Selected inflammatory diseases of older dogs

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Recent onset inflammatory skin disease in an old dog

- Sudden onset of atopic dermatitis or food-related allergy in a 7+ year old dog is rare/uncommon, unless moved.

- Flea allergy, sarcoptes and adult onset demodex are more common as recent onset in older dogs.
Toxic Cutaneous Immunological Drug reactions

- Drug macro-molecules may be directly antigenic
- Binding to cell membrane or nucleic acids => loss of self antigens
- Drug/antibody complexes depositing in blood vessel walls => vasculitis
- Drugs directly provoked autoantibodies

Revisable = Drug dependent
Irreversible = Drug induced
• Uncommon idiosyncratic events (except Doberman <-> sulphonamides

• Most commonly associated with:
  – B-lactam antibiotics (Amoxicillin, cephalexin etc)
  – Anti-inflammatory drugs Carprophen
  – Vaccines
  – Sulphonamides, other antibiotics and antifungals (itraconazole griseofulvin)
  – Phenobarbitone
  – **ANY OTHER DRUG**

Can begin at any time

• IgE mediated urticarial reactions immediate

• Commonly begin 3-14 days after drug initiated.
Wide Variety of Clinical Signs
Initially acute onset erythema +/- pruritus and fever

<table>
<thead>
<tr>
<th>Erythema multiforme</th>
<th>Vasculitis</th>
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</thead>
<tbody>
<tr>
<td>- Target lesions =&gt; ulcers</td>
<td>- Oedema erythema</td>
</tr>
<tr>
<td>- +/- mucosal lesions (Major)</td>
<td>- Demarcated ulcers</td>
</tr>
<tr>
<td></td>
<td>- Necrosis of extremities</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-induced pemphigus</th>
<th>Non-specific erythemaous maculo-papular reactions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>- Steven-Johnson syndrome/toxic epidermal necrolysis</td>
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</table>

<table>
<thead>
<tr>
<th>Fixed drug reactions</th>
<th>Urticaria</th>
</tr>
</thead>
</table>
Erythema Multiforme (major) Dog
Cephalexin

www.excellenceindermatology.jp
Drug-induced pemphigus
B-lactam antibiotics
Steven-Johnson syndrome/toxic epidermal necrolysis
Non-specific macular / erythrodermic reaction
Carprofen
VASCULITIS
Diagnosis of drug reactions

• Often severe and acute onset

• History of drug administration

• Compatible clinical signs

• Compatible histological findings (Don’t wait!, not always specific)

• Resolution of the symptoms on withdrawal of the drug (not always!)
Treatment of drug reactions

• Withdrawal of all suspect medications

• Short term corticosteroids. Evidence? Risk/Benefit

• Support treatment as per burns

• Antibiotics if sepsis risk (eg enrofloxacin + clindamycin)

• Long term appropriate immunosuppression if Dx confirmed and fails to resolve on drug withdrawal
Hepatocutaneous syndrome (Metabolic epidermal necrolysis)

- Degeneration and hyperplasia of keratinocytes associated with:
  - Chronic liver disease
  - Diabetes mellitus
  - Pancreatic glucagonoma. Less common in dogs vs humans

- Aetiopathogenesis unclear (defective protein and/or zinc metabolism???)

- May have a heritable component in Shih Tzus

- Older dogs.

- Skin signs may present before signs of liver disease
Hepatocutaneous Syndrome

- **Necrotizing dermatitis + hyperkeratosis**
- Footpad hyperkeratosis +/- fissures
- Erythema and erosion with hyperkeratosis at:
  - Mucocutaneous junctions (lips, nasal planum and genitalia)
  - Friction points (elbows, hocks and distal extremities)
Red Hyperkeratosis
White Necrosis and degeneration
Blue Basal cell proliferation

www.vetbook.org
+ infection
Laboratory Findings - Variable

- Elevated liver enzymes
- **Decreased albumen**
- Elevated post-prandial serum bile acids
- Hyperglycemia
- Non-regenerative anemia.
- Ultrasound may reveal changes to the hepatic parenchyma that are more severe than suggested by biochemistry.
### Table 4: Serum biochemistry results in six dogs with Metabolic Epidermal Necrosis.

