CLINICAL MANAGEMENT

In humans, EBA is considered difficult to manage and typically requires more systemic glucocorticoid therapy. Colchicine is considered one of the initial treatments to add to glucocorticoids, and IVIG is considered a good option for resistant cases.26 One dog with EBA went into remission with combinations of glucocorticoids, azathioprine, colchicine, and a treatment with IVIG.26 This resulted in complete resolution, which was maintained after stopping therapy. Ten other cases were described; five were euthanized, but four went into remission with either prednisone alone (1-2 mg/kg every 12 hours) or with azathioprine or colchicine added. Over time, doses were tapered, and three dogs were withdrawn from therapy and stayed in remission for over a year of follow-up. The rapid progression, severe oral involvement, and generalized disease would explain why many cases were euthanized, but the results suggest aggressive combination therapy may be effective and, in contrast to many skin conditions, eventually result in a cure.

ACQUIRED JUNCTIONAL EPIDERMOLYSIS BULLOSA

This is a newly described variant of AJSBD reported in five dogs.3 All these dogs have IgG autoantibodies to laminin 332. Laminin 332, previously called laminin 5, epiligrin, and kalinin, is a main adhesion molecule of the basement membrane. The dogs’ clinical presentation resembled EBA, but none were Great Danes. They ranged from 0.8 to 8 years of age at onset, with no breed or age predilection apparent in this small number of cases. All had ulcers and vesicles. All cases had oral and ear lesions, four had paw lesions, and three had nasal or perinasal lesions.

All five dogs had acellular vesicles that contained erythrocytes, and three dogs had subepidermal neutrophilic inflammation. Two of the dogs with subepidermal inflammation had some eosinophils present. If the dogs appear clinically similar to BP and have anti-laminin 332 autoantibodies the name mixed auto-imune subepidermal blistering dermatosis was proposed.3

LINEAR IMMUNOGLOBULIN A DISEASE

Linear IgA disease (LAD), also called linear IgA bullous dermatosis, is an autoimmune blistering disease of humans. It is characterized by IgA and sometimes IgG autoantibodies against processed extracellular components of collagen XVII. This includes a 120-kD protein named LAD-1 or a smaller 97-kD portion. The lesions affect the skin and sometimes mucosa. There is one report of two dogs that meet the criteria for the diagnosis of LAD in humans; they both had IgA antibodies against LAD-1.28 A 3-year-old spayed female Labrador retriever cross and 4-year-old castrated male Briard presented for predominantly ulcerative lesions that affected the oral cavity and footpads in both dogs. Erosions and crusted lesions were seen, but vesicles and bullae were not reported. In addition, there were some cutaneous lesions that involved skin sites subjected to trauma, such as the axillae, sternum, groin, and extremities. Histologic examination revealed mixed inflammatory, hemorrhagic, subepidermal vesicles without eosinophils. Direct immunofluorescence showed that vesicles occurred above collagen IV. Canine salt-split skin showed the IgG or IgA autoantibody-labeled antigen located on the basal aspect of the epidermal side of the artificial clefts. Circulating IgA and IgG autoantibodies targeted the 120-kD linear IgA bullous dermatosis antigen (LAD-1) of the extracellular processed portion of collagen XVII. Treatment results were not reported.

LUPUS ERYTHEMATOSUS

LUPUS ERYTHEMATOSUS IN MAN

Lupus erythematosus encompasses a varied spectrum of disease processes affecting man, united by the presence of a spectrum of immunologic abnormalities. The classic prototype is systemic lupus erythematosus, or SLE, which is the most serious manifestation and is associated with a variety of potentially fatal internal diseases. The overall prevalence is reported to range from 12 to 50.8 cases per 100,000 persons in different countries.216 In addition, and not included in these data, are a large number of variants, some well defined and others less so, that have wide-ranging morbidities and mortalities. The following discussion on its etiology and pathogenesis is based predominantly upon research findings in SLE in man, which in turn is compared with the current knowledge in the dog and cat.

Classically, lupus can be considered as resulting from the effects of three triads at three different levels that have been referred to as three troikas, named after the three-horse Russian carriage,221 in that each horse pulls independently, but with each contributing to the final outcome. The three troikas, with their contributing factors are listed in Box 9-1.

ETIOLOGY IN MAN COMPARED TO ANIMALS

The etiology of SLE comprises genetic, hormonal, and environmental factors. That genetic factors are evident in man comes first from a study of monozygotic and dizygotic twins in which it was shown that concordance for the disease in the former was eight times greater than in the latter.214 That it was still not 100% can be accounted for by variability in environmental triggers. The mode of inheritance, however, appears to be exceedingly complex, with a number of different loci linked to increased disease susceptibility.216-218

In genetic studies in the dog, one first looks for evidence of breed susceptibility, and in two studies a breed predisposition for the German shepherd dog has been shown.219,220 Three attempts have been made to develop breeding colonies. The first of these was established by Lewis and Schwartz in the United States from the mating of two dogs with spontaneous SLE. Despite the incidence of high ANA titers, it was 10 years and 5 inbred generations before any evidence of SLE emerged.221 Another more successful attempt was made by Monier et al. in France from the mating of an affected German shepherd dog with a Belgian shepherd.222 The incidence of ANA and clinical signs increased with each inbred generation, and by the third, 5/6 dogs had positive ANA titers, and 4/6 had clinical signs

Box 9-1 Etiopathogenesis of Systemic Lupus Erythematosus: The Three Troikas

<table>
<thead>
<tr>
<th>Etiology</th>
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<tbody>
<tr>
<td>Genetic factors</td>
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<td>Hormonal factors</td>
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<td>Environmental factors</td>
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<table>
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<th>Etiopathogenesis</th>
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<td>T-cell dysfunction</td>
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<tr>
<td>Polyclonal B-cell activation</td>
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<td>Cytokines</td>
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<th>Pathogenesis</th>
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<td>Immune complex-mediated damage</td>
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<td>Direct damaging effects by autoantibodies</td>
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<tr>
<td>Functional effects of autoantibodies</td>
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compatible with SLE. Hubert et al. investigated another colony of German shepherd dogs that were being bred for show and sale. Here, a deliberate attempt was made to outbreed, and the incidence of ANA and clinical signs decreased with each generation.233 One study of canine SLE showed an association with DLA-A7,234 and another interesting study examined major histocompatibility complex (MHC) class I polymorphism in Nova Scotia duck tolling retrievers who develop an SLE-like disease characterized by polyarthritis and meningitis/arteritis with frequently positive ANA tests. Significant associations were found with certain haplotypes.235 More recent studies on this highly inbred breed used a genome-wide association approach, which identified five loci on chromosomes 3, 8, 11, 24, and 32 that were strongly associated with the disease.236 That genetic factors are involved in canine SLE is thus clear, although the disease cannot be ascribed to genetic influences alone.

