Cutaneous lymphoproliferative disease in cats and dogs

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Lymphoproliferative disease in animals consists of lymphoid leukaemia's (originate in bone marrow or spleen) and lymphomas (originate in lymphoid tissue other than bone marrow) although there is overlap as lymphoma can become leukemic (Stage V) and lymphoid leukaemia's can infiltrate other organs including lymphoid tissue and skin.

Classification

Lymphoma is classified according to anatomical location, cell morphology, immunophenotype, anatomic distribution within lymphoid organs, molecular characteristics and biological behaviour (when known). The current REAL classification system for lymphoma in animals adopted by the World Health Organisation will constantly evolve with technological advances in molecular diagnostics and more robust clinical data on prognosis based on biological behaviour and response to treatment.

Immunophenotype (T cell, B cell)

Lymphoproliferative disease can be immunophenotyped by:

- Immunohistochemistry
  - Histology
    - Fixed tissue.
- Immunocytochemistry
  - Cytology
    - Smears
- Flow cytometry.
  - Blood or aspirates.
    - Counts
    - Measures cell size.
    - Requires live cells.
    - Does not differentiate between neoplastic and reactive populations.
    - Limited to surface antigens in commercial laboratories.

Cytology

- Best for cell morphology.
- Size (small, intermediate, large).
- Immunocytochemistry.

Histology

- Best to assess architecture and infiltration pattern.
- Immunohistochemistry.

Biological behaviour and response to treatment

- Aggressive vs indolent.

Flow cytometry

- Requires live cells.
- Immunophenotype
- Enumeration
- Size
- Only assesses surface antigens in commercial laboratories

PARR (PCR for Antigen Receptor Rearrangements)

- Identifies clonal populations of lymphocytes based on variability of lymphocyte receptor components
  - Differentiates between reactive and neoplastic lymphocytes
- Can be done on cytology and histology samples
- Can identify immunophenotype but immunohistochemistry and flow cytometry preferred

Grading

- Grading is a histological term that refers to the average mitotic rate of neoplastic lymphocytes per 400x field (hpf)
  - Low=0–5 mitotic figures/hpf
  - Medium=6–10 mitotic figures/hpf
  - High = >10/hpf
- Grading is **not** a clinical term to indicate biological behaviour or prognosis

Staging

- Separate WHO staging system for multicentric lymphoma in dogs and cats
- Tumour, Node, Metastasis, Blood (TNMB) can potentially apply to primary lymphomas at other sites, but clinical significance limited at this stage.

Location

Lymphoproliferative disease can potentially involve all tissues secondarily but the most common primary locations in dogs and cats are multicentric, gastrointestinal (GI), mediastinal and cutaneous. Less common primary locations include splenic, ocular, hepatic, central nervous system or pulmonary.

Cutaneous lymphoma

Cutaneous lymphoma is generally categorised as epitheliotropic or non-epitheliotropic. Lymphoid leukaemia's can also involve ethe skin and there are also non-neoplastic entities which can histologically (and sometimes clinically) resemble lymphoproliferative disease.

Dogs

Approximately 1% of skin tumours in dogs are due to lymphoproliferative disease with 5% of all canine lymphomas involving the skin. Almost all cutaneous lymphoproliferative diseases are considered categories of peripheral T cell lymphomas. Apart from plasmacytomas/plasmacytosis, B cell lymphoproliferative disease involving the skin is extremely rare.

Resident T lymphocytes within the epidermis and dermis are predominantly $CD8^+$ T cell receptor (TCR) $\alpha\beta$ subtypes which are part of the acquired cell mediated immune response as they require antigen presentation with over 95% within the dermis. TCR $\gamma\delta$ T cells are <10% and are part of the innate immune system not requiring antigen presentation for activation.

