ANIMAL MODEL OF HUMAN DISEASE

Systemic Lupus Erythematosus

Animal Model: Canine Systemic Lupus Erythematosus

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Clinical Features

Canine systemic lupus erythematosus (SLE) is a multisystem disorder characterized by the simultaneous or sequential development of hemolytic anemia, thrombocytopenic purpura, proteinuria, dermatitis and symmetrical polyarthritis. Young adult female dogs are most commonly affected. There is no known breed disposition for the disease, nor have instigating factors such as exposure to drugs, chemicals, sunlight or known infectious diseases been evident in the history of affected animals.[1,2]

The anemia is characterized by acute severe hemolytic crises accompanied by a positive direct antiglobulin (Coombs) test. Eluates prepared from affected red blood cells will sensitize normal canine erythrocytes to an indirect antiglobulin test, thereby confirming that an autoantibody is responsible for red cell destruction. Thrombocytopenic purpura often accompanies the hemolytic crisis and is characterized by the sudden onset of petechiae and ecchymoses in the skin and mucous membranes, hematuria, epistaxis and melena. To date, autoantibodies to either platelets or megakaryocytes have not been reported in affected animals. Consequently, it is probable that circulating soluble immune complexes, in which neither the antibody nor the antigen have a relationship to thrombocytes, are exerting a cytotoxic effect on platelets which results in purpuric bleeding. Persistent loss of urinary protein characterizes the nephritis present in this disease, and renal failure is a frequent cause of death. Recurrent, progressive, symmetrical polyarthritis of the peripheral joints imitates, in every respect, classic human rheumatoid arthritis.[3,4]

The most important serologic abnormalities of this disease in dogs include autoantibodies against nucleoprotein, DNA, RNA, DNA-histone complexes, thyroglobulin, IgG and erythrocytes. The lupus erythematosus (LE) cell test is highly specific for systemic lupus erythematosus in dogs and is frequently accompanied by a positive fluorescent test for antinuclear antibodies.[5]

Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR 00301 from the Division of Research Resources, US Department of Health, Education and Welfare, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

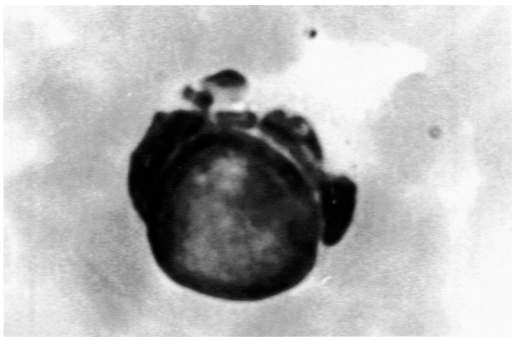

Fig 1—LE cell from a dog with canine SLE.

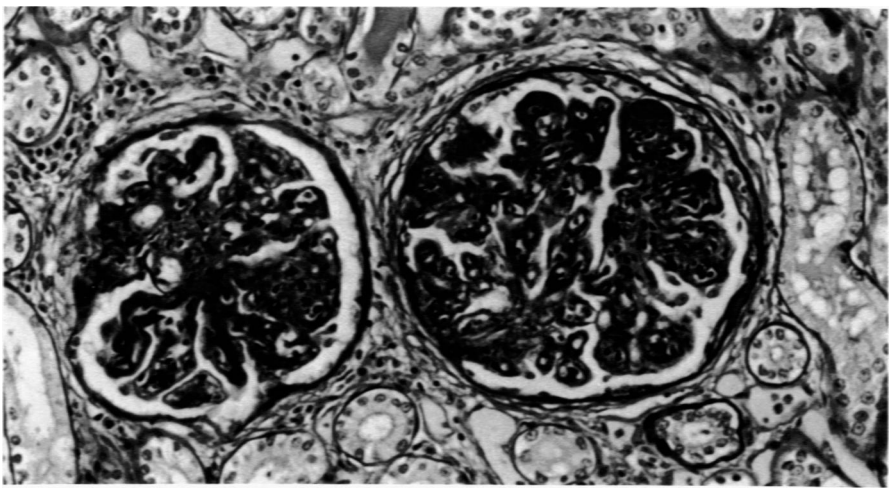

Fig 2—Chronic membranous glomerulonephritis in canine SLE. Primary lesion in the glomerulus, with thickening of capillary walls and deposition of PAS-positive material in the mesangium. Intratubular protein casts and periglomerular accumulations of plasma cells accompany the glomerular changes.

