BRITISH VETERINARY DERMATOLOGY STUDY GROUP

SPRING MEETING • APRIL 2015

Danny Does Derm...

Crowne Plaza Hotel, Birmingham City Centre
Wednesday 8th April 2015

SPRING PROCEEDINGS

2015
BRITISH VETERINARY DERMATOLOGY
STUDY GROUP SPRING MEETING

Crowne Plaza, Birmingham City Centre
8th April 2015

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Allergic skin diseases are very common in the cat, accounting for 32.7% of our feline dermatology cases over a 15-year period. The most common cutaneous allergies in cats are atopic dermatitis, flea-bite allergy, and food allergy. The four classic cutaneous reaction patterns in allergic cats are:

1. Papulocrustous dermatitis ("miliary dermatitis"). Most common on back and neck.
2. Eosinophilic granuloma complex (eosinophilic granuloma, eosinophilic plaque, indolent ulcer).
   a. **Indolent Ulcer**: well-circumscribed, red-brown, alopecic, glistening, raised border, nonpruritic, especially upper lips.
   b. **Eosinophilic Plaque**: well-circumscribed, raised, flat-topped, erythematous, oozing, eroded-to-ulcerated, intensely pruritic, especially abdomen and medial thighs.
   c. **Eosinophilic Granuloma**: well-circumscribed, raised, firm, papulonodular-to-linear, yellow-pink-to-erythematous, variably pruritic, especially lips and caudal thighs.
3. Symmetrical, initially lesionless pruritus. Most common on face, ears, and neck.
4. Symmetrical self-induced hair loss with normal underlying skin. Most common on abdomen, back, and legs.
It is very important to remember that these reaction patterns: (a) do not indicate a specific allergy, (b) can be seen in various combinations in the same cat, and (c) can be produced by nonallergic diseases (Tables 1-4). Cats rarely develop urticaria, angioedema, exfoliative dermatitis, or plasma cell pododermatitis in association with their allergies.

The approach to each reaction pattern thus involves a thorough history and physical examination, and various combinations of:

1. Skin scrapings.
2. Combinations.
3. Fecal flotation.
4. Cytology.
5. Trichography.
6. Culture.
7. Stopping current drug(s).
8. Response to therapy.
10. “Allergy testing” (blood, skin).
11. Skin biopsy.

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<td>Food allergy</td>
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REFERENCES


FELINE ATOPIC DERMATITIS

Feline atopic dermatitis (FAD; feline atopy) owes its birth and current level of interest and investigation to Dr. Lloyd M. Reedy, whose landmark article on intradermal testing and allergen-specific immunotherapy (hyposensitization) in cats was published in 1982. FAD is now a widely accepted clinical and therapeutic reality.

Atopic dermatitis (AD) is defined as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE most commonly directed against environmental allergens. It is currently believed to be a multifactorial disease, most likely resulting from a complex interaction between host and environment.

The genetic aspects of AD in cats have not undergone the depth of investigation that they have in humans and dogs. However, AD has been reported in related cats and littermates. IgE has been characterized in the cat, and the immunopathogenesis of AD in cats is similar to that described in humans and dogs.

The prevalence of FAD is unknown, but the condition is generally believed to be the second most common allergic skin disease of cats in areas of the world where flea-bite hypersensitivity is common. In a recent study, FAD accounted for 10.3% of the dermatologic diagnoses, and 0.88% of the total cat population, at a university clinic.

The clinical signs of FAD may be initially seasonal (e.g., cold weather in association with house dust mites and indoor molds; or warm weather in association with pollens and outdoor molds), or nonseasonal, or progress from a seasonal to a nonseasonal disease with the passage of time. The most common cutaneous reaction patterns associated with FAD are papulocrustous dermatitis (“miliary dermatitis”), symmetrical initially nonlesional pruritus, symmetrical self-induced hair loss, and the eosinophilic granuloma complex. These reaction patterns are reportedly seen in various combinations in any given cat.

The diagnosis of FAD is based on compatible historical and clinical findings, and the ruling out of all conditions that can produce similar clinical reaction patterns. Management of FAD includes allergen avoidance, allergen-specific immunotherapy, various anti-inflammatory medications, and combinations of these.

Our purpose was to report the results of a retrospective study of 194 cats with AD.

