

All in the Family: Chronic Dermatitis & German Shorthaired Pointers

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A 22-kg, 6-year-old, spayed German shorthaired pointer was presented with a history of chronic dermatitis since being adopted from a shelter 1 year earlier. Previous medical history and travel history before adoption were unknown.

History

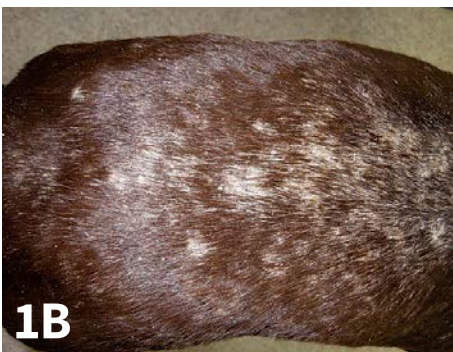
At the time of adoption from a local shelter, the patient was presented to the general practitioner for client-reported allergic skin disease. Reported signs included pruritus and a generalized crusted dermatitis. There was no response to treatment by the general practitioner with antiseptic-shampoo

therapy and administration of cephalexin at 10 mg/kg every 8 hours, hydroxyzine at 1 mg/kg twice a day, and prednisolone at 1 mg/kg twice a day. The patient was not being treated at initial examination.

Examination

Presenting concerns included persistent dermatitis, pruritus, and progressive malaise. The clients reported that the dog seemed hesitant to rise or walk, as if painful. Skin lesions at presentation consisted of generalized patchy alopecia, intense erythroderma, and fine adherent scales. Lesions were most evident on the pinnae, dorsal muzzle, dorsum of the head, and flank regions. A patchy-to-diffuse dermatitis consisting of excessive scale and crust was noted on the body. Mild lichenification with slight scaling affected glabrous regions of the chest and

Skin lesions consisted of generalized patchy alopecia, intense erythroderma, and fine adherent scales.



▲ At presentation, there was a generalized and diffuse loss of hair coat with fine scaling (A). Thicker crusts were noted on the dorsum of the body (B). The pinnae were erythematous, with patches of adherent scale and crust (C).

ventral abdomen. The patient appeared mildly lethargic and stiff. There was no joint swelling, and pain could not be elicited with joint palpation. Mild pruritus was evident (Figure 1).

Diagnostic Results

Samples for routine blood work and histopathologic examination of skin biopsies were submitted for this patient.

CBC and serum chemistry panels were normal except for an elevated globulin of 5.1 g/dL (reference range [RR], 2.4-4.0), and total protein of 7.8 g/dL (RR,

5.5-7.5), and mild thrombocytopenia of $91 \times 10^3/\mu\text{L}$ (RR, $143\text{-}448 \times 10^3/\mu\text{L}$).

Histopathologic abnormalities from skin tissue included moderate acanthosis with laminated-to-compact hyperkeratosis and a superficial dermal mild-to-moderate band-like infiltrate of lymphocytes, pigmented macrophages, plasma cells, and few neutrophils. Sebaceous glands were absent. There was blurring of the dermoepidermal junction, and the basal cell layer showed extensive squamization with mild vacuolar alterations and scattered apoptotic keratinocytes.

ASK YOURSELF

- ▶ Based on the clinical findings and history, which of the following differential diagnoses is the **least** likely?
 - Staphylococcal folliculitis (pyoderma)
 - Discoid lupus erythematosus
 - Cutaneous leishmaniasis
 - Exfoliative cutaneous lupus erythematosus
- ▶ What are the **most** appropriate diagnostic test(s) to consider in this case?
 - Skin scraping for cytologic examination
 - Routine CBC and serum chemistry panel
 - Skin biopsy for histopathologic examination
 - All of the above
- ▶ Pending test results, which treatment option would be the **most** appropriate to begin?
 - Cephalexin 25 mg/kg twice a day
 - Ketoconazole 10 mg/kg once a day
 - Prednisolone 0.5 mg/kg twice a day
 - Chlorhexidine-containing shampoo every other day

DID YOU ANSWER?

