Paraneoplastic and Immune-Mediated Skin Diseases in Cats

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Paraneoplastic syndromes (PNS)

Non-cancerous neoplasia-related disorders that occur at a site distant from the primary tumor or metastasis

- Indirect effects of cancer
- May be the initial clinical sign

Cutaneous

- 30 disorders reported in humans
- Precede, follow, or coincide with neoplasia
- Other: Endocrine, Blood, GI, Neurological, Renal

Paraneoplastic skin diseases

- Feline Paraneoplastic Alopecia
- Feline Thymoma-Associated Exfoliative Dermatitis
- Metastatic Pulmonary Carcinomas

Metabolic diseases

- Cutaneous Xanthomas
- Hyperadrenocorticism
- Feline Skin Fragility Syndrome

Feline paraneoplastic alopecia (FPA)

Clinical presentation

- Ventral alopecia & 'glistening' translucent skin
- Secondary Malassezia common
- Dry, fissured, peeling foot pads
- Pruritus (often intense)/grooming
- Rapid onset (days to weeks)
- Age: 7-16 years old (median 13 years)
- Systemic CS: V+, D+, weight loss, lethargic, abdominal distention, anemic, ↑WBC, lethargy, emaciated

Tumor

- Visceral carcinomas
- Bile duct carcinoma
- Pancreatic tumors
- Exocrine pancreatic adenocarcinoma
- Hepatic carcinoma
- +/- metastases (liver, lungs)

FPA

Diagnosis

- CS, PE, HX, US, CT, Biopsy, Trichogram
- R/O metabolic, fungal, parasitic disease
    - DDX: demodicosis, dermatophytosis, self-induced alopecia, endocrine disease (Cushing-63% alopecia, Hyperthyroidism, telogen effluvium/defluxion), feline symmetrical alopecia, alopecia areata

Treatment

- removal tumor (symptomatic relief)
- recurrence or metastases
- Secondary infection
- Malassezia Dermatitis

Feline thymoma-associated exfoliative dermatitis (FTED)

- AKA: Feline Paraneoplastic Exfoliative Dermatitis (PNED)
- Pathogenesis: T-cell–mediated process (CD3+): abnormal antigen presentation of neoplastic thymic epithelial cells (immature auto-reactive T-cells attack keratinocytes)
- Older cats; especially orange male cats
- FTED
- Cutaneous Signs
    - Initially non-pruritic, mild to very erythematous dermatitis exfoliative/scaling head & ears → generalized (trunk, chest, limbs)

    - Later: brown, waxy, keratosebaceous debris in digits/claw beds & ears (+/- pruritus/infections)
- Systemic signs
    - May be otherwise healthy at the onset +/- lethargy
    - Respiratory distress & recurring respiratory infection
- Neoplasia
    - Humans: lymphomas & leukemias
    - Cats: thymoma or thoracic lymphoma
- Diagnosis
    - CS, PE, HX, Biopsy, Radiograph
- Treatment
    - Removal of thymoma (and sternal LNs) resolves dermatitis
    - +/- chemotherapy and/or radiation therapy
    - Prognosis usually poor
- Imidicloprid (Godfrey-JSAP, 1999)

Metastatic Pulmonary Carcinomas (MPC)

- Mean Age: 12.7 years
- Presenting Complaint
    - Lameness (primarily weight-bearing digits & P3)
    - Ventral abdomen (fat pad)
    - Rarely have respiratory signs (despite the pulmonary brochogenic carcinoma) +/- other sites
- Prognosis
    - Mean Survival: 58 days from initial presentation
- Treatment
    - Amputation of digits rarely palliative since development of lesions in other digits

Cutaneous Xanthomas (CX)

