# Lupus and other cytotoxic skin diseases in dogs and cats

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Cytotoxic dermatitides have previously been referred to as lichenoid-interface or interface dermatitis and are usually immune mediated diseases characterised by keratinocyte death (apoptosis) mediated by cytotoxic T lymphocytes or NK cells.

The underlying cause is often not known but genetic/breed predispositions, drug, pathogen and ultraviolet radiation (UVB) associations have been identified for some diseases. These antigenically alter keratinocytes, provide haptens to cell surface molecules or cause dysfunction in the innate or acquired immune system which results in cell mediated destruction of keratinocytes by NK cells and cytotoxic T cells respectively.

Keratinocyte cell death can be individual cells or groups of cells, limited to the stratum basale (interface) or all layers of the epidermis (panepidermal) with or without follicular epidermal and/or adnexal involvement. Clinically these present as erosive, vesiculobullous to depigmenting diseases and are often bilaterally symmetrical. Due to loss of structural integrity of the epidermal barrier, ulceration and secondary bacterial infection are common.

The dermal inflammatory cell infiltrate can be variable (cell poor vs cell-rich) but is usually lymphocyte-predominant in areas not associated with ulceration or mucocutaneous junctions where neutrophils and plasma cells can predominate. Lymphocytic exocytosis into the overlying epidermis associated with apoptotic cells is also a histological feature of cytotoxic disease along with hydropic degeneration at the dermal-epidermal junction and with the epidermis. Pigmentary incontinence

The most common cytotoxic diseases seen in animals are interface diseases including the cutaneous lupus erythematosus group which have strong genetic/breed associations. Cytotoxic disease associated with drugs in companion animals are usually panepidermal and include erythema multiforme, Steven Johnson Syndrome and toxic epidermal necrolysis the latter two of which are extremely rare, acute onset, severe and potentially life-threatening. Infectious causes of cytotoxic dermatitis in companion animals are less common than humans but florid histological interface cytotoxic changes can be seen with resolving viral papillomas in dogs.

Clinically the most commonly encountered diseases of the cutaneous lupus erythematosus (CLE) group are discoid lupus erythematosus, symmetric lupoid onychitis (SLO), mucocutaneous lupus erythematosus and vesicular cutaneous lupus erythematosus. The pathogenesis of canine CLE is not completely understood, but it does appear that human CLE and canine CLE are similar with CD8+ T cells targeting epidermal keratinocytes with excessive secretion of interferons (IFNs) from the type I, II and III families. CLE variants have been described as the “archetypal interferonpathies”.

Discoid lupus erythematosus (DLE) is a relatively benign disease with no systemic involvement. There is a breed predilection for collies, German shepherds, Shetland sheepdogs and Siberian huskies. Sun exposure aggravates the disease suggesting that photosensitivity plays a role in the pathogenesis.

Lesions of DLE are often confined to the nasal planum but can also involve the lip margins, muzzle, periorbital region and pinnae. Depigmentation is a feature, along with erythema and scaling. Early depigmentation is evident on the nasal planum as a slate blue/grey change in colour with loss of the normal cobblestone appearance. Later lesions include erosion, ulceration and crusting. Ulceration can be deep and result in loss of nasal cartilage, which can lead to profuse haemorrhage. Scarring can be significant which is in contrast to the other diseases in this group.

Cytology of any exudate, from beneath crusts and from eroded or ulcerated surfaces should be utilised to identify secondary infection, which is very common. Infection can be treated topically or in combination with systemic antimicrobial therapy based on cytological findings. The main differential diagnosis for DLE is mucocutaneous pyoderma and these can be indistinguishable on histology. To help with making a diagnosis it is advisable to implement antimicrobial therapy (topical +/- systemic) for three weeks prior to taking biopsies. If the lesions significantly improve or resolve then DLE is unlikely, but if the lesions persist then this is the ideal time to biopsy. Include this information on the submission form for the pathologist.

