

Systemic Lupus Erythematosus in Dogs and Cats

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Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple systems and has been reported in humans, dogs, and cats. Although known since the 19th century in humans, SLE was not recognized in the dog until 1965.¹ Since the first case report, a number of cases have been documented in the dog. On the other hand, the first case of SLE to be suspected in the cat was in 1971,² and only five further cases have appeared in the literature.^{3,4,5,6}

The incidence of SLE in dogs and cats has not been estimated; however, the incidence in humans has been speculated to be approximately 5 cases per 100,000 population.⁷ In humans, the disease is much more common in females (approximately 75% of cases). However, review of cases in the dog reveals no sex predilection,⁸ and there are too few cases in the cat to comment. The most common age group affected in the dog is 2 to 8 years, and no breed predilection has been determined.⁹

ETIOLOGY AND PATHOGENESIS

The cause of SLE is unknown. However, genetic factors, viruses, immunologic disorders, pharmacological agents, and environmental factors have been suspected. Quimby et al.,¹⁰ in work with dogs, postulates the existence of genes in SLE: those that permit a general disposition to autoimmunity (Class I) and those that determine the phenotype of the disease (Class II). Permissive alleles of Class I genes are associated with the production of autoantibodies, whereas Class II genes determine manifestations of the disease. The development of SLE results from interaction between genes of both classes.

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The possibility of a viral cause comes from work where cell-free filtrates of SLE cases were injected into pups, and antinuclear antibodies were produced.¹¹ However, none of the animals in this study developed clinical signs of SLE.

Evidence that an immunologic disorder contributes to the pathogenesis of SLE comes from work in the New Zealand Black and New Zealand White mice. These mice provide an animal model for the study of SLE in humans and have been shown to lose suppressor T-cell activity with age.¹² The loss of this activity has been associated with the onset of clinical signs.

Many drugs have been reported to cause the production of antinuclear antibodies in people. A recent report¹³ has shown that hydralazine is capable of causing the production of antinuclear antibodies in dogs, although the dogs in this study remained clinically normal.

Finally, certain environmental factors have been incriminated in the pathogenesis of SLE. For instance, ultraviolet light has been thought to exacerbate the skin lesions in SLE.¹⁴

An autoimmune disease is caused by an immune response directed against an individual's own tissues. In SLE, autoantibodies are directed against: nuclear antigens including native DNA, RNA, histones, and nucleoproteins; cellular surface antigens on leukocytes, erythrocytes, and platelets; and against certain cytoplasmic antigens such as lysosomes and ribosomes.¹⁵

The mechanism involved in damage to tissues in SLE is primarily a Type III hypersensitivity reaction where immune complexes are deposited in various tissues, principally along blood vessels and basement membranes. The immune complexes are composed of autoantibodies and antigens which activate complement. Complement activation, in turn, attracts neutrophils to set up an inflammatory response. Autoantibodies directed against hema-

topoietic cells result in a Type II hypersensitivity,¹⁵ wherein autoantibodies bind to the cell involved (for example an erythrocyte) and either lyse the cell by activation of complement or cause phagocytosis of the cell.

CLINICAL SIGNS AND LESIONS

Clinical signs of SLE are extremely variable. SLE is classically described as having four syndromes: autoimmune hemolytic anemia, thrombocytopenia, symmetrical polyarthritis, and immune complex (membranous) glomerulitis. Dermatologic lesions are also very common.⁸ Pleuritis, meningitis, and gastrointestinal disorders such as ulcerative colitis are encountered much less frequently.¹⁶ The disease in a particular animal may have any or all of the above syndromes involved, and the development of various clinical signs may occur in any order.¹⁷

TABLE 1
Incidence of Signs in 29 Cases of Definite or Probable SLE in Dogs Seen at the University of Pennsylvania¹⁷

Signs	Incidence (%)
Musculoskeletal system	58.6
Skin	44.8
Anemia (Coombs' positive)	27.5
Glomerulonephritis	20.7
Thrombocytopenia	13.8
Leukopenia	10.3
Fever	41.4
CNS signs	6.9

Musculoskeletal signs: This system is the one most frequently involved in canine cases (Table 1).^{17,18} There are two forms of musculoskeletal involvement: polyarthritis and polymyositis. The arthritis associated with SLE, in contrast to rheumatoid arthritis, is nonerosive.¹⁶ About 50% of cases have widespread joint involvement (more than 5 joints).¹⁶ These dogs present with a rigid walk and take short steps; some refuse to walk. Dogs with fewer joints involved may present with posterior weakness and migratory lameness. Some dogs may appear to have only one joint involved, but synovial fluid exam often shows several joints to be affected, one having more intense inflammation than the others. Fluctuation of clinical signs with time is common. There are often visible enlargements of joints, especially in the carpus and tarsus.

