Psoriasiform-lichenoid-like dermatosis in three dogs treated with microemulsified cyclosporine A

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- Cyclosporine is reported to be effective for the treatment of various cutaneous autoimmune disorders in dogs; adverse reactions have generally been limited to gastrointestinal tract disturbances and cutaneous eruptions.
- Dogs being treated with microemulsified cyclosporine A may develop antimicrobial-responsive cutaneous reactions similar to psoriasiform-lichenoid dermatitis.
- Such reactions may represent atypical staphylococcal infections.

A 2-year-old 7-kg (15.4-lb) sexually intact male West Highland White Terrier was referred for treatment of presumptive epidermal dysplasia of 1 year’s duration. Previous treatments had included antimicrobials and lime-sulfur rinses without effect. At the time of initial examination, lesions consisted of severe lichenification, hyperpigmentation, erythema, and exudation affecting the ventral aspect of the abdomen, ventral aspect of the neck, cranial aspects of the antebrachia, and the interdigital regions. Examination of epidermal exudates revealed *Malassezia pachydermatis* and coccoid bacteria (presumed to be staphylococci). Initial treatment included frequent bathing, clindamycin (11 mg/kg [5 mg/lb], PO, q 24 h), and ketoconazole (7 mg/kg [3.2 mg/lb], PO, q 24 h). Microemulsified cyclosporine A (3.5 mg/kg [1.6 mg/lb], PO, q 24 h) was also prescribed. Substantial improvement was noticed after 4 weeks of treatment, and administration of clindamycin and ketoconazole was continued for an additional 4 weeks at 3 days per week. The dosage of cyclosporine A was decreased to 3.5 mg/kg, PO, every 48 hours.

Nine weeks after treatment was begun, multiple punctate, whitish, crusted, 2- to 6-mm-diameter papillomatous plaques were seen on the ventral aspect of the abdomen (Fig 1). Overgrowth of gingival tissue was also noticed. The dog appeared otherwise healthy. Biopsy specimens were obtained from the skin and gingival lesions. Histologic examination of the skin biopsy specimens revealed plaque-like areas of marked, irregular acanthosis with parakeratosis and occasional collections of degenerate neutrophils (microabcesses) within the stratum corneum. A single, small pustule consisting of neutrophils with small numbers of coccoid bacteria and a larger colony of coccoid bacteria was seen in the epidermis. The superficial portion of the dermis had a moderate, band-like infiltrate composed primarily of lymphocytes with smaller numbers of plasma cells and neutrophils. There was moderate exocytosis of lymphocytes in the lower layers of the epithelium. A morphologic diagnosis of psoriasiform-lichenoid dermatitis was made. Histologic examination of the gingival biopsy specimens revealed mild to moderate hyperplastic, lymphoplasmacytic stomatitis.

Although biopsy specimens were not submitted for bacterial culture, coccoid bacteria seen in the biopsy specimens were presumed to be staphylococci on the basis of their physical appearance (short chains to irregular clusters). An aberrant immunologic response to bacterial infection was suspected. There was no evidence of papillomavirus infection (eg, koilocytosis, giant keratohyalin granules, or basophilic intranuclear inclusions). Cephalexin (35 mg/kg [16 mg/lb], PO, q 12 h) was prescribed, and the dosage of cyclosporine A was reduced to 3.5 mg/kg, PO, twice weekly. Lesions resolved within 1 week after this change in treatment, and there were no recurrences in the subsequent 18 months.

A 3-year-old 38-kg (84-lb) sexually intact male Labrador Retriever was referred with a 2-year history of severe pruritus that failed to respond adequately to antimicrobials, corticosteroids, or a trial of feeding a restricted-ingredient food. Results of a serum ELISA for atopy were negative. Histologic examination of skin biopsy specimens revealed moderate superficial, perivascular, mastocytic, and histiocytic dermatitis with hyperkeratosis and acanthosis and secondary bacterial folliculitis. Generalized, severe erythroderma with scaling and malodor was evident on examination. Cytologic examination of epidermal exudates revealed many coccoid bacteria and smaller numbers of *M pachydermatis*. Results of intradermal allergy testing were strongly positive for environmental, insect, weed, grass, and mold allergens, although results of follow-up serum allergy testing were again negative. There was no...
change in pruritus when the diet was changed from a restricted-ingredient food to the previous commercial diet. Treatment included frequent bathing, cephalixin (26 mg/kg [12 mg/lb], PO, q 12 h, every day until lesions healed and then 3 consecutive days per week), diphenhydramine (2.6 mg/kg [1.2 mg/lb], PO, q 12 h), and prednisone (10 to 20 mg, PO, once to twice weekly as needed for pruritus). Hypoposensitization was initiated.