Management of DLE should include measures to reduce sun exposure. Apart from UV light exacerbating DLE, the depigmented areas are highly susceptible to solar damage ranging from solar dermatitis, actinic keratosis, solar vasculopathy and solar-induced neoplasia.

DLE can be managed successfully with a topical glucocorticoid (e.g. mometasone) or calcineurin-inhibitor (e.g. tacrolimus). Topical treatment needs to be applied every 12 hours for 4-6 weeks, and then application is tapered for maintenance.

If topical treatment is unsuccessful alone or not practical, then systemic medications are required. The immunomodulatory combination of doxycycline and niacinamide has traditionally been the first option +/- prednisone at an initial dose of 0.5-1.0mg/kg until the lesions are in remission before tapering down and then off the prednisone. DLE can then usually be maintained with a tapered dose of doxycycline/niacinamide + topical therapy. However, the use of doxycycline in this way is a concern in this age of antimicrobial stewardship.

Oclacitinib (Apoquel) is being utilised off-label for the different forms of cutaneous lupus erythematosus (CLE) and has been very effective, with relatively rapid responses. Oclacitinib is a nonselective Janus kinase (JAK) inhibitor that binds predominantly to JAK1. Oclacitinib has the potential to inhibit the activation of JAK receptors of several cytokines in addition to IL-31 including IL-2, IL-15, IFNα and IFNγ. The inhibition of IFN signalling is of particular relevance for CLE as it could directly target the pathogenesis of the disease. Oclacitinib is well tolerated with very few side effects, and we are comfortable using it once daily long term for atopic dermatitis. The dose used in dogs for CLE ranges from 0.45mg/kg twice daily to 1.8mg/kg once daily, which is off-label dosing, and the long-term side effects of twice daily and higher dosing needs to be considered. Regular monitoring of blood counts is important, especially when given twice daily in the long term, because of its potential inhibition of JAK2 that could impact haematopoiesis.

The prognosis for DLE is good, but some form of maintenance therapy will need to be continued lifelong.

Mucocutaneous lupus erythematosus has a breed predilection for German shepherd dogs and their crosses and females are more commonly affected than males. The age of onset is typically between 4-8 years of age. As the name suggests the lesions target the mucocutaneous junctions and are usually symmetrically distributed. Commonly affected areas are the anus, vulva and prepuce. Lesions can also involve the lip margins, around the eyes and the nasal planum. It is rare for lesions to occur in the mouth. A common presentation is pain urinating or defaecating, but dogs are usually not systemically unwell. Typical lesions are erosions and ulcerations, crusting and hyperpigmentation. Differentials to consider are mucocutaneous pyoderma, mucous membrane pemphigoid and erythema multiforme. Cytology should be performed to identify secondary microbial infection. Histology is needed for a definitive diagnosis and as for other ulcerative diseases, taking biopsies after treatment for pyoderma will help increase the diagnostic quality of the biopsies.

Treatment has traditionally included doxycycline/niacinamide, prednisone, cyclosporine and other immunosuppressive therapy. Identifying and managing secondary pyoderma is also important. More recently, oclacitinib is being used off-label with promising results.

Vesicular cutaneous lupus erythematosus (VCLE) is seen almost exclusively in collie-related breeds suggesting that there is a strong genetic predisposition. The lesions affect the glabrous skin of the abdomen, axilla, groin and medial hindlegs. There can also be lesions of the mucocutaneous junctions, concave pinnae and oral cavity. In the early stage the lesions are vesicles, but these are fragile and slough easily leaving erosions and ulcers which are more typically seen. The erosions/ulcers on the ventrum are often in a serpiginous pattern which is unique.

Secondary infection of erosions/ulcerations is common. The main differential diagnosis for VCLE is erythema multiforme.

Management is as for the other CLE variants, with oclacitinib replacing more traditional immunosuppressive combinations as the first line treatment.

