Discoid Lupus Erythematosus (DLE)

DLE in dogs is seen primarily in younger dogs (2-4 years of age) as a depigmenting and inflammatory disease of the nasal planum, bridge of the nose, periocular region, mucocutaneous areas of the lips, and occasionally the pinna. A variant of the disease (or perhaps a different disease?) is seen primarily in Australian shepherds and “white” dolicocephalic dogs, resulting in very severe atrophy and erosion of the planum. DLE usually sun sensitizes the skin. The histology of DLE classically involves variable epidermal atrophy and hyperplasia, hydropic degeneration, and single cell necrosis within the basal cell layer and a superficial dermal accumulation of lymphocytes, lymphocytes and plasma cells, or predominantly plasma cells. The infiltrate may be band-like (lichenoid reaction) and may obscure the dermoepidermal junction. There is usually pigmentary incontinence and variable thickening of the basement membrane. Interestingly, in the author’s experience, only about half of the patients with clinical signs consistent with the disease have classic histopathology. The other half has a superficial dermal mononuclear dermatitis, but lacks the other changes of DLE. This may represent a DLE-like disease whose clinical presentation and response to medication mimics DLE. It has also been recently shown that the histopathology of mucocutaneous pyoderma affecting the planum (more common in German shepherds) may also overlap with that of DLE. Therapy for DLE has included sun restriction, sunscreens, topical glucocorticoid (e.g., betamethasone ointment, fluocinolone/DMSO [Synotic]), oral vitamin E (400-800 IU BID), omega 6/omega 3 fatty acids, topical 0.1% Tacrolimus (BID administration producing response in 65-75% of cases), oral tetracycline or doxycycline and niacinamide (producing 50-60% responses), oral prednisone /prednisolone, prednisolone and azathioprine, or gold salts. DLE is only rarely encountered in cats.

Vesicular Cutaneous Lupus Erythematosus (also known as ulcerative dermatosis of collies and Shetland sheepdogs)

This disease is presented as focal areas of erosion and ulceration (annular, poycyclic, serpiginous) over the ventral abdomen, groin, and axilla and only occasionally over mucous membranes. The onset of the disease is usually in summer and can recur in subsequent spring and summers. Histology shows apoptosis of epidermal basal cells and an interface dermatitis characterized by lymphocytes and vesiculation at the dermo-epidermal junction. DIF often shows a strong linear Ig deposit at the dermal-epidermal junction (“lupus band”). ANA titers are negative, but antibodies to extractable nuclear antigens (Ro/SSA or La/SSB) are positive in 80% of cases. Response to therapy with glucocorticoids at immunosuppressive dosages or glucocorticoids and azathioprine has been good. Some individuals will be benefited by tetracycline or doxycycline and niacinamide. Focal lesions may respond to topical 0.1% tacrolimus. Sunscreens and sun restriction are indicated.

Exfoliative Cutaneous Lupus Erythematosus (also known as hereditary lupoid dermatosis of the German shorthaired pointer)

To date, the German shorthaired pointer is the only breed affected. In one study, the median age of onset was 10 months; females were overrepresented (2:1). Skin changes include heavy, adherent scale (follicular casting), alopecia, and focal areas of crusting with variable degrees of erosion and ulceration affecting primarily the muzzle, pinnae, and dorsal trunk. The disease may become generalized. Lymphadenopathy, pain, pruritus, and pyrexia are variable. Histologic changes include moderate to severe hyperkeratosis, lymphocytic interface dermatitis, and focal apoptosis (singly necrotic keratinocytes) diffusely throughout the stratum spinosum. Direct immunofluorescence of affected skin shows the deposition of IgG in the epidermal basement membrane. Serum indirect immunofluorescence may reveal circulating anti-hair follicle IgG antibodies. The disease is generally poorly responsive to therapy. Topical oil therapies, as for sebaceous adenitis, may improve scaling. Fatty acids and tetracycline or doxycycline and niacinamide may produce some mild improvement. Variable responses are noted to immunosuppressive dosages of glucocorticoids or glucocorticoids and azathioprine, oral cyclosporine (5-10 mg/kg q 24 hrs or BID), or leflunomide.
Other Poorly Characterized Forms of Cutaneous Lupus Erythematosus

Cutaneous Lupus (Widespread DLE?)
Individuals who have more generalized cutaneous inflammatory disease (not restricted to the face as for DLE), which histologically looks like lupus, but for whom ANA titers are negative and who do not go on to develop more systemic disease (as might be expected with SLE), have been suggested to have cutaneous lupus (as seen in man). Successful therapies have included tetracycline or doxycycline and niacinamide, oral glucocorticoids, glucocorticoids and azathioprine, or cyclosporine.