A hormonal influence is evident from the fact that in humans, lupus occurs predominantly in young adult women, with a female-to-male incidence ratio of 8:1 to 15:1, depending upon the age group.237 Further evidence of a hormonal influence comes from a study of the New Zealand black/New Zealand white F1 hybrid mouse model (NZB/NZW), which spontaneously develops an SLE-like disease. The onset of disease and concomitant immunologic abnormalities is accelerated by estrogens and retarded by androgens and antiestrogens.228,229

Whether or not a sex bias exists in canine SLE is controversial. Many female dogs are, of course, spayed, and the exact proportion of intact and spayed animals reported in studies is not always noted. Additionally, some males may be castrated. In fact, the two largest studies have shown a male bias.205,221 Only one study has noted a female bias, and in this report 23/30 affected animals were female.229 Some doubts exist as to the validity of these data, because some animals did not satisfy the currently accepted diagnostic criteria.

The third consideration regarding etiology is that of environmental influences. The influence of UV light can clearly both initiate and aggravate clinical signs in man. It is hypothesized that in genetically susceptible individuals, both UVA and UVB cause nuclear damage to basal cells, leading to nuclear antigen expression on the cell surface. In turn, this induces both antibody and cell-mediated damage to epidermal cells, leading to apoptosis and cell death. This then leads to a lymphohistiocytic infiltrate and immunoglobulin deposits at the dermoeidermal junction. It is also appropriate to consider drug-induced lupus under this heading. Many drugs are known to cause lupus-like symptoms in man, including isoniazid, phenytoin, procainamide, chlorpromazine, and the antihypertensive drug hydralazine, the latter being the most potent in inducing classic signs of SLE.230,231 Finally, there is the possible role of infective agents. There is a remarkably high level of Epstein-Barr virus infection in young patients with SLE,232 and a possible role for other viruses has been proposed. In support of a role for an infective agent is the observation of much higher levels of DNA binding (i.e., ANA) in sera of scientists working in laboratories that process sera from patients with SLE than in the general population.234

UV light exposure in animals is also believed to have a contributory role. Certainly, the distribution of skin lesions in SLE and in discoid lupus shows a predisposition for sun-exposed areas, and the therapeutic benefits of restriction from sunlight exposure both argue for such a role, although controlled studies are lacking. Similarly, although adverse drug reactions in dogs sometimes mimic the cutaneous signs of SLE, reports are largely anecdotal, and although hydralazine has been shown to induce ANA in beagles, no adverse signs resulted.235 Of great interest, however, is the lupus-like syndrome produced in hyperthyroid cats following treatment with propylthiouracil.236 In experimental studies, 53% of cats became ill following administration of 150 mg daily. Clinical signs included weight loss, lethargy, lymphadenopathy, a Coombs-positive anemia, and positive ANA titers.237 Interestingly, administration of propylthiouracil was without effect, implying that the sulfur atom is crucial in this effect. It appears that all drugs that induce lupus-like syndromes in man and animals have one feature in common: the ability to interact in vitro with DNA or nucleoproteins, thus rendering them more antigenic.235

Canine studies have also implicated a possible role of infective agents. Cell-free extracts of spleens from the offspring of dogs with SLE were injected into puppies, mice, and rats.238 The puppies and mice (but not the rats) later developed positive ANA titers. Some of the mice developed lymphomas, and cell-free extracts from these were able to induce positive ANAs in puppies following injection. None of these animals, however, developed overt SLE. The occasional finding of normal animals with high titers of ANA, together with anecdotal reports of clusters of both dogs and cats with high titers are also supportive of the existence of an infective agent.

Much controversy has existed over the years as to whether any putative infective agent can cross the species barrier from man to dog or vice versa. Many of the studies that implicated transmission of an infective agent from dogs were either anecdotal or poorly controlled,239,240 despite publication in highly reputable journals. For example, one described two dogs that lived in the home of a rheumatologist whose mother-in-law had suffered from SLE for over 35 years. One had clinical signs compatible with SLE and a positive ANA. The other also had a positive ANA and purportedly had ocular Sjögren syndrome, a well-defined immune-mediated disease of man accompanied by keratoconjunctivitis.241 Limited but well-controlled studies that involved serologic testing of a number of lupus-associated autoantibodies failed to detect significant differences between sera from dogs in households with one or more lupus patients and the general population.242,243 A study from Taiwan has reopened the question, however, and provided evidence of a transmissible agent that can pass from man to dog.244 This study involved clinical and serologic examinations of 59 dogs owned by 37 patients with SLE. 187 randomly selected pet dogs owned by healthy people, and 650 dogs seen as outpatients at a University Teaching Hospital. The incidence of positive ANA among the three groups was 18.64%, 4.81%, and 5.23%, respectively. SLE in the canine patients was diagnosed strictly according to the recently accepted criteria, and this revealed 3 cases from the 59 dogs living in lupus households (5.08%), none from among the 187 pets from non-lupus households, and 6 (0.92%) from among the 650 outpatients. The incidence of ANA was significantly greater in the dogs from lupus households than the other two groups (P = 0.001 for both by χ²), as was the incidence of clinical SLE (P = 0.013 and 0.032 by two-sided Fisher exact test) respectively. The prevalence of SLE among pet dogs of SLE patients was estimated at 508 per 10,000, as compared with the estimated incidence in the general U.S. population of 27 per 100,000.245 Thus persuasive evidence was provided of infectivity that can pass from man to dog. The question of whether the reverse can occur must await results of further studies.