Pathologic Features

Thymic lesions, characterized by the presence of lymphoid follicles with well-developed germinal centers in the relatively acellular medullary portion of the organ, are frequently found in affected animals. These follicles may occur singly or appear as clusters, simulating the appearance of lymph nodes within the lobules of the thymus. The renal lesion is characteristic of chronic membranous glomerulonephritis, with thickening of glomerular capillary basement membranes and focal accumulations of lymphocytes and plasma cells around affected glomeruli. Not all glomeruli are affected to the same degree, but diffuse glomerulosclerosis eventually leads to progressive renal failure. Joints affected with the rheumatoid lesion are characterized by congestion and infiltration of the synovia by lymphocytes and plasma cells, focal necrosis of collagen, desposition of compact fibrin, and necrotizing vasculitis. Villous proliferation of the synovium and fibrovascular connective tissue into the joint space contributes to pannus formation

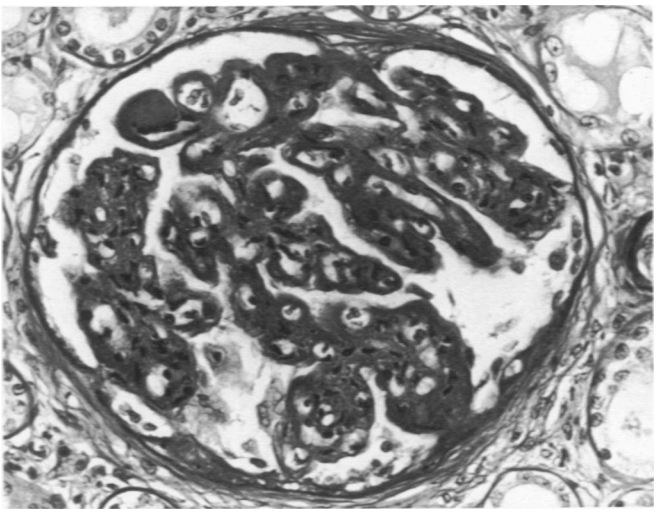

Fig 3—Chronic membranous glomerulonephritis in canine SLE with foci of acute glomerulitis and "wire loop" formation.

between opposing articular surfaces. Focal necrosis of articular cartilage produces a pitted articular surface to which fibrin tags are adherent, and subcondral bone resorption is associated with intraocceous fibrosis. In addition, fibrinoid lesions in small muscular arteries and acute focal necrotizing vasculitis may be found in other tissues.

Comparison with Human Disease

Canine SLE mimics, in virtually every respect, the clinical, serologic and pathologic features of the human disorder.[6,7] The familial instance of the human disease or its serologic markers[8-10] has led to a detailed genetic analysis of inbred offspring derived from dogs affected with SLE.[11] Data collected from more than 400 animals produced in this breeding program does not support the premise that canine SLE is solely due to an inheritable defect. On the contrary, it would appear that the genetic markers for this disease occur in response to the presence of a vertically transmitted viral agent. Further, cell-free filtrates prepared from asymptomatic seropositive dogs induce the formation of antinuclear antibodies when injected into newborn normal mice. Some recipient mice develop lymphoid tumors after the production of antinuclear antibodies; cell free filtrates from these murine lymphomas will, in turn, induce the formation of antinuclear antibody and positive LE cell tests in recipient newborn puppies.[12]

Availability

Canine SLE occurs in approximately 1 of every 5000 admissions to a veterinary hospital. A colony of dogs derived from affected animals has been established by Dr. Robert M. Lewis and members of this colony are available for study.

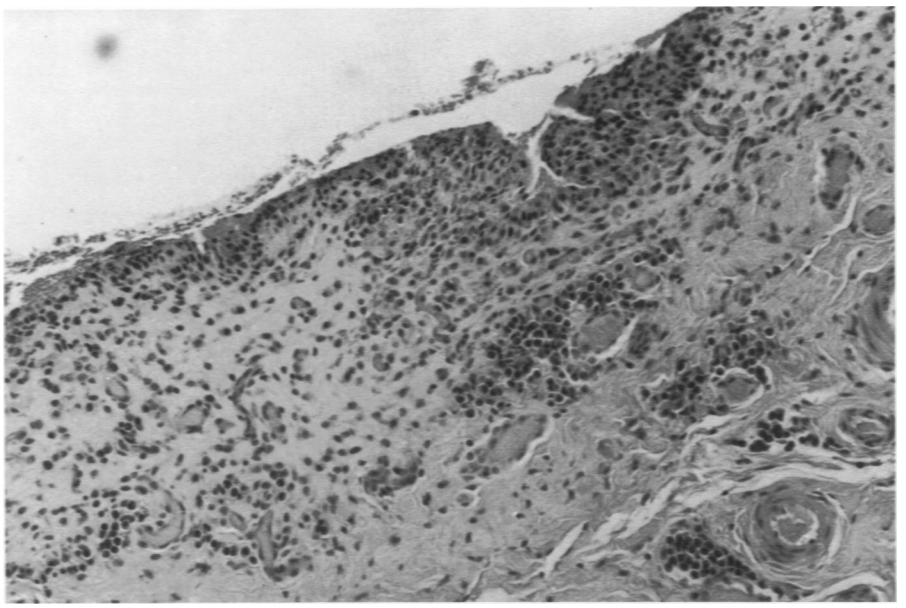

Fig 4—Synovial membrane from a dog with canine SLE and symmetrical (rheumatoid) polyarthritis. Proliferation of synovial cells, perivascular aggregates of lymphocytes and plasma cells, and deposition of compact fibrin on the articular surface are consistent features of the lesion.

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