Erythema multiforme (EM) is a cytotoxic disease with a different pathogenesis to the CLE group, as explained above. EM can present with a wide range of lesions which can range from erythematous macules, plaques or papules to ulcerations. It can also present with generalised scaling, erythema, crusting and alopecia. There has also been described a hyperkeratotic form, which is also called "old dog" EM. There are a number of triggers that can induce EM, and an investigation into the trigger should be launched, but it is not uncommon that cases are idiopathic. If the trigger can be identified and removed or managed, then mild cases of EM may resolve without treatment. However, in more severe cases or when the trigger cannot be removed then immunosuppressive therapy and supportive therapy is required. Immunosuppressive therapy usually includes glucocorticoids alone or in combination with cyclosporine, azathioprine, mycophenolate. Intravenous immunoglobulin has been used in very severe or refractory cases. There is one report of two dogs with a rapid response of hyperkeratotic EM to oclacitinib.

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| Disease | Keratinocyte cell death | | | Species | Breeds | Lesion type | Distribution |
|---|---|---|---|---|---|---|---|
| | Interface | Panepidermal | Follicular | | | | |
| Discoid lupus erythematosus - Localised | Y | N | Y | Canine | German Shepherds | CU, D | Nasal planum and facial mucocutaneous junctions |
| Discoid lupus erythematosus - Generalised | Y | N | Y | Canine | Chinese Crested | CU,D | Trunk, abdomen, lateral limbs |
| Mucocutaneous lupus erythematosus | Y | N | N | Canine | German Shepherds | CU, D | Genitals, mucocutaneous junctions |
| Exfoliative cutaneous lupus erythematosus | Y | N | Y | Canine | German Shorthaired Pointer<br>Magyar Vizsla | HK, A | Trunk, pinna, muzzle, abdomen |
| Vesicular lupus erythematosus | Y | N | N | Canine | Rough Coated and Border collies<br>Shetland Sheepdog | CU, V | Ventrum, axilla, groin, pinna |
| Pemphigus erythematosus | Y | N | N | Canine | German Shepherds<br>Collies<br>Shetland sheepdogs | CU | Nasal planum, pinnae and muzzle |
| Thymoma-associated exfoliative dermatitis | Y | Y | N | Feline | | HK, A | Head, pinnae and neck |
| Lupoid onychitis | Y | N | N | Canine | German Shepherds<br>Gordon Setters<br>Bearded collies | O | Digits |
| Uveodermatologic syndrome | Y | N | N | Canine | Akita, Husky, Samoyed | D<br>Uveitis | Nasal planum, periocular, perioral, oral |
| Ischaemic dermatopathies (5 subtypes) | Y | N | Y | Canine | Familial Type: Rough Coated Collies<br>Shetland Sheepdog<br>Jack Russell Terrier | A, HK | Pinna, vaccination sites, periocular |
| Drug reactions | Y | N | N | Canine | | CU, D | Mucocutaneous junctions, mucous membranes |
| Epitheliotrophic lymphoma | Y | Y | Y | Both | Boxers<br>English Cocker Spaniels | CU, D | Mucocutaneous junctions, haired skin, mucous membranes |
| Classic Erythema multiforme | N | Y | Y | Both | German Shepherds<br>Pembroke Welsh Corgis | CU | Ventrum, axilla, groin, pinna |
| Hyperkeratotic erytheme multiforme | N | Y | Y | Canine | | HK | Ventrum, axilla, groin, pinna mucocutaenous junctions |
| Steven-Johnson Syndrome | N | Y | Y | Both | | CU, V | Trunk, axillae, inguinal, mucocutaneous |
| Toxic epidermal necrolysis | N | Y | Y | Both | | CU, V | Trunk, axillae, inguinal, mucocutaneous |
| Staphylococcal toxic shock syndrome | N | Y | Y | Canine | | CU, V | Head, extremities |
| Proliferative necrotising otitis externa | N | Y | N | Feline | | CU, HK | External ear canals and pinnae |

CU=crusting / ulcerative; D=depigmenting; HK=hyperkeratotic; N=nodular; HP=hyperpigmented; A=alopecia; V=vesicular
O=onychomadesis