- Background:
    - Rare, benign, granulomatous lesions (skin, SQ tissues, tendons & internal organs)
- Previous trauma sites (rare) or idiopathic (one report)
    - Cutaneous Clinical Signs
    - White-yellow-pale plaques; nodules; papules with borders that appear erythematous
- Pathological hyperlipidaemia
- 1o or 2o to disturbances of lipid synthesis, metabolism & transportation
- CX: Primary Etiologies
    - Primary: (cat, dog, human)
        - Familial hypertriglyceridaemia: ↑ chylomicrons & VLDL in serum ↑ cholesterol (not always)
            - Hyperlipidemia
                - ↑ total plasma [TG and/or cholesterol]
                - indicated by plasma lipemia if significant ↑TG (not with hypercholesterolaemia alone)
- Hyperchylomicronemia
- Quick Review: TG & Cholesterol
- Common Manifestations of ↑TG
    - Cats: DM, peripheral nerve paralysis, ocular
    - Dogs: DM, pancreatitis, GI
- Common manifestations of ↑ Cholesterol
    - causes few clinical abnormalities (dogs/cats)
    - Endocrine (e.g., hypothyroidism in dogs)
    - corneal lipid deposits or atherosclerosis (humans)
- CX: Secondary Etiologies
- Secondary: (more common)
    - Drugs (cats): Estrogens, progesterone, corticosteroids & retinoids
    - Diet-induced (exacerbates the familial form)
    - DM (cats and dogs)
    - may also cause hypercholesterolaemia
    - Humans (pediatrics): leukemia
    - Cutaneous Xanthomas (CX)

- Where?
    - Face: head/neck/pinna
    - Footpads
    - SQ over Bony Prominences
    - Other: Limbs and Trunk
- Who?
    - Young to mid-age cats
    - Dogs, horses, birds, reptiles, humans
- DX/TX:
    - Determine underlying problem with lipid metabolism
    - Feed Low Fat Diet
    - Oils are rich in Ω-3 fatty acids (↓VLDL)
    - Gemfibrozil (Lopid®) ?
    - HMG CoA-reductase inhibitors ?
    - Bile acid sequestrants (↓LDL & cholesterol)
    - TX concurrent disease (e.g., dermatophytosis and demodicosis)

Feline Skin Fragility Syndrome (FSFS)

- Any age, sex, breed
- Clinical signs
    - skin tents very easily
    - Minor trauma causes large gaping wounds (difficult to repair)
    - 'Paper thin' skin (like rabbit skin)

Feline Skin Fragility Syndrome (FSFS)

- Associated with
    - Hyperadrenocorticism (HAC) > 80% w/ DM
        - Pituitary Adenoma/Pituitary Dependent (81%)
        - Adrenal Hyperplasia/Tumor (11%): 64% benign & 36% malignant carcinomas
        - Secondary HAC:
    - Progestagen use (Ovaban®; magesterol acetate), glucocorticoids
    - Hepatic Neoplasia
- Hepatic Lipidosis
    - Diagnosis
    - History, clinical signs, physical exam
    - Biopsy (HAC= ↓dermal collagen)
- US, ACTH Stimulation Test
    - Treatment
    - Avoid any trauma to skin
    - Antibiotics PRN
        - Address Underlying Trigger:
        - Stop steroids or Ovaban® (iatrogenic)
            - Treat HAC
            - Ketoconazole (10- 15 mg/kg/d) (hepatopathy)
    - Metyrapone (65 mg/kg q 12 hours)
    - +/-Surgery: Bilateral Adrenalectomy
- Prognosis
    - Over time, can gradually improve (takes months)
- Auto-immune/(Immune-mediated) Feline Skin Diseases
- Auto-immune Disease (primary)
    - Antibodies or activated lymphocytes develop against normal body constituents
    - Lack of control of or bypass of normal control mechanisms
    - Example: Pemphigus foliaceus
- Immune-mediated Disease (secondary)
    - Antigen is foreign to the body
    - Example: drugs, vaccine, bacteria, viruses, UV light, etc.
        - DLE (alteration of antigen from UV light)

Potential mechanisms

- T-cell malfunction
- Abnormal MHC II expression (CD4+)
- Cytokine & receptor ligand abnormalities
- Auto-antigen modification
- Cross-reacting antigens
- Inappropriate IL-2 production
- Mutations in receptor affinity
- Idiopathic
- Hypersensitivity
    - Type II (auto-antibodies to self-proteins; e.g., PF)
    - Type III (immune complex; e.g., SLE/DLE)
- Other
    - Genetic
    - Hormones
    - Physical (i.e., UVL) and Biological Factors (i.e., infectious)