After 1 year of treatment, there was minimal improvement. Microemulsified cyclosporine A (2.6 mg/kg, PO, q 12 h) was prescribed, and hypoposensitization was discontinued. A substantial response to treatment was noticed within 2 months, and the dosage of cyclosporine A was gradually decreased to 2.6 mg/kg, PO, 3 times weekly. At irregular intervals, cephalixin and ketoconazole were prescribed for 14 to 21 days to treat infections.

Two years after treatment with cyclosporine A was begun, multiple, punctate to coalescing, erythematous, pigmented, crusted plaques were noticed on the ventral aspect of the abdomen (Fig 2). Results of a CBC and serum biochemical analyses were unremarkable. Fungal culture of broken hair shafts and epidermal debris did not yield any growth. Cytologic examination of epidermal exudates revealed hair shafts surrounded by adherent, irregular clusters of coccoic bacteria considered most likely to be staphylococci. Biopsy specimens were not obtained. The dog was treated with clindamycin (11.8 mg/kg [5.4 mg/lb], PO, q 24 h), and the dosage of cyclosporine A was decreased to 2.6 mg/kg, PO, twice weekly. All lesions healed without complications, and there were no recurrences during the subsequent 12 months.

A 2-year-old 30-kg (66-lb) sexually intact male Collie was referred because of a 3-month history of facial and pedal dermatitis. On initial examination, there were multiple annular lesions consisting of erythema, exudation, erosions, and ulcers involving the face, feet, inguinal region, scrotum, and axillae. Severe oral ulceration was also evident. A diagnosis of probable erythema multiforme was made on the basis of results of histologic examination of biopsy specimens, but no underlying cause was identified. Results of a CBC and serum biochemical analyses performed prior to initiation of treatment were unremarkable. There was no history of drug or supplement administration. A feeding trial with a restricted-ingredient diet was initiated, and the dog was treated with azathioprine (1.5 mg/kg [0.68 mg/lb], PO, q 24 h), pentoxifylline (13 mg/kg [5.9 mg/lb], PO, q 12 h), and prednisone (3 mg/kg [1.4 mg/lb], PO, q 24 h). The severity of clinical signs was reduced with this treatment, and treatment was maintained with azathioprine (2.5 mg/kg [1.1 mg/lb], PO, twice weekly) and prednisone (2 mg/kg [0.9 mg/lb], PO, twice weekly). However, lesions continued to develop. Two years after treatment was begun, a substantial increase in the number of lesions occurred. Treatment with prednisone was discontinued, and treatment with dexamethasone (0.26 mg/kg [0.12 mg/lb], PO, 3 times weekly), doxycycline (6.7 mg/kg [3.0 mg/lb], PO, q 12 h), and niacinamide (500 mg, PO, q 12 h) was initiated. Lesions again improved, but substantial weakness of the tissue over pressure points developed, resulting in proliferative granulation tissue. Treatment with microemulsified cyclosporine A was begun at a dosage of 3 mg/kg, PO, every 24 hours. The lesions healed, and treatment with dexamethasone was discontinued. The dosage of cyclosporine A was decreased to 3 mg/kg, PO, every other day after 4 weeks and then to 3 mg/kg, PO, twice weekly after 8 weeks. Eight months after beginning treatment with cyclosporine A, thick crusts and scales with underlying erythema developed on the lateral aspects of the elbows and carpi and in the ungual folds. Severe gingival overgrowth was also present, along with generalized hirsutism. Hyperplastic gingiva was resected with electrocautery. Histologic examination of skin biopsy specimens revealed irregular acanthosis with severe hyperkeratosis and patchy parakeratosis. The stratum corneum contained scattered, small collections of degenerate granulocytes. The superficial dermis had a moderate, band-like infiltrate primarily of plasma cells. There was blurring of the dermoeipidermal junction associated with upward migration of inflammatory cells. Lymphocyte satellitosis with individual necrotic keratinocytes was present in the basal and spinous cell layers. Several clusters of coccoic bacteria were observed in the follicular infundibula. A morphologic diagnosis of psoriasiform-lichenoid dermatitis was made. Bacterial culture of a skin biopsy specimen yielded a coagulase-positive Staphylococcus spp. Clindamycin (15 mg/kg [6.8 mg/lb], PO, q 24 h) was prescribed, and the dosage of cyclosporine A was decreased to 3 mg/kg, PO, once weekly. The more recent lesions healed with this treatment, but the original lesions associated with erythema multiforme returned after 1 month. These lesions improved when the dosage of cyclosporine A was increased to 3 mg/kg, PO, twice weekly. Trough serum cyclosporine concentrations were measured both during once weekly and twice weekly drug administration and were reportedly < 200 and 310 ng/mL, respectively (reference range, 200 to 500 ng/mL). Mild lesions of atypical pyoderma remained on the lateral aspects of the limbs when cyclosporine A was administered twice weekly (Fig 3); these lesions were managed with various antimicrobials and considered less severe than the lesions associated with erythema multiforme.