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Cases</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total proteins (g/dl)</td>
<td>8.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>ND</td>
<td>1.70</td>
</tr>
<tr>
<td>Serum urea nitrogen (mg/dl)</td>
<td>12.1</td>
<td>7</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>ND</td>
<td>0.5</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>ND</td>
<td>228</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>ND</td>
<td>0.21</td>
</tr>
<tr>
<td>Alkaline phosphatase – AP (U/L)</td>
<td>3135</td>
<td>131</td>
</tr>
<tr>
<td>Alaninoaminotransferase – ALT (U/L)</td>
<td>305</td>
<td>79</td>
</tr>
<tr>
<td>Creatine kinase – CK (U/L)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>6.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>ND</td>
<td>8.4</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>ND</td>
<td>5</td>
</tr>
</tbody>
</table>

ND: Not done.
Hepatocutaneous syndrome
Diagnosis

• DDX includes:
  – Zinc responsive dermatitis
  – Immune mediated disease (pemphigus, vasculitis)
  – Mucocutaneous pyoderma
  – Naso-digital hyperkeratosis

• Definitive diagnosis:
  – Histopathology (without secondary infection)
  – Demonstration of underlying cause
Pemphigus foliaceus

Muco-cutaneous pyoderma

Idiopathic naso-disital hyperkeratosis

Zinc responsive dermatosis
Prognosis is often poor unless underlying disease can be corrected.

Treatment reports mostly single case

**Amino acid supplements**
- IV infusions Hypertonic, irritating. Central line/large catheter. 25-40ml/kg slowly over 7-12 hours every 3-7 days. Then as required to maintain remission. May improve interval to add lipid supplement
- Oral body builder supplements. 1 adult dose/5kg Xylitol free! Can base on amino acid levels.
- Other supplements: Scrambled eggs, onion free chicken stock.
Other support treatment

- Zinc supplements
- Moisturizing hyperkeratosis areas
- Essential fatty acids
- Treatment of secondary bacterial and yeast infections
- Octreotide – glucagonoma: Somatostatin analogue that inhibits glucagon release. 2μg/kg bid
- Corticosteroids topical and systemic
  - Decrease hyperkeratosis
  - Relieve inflammation and pain
  - May make underlying condition worse
- Apoquel (Oclacitibib) if pruritic
Epitheliotropic Lymphoma

• Majority malignant cytotoxic-T cells, probably memory cell class. Minority cases natural killer cells

• The primary target is the epidermis, in particular the hair follicles +/- mucus membranes. The dermis is later involved by invasion.

• Non-epitheliotropic lymphoma may involve the skin but involvement is primarily of the dermis. Nodular with other organ involvement
Epitheliotropic Lymphoma

Human classification:


• Mycosis fungoides involves both the epidermis, dermis +/- mucus membranes.

• Sézary’s syndrome. Leukemia. Circulating malignant lymphocytes. Less common
Clinical picture
Pleomorphic and Variable

• Older animals.
• Pruritus common
• Classification based on stage. Frequent overlap
  – Erythemic macule(s)
  – Erythemic plaque
  – Exfoliative Erythroderma
  – Tumor stage (ulcers and nodules) advanced and aggressive
Diagnosis of EL
The variability makes definitive visual diagnosis difficult.

- Onset of (severe) inflammatory skin disease in an older dog, possibly accompanied by pruritus
- Allergic skin disease, other than flea allergy and sarcoptes, it is uncommon to begin in older age.
- Potential differentials include:
  - Hepatocutaneous syndrome
  - Adult onset Demodex
  - Immune mediated disease (including drug reactions)
    - Pemphigus
    - Erythema multiforme
    - Nodular paniculitis
  - Other tumours
  - Nodular infections
  - Histiocytosis
Cytology

Wipe and blot and scrape

Round cell pattern

Often heavy presence of neutrophils associated with secondary infection +/- bacteria

DDx cytology = other round cell tumours or (pyo)granuloma

Palumbo et al 2015
http://dx.doi.org/10.1590/1678-4162-7575
Histopathology and Immuno-histochemistry

- Epidermal and adnexal trophism
- Majority CD3+ (T cell), CD79 – (B cell), CD8+ (cytotoxic t cell), CD4- (T-helper)
- Minority CD3+/CD8- /CD4- (natural killer cells)
- Not prognostic
Treatment and Prognosis

• Guarded. 3-6 months in most cases. Not related to immunohistchemistry

• Chemotherapy likely to have enhanced quality of life.