Diagnosis

- Clinical Features (Signalment, HX, PE)
- Cytology (Tzanck Preparation)
- Micro-bacterial Finding
    - Negative fungal culture
    - Bacterial culture & sensitivity/antibiotic response
- Immunodiagnostic Tests
- Histopathology

Pemphigus foliaceous

- Acantholysis → Acantholytic Cell
- separate and rounding-up of a keratinocyte
- acantholysis (epidermal detachment)
- desmoglein

Background

- Humans (erythema/vesicles +/- pustules), dogs, cats, horses, goats, llamas
- Clefts filled with suppurative exudates
- Pustular-crusting dermatitis (no vesicles)
- Desmoglein-1 (everywhere in the skin) below stratum corneum
- Auto-Abs to dsg1 (150-160kd glycoprotein; cadherin group of adhesion molecules)
- Only the epidermal desmosomes are affected
- NO mucosal lesions! (would need to affect dsg-3)
- PF
- History
    - Lesions across the face and body
    - Acute flare-ups overnight are reported +/- intrinsic cyclicity
    - Crusting (ear, eye, dorsal muzzle, planum nasale- and generalized→ back etc.)
    - May wax/wane
    - Season/UV light/Photoexacerbated (suggested)
    - Lack ABX and Anti-fungal response
    - Precipitating Factors: genetics, UV light, drugs, infection, allergy
    - Systemic Illness: lethargy, fever, decreased appetite, lymphadenopathy, etc. (sometimes)

(3) Classes/forms

1. Spontaneous: No previous skin disease or drug exposure
2. Drug & Food induced—lime-sulfur, itraconazole, ipodate (cats)
3. Chronic skin disease-

History of chronic skin disease (1-2 years of uncharacterized pruritic skin disease/allergies)

Clinical signs (cats)

- Intrinsic cyclicity flare-ups
- Same as dog, but pustules very short lived
- Lesions: serous-hemorrhagic crust, scale, alopecia
    - Dorsal muzzle, periorbital, pinnae = FACE

- Peri-mammary gland/nipples/peri-areolar
- Paronychia/claw beds/claw folds
- Trunk (bilaterally symmetrical), Tail, Legs, Chin
- Ventrum
- Generalization (less common than dogs)
- Other: lethargy, weight loss, anorexia
- Not FeLV/FIV+; Neutrophilia +/- eosinophilia
    - Differential Diagnosis: Pyoderma, Dermatophytosis, Demodicosis, Seborrheic skin disease, Cutaneous Adverse Drug Reaction, Superficial necrolytic dermatitis
    - Diagnosis: Biopsy
    - Skin biopsy
        - Confirmative- subcorneal pustules w/ acantholytic cells (often in "rafts"), neutrophils, eosinophils (biopsy/"pustule-watch"- from non-traumatic area); dermatophytosis may look similar (*)

Treatments (cats)

- Glucocorticoids (topical/systemic)
    - Cats: #1 choice is Triamcinolone (least side-effects, most likely to achieve remission; 1/7th to 1/10th dose of prednisolone
- Prednisolone/ Methylprednisolone (1.0-2.2 mg/kg; taper gradually to maintenance dose (0.5-2.0 mg/kg EOD)
- Alkylating agents
    - Chlorambucil (Leukeran®) (cats; 0.1-0.2 mg/kg PO q24-48 hrs)
    - Chrysotherapy-
    - Aurothioglucose (Solganal®-IM)
    - Auranofin (Ridaura®-PO)
- Cyclosporine (Atopica®)- may be effective