**PATHOGENESIS**

Hallmarks of the immune dysregulation that accompanies SLE can be categorized under T-cell dysfunction, polyclonal B-cell activation, and abnormalities in cytokine profiles and function, and these can be considered the second triad.

Lymphopenia is a feature of SLE and parallels disease activity.246 T cells, especially the cytotoxic/suppressor CD8⁺
cells, are primarily affected, with relatively normal helper CD4+ activity. In turn this is associated with lymphocyte-toxic autoantibodies of varying specificity. Perhaps for this reason, lymphocytes from SLE patients exhibit enhanced spontaneous apoptosis, which in turn releases more nuclear antigens, which then upregulates the antinuclear antigen responses. Recently the importance of a T-cell subset that is CD4+ and CD8− has been recognized as specifically enhancing production of pathogenic autoantibodies. Cytotoxic functions, both those resulting from natural killer (NK) cells and antibody-dependent cytotoxicity, are defective in SLE, which would lead to defective elimination of any possible viral agent. Since the recent identification of regulatory T cells (T-reg cells), which are CD4+, CD25+, and express forkhead box P3 (Foxp3), much research has focused on their role in SLE with conflicting results. Most have shown a reduction both in the numbers and suppressor function in active, untreated disease as compared with inactive disease, although the abnormalities may normalize after corticosteroid treatment. Others have either failed to find significant differences between SLE patients and normals, or have actually shown an increase of the subset. Yet another study showed normal levels but demonstrated that they were dysfunctional under the influence of interferon (IFN)-α from antigen-presenting cells. This area is thus highly controversial. The discordant results may reflect differences in patient selection or experimental methodology. Less controversial is the issue of B-cell function. Indeed the main immunologic event is B-cell overactivity, with a significant increase over normals in the number of spontaneously secreting B cells. This results in the characteristic hypergammaglobulinemia, and polyclonal activation engenders production of the plethora of autoantibodies associated with the disease. The immune response is also somewhat skewed toward a Th2 rather than a Th1 response. This may be reflective of the overproduction of IL-10 by SLE patients, which is suppressive both to IL-1 and IL-2 and favors Th1/2 polarization.

One in-depth study of T-cell subsets in dogs has shown significant abnormalities. Animals in the active stage of the disease were strikingly lymphopenic, with mean counts of 1050 x 10⁶/liter as compared with 2013 x 10⁶/L in controls. CD4+ and CD8+ cells in the affected animals comprised 56.7% and 10.9%, respectively, as opposed to 40.5% and 18% in controls. This translates to a very striking reduction in CD8+ cells. Treatment with prednisone and levamisole not only induced clinical remission but also normalized the CD4+CD8+ ratio. As yet there have been no studies of T-reg cells in canine SLE.

As a result of the immune dysregulation noted in the discussion of etiopathogenesis, which in turn is under the influence of the genetic, hormonal, and environmental factors alluded to, a plethora of autoantibodies develop. The diversity of these antibodies, and the fact that they tend to be broadly cross-reactive with other autoantigens to varying extents, accounts for the wide diversity that is the clinical spectrum of SLE. No two cases are the same. These autoantibodies can cause damage to the tissue bearing the inciting autoantigen or cross-reacting autoantigen(s) directly, or they can interfere with the function of the antigen; alternatively, damage can result from immune complex deposition and complement activation.

The hallmark of SLE in man is the presence of antibodies to double-stranded DNA (dsDNA), although antibodies against numerous other nuclear proteins also are seen. Not only do anti-dsDNAs lodge in the renal glomerulus via the normal filtration mechanism, but in some instances they have been shown to cross-react with constituents of the glomerular basement membrane, including heparan sulfate and laminin. The latter could also account for the preferential deposition in the BMZ of the skin. It is also the case that DNA free in the circulation may bind to tissues and thus attract anti-DNA antibody. Because laminin is one such protein to which DNA binds readily, this could also account for deposition of antibody in the basement membrane of the skin.

Other autoantibodies commonly associated with SLE in man are the heterogeneous lupus anticoagulants and antiphospholipid antibodies. Lupus anticoagulants are defined as immunoglobulins that interfere with in vitro phospholipid-dependent tests of coagulation. They were originally described in SLE patients with bleeding tendencies. Paradoxically, the abnormality is associated most commonly with thrombotic tendencies, and this is associated with the presence of antiphospholipid antibodies. The latter are themselves heterogeneous, and most are directed against phospholipid complexes with plasma proteins, especially β₂-glycoprotein 1. These antibodies are probably responsible for many cases of thrombocytopenia and hemolytic anemia seen in SLE, and possibly also with the commonly encountered leucopenia.

The spectrum of antinuclear antibodies encountered in canine SLE is discussed later under Diagnosis. Veterinary patients are not routinely screened for antiphospholipid antibodies and/or lupus anticoagulant, and only one case each in a dog and a cat have been reported. The potential pathogenicity of autoantibodies against heparan has been directly demonstrated by a study in which an SLE-like disease was induced in 8 dogs by injections of 200 µg of heparan sulfate from bovine kidney in adjuvant. All developed skin disease typical of canine SLE, with linear basement membrane deposits of immunoglobulin, glomerulonephritis, and 3/8 developed joint disease.

Another interesting recent study demonstrated the presence of autoantibodies in dogs with SLE directed against the T-cell co-stimulatory molecule CILA-4, which the authors proposed could be a driving force in modulating the immune response in the disease.

CLINICAL SPECTRUM

The spectrum of the skin lesions associated with lupus erythematosus in man has recently been redefined by Sontheimer. Although many of the entities described have yet to be identified in animals, it is recommended where possible that these criteria be adopted when reporting the various syndromes.

SYSTEMIC LUPUS ERYTHEMATOSUS IN THE DOG

SLE is a multisystem disease in which the varying signs may commence in varying combinations and at varying times. The appearance of one or more signs simultaneously generally implies a poorer prognosis. There are no age predilections and probably no sex predisposition, as discussed earlier. There is a convincing breed predisposition for the German shepherd dog. Onset is generally insidious, although acute hematologic signs may develop, which may lead the clinician to overlook milder and more chronic signs. The reported incidence of the different clinical signs is highly variable, probably reflective of the bias of the individual clinician.