MATERIALS AND METHODS

A retrospective study was conducted on 194 cats with AD examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) from 1988 to 2003. Inclusion criteria were the following:

1. Historical and clinical findings consistent with AD.
2. The exclusion of other conditions that mimic the clinical aspects of AD. This was accomplished by skin scrapings, flea combings, trichography, cytology, skin biopsy, novel diet trials, and response to therapy as appropriate to each case.
3. Complete resolution of clinical signs with the administration of systemic glucocorticoids.
Medical records were reviewed for the following information:

1. Breed, sex, and age of onset of clinical signs.
2. Seasonality of clinical signs.
3. Cutaneous reaction pattern(s).
4. Results of allergy testing.
5. Therapeutic protocols and results.
6. Follow-up period.

Breed, age, and sex data for cats with AD were compared with those for the general CUHA cat population for the same time period using the relative risk (RR) calculation.

\[
RR = \frac{\text{data for AD cats}}{\text{data for CUHA cats}}
\]

An RR of 2.0 or greater was considered significant.

Allergy testing was performed as follows:

1. Elimination diet trial with a home-cooked or limited ingredient commercial food selected on the basis of a detailed dietary ingredient history. Diets were fed for 4 to 6 weeks. If a reduction in clinical signs was seen in 4 to 6 weeks, the elimination diet was continued until maximum improvement was seen. Cats whose clinical signs improved while consuming the elimination diet were then fed their previous diet for 7 to 10 days in order to reproduce each patient’s clinical signs.
2. Intradermal testing (antigens from Greer Laboratories, Lenoir, North Carolina, USA) with 59 allergens as previously described.
3. Allergen-specific immunoglobulin E (IgE) serology (liquid phase immunoenzymatic testing: VARL Liquid Gold®, Pasadena, California, USA).

Cats were treated with one or more of the following protocols according to the owners’ wishes:

2. Prednisolone or prednisone, 2 mg/kg by mouth, every 24 hours until clinical signs were resolved. For maintenance, alternate-day therapy was used.
3. Dexamethasone, 0.2 mg/kg by mouth, every 24 hours until clinical signs were resolved. For maintenance, dexamethasone was administered every 48 to 72 hours or as needed.
4. Methylprednisolone acetate, 20 mg/cat subcutaneously, every 2 weeks until clinical signs were resolved (2 or 3 injections required). For maintenance, methylprednisolone acetate was administered no more frequently than every 3 months.
5. Chlorpheniramine, 2 mg/cat by mouth with food, every 12 hours.
6. Clemastine, 0.67 mg/cat by mouth with food, every 12 hours.
7. Cyproheptadine, 2 mg/cat by mouth with food, every 12 hours.
8. Amitriptyline, 1 mg/kg by mouth with food, every 12 hours
9. Hydroxyzine, 2 mg/kg by mouth with food, every 12 hours.
10. A commercial omega-6/omega-3 fatty acid-containing supplement (DVM Derm Caps Liquid®, DVM Pharmaceuticals, Miami, Florida, USA), 1 ml/9 kg given by mouth, every 24 hours. This product contained linoleic acid, γ linolenic acid,
doxycycline, and eicosapentaenoic acid.

11. Cyclosporine, 5 mg/kg by mouth with food, every 24 hours.
12. Allergen-specific immunotherapy (ASIT; hyposensitization) with aqueous antigens (Greer Laboratories, Lenoir, North Carolina, USA) as previously described.

RESULTS

AD was diagnosed in 13.8% (194/1,407 cats) of the feline dermatology cases and 0.9% (194/22,135 cats) of all cats examined at the CUHA over a 15-year period. Seventy-seven of 194 (40%) cats were first-opinion consultations, and 117/194 (60%) cats had previously been seen by one or more veterinarians. Domestic shorthair cats accounted for 77.8% (151/194) of the cats with AD, and 79.6% of the CUHA cat population (RR = 0.98). AD was also diagnosed in domestic longhair (15 cases), Himalayan (8 cases), Persian (7 cases), Siamese (4 cases), Abyssinian (4 cases), Maine Coon (2 cases), and Egyptian Mau, Manx, and Tonkinese (1 case each) cats. Himalayans (RR = 3.15), Persians (RR = 2.25), and Abyssinians (RR = 7.0) were over-represented.

