic tissue. There is usually no inflammatory response.

c. Flagellates

- *Histomonas*

    i. found primarily in gallinaceous birds-may be nonpathogenic or incidental finding in other species.

    ii. birds usually presented with weakness and diarrhea.

    iii. faecal exam may be diagnostic, but no specific hepatic test available. Enzymes may be elevated in cases of severe hepatic involvement.

    iv. primary lesions in gastrointestinal tract with hepatic lesions developing secondary to dissemination via the blood.

    v. grossly affected livers have multiple large necrotic lesions usually described and being depressed and yellow-green.

    vi. histologically there is severe necrosis, a pleocellular inflammatory reaction and organisms present in the lesions. Organisms can resemble macrophages and may be difficult to find in some cases.

- *Trichomonas*

    i. pigeons are the primary host but other avian species may be affected. World-wide incidence.

    ii. organism spread by direct contact or contaminated environment.

        iii. primary infection in the upper gastrointestinal tract, but velogenic strains of the organism may become septicaemic and can affect the liver.

    iv. gross changes are nonspecific and included swelling and multifocal necrosis.

    v. histologically there is necrosis and a variable inflammatory infiltrate that is initially heterophilic with progression to a more mononuclear response with chronicity. Specificity of the lesion is due to finding organisms, usually at the periphery of the necrotic foci.

5. Metazoan parasitic infection

    a. Trematodes

    - complicated life cycle. Hepatic lesions in birds usually related to incidental infection by intestinal flukes, or as a part of systemic infection by schistosomes. Primary hepatic fluke infection has been reported in Emus.

    - a variety of avian species affected. Schistosomes may be more common in waterfowl, but have been reported in small passerines. Incidental intestinal fluke infection is seen sporadically in psittacine birds.

    - gross lesions usually not apparent. Flukes can be found in birds that have chronic liver disease of undetermined cause, but are usually considered secondary/incidental. In Fascioliasis of Emus the lesions are similar to those in ruminants. There may be tracts in the parenchyma and bile ducts are thickened, fibrotic and may be mineralized.

    - histologically wandering intestinal flukes found in dilated bile ducts. There may be a minimal inflammatory reaction in some cases. Schistosomes are found in dilated, congested sinusoids. Inflammation is usually only associated with eggs that may be degenerating. The histologic reaction to Fasciola infection is characterized by accumulation of eosinophils, as well as macrophages and lymphocytes. There may be granuloma formation with giant cells and there is variable fibrosis.

B. **Noninfectious disease**

1. Nutritional/metabolic disorders.

a. ***Visceral urate deposition [gout]***

- deposits in liver as a part of generalized visceral gout. The exact pathogenesis may not always be obvious, but the condition is usually secondary to renal disease or inadequate water intake. Any species of avian can be affected.

- histologically urates are usually crystalline in parenchymal organs, with needle-like crystals being radially arranged. There can be associated necrosis and an inflammatory reaction that is primarily heterophilic.

b. ***Hepatic lipidosis***

- fatty liver can be a problem in a wide variety of birds. In chickens it may be due to a biotin deficiency, but the exact cause/pathogenesis in pet species is often not determined in individual cases. Excessive fat intake, inadequate utilization or hepatic enzyme defects are all possible causes.

- in pet birds it seems to be more common in amazon parrots, cockatiels. budgerigars and macaws, as well as young cockatoos.

- cockatoo chicks usually present with a swollen abdomen and obviously enlarged liver, but clinical signs in adult birds are not specific.

- elevations in hepatic enzymes are inconstant. Bile acids may also be elevated.

- Grossly affected livers are enlarged, pale and /or yellow and friable.

- histologically in uncomplicated cases hepatocytes are variably vacuolated and swollen.

c. ***Amyloidosis***

- seen in a variety of birds. Most common in waterfowl, and of pet species most commonly seen in small passerines.

- usually secondary amyloidosis. Primary causes include chronic disease and environmental stress. In severe cases, it can lead to hepatic failure.

- characterized by deposition of biochemically distinct proteins in tissue. Pathogenesis not completely understood, but may involve problems in degradation [by cells of the mononuclear phagocyte system] of soluble precursors in the circulation.

- no specific antemortem test available

- affected livers are usually enlarge pale and firm or friable. On gross examination they must be distinguished from fatty livers.

- histologically amyloid is pale eosinophilic or amphophilic and the amount present is variable. It accumulates in extracellular spaces and compresses the adjacent parenchyma.

d. ***Iron metabolic disorders***

- most common in mynahs and toucans [and related species], also reported in psittacines, particularly lories. Although some birds may have hemochromatosis, this name is not appropriate for most cases seen. The pathogenesis of the condition may be related to the dietary intake of iron, but it also may vary in different species. The disease may be hereditary in toucans.

- birds may present with a variety of clinical signs due to variable involvement of the liver.

- enzymes may be elevated due to hepatocyte damage, but are normal in many cases. Blood iron testing may not be definitive in all species.

- grossly the liver is enlarged and discolored. The color is usually gold-brown and small, scattered dark foci may be seen.