- ▶ The least likely differential diagnosis is discoid lupus erythematosus, an autoimmune disease characterized by depigmentation and crusting affecting the nasal planum, lip margins, and eyelid margins. Crusts often extend onto the pinnae and dorsal muzzle. Lesions are primarily confined to the head, and systemic signs are absent; in this case, lesions were generalized, and the nasal planum was not affected. Clinical lesions in this case are similar to those found in cutaneous leishmaniasis. Although not a disease endemic in the patient's current location, the travel history before adoption was unknown. Staphylococcal folliculitis (pyoderma) typically presents with pustules progressing to crusted papules. Over time, lesions enlarge to produce punctate alopecic patches with peripheral scale and epidermal collarettes. This patient's lesions consisted of generalized and diffuse fine scaling with no evidence of epidermal collarettes. Diffuse scaling can develop with chronic superficial pyoderma, especially in cases concurrently treated with corticosteroids, but there was no reported response to antiseptic shampoo therapy or to antibiotics.
- ▶ All of the diagnostic procedures listed are appropriate in this case. Demodicosis can cause patches of alopecia with inflammation and crusts. Blood work is appropriate in order to establish a baseline prior to treatment as well as to assess potential causes of systemic signs in this case. The benefit of skin biopsy here is to establish a definitive diagnosis and/or to exclude other differential diagnoses. Skin biopsies are often obtained when in-house diagnostics are negative and initial therapy is not effective.
- ▶ A chlorhexidine-containing shampoo every other day is the most appropriate first treatment option. Without confirmation of either a bacterial or a fungal skin infection, empiric treatment with systemic antiinfection medications is questionable. Conversely, treatment with prednisolone before the exclusion of infection would be detrimental in this patient as corticosteroids may worsen ongoing infection and/or occult demodicosis.

ECLE is a unique, heritable disease that causes signs similar to subacute cutaneous lupus erythematosus in human beings.¹

Diagnosis

Exfoliative cutaneous lupus erythematosus (ECLE)

Discussion

ECLE is a familial form of lupus found in German shorthaired pointer dogs. ECLE is a unique, heritable disease that causes signs similar to subacute cutaneous lupus erythematosus in human beings.¹ Lesions develop in young adult dogs (ages 6 months to 2 years 9 months) consisting of scaling and alopecia ini-

tially affecting the face, pinnae, and dorsum with eventual generalization. In addition, dogs often exhibit lameness, pain, and pyrexia. Anemia and thrombocytopenia develop in chronic and severe cases.²

An autosomal recessive mode of inheritance caused by a mutant gene on canine chromosome 18 has been proposed.¹ IgG deposition at the basement membrane and circulating antifollicular and anti-sebaceous IgG antibodies have also been identified.³



Treatments include topical antiseborrheics, essential fatty acid supplements, tetracycline-niacinamide, hydroxychloroquine, cyclosporine, and adalimumab, with poor overall success.

▲ After 1 year of treatment with leflunomide, the hair coat appears normal and shiny (A), with near-normal hair coat regrowth on the dorsum (B). The pinnae appear normal, with hair coat regrowth on the concave surfaces and with an absence of scales (C).

The prognosis for affected dogs is poor-to-guarded.⁴ Treatments include topical antiseborrheics, essential fatty acid supplements, tetracycline-niacinamide, hydroxychloroquine, cyclosporine, and adalimumab, with poor overall success.⁴⁻⁷ Transient response to corticosteroids with azathioprine was reported in 1 dog.³ Most patients are euthanized by 4 years of age because of progressive dermatitis and worsening joint pain and stiffness.⁶

A previous patient diagnosed with ECLE has been successfully treated with

leflunomide by the author for over 4 years. Because of a reported poor prognosis and the lack of response to previous therapy, treatment with leflunomide was initiated in this patient. Leflunomide has antiproliferative activity for rapidly reproducing cells—especially lymphocytes—inhibiting autoantibody production by B-cells and decreasing proliferation of autoimmune T-cells.⁸

Treatment & Outcome

Initial leflunomide treatment dosage was 80 mg/day (3.5 mg/kg/day). At

ECLE = exfoliative cutaneous lupus erythematosus

4 weeks, lesions were significantly less erythematous, and the patient was reported to be less painful and less depressed. However, significant pruritus developed and the patient was prescribed oclacitinib 9.8 mg twice a day (0.5 mg/kg twice a day) for 14 days, reduced to once a day for maintenance of comfort. After 1 year of treatment, the patient remains stable and comfortable, with no signs of malaise or stiffness. The patient continues to be administered leflunomide 80 mg every other day and oclacitinib 9.8 mg daily (Figure 2, previous page). To the author's knowledge, this article is the first to report the successful treatment of ECLE with leflunomide. Additional case experience using leflunomide, with or without oclacitinib, is needed to document the efficacy of this treatment for ECLE. ■

The author extends thanks to Andrea Cannon, DVM, DACVD, for assistance with these cases.

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ECLE = exfoliative cutaneous lupus erythematosus

NexGard® (afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description: NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-(2,2,2-trifluoroethyl)amino]ethyl.

Indications: NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), Lone Star tick (*Amblyomma americanum*), and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Dosage and Administration: NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:

Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:

Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:

There are no known contraindications for the use of NexGard.

Warnings:

Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

Adverse Reactions:

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N ¹	% (n=415)	N ²	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

¹Number of dogs in the afoxolaner treatment group with the identified abnormality.

²Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

Mode of Action:

Afoxolaner is a member of the isoxazolone family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:

In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥ 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days.

Animal Safety:

In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistry, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:

Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:

NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

NADA 141-406, Approved by FDA

Marketed by: Frontline Vet Labs™, a Division of Merial, Inc. Duluth, GA 30096-4640 USA

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1050-4493-03

Rev. 1/2015