  **Corticosteroids**
  
  Risk = severe suppression and Cushing’s syndrome.
  Proton pump inhibitor or H2 Blocker (GI ulcers)
  Topical in combination

**Monotherapy** (author’s protocol)
2mg/kg prednisolone once daily for 14 days then reducing by 25% every 10-14 days to a target of 1mg/kg every 2nd day if possible

**With CCNU** (author’s protocol)
Prednisolone 2mg/kg day 1-12 of CCNU cycle
CCNU Loumustine

• Orally every three weeks. (60 – 70 mg m2)
• Haematology and biochemical profile to beginning and 12 days after each individual dose.
• Potency between compounding pharmacies varies
• Side effects (Heading et al 2011, 206 cases)
  – Neutropenia 57%  Thrombocytopenia 14%
  – Anaemia 34%  ALT increase 49%
  – GI signs 39%  Vomiting 24%  Potential renal toxicity 12%

• Suspend treatment if neutrophils <2000, ALT > 400-500 or other critical indices indicate
• Modify dose if re-occurring
Controversies
CCNU +/pred vs Pred monotherapy

- 46 cases, multi-institutional CCNU only
  Risbon et al 2006
  - Survival time not evaluated
  - Response rate 83% with 32% complete remission and 50% partial
  - Median cycles to response = 1
  - Median response duration 94 days (22–282)

- 30 cases Fontaine et al 2009
- Median survival times (months)
  - CCNU 6
  - Prednisolone monotherapy 4.5
  - No treatment 3
- Due to small sample size, no statistical difference
- Quality of life improved regardless of which treatment
Other treatment modalities based on small numbers of cases or individual reports:

- **Fatty acid supplementation**: High doses of sunflower oil (75% linoleic acid – omega-6). If tolerated, this represents a benign, inexpensive adjunct treatment.

- **Retinoids: Isotretinoin** (2mg/kg SID) combined with prednisolone (2mg/kg SID). Retinoids have a relatively good safety profile in dogs but owners need to be aware of their teratogenic potential if women of child-bearing age are exposed.

- **Interferon**: Anecdotal reports that human interferon-α (Roferon Roche) sub-lingual/ buccal pouch 20,000 IU daily) or recombinant feline interferon-ω at 1-3 million IU/m² body surface area three times weekly. **Benign adjunct**

- **Radiation** of spot lesions

- **Topical nitrogen mustard. RISK**
Calcinosis Cutis

- Deposition of calcium salts into all layers of the skin beginning in the perifollicular dermis
- Almost always associated with canine Cushing’s syndrome
- Not specific for spontaneous (adrenal or pituitary) or iatrogenic
- Occasionally seen in hypercalcemia and hyperphosphatemia associated with renal, neoplastic or parathyroid.
- Very rarely, idiopathic
Classical lesions

- Pale pink plaque
- White areas often detectable
- Often pruritic
- May be infected
**Signalment:**
- Signalment: Female desexed, Staffordshire
- Bull Terrier, 3.5 years of age
- **Severe pruritus and owner complained of “lumpy” skin**
- Receiving prednisolone 10mg every second day for last 9 months.
Treatment of Calcinosis Cutis

- Treat the underlying disease
- Tetracyclines chelate calcium and have an antiinflammatory effect. Minocycline 5mg/kg 2x day
- DMSO topically
  - Initially twice daily (if tolerated) then daily
  - Beware drying. Use moisturiser
  - Owner protection
- Treat infections
- Oclacitinib (Aopquel) for pruritus
THANK YOU