CLINICAL FEATURES

DERMATOLOGIC SIGNS

Skin lesions are seen in some 40% to 50% of cases. The appearance is highly variable and ranges from trivial, mild alopecic scarring lesions to widespread ulceration (Fig. 9-21). Symmetry of the lesions is often a striking feature. Some present
with a pruritic seborrheic dermatitis, and in others mucocutaneous ulceration is seen, which may spread to involve other parts of the body. Loss of pigment from the nose or periocular region may be seen, as may erythema, ulceration, and crusting of the nose that is typical of discoid lupus erythematosus. Focal areas of alopecia are often noted that may extend to involve large areas. In some cases, lesions appear largely restricted to the hairless light-exposed areas, and photosensitization appears to be involved. Focal ulceration of the footpads suggestive of a vasculitis may occur, as may more diffuse crusting pad lesions (Fig. 9-22).

Two recently reported cases have presented unusual findings. Vesiculation and ulceration are not generally major features, but a 4-year-old castrated male bichon frisé was described as showing severe erosive lesions of the right elbow, axilla, and lateral thorax. Histopathology revealed a noninflammatory subepidermal cleft, and immunologic studies showed circulating anti-basement membrane antibody, which bound with the NC1 domain of recombinant human type VII collagen. Other clinical signs were a Coombs-positive anemia, thrombocytopenia, pleuritis, hepatitis, and a persistent proteinuria suggestive of glomerulonephritis. The authors proposed that this represented the canine equivalent of type 1 bullous SLE of man. In the other case, the patient presented with a Coombs-positive anemia, thrombocytopenia, and polyarthritis with an ANA titer of 12,240. Instead of cutaneous signs of SLE, however, there were clinical, histologic, and immunologic features of pemphigus foliaceus. This appears to be a case of concomitant SLE and pemphigus—a phenomenon noted occasionally in man. The dog subsequently developed lymphoma.

JOINT DISEASE

Overall, this is the most common presenting sign in canine SLE, affecting 40% to 90% of patients. The distinction from other types of immune-mediated polyarthritis is not always easy. In a study from western Canada, 17/83 cases presenting with polyarthritis of immunologic origin were accorded a final diagnosis of SLE. The arthritis is generally symmetrical, multarticularg, nondeforming, and nonserosive. Onset may be sudden or insidious, and although the affected joints are swollen and painful, radiographic changes are minimal apart from soft-tissue swelling. In advanced cases, involvement may extend to the temporomandibular joints.

HEMATOLOGIC CHANGES

Anemia is evident in some 30% to 60% of cases. These can be either immune mediated with a positive Coombs test, or an anemia of chronic disease, in approximately equal proportions. Thrombocytopenia, evidenced by petechial or ecchymotic hemorrhages, bleeding from any of the natural orifices, or excessive bleeding following surgery is seen in some 10% to 25% of cases. Leucopenia or leucocytosis is seen with approximately equal frequency in 20% to 30% of cases, but only the former is of relevance in making the diagnosis. In most instances, any leucopenia is the result of severe lymphopenia.

GLOMERULONEPHRITIS

Profuse proteinuria is evident in some 50% of cases, and this may proceed to azotemia and renal failure. Renal biopsies usually reveal a proliferative membranous glomerulonephritis, and direct immunofluorescence or immunohistochemistry reveals deposits of immunoglobulin and complement.

ULCERATIVE STOMATITIS

This may involve the buccal mucosa, the hard or soft palate, or more rarely the tongue, and is seen in 10% to 20% of cases. Histopathologic findings are similar to those seen in the skin of affected patients.
SEROITIS
Pleuritis or pericarditis is seen in 5% to 10% of cases, but when involvement is minor, these changes may escape detection, and hence the incidence may be underestimated.

NEUROLOGIC ABNORMALITIES
Convulsions, behavioral changes, or evidence of a polyneuropathy (e.g., hyperesthesia) is seen in a small proportion of cases.25,27

OTHER LESS SPECIFIC SIGNS
Fever is present in some 60% to 90% of cases, although this may be cyclical and thus escape detection. Characteristically it is not antibiotic responsive, but responds briskly to corticosteroids. Symmetrical mild to moderate lymphadenopathy and splenomegaly are often observed.

SEROLOGIC FINDINGS
SLE is classically associated with autoantibodies to nuclear antigens, and many clinicians maintain that a definitive diagnosis is not tenable in the absence of such evidence. A number of techniques are available for their demonstration, and the varied specificities have differing significance.

LE CELL PHENOMENON
In earlier studies, this test employing either heparinized or clotted blood was the most widely employed. It is based on the ability of antinuclear antibodies to opsonize free nuclear material for phagocytosis by neutrophils to yield the classic LE cell, which is a neutrophil containing an engulfed mononuclear cell nucleus. Indeed, spontaneous LE cells are occasionally encountered in joint taps of dogs with SLE-associated arthritis, and may even be found in conditions unrelated to SLE, such as lesions from deep pyodermas. A perceived lack of sensitivity has led to abandonment of this test.

ANTINUCLEAR ANTIBODY BY IMMUNOFLUORESCENCE
This is the preferred test for routine use. Substrates employed have included mouse leukocytes, mouse and rat liver, and various tissue culture cell lines, particularly HeLa and Hep-2 cells (Fig. 9-23). The reported sensitivity varies between laboratories and with the substrate employed. In reporting results, both the titer and staining pattern must be documented.

Positive titers, even at high levels, may be found in sera from normal dogs and from dogs with miscellaneous disease states. In a study of sera from 100 normal dogs sampled at the time of presentation for routine heartworm prophylaxis, four were positive at greater than 1/40, with two showing titers of 1/320.280 Very interesting are reports of clusters of normal animals showing high ANA titers. A line-bred colony of English cocker spaniels was investigated following the diagnosis of SLE in one animal. Of 58 normal dogs in the kennel, 46.5% had positive titers as compared with 0/25 from a control kennel.281 A relatively high incidence of positive ANAs is also seen in a number of chronic diseases of microbial or parasitologic etiology. In one study, 10% to 20% of sera from animals seropositive for Bartonella vinsonii, Ehrlichia canis, and Leishmania infantum had positive ANA titers.282 The latter is of great importance because the dermatogetic signs associated with leishmaniasis are strikingly similar to those seen with SLE.