Epitheliotropic lymphoma

1. Pagetoid reticulosis.
   a. Restricted to superficial and follicular epidermis.

   b. Predominantly γδ T cells.
2. Mycosis fungoides.
   a. Roughly equal CD8+ ab and gd T cells (cytotoxic T cells).
   b. Epidermal, dermal, adnexal involvement.
   c. Often mucocutaneous involvement.
   d. Mimics other dermatologic diseases.
      i. Allergies
         - Erythema
         - Pruritus
      ii. Immune mediated disease.
         - Cytotoxic, e.g. DLE.
            - Depigmentation
         - Vesiculobullous
            - Vesicles and ulcers
         - Pemphigus foliaceus.
            - Crusts
      iii. Endocrinopathies.
         - Alopecia
      iv. Keratinisation defects.
         - Crusts and scale.
      v. Vasculitis
         - Pawpad lesions.
         - Linear lesions.
         - Depigmentation
      vi. Other neoplasia.
         - Can form nodular masses.
3. Sezary syndrome.
   a. Epitheliotropic lymphoma with progression to leukaemia.
   b. Very rare in dogs.
4. Diagnosis
   a. Cytology rarely diagnostic as lesions usually too superficial.
      i. Tumour form.
      ii. Impressions smears of eroded areas.
   b. Histology best.
      i. Non-ulcerated or depigmented lesions.
      ii. Multiple biopsies.
5. Prognosis poor.
   a. Survival similar for MF and PR.
      i. Median survival ~6 months.
      ii. Histological prognosis (Dettwiler *et al.* 2023).
         - Poor prognosis.
            - Dogs with haired skin involvement.
            - Erosions, ulcers, crusts and nodules.
            - Histology
               - Mitotic activity. >7mf/hpf.
               - Panniculus involvement.
               - Call and nuclear diameter.
   b. Sezary syndrome worst prognosis.

Non-epitheliotropic cutaneous lymphoma

1. Peripheral T cell lymphoma.
   a. Subcutaneous panniculitis-like T cell lymphoma.
      i. Very rare.
      ii. Single or multiple subcutaneous skin masses.
      iii. Frequent necrotic foci.

   iv. Clinically aggressive with short median survival.
   b. Pleomorphic small / medium-sized (Inflamed T cell lymphoma).
      i. Mixed population of small and large lymphocytes with other inflammatory leucocytes.
      ii. DDX reactive histiocytosis clinically and histologically.
         - Need PARR and Thy-1 IHC.
2. Anaplastic large T cell lymphoma.
   a. Multifocal dermal/subcutaneous nodules.
      i. Monomorphic population of large lymphocytes with high mitotic rate (high grade).

Angiocentric lymphoma

1. Not a specific entity – Pathological progression of multiple entities.
   a. T or B cell.
   b. Vasculocentric infiltration +/- vasculotropism / vasoinvasion.
      i. Can lead to vascular occlusion/disruption resulting in necrosis.
         - Dermal / subcutaneous nodules with necrotic centres (donut-shaped).
   c. Lymphomatoid granulomatosis.
      i. Primary pulmonary angioinvasive lymphoma.
         - May have cutaneous involvement.
         - Usually B cell.

Cutaneous lymphocytosis / pseudolymphoma

1. Focal nodular to multifocal alopecia, erythema, scale.
2. Trunk > limbs > abdomen / flanks.
3. Variable prognosis – may progress to lymphoma.
   a. Need clonality to differentiate.
4. Can get lymphadenopathy.
5. Antigenic stimulation.
   a. Drug-induced.
   b. Chronic hypersensitivity (arthropods).
6. Cytology and histology.
   a. Can be monomorphic population of lymphocytes.
   b. Usually low numbers of other inflammatory cells, e.g. eosinophils with chronic insect bite hypersensitivity.

Chronic lymphoid leukemia

1. Rare cutaneous manifestation.
2. Lichenoid band of small lymphocytes in superficial dermis.
3. Resembles cutaneous lymphocytosis.
4. Check haematology for lymphocytosis and cytopenias +/- bone marrow cytology.

Cutaneous plasmacytosis

1. Very rare.
2. Multiple cutaneous plasmacytomas (3–100).
3. Can have lymph node involvement.
4. No monoclonal gammopathy.
5. ~70% response to chemotherapy (melphalan and prednisone or lomustine) with disease-free interval for 153 days.
6. Median survival after treatment 542d.

Cats

1. Only 1.7% of feline lymphoma involves the skin.
2. Older cats.

3. Prognosis not affected by presence of epitheliotropic.
    a. Median survival.
        i. Non-treated ~ weeks.
        ii. Treated
            - ~50% response.
            - ~10% complete remission.

Non-epitheliotropic lymphoma

1. Most common 87%.
2. Nodules and masses.
3. Often higher grade.
4. Can be cutaneous manifestation of systemic disease.
    a. T cell > B cell lymphoma.
5. Tarsal lymphoma.
    a. Predominantly B cell.
    b. Subcutaneous
    c. Often systemic disease, regional lymph node involvement or other skin lesions.
    d. Poor prognosis.

Epitheliotropic lymphoma

1. 13%
2. Erythematous plaques, patches and erosions.
3. T cell lymphoma.
4. Median survival up to 10.25 months.

Cutaneous lymphocytosis / pseudolymphoma

1. Focal/multifocal lesions>diffuse.
2. Alopecia > erythema > scale > papules > nodules.
3. Head and neck > distal limbs.
4. May be an indolent lymphoma as can be clonal and systemic lymphoid infiltration.
5. Antigenic stimulation.
    a. Drug-induced, e.g. Phenobarb.
    b. Chronic hypersensitivity (arthropods).