Perianal (and Perivulvar?) LE
Perianal and perivulvar LE is a rare disease. Clinical signs include perianal depigmentation, erosions and ulcers, dyschezia, and frequent hematochezia and constipation. In the veterinary literature, there are reports of two dogs that were treated with prednisolone (2 mg/kg/day) and remained in remission when the glucocorticoid was stopped. Four responded to prednisone and azathioprine, but required alternative-day prednisolone or azathioprine to control the problem. One dog was controlled with tetracycline and niacinamide.

Lupus-like Diseases

Canine Lupoid Onychodystrophy
The most common cause of 20-nail onychomadesis in dogs has been referred to as a lupus-like or lupoid syndrome. It has been recognized in many breeds, including the German shepherd, miniature schnauzer, golden retriever, Labrador retriever, rottweiler, boxer, greyhound, and mixed breeds. There is a recent report of what appears to be a very similar presentation in 18 Gordon and 4 English setters from Norway. There appeared to be a familial predisposition to this problem in this study group.

Based on the “lupoid” nature of the inflammatory changes seen on histopathologic examination and response to therapies (e.g., glucocorticoids), this syndrome is likely an immune-mediated disease. It is important to note that rare cases with the same clinical presentations and histologic changes have been noted to respond completely to systemic antibiotic therapy. Although these may have represented bacterial infections, it is more likely that they may have been individuals who underwent spontaneous remission following clearance of secondary infections. A small percentage of patients with this clinical presentation and “lupoid” histologic changes have responded to restrictive diets (suggesting that food sensitivity was the source of the problem). Although the author does not routinely place affected individuals on a restrictive diet trial, this diagnostic is utilized for refractory cases. Some have suggested that the syndrome may be a reaction to vaccination, although this has not been borne out in reviews done to date.

The age of onset is variable, but tends to be in younger dogs, 1–8 years of age. Both sexes are affected. Onset of nail loss is usually acute. Affected claws are often painful, pruritic, and result in lameness. Progression to 20-nail loss may be rapid (over 2–4 weeks) or protracted (over 4–6 months). Onychorrhexis is variable. Paronychia is generally absent, as is a proximal, reactive lymphadenopathy or systemic involvement. Left untreated, the tendency is to have partial regrowth of abnormal, friable nail that continues to be sloughed/pulled off. There is generally no history of other related skin disease. Diagnosis is based on rule out and histologic evaluation of P3 (P3 amputation or “punch” biopsy). There is usually widespread hydropic degeneration of the basal cell layer of the epidermis, single epidermal cell necrosis (usually in the basal layer), a superficial dermal inflammatory infiltrate of lymphocytes and plasma cells, and marked pigmentary incontinence. Dermoeipidermal separation may be noted. Secondary bacterial infections (especially *Staphylococcus intermedius*) are common.

Consideration is given to removal of loosened claw plates. These will be invariably lost, in spite of the therapies outlined below. This is generally done at the time of anesthesia for purposes of diagnostic P3 amputation (biopsy). Systemic antibiotic therapy is indicated for secondary bacterial infection. Support for the immune-mediated nature of this disease is provided by the fact that the disease does respond to immunosuppressive dosages of glucocorticoids. However, several alternative therapies are also available. After several months of successful therapy, discontinuation of medication should be attempted. Spontaneous resolutions have been noted.

Because several therapeutic alternatives for this disease are relatively innocuous (e.g., tetracycline and niacinamide, doxycycline and niacinamide, or pentoxifylline), they may be tried prior to the establishment of a definitive diagnosis.
Therapeutic alternatives for the disease have been reviewed.5

Fatty acid therapy (omega 3 and omega 6 products such as Derm Caps, DVM; routine bottle dosages) have been noted by some to successfully treat this disease. Others have suggested more aggressive dosages (e.g., 50–60 mg/kg/day of combined EFA and DHA). The author has had poor response to this treatment and therefore only uses fatty acids as an adjunctive treatment in affected individuals.

