Impact of Lab Animal Diseases on Toxicological Pathology

Goals of the Talk

1. Provide brief background of toxicologic pathology of certain organ systems
2. Compare/contrast toxicologic pathology and lab animal diseases of each system
3. Discuss briefly drug-induced conditions that mimic common lab animal diseases
4. Compare/contrast histopathology between drug-induced and naturally occurring disease

Organ Systems to be Discussed

1. Liver
2. Pancreas
3. Respiratory Tract
4. Integumentary System
The Liver

- Adverse drug reactions less common than skin and gastrointestinal tract
  - Not predicted by animal studies; either allergic or non-allergic idiosyncratic in nature
- Hepatic toxicity is a challenge to contemporary hepatology in humans:
  - Apparently safe drugs occasionally produce severe adverse reactions in liver, e.g. aspirin
  - Hepatic drug reactions very difficult to diagnose b/c drug-induced injuries clinically mimic most hepatobiliary disease
  - Hepatic toxicity a common reason for termination of development of a new drug

Normal Liver

Toxicologic Pathology: Liver, Overview

- Hepatitis (Inflammation)
- Hepatic Necrosis
- Cellular changes associated with toxins
  - Hepatic fatty change (steatosis)
  - Hepatocellular hypertrophy & hyperplasia
  - Clear cell change
    - Characterized by presence of clear cytoplasm & accumulation of glycogen in liver
  - Peroxisomal proliferation, associated with hepatic carcinoma in rodents
Steatosis
*Imidazole antifungal agent*

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Hepatocellular Hypertrophy
*Phenobarbitone*

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Peroxisomal Proliferation
*Clofibrate*
Lab Animal Liver Diseases

**Rodents**
- Tyzzer’s Disease
- Mouse Hepatitis Virus infection
- Pseudotuberculosis
- Helicobacter infection
- Salmonellosis
- Hepatic cysticercosis
- Others

**Nonhuman Primates**
- Herpes B Virus infection
- Simian Varicella Virus infection
- Fatty Liver Syndrome
- Vitamin D deficiency
- Protozoal Merocysts
- Athesmiasis
- Cirrhosis
- Others

Inflammation/Hepatitis

- Characterized by small aggregates of acute/chronic inflammatory cells grouped around small zones of necrotic or degenerate eosinophilic hepatocytes.
- Granulomas can be caused by particulate forms of a drug or metabolite precipitating in liver:
- **Hepatitis** – characterized by scattered foci of hepatocellular necrosis, vascular dilatation, hemorrhage, intranuclear inclusions

Drug-Induced Inflammation/Hepatitis

**Griseofulvin**

**Corynebacterium parvum**
Naturally Occurring Inflammation/Hepatitis

**Mouse Hepatitis Virus**

**Mycobacteria**

http://www.microscopyu.com/galleries/pathology/hepatitis.html

Naturally Occurring Inflammation/Hepatitis

**Salmonellosis**

**Helicobacter infection**

http://pathology.utscavma.org/?page_id=12

Hepatic Necrosis

- Occurs spontaneously in lab animals, but can be caused by high doses of therapeutic agents
  - Result of indirect mechanisms e.g. tissue anoxia, biliary stasis, disturbance of blood supply

- Types of Necrosis:
  - Focal, Centrilobular, Periportal
  - Single cell necrosis (apoptosis)
**Drug-Induced** Hepatic Necrosis

*Experimental Antiproliferative Anticancer Drug*

Presentation: Srinivas S. Rao, D.V.M., Ph.D., MBA, Diplomate, ACVP

**Naturally Occurring** Hepatic Necrosis

*Tyzzer's Disease*  
*Mouse Hepatitis Virus*

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**Hepatocellular Carcinoma**

- Malignant tumors resembling hepatic parenchymal cells
- Occurs spontaneously in rodents with advancing age, rare among dogs and primates.
- Can develop in response to genotoxic carcinogens  
  - e.g. diethylnitrosamine, phenobarbital
- In humans, most common primary malignant liver tumor, associated with chronic hepatitis and cirrhosis

Presentation: Srinivas S. Rao, D.V.M., Ph.D., MBA, Diplomate, ACVP
Drug-Induced Hepatocellular Carcinoma

Diethylnitrosamine

Naturally Occurring Hepatocellular Carcinoma

Associated with hepatitis virus, cirrhosis

The Pancreas

Two basic anatomical patterns among lab animals:

- Mesenteric (rabbit, rat, mouse)
  - diffusely distributed in mesentery of small bowel
- Compact (hamsters, dogs, monkeys)

Drug metabolizing enzymes present in exocrine pancreatic tissue, inducible by certain chemicals

- Expression of enzymes vary among lab animal species
- Patients with chronic pancreatitis and pancreatic cancer are associated with altered immunoreactivity to these enzymes
Normal Pancreas

Toxicologic Pathology: Pancreas, Overview

- Pancreatitis/Inflammation
- Atrophy
- Pancreatic Necrosis
- Amyloid deposits
- Insulitis
- Duct Proliferation
- Hypertrophy, Hyperplasia, Neoplasia
  - Adenoma
  - Carcinoma

Lab Animal Pancreatic Diseases

Dog (most toxicologic studies performed in dogs)
- Pancreatitis
- Pancreatic Tumors
- Insular Amyloidosis
- Multifocal Fat Necrosis
- Diabetes
- Others
Pancreatitis