Plasma cell pododermatitis

- Background
    - Cats with this uncommon syndrome (collapsed footpads)
    - FIV negative (some studies) and FIV positive (over-represented in studies); no major gender predilection (male>female)
    - Concurrent plasmacytic stomatitis, renal amyloidosis, or immune-mediated glomerulonephritis have been reported
- Etiology
    - Immune-mediated (suspected): persistent hypergammaglobulinemia, marked plasma cell tissue infiltrate and the beneficial response to corticosteroids
    - Possible hypersensitivity (e.g., may be seasonality) +/- response to special diet
- Clinical signs
    - Soft, non-painful spongy swelling of one or more (multiple) footpads → often progressing to painful ballooning footpads +/- ulceration and/or bleeding
    - May have a dry, exfoliative, scaling/peeling appearance
    - Present primarily in the metatarsal and metacarpal footpads and rarely in the digital footpads
    - Secondary infection (abscess) +/- systemic signs
    - CBC= thrombocytopenia
- Diagnosis
    - Clinical signs, physical examination, and history
    - Aspirate/impression smear and cytology
    - Biopsy: intense inflammatory infiltrate (mature plasma cells with prominent Russell bodies in a perivascular pattern; if ulcerated, may detect a large number of neutrophils and macrophages +/- vasculitis
- Differential diagnosis
    - Food allergy, atopy, eosinophilic granuloma +/- contact (litter), Anatrichosoma spp. (nematode), thermal burn
- Treatment
    - Doxycycline 5mg/kg PO BID
    - +/- Corticosteroids oral and/or injection(dexSP, Depo, triamcinalone)
    - Pentoxifylline
    - +/- Solganol® (gold salt)
    - +/- NSAID (meloxicam_--not with corticosteroids
    - Surgery (widespread surgical excision)

Discoid Lupus Erythematosus (DLE)

- Background
    - Rare; Ag-Ab complexes at basement membrane zone; controversial

- Clinical Signs
- Nasal depigmentation, erythema, erosions, and crusting
- Atypical form may exist: pruritus marked truncal exfoliation, and vesicles and papules on the periocular margins and mucocutaneous junctions
- Diagnosis
- Lesion distribution, clinical signs
- Biopsy
- Direct immunofluorescence (Michel's solution): Ig deposition at the basement membrane
- Biopsy

- Differential diagnosis
  - Mosquito bite hypersensitivity, dermatophytosis, herpes, other
- Treatment
  - Oral vitamin E, topical glucocorticoids, omega 3 fatty acids, and avoidance of sunlight
  - Oral tetracycline + niacinamide

Systemic Lupus Erythematosus (SLE)

- Background
  - Rare with cats; multisystemic auto-immune disease (may involve skin)
- Etiology
  - multifactorial, complicated, antinuclear auto-Ab's to components of chromatin (DNA), circulating Abs lodge in a variety of tissues → damage
  - photosensitivity reactions (skin lesions)- UV A & B, Type II & III hypersensitivity
  - Breeds
- Siamese, Persians, Himalayans
  - Clinical Signs (cat)
- Systemic- hematological abnormalities (anemia), neurologic signs, fever,
  - lymphadenopathy, polyarthropathy, myopathy, renal disease, pulmonary disease, unresponsive to antibiotics
    - Skin- Face/Pinna/Paws, seborrheic dermatitis, exfoliative erythroderma,
    - Scaling, crusting lesions-alopecia/scar/oral ulcer
  - Maculopapular/Papulonodular
    - Erosive/Ulcerative
    - Alopecia
    - Pigmented
    - Pruritus
    - Diagnosis
    - Clinical Signs, history, physical examination
- Diagnostic work-up (imaging, ANA test, etc.):
  - Urinalysis: protienuria
  - Immunopathology: positive lupus band (deposites of granular deposits of immunoglobulin and complement at the Dermoepidermal junction)- suggestive
    - Blood Test:
    - ANA: 90% have + ANA (detect abs vs. cell nuclei); good screening, many false positives (serum)
    - LE: lacks sensitivity, good screening tool
      - Skin biopsy
        - Interface dermatitis with thickened BM; subepidermal vacuolar change "bubblies"; lichenoid; pigmentary incontinence (biopsy slate blue depigmenting lesions b/c dermal melanin); hydropic degeneration of basal cells; apoptosis; Civatte bodies (attack keratinocytes)

Treatment

- Glucocorticoids
- Chlorambucil
- Chrysotherapy
  - Aurothioglucose; (Solganal®)-50% gold
  - Sodium Aurothiomalate (Myochrysine ®)
  - Auranofin (Ridaura®)-29% gold
- IVIG
- Cyclosporine