The combination of tetracycline and niacinamide appears to benefit 5–60% of patients (500 mg of tetracycline and 500 mg of niacinamide or 250 mg of each for patients less than 10 kg) are given q 8 h. until the claws are significantly regrown (3–6 months). The frequency of administration of both drugs is then decreased to q 12 h for 2 months, then both are given once per day. If the claws remain intact after 4–6 months of once per day therapy, treatment is stopped. Recurrence of signs would warrant indefinite maintenance therapy. The trial treatment period for this drug combination is 3 months. Significant nail regrowth is generally noted within 2–3 months; complete regrowth often takes 4–8 months. For responders, about half of patients will regrow normal claws; others will regrow claws that are dystrophic (short, friable, malshaped). The combination of doxycycline (5mg/kg BID) and niacinamide (500 mg total dose BID or TID) has also proved to be effective.

Pentoxifylline at a dosage of 10–25 mg/kg BID to TID (author most commonly uses 15 mg BID) is noted to benefit about 50–60% of cases. In the author’s hands, this drug has primarily been used in tetracycline and niacinamide failures.

Prednisone or prednisolone is also effective (starting at 2.2 mg/kg/day for 2–4 weeks, then half this dose for 2–4 weeks, then gradually reduce to the lowest every other day dose required for maintenance). A “steroid sparing effect” may be achieved with the concurrent use of azathioprine at routine dosages/dosage regimens.

To date, the author is not aware of patients that have been treated with cyclosporine for this disease.

For refractory cases, or patients who are intolerant of the above therapies, consideration should be given to 20-nail, P3 amputations. This procedure does appear to be tolerated well.3

Of the Norwegian Gordon and English setters noted above, 2 dogs were euthanized because of the disease and 2 had regrowth of normal claws (one was treated with polyunsaturated fatty acids, the other was treated with fatty acids, prednisolone, and niacinamide), but most of the dogs had persistent disease in the face of fatty acid therapy.

The Subepidermal Bullous Diseases

This group of diseases is made up of, in order of decreasing incidence, mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), and bullous pemphigoid (BP). Antibodies are produced to antigen (collagen type XVII for BP and MMP, collagen type VII for EBA) located at the dermoeipidermal junction and important for binding the basal keratinocyte to the basement membrane zone. Histopathologic examination shows subepidermal clefting and vesicle formation. Acantholysis does not occur. Differentiation is based on histopathology and immunodiagnostics (direct and indirect immunofluorescence, Elisa or immunoblotting). Because of the depth of skin involvement, it is more likely to see intact vesicles or bulla with these diseases. However, they may be transient and lesions may present as erosions and ulcers. MMP shows involvement of the oral cavity, lips, nose, inner pinna, and genital area. German shepherds are overrepresented. With BP, lesions are most common in the oral cavity, mucocutaneous junctions, pinna, axilla, and inguinal areas. EBA is usually a disease of younger dogs (< 15 months) involving the mouth, face, axilla, abdomen, groin, and footpads. Great Danes appear predisposed. MMP may respond to prednisolone, with or without azathioprine or chlorambucil, or tetracycline and niacinamide, or dapsone. BP may respond to prednisolone with or without azathioprine or tetracycline and niacinamide. EBA is more difficult to treat than BP or MMP. Some dogs may respond to prednisolone with or without azathioprine.4

Vasculitis

The pathomechanisms of cutaneous vasculitis are thought to involve Type III (immune complex) hypersensitivity reactions, although multiple mechanisms likely play a role. Cutaneous vasculitis may be associated with underlying diseases (infections, food sensitivity, insect bites, malignancies, SLE), drugs, or vaccines or may be idiopathic (50% of cases). Predisposed breeds include Jack Russell terriers, German shepherds, greyhounds, Scottish terriers,
Lesions are often noted in “pressure” areas and extremities (e.g., pinnae, tip of tail, nasal planum, paw pads, scrotum). Clinical manifestations include lymphedema (often confined to one leg), purpura, erythematous urticarial plaques, infarcts and “punched-out” ulcers, hemorrhagic bullae, and subcutaneous nodules/plaques (panniculitis due to septal vasculitis). More well-defined syndromes include proliferative thrombovascular necrosis of the pinnae; cutaneous and renal vasculopathy (Alabama rot) of greyhounds, familial cutaneous vasculopathy of German shepherds, familial pyogranuloma and vasculitis of Scottish terriers, focal cutaneous vasculitis and alopecia at the sites of vaccination—especially rabies vaccine, widespread ischemic dermatopathy associated with vaccination, familial vasculitis of shar-peis, acute febrile vasculitis of young shar peis, and dermal arteritis of the nasal philtrum (especially in St. Bernards and Newfoundlands). Diagnosis is by biopsy followed by diagnostics required to define underlying causes.