Synovial fluid leukocyte counts average 74,500 cells/mm³ with the majority of cells being neutrophils.¹⁶ Radiography reveals no joint



Fig. 1. AP view of a canine tarsal joint with soft tissue swelling.

abnormalities, although soft tissue swelling may be observed. Histopathologically, the synovium is found to be thickened from infiltration of inflammatory cells. The greatest number of cells is found adjacent to or contained within the synovial cell layer.¹⁶

Polymyositis, although much less common than polyarthritis, may occur. The most prevalent clinical signs of polymyositis are muscular atrophy and weakness in addition to dysphagia from megaesophagus.¹⁹ Pathologic lesions consist of myofiber necrosis and phagocytosis, perivascular and interstitial infiltrations of mononuclear cells, and type I and II myofiber degeneration and vacuolation.¹⁹

Dermatologic Signs: Cutaneous manifestations are exhibited in about 50% of SLE cases in the dog, and 33% of the six cases reported in cats were presented with skin lesions.⁴ Lesions are extremely variable but usually involve the nose, head, and ears, and often show symmetry.¹⁷ Lesions are alopecic, crusted, and scarred, and exhibit a chronic onset.²⁰ There is a bullous phase in both the cat and the dog which is transient,⁴ but lesions are rarely ulcerative.²¹ There may also be evidence of a chronic bacterial skin disease, but the condition is nonre-

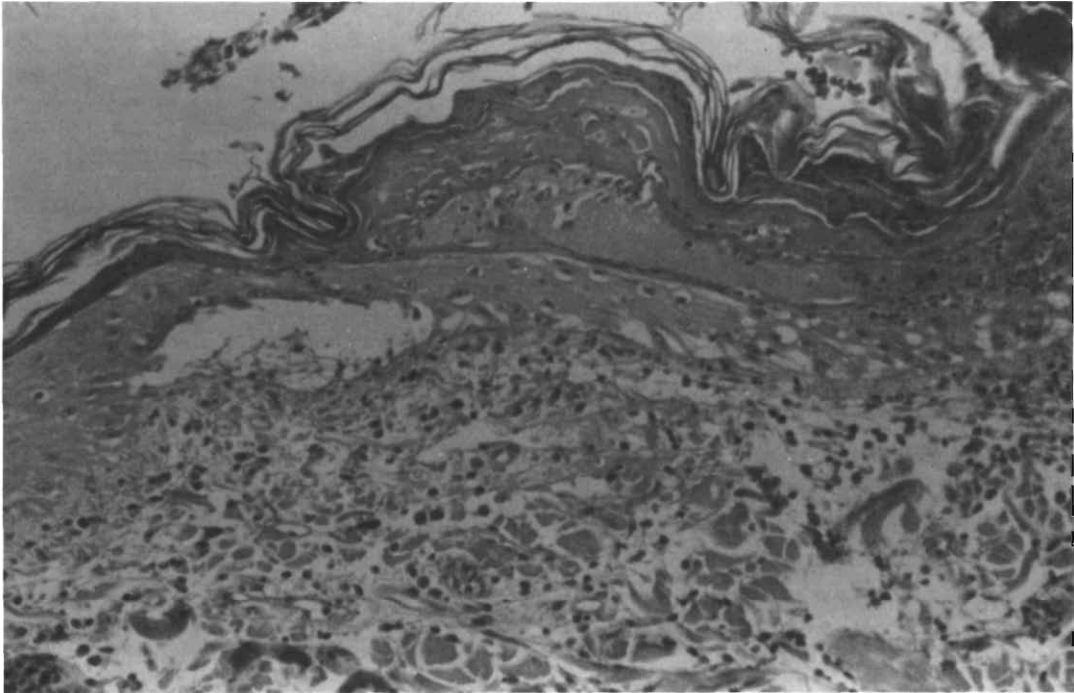


Fig. 2. Skin biopsy from a dog with SLE. Notice the hydropic degeneration of the basal cell layer and the dermal-epidermal cleft. ($\times 51$)

sponsive to antibiotics.⁴ Another form of the disease, discoid lupus erythematosus (DLE), exists in the dog. The lesions of DLE are usually confined to the nasal area and may have ulcerations of the tongue.¹⁹ However, in contrast to SLE, DLE is usually negative for both the antinuclear antibody (ANA) and lupus erythematosus (LE) cell tests, and involves no systems other than the skin.

Histopathologically, there is hyperkeratosis with keratotic plugging around the appendages.¹⁷ Hydropic degeneration occurs in the basal cells of the epidermis, and there is edema of the dermis with fibrinoid deposits around collagen. Extravasation of erythrocytes in the upper dermis may be seen as well as pigmentary incontinence.