A number of patterns are seen, including homogeneous coarse or fine speckled (Fig. 9-23, A), homogeneous/speckled, membrane (Fig. 9-23, B), and nucleolar (Fig. 9-23, C), the latter being less specific for SLE and more suggestive of unclassified immune-mediated disease. One study suggested that a homogeneous pattern is seen most commonly with multiple organ disease, including hematologic abnormalities, whereas a speckled pattern more frequently accompanies cases of lupus arthritis.283

SPECIFICITY OF ANTINUCLEAR ANTIBODIES
Classically, ANA in man has activity against dsDNA. Early canine studies suggested that this held true for the dog, but it
was later shown that the standard precipitation assay under-
taken for anti-dsDNA in man (the Farr assay) routinely yielded
false-positive results. This was shown to be due to the presence
in canine (and feline) sera of an acidic β-globulin that binds
nonspecifically to DNA. Subsequent studies using ELISA
techniques with highly purified DNA and also indirect immu-
nofluorescence employing *Crithidia luciliae* whose kinetoplast is
composed of dsDNA confirmed that very few cases of classical
canine SLE have demonstrable anti-dsDNA antibodies. Thus,
testing for anti-dsDNA is no longer employed. Also, the
measurement of antibodies to single-stranded DNA is of no
value, with reactivity seen in sera from a multiplicity of
diseases.

Histones are nucleoproteins associated with DNA, and the
presence of antihistone antibodies is highly correlated with a
positive diagnosis of SLE. In one study, 71/100 sera from dogs
fulfilling four or more criteria for SLE showed positive results,
compared to only 6.7% of normals. The majority of sera recog-
nize H4 and/or H3, with a smaller proportion recognizing H2A
and H2B. This contrasts with the situation in man, where H1
and H2B are the dominant autoantigens. Other sera detect
ribonucleoprotein or the associated Sm antigen to cytoplas-
ic antigens Ro/SSA and La/SSB, and most importantly to
heterogeneous nuclear ribonucleoprotein G (HnRNP G). In
earlier publications, this was termed type 1, or T1. This
antibody specificity appears to be uniquely canine, is the most
specific marker for canine SLE, and the antigen has been pre-
pared in recombinant form.

**DIAGNOSIS**

Histopathology classically reveals a lichenoid or hydropic inter-
face dermatitis that hags the dermoeipidermal junction and may
extend to the hair follicle and outer root sheath. Apatosis of
basal or suprabasal cells may occur, as may subepidermal vacu-
olar alteration, with focal thickening of the basement mem-
brane and pigmentary incontinence. Subepidermal vesicles,
leukocytoclastic vasculitis, and occasionally a lupus panicula-
tis are also encountered.

Direct immunofluorescence or immunohistochemistry in
most cases reveals linear deposits of immunoglobulin and com-
plement at the dermoeipidermal junction (Fig. 9-24).

The onset of SLE is generally insidious, and the clinical
signs can appear in random associations and in random order
over months or years. The diagnosis of SLE is not an easy one.

![Linear deposits of immunoglobulin (Ig)G at the dermoeipider-
mal junction in a case of systemic lupus erythematosus.](image)

**Table 9-4** Criteria for Diagnosis of Canine Systemic Lupus
Erythematosus*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Erythema</td>
<td>Redness in areas of skin that are thin or poorly protected by haircoat (particularly face)</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Depigmentation, erythema, erosions, ulcerations, crusts, and keratotic scaling that selectively affect the face (e.g., nasal planum, forehead, lips, and periocular region)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Rash resulting from an unusual reaction to sunlight</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration; usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized mainly by pain during movement (progressive forced flexion-extension); swelling or effusion are often not very marked</td>
</tr>
<tr>
<td>Serositis</td>
<td>Presence of a nonseptic inflammatory cavity effusion (pleuritis or pericarditis)</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>Persistent proteinuria (&gt;0.5 g/L or &gt;3+ if quantification is not performed) or cellular casts (red blood cell, hemoglobin, or mixed)</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>Seizures or psychosis in the absence of offending drugs or known metabolic disorders (e.g., uremia, ketoacidosis, or electrolyte imbalances)</td>
</tr>
<tr>
<td>Hematologic disorders</td>
<td>Hemolytic anemia (with reticulocytosis) or leukopenia (&lt;3000/mm³ total on two or more occasions) or lymphopenia (&lt;1000/mm³ total on two or more occasions) or thrombocytopenia (&lt;100,000/mm³ in the absence of offending drugs)</td>
</tr>
<tr>
<td>Immunologic disorders</td>
<td>Antithione (antibody to histone at an abnormal titer) or anti-Sm (antibody to the Sm nuclear antigen) or anti-γ type 1 (antibody to a 43-kD nuclear antigen) or T-cell subsets (striking decrease in CD8 population &lt;200/mm³) or a CD4+:CD8: ratio &gt; 4.0)</td>
</tr>
<tr>
<td>Aminuclear antibodies (ANAs)</td>
<td>Abnormal titer of ANAs shown by immunofluorescence or an equivalent assay in the absence of drugs known to be associated with their formulation</td>
</tr>
</tbody>
</table>

*Adapted from the 1982 revised American Rheumatism Association Criteria,
serologic abnormalities may precede the onset of clinical signs by some years.222

**CLINICAL MANAGEMENT**

The wide clinical spectrum encountered in this disease means that no two cases are the same, and thus the treatment has to be individualized for each case. Oral glucocorticoids are the mainstay of the approach and are given initially in high doses, such as 2 to 4 mg/kg of prednisolone or equivalent doses of other glucocorticoids. In acute cases, concomitant cytotoxic drugs such as azathioprine or chlorambucil are given, with the dose of glucocorticoids reduced by some 50%. If immune-mediated anemia is present, intravenous cyclophosphamide may be selected and followed up by oral dosage. Where there is immune-mediated thrombocytopenia, some clinicians advocate the use of vincristine. The disease has an unpredictable course and may wax and wane. Caution is required to avoid overtreatment.

Plasmapheresis has been employed in treating four dogs that were refractory to conventional treatment, with three having a good response lasting from 1 to 6 months, and a marked fall in ANA titer.179 There was also a rise in total hemolytic complement, indicating a reduction in immune complexes, and perhaps also indicating a pathogenic role in these cases.