Treatments include management/elimination of known triggering factors and immunomodulatory drugs. Drugs used for this and the idiopathic forms of the disease include prednisone/prednisolone or methylprednisolone (2 mg/kg/day initially), pentoxifylline (15–25 mg/kg BID to TID), tetracycline and niacinamide (250–500 mg of each TID to start), azathioprine and prednisone (azathioprine at 2 mg/kg/day to start), and cyclosporine (5 mg/kg/day to start).

Sterile Granuloma and Pyogranuloma Syndrome
In dogs, lesions are typically well demarcated, firm, variably alopecic dermal plaques or nodules, most commonly located over the head, neck, and trunk. Lesions may ulcerate. They may wax and wane in severity. Similar lesions have been noted in cats. Histologically, granulomatous and pyogranulomatous inflammation extends from the dermis to the panniculus and often to the deeper subcutis. Mandatory differential diagnoses include infectious pyogranulomas (to be ruled out with stained impression smears; special stains of biopsies, culture, and PCR testing). Sterile pyogranuloma and pyogranuloma syndrome is commonly confused with cutaneous reactive histiocytosis. Differentiation may be made histologically, but in some cases it may take immunohistochemistry to identify the histiocytes of cutaneous histiocytosis as dendritic cells, whereas macrophages are the predominant large mononuclear cell of sterile granuloma and pyogranuloma syndrome. If lesions are solitary, they may be resolved by surgical excision. Multiple lesions are treated with glucocorticoids, tetracycline or doxycycline/niacinamide, or glucocorticoids and azathioprine. More recently, excellent responses have been noted to cyclosporine therapy (5 mg/kg/day).

Sterile Idiopathic Panniculitis (SIP)
Panniculitis is an inflammatory condition of the subcutaneous fat, characterized by cutaneous nodules that often become ulcerated and develop draining tracts. Lesions may be solitary. Multiple lesions are most commonly truncal in distribution. Patients with multiple lesions may also have intermittent or continuous constitutional signs, including poor appetite, depression, lethargy, and pyrexia. Dachshunds and poodles are predisposed. Diagnosis is by biopsy and rule out. Other potential causes of panniculitis include infections (bacterial, mycobacterial, actinomycetic, fungal), lupus erythematosus, drug eruption, erythema nodosum, arthropod bite, foreign body, trauma, pancreatic disease (inflammation, neoplasia), vasculitis, and vitamin E deficiency. Therapies for SIP have included prednisone/prednisolone (starting at 2 mg/kg/day), oral vitamin E (400 IU BID), or oral potassium iodide. More recently oral cyclosporine has been very beneficial in treating this disease (5 mg/kg/day). Some individuals who have been in prolonged remission may eventually be able to have all therapies discontinued.

Erythema Multiforme and Toxic Epidermal Necrolysis
Erythema multiforme is an acute dermatitis characterized by any combination of erythematous macules, papules, urticarial plaques, vesicles, bullae, erosions, or ulcers. Mucous membranes can be involved. Histologically it is typified by single-cell necrosis (apoptotic cells) within the epidermis. Although many cases in dogs are idiopathic (possibly viral induced), the immune-mediated destruction of keratinocytes can also be triggered by drugs, infections, foods, and neoplasia. Therapy is directed at removing the underlying cause. Spontaneous remission is possible. Progressive disease can be treated with glucocorticoids, starting at immunosuppressive dosages (i.e., 2 mg/kg/day of prednisone or prednisolone). Severe, refractory disease has been significantly benefited by intravenous human immunoglobulin (e.g., 5% to 6% solution prepared with saline; 0.5 to 1 g/kg infused IV over a 4–6 hour period, once or twice, 24 hours apart). More recently, oral cyclosporine (5–10 mg/kg/day) has been shown to be effective in treating this disease.
Toxic epidermal necrolysis is a vesicobullous disease of the skin and mucous membranes characterized by widespread skin and mucous membrane erosions and ulcers and histologically by full-thickness necrosis of the epidermis. It is most commonly associated with reactions to drugs. Therapy is symptomatic and supportive. Glucocorticoids are variably effective and should only be considered for progressive disease. Intravenous immunoglobulin has been reported to be of benefit in humans. There are anecdotal reports of benefit in dogs and cats.

**References**