Hematologic Signs: Immune-mediated thrombocytopenia (platelet factor 3 [PF-3] positive) may cause presenting signs such as petechiae and ecchymoses in skin and mucous membranes, hematuria, melena, and epistaxis.^{17,22} One study found that about 10% of dogs with autoimmune thrombocytopenia also had SLE (based on a positive LE cell test).²³ Platelet levels are decreased below 100,000 platelets/mm³ and megakaryocytes are very numerous in the bone marrow.²²

A more frequent SLE manifestation than

thrombocytopenia is autoimmune hemolytic anemia (AIHA),¹⁷ which is Coombs' positive. About 17% of dogs with AIHA have the condition as a consequence of SLE.²⁴ Of SLE reported in the cat, two cases have had AIHA and one has had thrombocytopenia as major signs.^{3,5,6} Animals with AIHA will show signs of weakness, pallor, and possible icterus.²² Spherocytosis, polychromasia, and reticulocytosis accompany the anemia.^{22,23} Hyperbilirubinemia, with more than 50% of the total serum bilirubin being unconjugated, may also be found. The plasma protein value will usually be normal or increased in these cases. A normochromic and normocytic anemia may also be seen in SLE. Approximately 70% of human SLE patients are afflicted with anemia resulting from chronic disease,⁴ and it is suspected a similar incidence is present in the canine.

Leukopenia may occur in SLE as a result of complement activation and the generation of chemotactic fragments.¹⁷ However, in lupus dogs with AIHA or with complicating infections, a leukocytosis with a left shift will be present.¹⁸

Renal signs: An immune-complex glomerulonephritis will reveal a proteinuria in the presence of a normal urine specific gravity, at least

early in the course of the disease before tubular function is involved. Hypoalbuminemia with subsequent edema formation may result. Histopathologically, thickening of Bowman's capsules and hyalinization of glomeruli are found.³

Fever: Many reports emphasize the presence of a fever (103–106°F).^{4,5,16,21} The fever may be intermittent or constant.

DIAGNOSIS

Diagnosis of SLE can be extremely challenging because of the variety of clinical syndromes that make up this disease. The diagnosis is based on clinical signs, clinical pathologic findings, pathologic abnormalities, serologic criteria and specialized immunologic tests. In man, SLE is diagnosed when a minimum number of diagnostic criteria, including clinical signs and laboratory findings, are detected. Several similar diagnostic schemes have been proposed to assist in diagnosing canine SLE. Other than employing several diagnostic criteria previously discussed, these diagnostic aids rely on specialized procedures that are discussed below.

The antinuclear antibody titer (test) is a procedure used to detect antibodies to a variety of nuclear antigens. This test is positive in a high percentage of clinical SLE cases, however the actual percentage of cases in which significant titers are reported varies from 40 to 100 depending on the study cited.^{4,18,25} Of the six reported cases of feline SLE, 50% have been ANA positive. The ANA titer is constant from day to day and is relatively corticosteroid resistant. If clinical remission is achieved, titers fall. Therefore, the ANA titer can be used as an indicator of disease activity. A high titer in a patient which has become clinically asymptomatic indicates disease exacerbation.⁴

To perform the ANA test, dilutions of serum from the suspected patient are applied over a substrate such as mouse layer cells.¹⁷ The preparation is then washed after a suitable incubation period. A fluorescein-conjugated anti-canine IgG serum is added, the system is incubated and the slide is then rinsed again. Both pattern of fluorescence (ring or speckled) and titer are obtained. Titers vary from lab to lab and also vary according to substrate used. Normal sera occasionally will have significant titers, therefore, the ANA test cannot be used as the only basis for diagnosis.⁸

The LE cell test is another major criterion used to diagnose SLE. The LE cell is a neu-

trophil which has engulfed nuclear material.³ A round structure representing the phagocytosed material is found in the cytoplasm of the neutrophil, compressing the nucleus to one side of the cell. Occasionally LE cells are seen in joint fluid from an animal with SLE, however it is primarily a laboratory phenomenon. The LE cell preparation requires much time and experience to perform.¹⁸ The procedure includes passing both serum and clot through a fine wire mesh.³ Collected material is then placed in a Wintrobe hematocrit tube and centrifuged for ten minutes at high speed. The buffy coat is used to make smears which are stained and examined for LE cells. A positive test is indicated when two or more LE cells are found.