Most impressive have been the reports from France of using a combination of prednisone and levamisole,219 a combination that might appear paradoxical. In a comparative study, one group of affected dogs was given prednisone alone at 1 to 2 mg/kg, which was tapered once control was effected. The second group received the same dose of prednisone supplemented with 3 to 7 mg/kg of levamisole on alternate days. The first group continued to receive prednisone for maintenance, whereas in the second group, prednisone was discontinued and levamisole alone used when and if there was recrudescence of clinical signs. The first group always responded well but relapsed when the prednisone was withdrawn. However, where combined therapy was employed, prolonged remission occurred in over 50% of cases, and when there was a relapse, levamisole alone was effective in inducing remission again.219 The treatment also resulted in elimination of the lymphopenia and normalization of the CD4:CD8 ratio.

The prognosis for long-term survival is guarded, although some cases are maintained for many years on low doses of the appropriate drug. Most of the cases in the French study were presented with joint disease, and follow-up of greater numbers with hematologic signs is needed to assess the long-term efficacy of the combination therapy.

In a study from Korea, gene therapy aimed at the CTLA-4 ligand on activated T cells was employed in treating the lupus-like disease induced by immunization with heparan sulphate.280 Dramatic improvement resulted, and it will be very exciting to see if similar results are obtained in the spontaneous disease.

**SYSTEMIC LUPUS ERYTHEMATOSUS IN THE CAT**

Although it is clear that an SLE-like disease occurs in the cat, the paucity of reported cases has precluded the in-depth investigations that have been undertaken on the canine condition. Apart from one series of 11 cases,268 most reports have detailed one or two cases only.296-301 That satisfied the diagnostic criteria to varying extents.299 The last of these was presented with symmetric dermatitis, thrombocytopenia, and an ANA titer of 1:160.300 This case later developed ulceration of the hard palate, justifying a diagnosis of definite SLE. Another case was of interest in that it had lupus anticoagulant in addition to hemolytic anemia, thrombocytopenia, probable neurologic disease, and an ANA titer of 1:4096—but still only satisfying three criteria and justifying a diagnosis of probable lupus.267 A further report identified three cases of definite SLE through ANA screening undertaken at the University of Florida.302

**CLINICAL FEATURES**

Some 50% of cases show dermatologic manifestations, including generalized seborrheic skin disease, exfoliative erythroderma, and erythematous crusting and scaling lesions, usually symmetrical and most commonly involving the face and ears. Glomerulonephritis and hemolytic anemia were evident in about half of the reported cases, and of interest is the fact that neurologic signs are seen more commonly than in the dog and similarly affect some 50% of cases. Fever is sometimes noted, although not with such regularity as reported for the dog, and lymphadenopathy, thrombocytopenia, and buccal or mucocutaneous ulcers are sometimes noted.

**DIAGNOSIS**

In the absence of any evidence to the contrary, it is proposed that the same diagnostic criteria used for the canine disease are applied to feline SLE. There are no data on the specificity of ANA activity, but it is important to note that animals suffering from some of the feline viral diseases have been reported to show high titers.302 Histopathology of typical skin lesions in feline SLE should reveal that same interface dermatitis with basal cell apoptosis and pigmented incontinence that are noted for the dog.301

**CLINICAL MANAGEMENT**

Corticosteroids represent the cornerstone of the therapeutic approach to feline SLE, supplemented if necessary by chlorambucil or cyclophosphamide, the latter usually for short periods. The paucity of cases does not permit accurate statements to be made as to the prognosis, which is probably guarded.

**DISCOID LUPUS ERYTHEMATOSUS**

**CANINE**

Discoïd lupus erythematosus (DLE), also referred to as cutaneous lupus erythematosus, is a relatively benign disease in which systemic manifestations are absent.303,304 In one study, 0.3% of canine cases presented to Cornell University Dermatology Clinic were accorded this diagnosis.403 This may be an underestimate because the condition is believed to be more common in sunnier climates, reflecting the fact that most cases are exacerbated, or possibly induced, by UV light exposure. It seems likely that most if not all cases that were previously diagnosed as “collie nose” or “nasal solar dermatitis” in fact represent either DLE or pemphigus erythematosus, and many clinicians now question the existence of the former two as clinical entities.

**CLINICAL FEATURES**

Clinical signs commence initially as depigmentation of the nose, which takes on a slate gray or bluish color change (see Fig. 9-1). There is a loss of the normal cobblestone architecture, and this is followed by erythema and scaling (Fig. 9-25, A). Erosions, ulceration, and crusting develop in chronic cases (Fig. 9-25, B). The lesions usually commence dorsally at the junction between the nasal planum and the haired skin or along the ventral or medial aspects of thealar folds. With time, the lesions usually extend up the nose and infrequently involve the sun-exposed parts of the ears and the periorbital region. Cases are reported with unusual distributions, such as the distal limbs, footpads, and perianal region.307,308 There is one report of chronic DLE developing into a squamous cell carcinoma.309

**DIAGNOSIS**

The diagnosis is made by a careful history and clinical examination and supported by histopathologic
findings consistent with those observed in SLE. Direct immunofluorescence or immunohistochemistry will usually reveal immunoglobulin deposits at the dermoepidermal junction. ANA testing is ordinarily negative, as are tests for other circulating autoantibodies. There is, however, one report of a 9-year-old Shetland sheepdog with DLE with a negative ANA, in which circulating autoantibodies were detected using salt-split skin. The antigens detected were at the basement of the cleft, and Western blot showed targeting of two proteins of 120 and 85 kD that did not correspond to any known basement membrane antigen. Important differentials include dermatomyositis, uveodermatologic syndrome, contact dermatitis, and SLE. The clinical signs are very similar to those reported for pemphigus erythematosus, but the distinction between the two is not critical on clinical grounds, because the therapeutic approach is similar.