- Characterized by inflammation and pancreatic necrosis
- Pathogenesis of disease not well understood in lab animals
- Has been associated with wide range of drugs:
  - Corticosteroids, diuretics, antibiotics, antimitotics, anti-HIV, and other analgesic or anti-inflammatory agents
- Occasionally occurs spontaneously in rodents
  - Uncommon in lab dogs, more common in pet dogs

Drug-Induced Pancreatitis

Naturally Occurring Pancreatitis

http://www.vetmed.wsu.edu/courses_vm546/content_links/DfDx/Cat%200Case%204/pancreatitis.htm
http://www.animalhealthcare.com/handouts/dogs/pancreatitis.htm
Islet Cell Neoplasia

- Composed mainly of insulin-producing B cells
- Characterized by a broad range of appearances such as large rounded islets, multilobulated islets, fibrosis, interspersed exocrine tissue, chronic inflammation
- Occurs spontaneously with advancing age or following administration of chemicals such as Streptozotocin treatment

Induced Islet Cell Neoplasia

Naturally Occurring Islet Cell Neoplasia
Respiratory Tract

- In humans, most important lung diseases are related to tobacco smoking
  - Therapeutic agents remain relatively minor cause of pulmonary toxicity in humans
- However, drug-induced conditions are increasingly frequent in clinical settings
  - Can produce excessive effects on pulmonary function, mediate allergic reactions, precipitate thromboembolism/hemorrhage, etc.
  - Increase in number of drugs associated with parenchymal pulmonary injury e.g. anticancer drugs

Normal Nasal Cavity

- Top of head (w/ hair follicles)
- Olfactory regions of nasal cavity
- Vomero – nasal organ
- Tooth
- Oral cavity
- Tongue

Toxicologic Pathology: Respiratory Tract, Overview

- Congestion
- Degeneration
- Inflammation
- Ulceration
- Edema
- Fibrosis
- Hemorrhage
- Neoplasia, Hyperplasia
- Emphysema
- Phospholipidosis
Lab Animal Respiratory Diseases

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<thead>
<tr>
<th>Rodents</th>
<th>NHP</th>
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<td>• Pneumonia</td>
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Dog

• Lung Cancer
• Histiocytosis
• Pneumonia
• Infectious Canine Hepatitis
• Others

Pulmonary Fibrosis

• Characterized by replacement of normal pulmonary structure by thickened collagenous matrix
  – Reduction in capacity for gas exchange
• Associated with chronic lung injury from a variety of causes
• Occurs in lab animals as a response to parasite infestation, or as result of anticancer drugs i.e. bleomycin

Drug-Induced Pulmonary Fibrosis

Bleomycin

H&E staining

Trichrome staining

Presentation: Srinivas S. Rao, D.V.M., Ph.D., MBA, Diplomate, ACVP
**Naturally Occurring Pulmonary Fibrosis**

- Inflammation with granulomas develops in lab animal lungs under variety of different circumstances
  - Common cause results from aspiration of stomach contents or food particles
  - Dogs, primates more liable for parasite infestation
  - Intra-tracheal or intravenous injection of relatively insoluble substances

**Granulomatous Inflammation**

**Drug-Induced Granulomatous Inflammation**
**Naturally Occurring** Granulomatous Inflammation

- Skin lesions among most common adverse reactions to clinical drugs
  - Non-steroidal anti-inflammatory drugs and penicillins associated with particularly high rate of adverse skin reactions
  - Incidence of skin carcinomas increases with duration of immunosuppressive therapy
- Skin may be particularly predisposed to drug hypersensitivity reactions
  - Inaugraded system of keratinocytes, Langerhans cells, and T lymphocytes mediates cutaneous immunosurveillance

**Integumentary System**

**Normal Skin Histology**
**Toxicologic Pathology: Skin, Overview**

- Inflammation
  - Injection site
  - Implanted biomaterials
  - Systemic drug administration
  - Granulomas
- Hyperplasia/Neoplasia
- Necrosis
- Skin Irritancy
- Dermatitis
- Cutaneous phototoxicity
- Steatitis
- Haematopoiesis
- Hyper/Hypo pigmentation
- Elastosis
- Atrophy
- Alopecia

**Lab Animal Skin Diseases**

**Mouse**
- Mousepox
- Staphylococcus
- Mites
- Squamous cell carcinoma
- Syrprocedural dermatitis
- Skin cancer
- Others

**NHP**
- Bacterial infections
  - Staphylococcus
- Viral infections
  - Papillomatosis, Herpes
  - SIV, Pox, etc
  - Cancer
  - Others

**Dog**
- Hyperpigmentation
- Allergies
  - Dermatitis
  - Amphotiasis
- Food
- Several bacterial/viral infections
- Fleas, Ticks, Mites
- Cancer
- Others

**Inflammation, Dermatitis**

- Can be induced by systemic drug administration, allergic reactions, phototoxicity, or implanted biomaterials
- Spontaneously occurs following loss of integrity of epidermal barrier
  - Localized infections, abrasions, minor trauma, excessive blood sampling
- Nature and distribution of lesions allow toxicologists to make clear distinctions between intercurrent and drug-induced changes
Drug-Induced Dermatitis

Anti-EGF treatment

Naturally Occurring Dermatitis

Dermatitis Herpetiformis