- the histologic appearance varies with the amount of iron deposited. Iron can be seen in hepatocytes and in Kupffer's cells and macrophages. There may be an associated inflammatory process that includes lymphoctyes and scattered heterophils. In severe cases there may be variable hepatic necrosis, and with chronicity fibrosis can develop. Prussian blue staining can be used to identify the pigment.

e. ***Chronic liver disease***

- not uncommon condition in psittacines, particularly amazon parrots, cockatiels, macaws and budgerigars.

- has been referred to as chronic-active hepatitis and hepatic cirrhosis.

- birds may present sick with signs referable to the liver, but in some cases they die without the owner observing any premonitory signs.

- there is an elevation of bile acids, AST, and AP. Electrophoresis may indicate chronic-active inflammation.

- the cause and pathogenesis are usually not determined. The lesions have been seen in cases of chronic infectious disease-particularly chlamydiosis, and exposure to bile excreted toxins. There is probably an immune-mediated component, and more than one primary cause.

- grossly affected livers are variable shrunken, pale and fibrotic. In extreme cases, there may only be small firm nodules in place of the normal liver.

- the histologic appearance varies with the stage of the disease. Early lesions consist of hepatocyte vacuolization, a pleocellular inflammatory infiltrate that is primarily in portal areas, bile duct proliferation and mild fibrosis. The lesion may progress to severe fibrosis and diffuse biliary hyperplasia. There does not seem to be a direct correlation between the stage of the lesion and the death of the bird.

f. ***Toxic liver disease***

- large number of hepatotoxins can affect the avian liver. All species affected.

- clinical signs usually not specific. If there is sufficient hepatocellular damage there may be enzyme elevations.

  i. vitamin D or vitamin D analog rodenticides. Liver lesions secondary and usually comprised of mineralization of basement membranes.

  ii. lead. Grossly there may be some hepatic enlargement. Histologic
  lesions noted include hemosiderosis and variable hepatocyte swelling.

  iii. zinc. Hepatic lesions can include hemosiderosis and erythrophagocytosis.

  iv. mycotoxins. Some are bile-excreted and can lead to periportal necrosis and inflammation. In chronic cases there is bile duct hyperplasia.

g. ***Miscellaneous***

- mineralization. Usually secondary to renal disease, nutritional problems [Ca/P imbalance] or vit. D toxicity.

- lipofuscinosis. Lipofuscin pigment accumulates in hepatocytes secondary to a variety of diseases. It is considered a “wear-and-tear” pigment and is due to excessive biologic oxidation at the cellular level. Vitamin E deficiency is one possible cause. The liver is a common location for lipofuscin accumulation.

C. **Neoplasia**

1. ***Epithelial***

a. Primary tumors. May be of hepatocellular or bile duct origin. Bile duct tumors more common and are reported in a wide variety of birds.

- bile duct proliferation, and possibly tumor formation, has been reported in association with internal papillomatosis, and the possibility of a viral etiology suggested.

- gross lesions consist of variably-sized nodules which vary from somewhat friable to firm. Hepatocellular carcinomas tend to be red-brown and bile duct carcinomas may be yellow-white.

- histologically hepatocellular carcinomas are comprised of moderately undifferentiated to poorly differentiated hepatocytes that form cords and nests. Hepatomas may contain well-differentiated cells, with the absence of portal areas being the only differentiation from hyperplastic nodules. Carcinomas are less well differentiated. Bile duct adenomas and carcinomas are characterized by proliferation of ductular structures, or nests,cords and individualized cells in the case of carcinoma.

b. Metastatic tumors.

- the liver can be a metastatic site for any carcinoma. Metastasis is not common, but renal, pancreatic and proventricular metastases are most common. Grossly these tumors present as variably-sized nodules and histology is necessary for differentiation.

c. Non-neoplastic epithelial proliferative lesions.

- hyperplasia and cyst formation seen in all avian species. May need histology to differentiate from neoplasia or granulomatous disease.

2. ***Mesenchymal tumors.***

a. Fibrosarcoma, lymphosarcoma, leiomyosarcoma, hemangioma and hemangiosarcoma, and myelolipoma all reported. May be primary or possibly metastatic.

b. No specific laboratory tests. May have elevated white count and lymphocytosis in some cases of lymphosarcoma.

c. No specific gross features except that hemangioma/sarcoma may be friable and hemorrhagic.

d. Histology typical of these tumors in any location and is used to differentiate the lesions.

- fibrosarcoma and leiomyosarcoma comprised of interlacing bundles of cells. Fibrosarcoma usually has a much high mitotic rate.

- hemangioma/sarcoma comprised of vascular channels and possibly solid foci in sarcoma. Determination of type based on histologic features of anaplasia.

- lymphosarcoma usually a sheet of immature lymphoid cells. Degree of effacement varies.

- myelolipoma comprised of well differentiated adipose cells and bone marrow elements.

3. ***Malignant melanoma***

   a. Primary can be in several tissues.

   b. If the liver is involved, multiple gray-black nodules may be present.

   c. Histologically the tumor is comprised of poorly differentiated melanocytic cells with variable cytoplasmic pigment.

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