**CLINICAL MANAGEMENT** The prognosis in DLE is good, and in most cases, effective control is achieved without the use of potent immunosuppression. It should be emphasized that reports of therapeutic efficacy are largely anecdotal, and there have been no controlled trials. Avoidance of direct sunlight is of obvious importance, and some cases are controlled by that means alone. Sunscreens have been advocated, but most animals will lick them off immediately, limiting their effectiveness. Some clinicians advocate use of a 1-month course of prednisone or prednisolone, initially at high doses, to bring the condition under control. Tetracycline-niacinamide in combination is reportedly effective in 50% to 70% of cases, but the response is slow, and 2 months is required for full effect. Doses advocated are 250 mg of each three times daily in dogs under 10 kg, and 500 mg of each for those over 10 kg. High doses of vitamin E (400 IU every 12-24 hours) and essential fatty acids have also been advocated. A report showed good efficacy of topical application of 0.1% tacrolimus, and topical corticosteroids are useful adjunctive therapy. In selected cases, rotation flap skin grafting may be very effective.

**FELINE**

DLE is rarely reported in cats. In contrast to the dog, nasal involvement is less prominent, and lesions commonly involve the face and ears. A recent report describes two cats with acute onset of an exfoliative dermatitis in which the histopathology showed a lymphocyte-rich interface dermatitis accompanied by mura interface dermatitis and apoptosis of keratinocytes. The diagnosis was cutaneous lupus erythematosus, and the cats responded to cyclosporine. Whether this should be considered a variant of DLE or a distinct entity is debatable. The diagnostic and therapeutic approach for feline DLE is the same as for the canine disease, and corticosteroids probably represent the initial therapy of choice.

**VESICULAR CUTANEOUS LUPUS ERYTHEMATOSUS**

An ulcerative condition affecting predominantly the ventrum of Shetland sheepdogs and rough collies has been known as a distinct entity for many years. It was first suggested that it was a manifestation of hydradenitis suppurativa, which is a staphylococcal infection involving the apocrine sweat glands. It was later suggested that the condition more likely represented BP or a variant of dermatomyositis, which is known to affect these breeds. An exhaustive study of a series of cases revealed that it is quite distinct from dermatomyositis, the main criterion being that the interface dermatitis is cell-rich rather than cell-poor, which is a characteristic of the latter disease. These authors went on to suggest that it should be termed vesicular cutaneous lupus erythematosus, which has similarities with subacute cutaneous lupus erythematosus (SCLE) of man.

Affected dogs are usually middle-aged to older, and not only is the onset usually in the summer months, but some animals exacerbate in the summer months, suggesting a role of UV exposure in the pathogenesis. The ventral abdomen, groin, and medial thighs are the major sites, and the condition is characterized by focal to confluent serpiginous areas of ulceration (Fig. 9-26). In addition, the mucocutaneous junctions are often affected, and the concave aspect of the pinnae and buccal mucosa may be involved. Though obviously painful, the lesions are generally nonpruritic. In contrast to SLE, clinical signs are generally confined to the skin, although one dog had a concomitant arthritis, another hypothyroidism, and some had granular casts in their urine.

Histopathologic findings are of a cell-rich interface dermatitis with some vesiculation at the dermoepidermal junction.
Apoptotic keratinocytes are often found. Immunohistochemistry reveals an infiltrate of predominantly T cells that tend to be CD8+ in the epidermis and CD4+ in the dermis. Direct immunofluorescence testing reveals focal or diffuse areas of IgG deposition in the BMZ in 50% of cases, but evidence of circulating autoantibodies against dermal antigens is not found on indirect immunofluorescence. ANA tests using Hep-2 cells are negative, but evidence of antibodies against extractable nuclear antigens is found in most cases, using both ELISA against purified human extractable nuclear antigens and immunoblotting using a Hep-2 cell extract. Of particular interest has been the finding of antibodies against Ro/SSA and/or La/SSB in sera from 55% of cases. This finding is characteristic of SCLE in man, and it is suggested that this could result from relocation of nuclear antigens to the cytoplasm and cell membrane due to UV damage.

Response to therapy and clinical course are quite variable. Corticosteroids are advocated in high doses initially, and azathioprine may be required in addition. Antibiotic therapy is obviously necessary in view of the extensive ulceration. Four out of the 11 cases responded completely, and in two cases therapy was discontinued without relapse during the subsequent period of observation (2.5 years and 9 months). In a report of a further case, there was a good response to cyclosporine A.

**EXFOLIATIVE CUTANEOUS LUPUS ERYTHEMATOSUS**

The first report of this condition, which is restricted to the German short-haired pointer, appeared in 1992. Since then, there have been a number of reports of multiple cases, the most recent of which described the clinical, pathologic, and immunologic features of 25 cases from multiple geographic locations. All describe the same clinical picture, and an autosomal recessive mode of inheritance is thought to be most likely.

Onset is generally during the young adult period, with the earliest reported case presenting at 10 weeks of age. Lesions are characterized by scaling and alopecia that typically commence on the muzzle, pinnae, and dorsal trunk, progressing to involve the limbs and ventral trunk (Fig. 9-27). Ulceration and crusting may develop and occasionally is severe. There may be a generalized lymphadenopathy and intermittent episodes of pyrexia. Another characteristic feature is evidence of episodes of pain presenting as stiffness and/or lameness, reluctance to move, and occasional crying out as if in pain. Although pain may be apparently localized to one or more joints, cytologic analysis of joint fluid is unremarkable, ruling out any suggestion of a lupus arthropitis. Laboratory assessment is usually unrevealing except for thrombocytopenia in 25% of cases. Any further characterization of the latter in terms of possible immune etiology was not reported.

Histopathology reveals an interface dermatitis comprising predominantly T lymphocytes and extending to the infundibulum of the hair follicles as a mural folliculitis. Apoptosis of the basal keratinocytes is frequently observed. Another striking feature is involvement of sweat and sebaceous glands that often leads to destruction of the latter in a pattern suggestive of sebaceous adenitis. ANA testing was essentially negative in these cases, but all showed evidence of immunoglobulin deposits at the dermoepidermal junction and the follicular basement membrane in some cases. Indirect immunofluorescence revealed the presence of autoantibodies against the hair follicle and basement membrane of the sebaceous glands in some cases, but there was no evidence of antibody activity against the dermoepidermal junction basement membrane.