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The previous report of cutaneous papillomatous hyperplasia in Beagles treated with cyclosporine A described clinical lesions of irregular, oval, sessile firm masses with histologic findings of hyperkeratosis and acanthosis, mild hyperplasia of hair follicles and sebaceous glands, and diffuse dermal infiltrations of lymphocytes and plasma cells. Biopsy specimens from 2 dogs described in the present report had similar lesions with parakeratosis, band-like lymphocytic infiltrates, and clusters of coccoid bacteria that were often in intraepidermal microabscesses. These histologic findings (epidermal hyperplasia, lichenoid dermatitis, and intraepidermal microabscesses) are identical to those found in psoriasiform-lichenoid dermatitis. Lesions of psoriasiform-lichenoid dermatitis in Springer Spaniels are typically erythematous, papillated plaques that begin on the pinnae and may generalize. The condition is not considered a classic hypersensitivity reaction and may represent an exaggerated reaction to staphylococcal infection; it reportedly responds to antimicrobial treatment. The similarity between findings in the dogs in the present report and findings in Springer Spaniels with psoriasiform-lichenoid dermatitis supports the hypothesis that these adverse reactions associated with microemulsified cyclosporine A may represent a dose-dependent, aberrant immunologic response to staphylococcal infection. The mechanism of this aberrant immunologic response, however, is not known.

Numerous studies have demonstrated both general inhibition of keratinocyte proliferation and stimulation of follicular keratinocyte growth by cyclosporine. Perhaps this paradoxical response of keratinocytes results in atypical clinical lesions (eg, suppression of growth on the epidermal surface and exaggeration of growth at the follicle may create a papillomatous appearance). High numbers of plasma cells were seen in biopsy specimens from 2 of the dogs described in the present report, and an increase in plasma cells is also found in dogs with gingival hyperplasia associated with administration of cyclosporine A. This may be associated with type 2 T helper cell-dependent activation of B lymphocytes, although this plasmacytic response and its role in cutaneous lesions require more clarification.

Unlike the situation in human transplant patients, in whom cyclosporine dosage is adjusted by carefully monitoring serum cyclosporine concentrations, cyclosporine dosages in dogs with dermatologic abnormalities tend to be modified on the basis of clinical results. Although expensive, monitoring of serum cyclosporine concentrations is recommended to decrease the risk of adverse reactions. As in the third dog described in the present report, some animals may metabolize the drug more slowly than others, resulting in substantial serum concentrations even with intermittent administration.

Cyclosporine is reported to be variably effective for the treatment of various cutaneous autoimmune disorders in dogs, including epidermal dysplasia in West Highland White Terriers and atopic dermatitis. A recently published trial of the use of microemulsified cyclosporine A for the treatment of dogs with atopic dermatitis reported a clinical response rate similar to that reported for prednisone. Adverse effects in that study included diarrhea and a cutaneous reaction in a single dog. In humans, adverse reactions most commonly include renal dysfunction, hirsutism, hypertension, tremor, and gingival hyperplasia.

The 3 dogs described in the present report all developed antimicrobial-responsive, psoriasiform-lichenoid-like dermatosis while being treated with microemulsified cyclosporine A. Reactions in these dogs possibly represent atypical staphylococcal infections.

Previous studies have reported the development of papillomatous-like reactions in dogs given microemulsified cyclosporine A at high dosages (10 mg/kg [4.5 mg/lb] to 45 mg/kg [20 mg/lb], PO, q 24 h). In contrast, dogs in the present report were treated at dosages of 3 to 5.2 mg/kg/d (1.36 to 2.36 mg/lb/d) initially, and reactions developed between 8 weeks and 2 years after treatment with cyclosporine A was begun. Two of the dogs were receiving the drug only twice weekly, and the third was receiving the drug every other day when reactions developed. Histologic lesions in 2 of these dogs were similar to lesions reported for psoriasiform-lichenoid dermatitis in Springer Spaniels.

All 3 dogs had substantial numbers of coccoid bacteria in biopsy specimens and exudates. In 2 dogs, these bacteria were presumed to be staphylococci on the basis of histologic or cytologic appearance, and in the third dog, Staphylococcus spp was isolated by means of bacterial culture. All 3 dogs responded rapidly to antimicrobial administration and a reduced dosage of cyclosporine A. The rapidity with which lesions resolved would be more consistent with a response to antimicrobial administration than with a decrease in cyclosporine A dosage, but this cannot be proven. In the third dog, the hyperplastic lesions worsened dramatically if antimicrobial administration was discontinued.