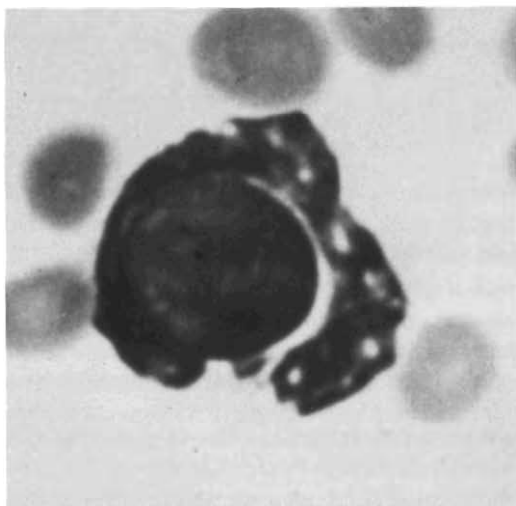


Fig. 3. Lupus erythematosus cell from a cat with SLE. (oil immersion)

The reported incidence of the LE cell phenomenon in naturally occurring SLE varies with different studies. In general 60–90% of SLE cases are positive.^{18,25} Four of the six reported cases of feline SLE were LE cell positive. The LE cell test is more specific for SLE than the ANA test.⁹ Unlike the ANA test, the LE cell test rapidly becomes negative with corticosteroid treatment.¹⁵

Direct immunofluorescence testing is a specialized procedure helpful in diagnosing SLE. Direct immunofluorescence (DIF) is used to detect immunoglobulin and complement deposited in the basement membrane zone at the dermal-epidermal junction or in the glomerular capillaries.⁹ When using DIF on skin, the test is referred to as the lupus band test. The lupus band test is a sensitive indicator of lupus ery-

thematous in lesional skin.⁴ Direct immunofluorescence of renal biopsy specimens will show a discontinuous granular deposition on the glomerular capillary loops.¹⁵ Direct, rather than indirect immunofluorescence, must be used in the dog since circulating autoantibody titers are low.⁹

Other immunologic criteria, although not specific for SLE, may aid the diagnosis by detecting autoantibodies directed at other tissues. These tests include the direct Coomb's test (anti-erythrocyte antibodies) and the platelet factor 3 test (for antiplatelet antibodies). A serum protein electrophoresis may detect an increase in the gamma globulin concentration which represents increased production of immunoglobulin.

TREATMENT

Treatment of SLE is centered around two categories of nonselective, nonspecific cell function modulating drugs, corticosteroids and cytotoxic agents.²⁶ Corticosteroids are used because they inhibit monocyte and macrophage function. Cytotoxic agents, on the other hand, are used to depress antibody production. When used together, the drugs exhibit a complementary action.

The drug of choice initially is prednisone or prednisolone at a dosage of 2–4 mg/kg body weight given orally and divided into two daily doses. The dosage is decreased as clinical signs go into remission. The decrease in dosage should be done by incrementally dropping the dosage by halves every two weeks until alternate day dosing is sufficient to maintain remission. Cessation of therapy may be attempted so long as the patient is monitored.²¹

Many cases will not respond to corticosteroids alone and will need cyclophosphamide or azathioprine in addition.²⁶ There are many acceptable treatment regimens. One regimen that may be followed is to use an oral dosage of 1.5–2.5 mg/kg of cyclophosphamide once for four consecutive days of the week. Azathioprine is administered at 2 mg/kg divided into two daily doses. Once remission is achieved, the prednisone dosage should be cut in half. If clinical signs subside for one full month, then azathioprine may be changed to an every-other-day regimen. If remission continues for an additional 2 to 4 months, cyclophosphamide and azathioprine may be discontinued completely. Prednisone may then be tapered off.

Patients with hemolytic anemia may require

splenectomy,¹⁸ since the spleen is the principle site of destruction of antibody-sensitized red cells and a major site of antibody production.²⁴ However, in dogs these two functions may be taken over by other sites and relapses will occur even in the face of splenectomy.²⁴ Some reports, nonetheless, show that as many as 50% of splenectomies performed in dogs will be successful in the treatment of AIHA.²² Splenectomy may also aid in the treatment of thrombocytopenia, although results are variable.²²

Since SLE has been associated with a loss of suppressor T-cell function, two drugs in addition to corticosteroids and cytotoxic agents, may be useful. Levamisole, because it is a T-cell modulator, may regenerate some of the lost T-cell function. Another drug which may regenerate regulation by suppressor T-cells is thymosin fraction V. This drug is derived from the bovine fetal thymus gland and will cross species barriers. Neither of these drugs has been reported to treat canine or feline SLE, although use of either drug could be attempted in a case which is nonresponsive to other therapy.

PROGNOSIS

Patients which are afflicted with hemolytic anemia and thrombocytopenia are the ones which will most often require cytotoxic agents and extensive therapy.¹⁸ However, most patients without these two syndromes will respond favorably to prednisone therapy and will remain in clinical remission for long periods of time. The principle prognostic component for SLE patients is the presence of glomerulonephritis.¹⁸ Many SLE patients with glomerulonephritis will progress into renal failure, and uremia will result in death.²²

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