This condition thus has many of the hallmarks of a lupus condition, although it does not come close to fulfilling the criteria for SLE.
Most dogs received symptomatic therapy with a variety of topicals and shampoo therapy some benefit, but in general the response to immunomodulatory therapy was variable. High doses of corticosteroids were deemed helpful, but the condition tended to relapse when the dosage was lowered. A recent study assessed the use of cyclosporine, hydroxychloroquine, and the tumor necrosis factor (TNF)-α antagonist adalimumab (Humira [Abbott Laboratories, Abbott Park, Ill.]). These treatments were given in a controlled environment, with the conclusion that none of these drugs had any significant effect on the eventual disease outcome, although transitory improvement was noted with cyclosporin, and hydroxychloroquine seemed to slow progression. Long-term management appears to be difficult and the prognosis guarded. IVIG therapy has been reported to be effective in humans, presumably via Fas (CD95) blockade.

**ALOPECIA AREATA**

Alopecia areata is an uncommon or infrequently recognized disease of dogs and a rare disease of cats. It is characterized by patches of nonscarring hair loss that grossly is non-inflammatory. The canine disease is believed to be a good homolog for the human disease, though that is considered common, having a lifetime incidence of 1.7% in the United States. Other than genetics and incidence, canine and human alopecia areata share many clinical and immunologic characteristics.

**CAUSE AND PATHOGENESIS**

Alopecia areata is of complex pathogenesis in both humans and dogs. Normal hair growth involves many interactions and changes in hormones, receptors, and cytokines within the hair follicle and matrix that result in repetitive cycling through different stages of growth (see Chap. 1 for complete description). In alopecia areata, normal cycling is interrupted; in humans, three different hair-growth cycle abnormalities have been described: dystrophic anagen, truncated cycling, and prolonged telogen. It is believed these abnormalities are induced by an immune-mediated mechanism that may be modulated by genetics and hormones. Environmental factors such as stress and resultant production of stress hormones, vaccinations, and infection may affect expression or development of disease. A case seen by one of the authors (CEC) was reported by the dog’s owner to have an acute exacerbation of alopecia areata following a stressful event. Even diet may play a role. One study showed high levels of the phytoestrogen genistein, which was shown to affect the onset and severity of the disease in a mouse model of alopecia areata. In both humans and dogs, a heterogenous group of antifollicular autoantibodies (IgG class) are demonstrated by both direct and indirect immunofluorescent studies.

Other methods such as immunoreactant deposition, immunoblotting, and immunoprecipitation have shown that antibodies target the bulbar and inferior part of the hair follicle, though trichohyalin appears to be the major antigen targeted in dogs. There is some evidence that hair bulb melanocytes may also be targeted, and clinically in the dog this is supported by the finding that some cases have lesions mainly affecting one color or dark hair; leukotrichia is a common sequela of the disease. In addition, CD4+ and CD8+ cells are found around affected hair follicle bulbs, and CD8+ cells are likely responsible for inducing the hair loss in humans and laboratory models. In dogs there were more CD8+ cells found within the hair bulbs, supporting a similarity to the human disease. In addition, many CD1d dendritic antigen-presenting cells are present in the perifollicular dermis.

Other observations in humans supporting an immunologic basis for this disease are (1) occasional association of alopecia areata with other immune-mediated diseases, especially autoimmune thyroid disease, (2) increased incidence of various autoantibodies in alopecia areata, (3) decreased numbers of circulating T cells, (4) abnormal presence of Langerhans cells in the follicular bulb, (5) increased expression of class I and II MHC antigens, (6) deposition of C3 or IgG and IgM or both at the BMZ of hair follicles in lesional and normal scalp as revealed by direct immunofluorescence testing, (7) therapeutic benefit and cytokine changes associated with the response that are seen by inducing delayed-type hypersensitivity, and (8) response to immunosuppressive therapies.

**CLINICAL FEATURES**

In dogs and cats, alopecia areata is characterized by focal or multifocal patches of asymptomatic noninflammatory alopecia, most commonly affecting the head or face. The disease has been reported once in the cat. There has only been one large study of 25 canine cases published, with age at onset ranging from 1 to 11 years, with a median of 5 years. No studies have evaluated breed predispositions compared to base populations, so all suggestions are suspect. Based on a review of the literature and the authors’ experience, it is suspected that the German shepherd dog, dachshunds, and beagles may be predisposed. The male-to-female ratio in 25 cases was 0.79. The initial lesion is alopecia in 92% of the cases, and leukotrichia was initially noted by the owner in 8%. Lesions start as sharply margined (70%) patches without erythema or scale. Leukotrichia was present at evaluation in 28% of the dogs, and melanodera was reported in 20%. Chronically alopecic areas may become variably hyperpigmented. Most commonly (72%), lesions appear on the head or face region, with the muzzle and perioral areas affected in 50% of the cases. Other facial sites and legs may also be affected. In 16% of the cases generalized though incomplete distribution may be seen. Lesions most often are multiple, with a tendency for a symmetric pattern in as many as 80% of cases. Hair regrowth may occur spontaneously, with the initially regrown hair being white, only to later be replaced by pigmented hair. White hair growth occurred in 75% of cases, and in half with long-term follow-up, the white hair persisted for multiple hair cycles. Occasionally, alopecia areata may be confined to the dark-haired areas of multicolored haircoats. Claw changes compatible with trachyonychia (roughening, ridging, vertical striations) were seen in one dog and were compared to those occasionally occurring in humans with alopecia areata.

**DIAGNOSIS**

The differential diagnosis includes traction alopecia, injection reactions, acquired pattern alopecia, topical steroid reaction, follicular dysplasia, dermatophytosis, demodicosis, staphylococcal folliculitis, pseudopelade, psychogenic alopecia, and endocrinopathies. Microscopic examination of hairs plucked from the margin of enlarging lesions may reveal a mixture of normal telogen, dysplastic, and “exclamation point” hairs—short, stubby hairs with frayed, fractured, pigmented distal ends whose shafts undulate or taper toward the proximal end. Definitive diagnosis is based on the insidious onset of asymptomatic well-circumscribed areas of noninflammatory alopecia and on skin biopsy.

**HISTOPATHOLOGY**

The characteristic early histopathologic findings include a peribulbar to inferior hair follicle accumulation of lymphocytes, macrophages, or dendritic cells and usually some plasma