Spayed females, castrated males, intact females, and intact males accounted for 47.9%, 36.6%, 10.3%, and 5.7%, respectively, of the cats with AD. These same sexes accounted for 38.2% (RR = 1.25), 38.8% (RR = 0.94), 10.9% (RR = 0.94), and 10.1% (RR = 0.56), respectively, of the total CUHA cat population. Hence, no sex predilection was evident.

The age at onset of clinical signs for AD cats varied from 3 months to 15 years. The age of 24 cats (12.4%) with AD was unknown. The age of onset was ≤ 3 years, 4 to 6 years, 7 to 9 years, and ≥ 10 years for 51.5%, 14.4%, 12.9%, and 9.2%, respectively, of the cats with AD. By comparison, these same age groups accounted for 46.4% (RR = 1.24), 17.0% (RR = 0.85), 12.7% (RR = 1.02), and 23.6% (RR = 0.39), respectively, of the total CUHA cat population. Hence, no age group was over-represented.

Clinical signs were nonseasonal in 131/194 (67.5%) of the cats. One hundred-twenty-one of these 131 cats (92.4%) had nonseasonal disease from the onset, and also had seasonal (summer or winter) increased severity of clinical signs. The other 10 cats initially had seasonal (spring through fall; summer; winter; fall) disease which became nonseasonal after 2 to 4 years.

Clinical signs remained seasonal in 63/194 (32.5%) cats:
1. Winter in 18 cats.
2. Fall and winter in 14 cats.
3. Spring and summer in 10 cats.
4. Summer and fall in 10 cats.
5. Spring, summer, and fall in 6 cats.
7. Fall in 1 cat.
8. Winter and spring in 1 cat.
9. Spring and fall in 1 cat.
The most common cutaneous reaction pattern in cats with AD was initially lesionless symmetrical pruritus (ILSP) which progressed to excoriations. It was present in 99/194 (51%) cats, as the only reaction pattern in 42 (21.6%) cats, and in conjunction with one, two, or three other reaction patterns in 47, 9, and 1 cases, respectively. The ILSP pattern affected one or more of the following body regions: face (71 cats; 71.7%), ears (63 cats; 63.6%), neck (34 cats; 34.4%), front paws (13 cats; 13.1%), and axillae (10 cats; 10.1%). Disease was isolated to the ears or paws in 8 (8.1%) and 3 (3%) cats, respectively.

The second most common reaction pattern was self-induced hair loss (SIHL) with no visible skin lesions. It was present in 89/194 (45.8%) cats, as the only reaction pattern in 38 (19.5%) cats, and in conjunction with one, two, or three other reaction patterns in 40, 9, and 1 cases, respectively. The SIHL pattern affected one or more of the following body regions: abdomen (63 cats; 70.8%), back (43 cats; 48.3%), legs (32 cats; 35.9%), medial thighs (7 cats; 7.9%), lateral thorax (7 cats; 7.9%), tail (7 cats; 7.9%), perineum (3 cats; 3.7%), and axillae (2 cats; 2.3%). In the 32 cats with involvement of the legs, all 4 legs were affected in 26 cats, the rear legs in 4 cats, and the front legs in 2 cats.

The third most common reaction pattern was miliary dermatitis (MD), which was present in 60/194 (30.9%) cats, as the only reaction pattern in 33 (17%) cats, and in conjunction with one, two, or three other reaction patterns in 17, 9, and 1 cases, respectively. The MD pattern affected one or more of the following body regions: back (44 cats; 73.3%), neck (20 cats; 33.3%), abdomen (10 cats; 16.7%), face (6 cats; 10%), ears (4 cats; 6.7%), legs (4 cats; 6.7%), trunk (3 cats; 5%), axillae (1 cat; 1.7%), and tail (1 cat; 1.7%). In 10 cats the MD was generalized.

The least common reaction pattern was the eosinophilic granuloma complex (EGC) which was present in 26/194 (13.4%) cats, as the only reaction pattern in 11 cats (5.7%), and in conjunction with one, two, or three other reaction patterns in 11, 5, and 1 cases, respectively. Eosinophilic granulomas were present in 13 cats (50%): upper lips (8 cats), hard palate (5 cats), chin (3 cats), caudal thighs (3 cats), lower lips (2 cats), and tongue (1 cat). Eosinophilic plaques were present in 11 cats (42.3%): medial thighs (9 cats), abdomen (8 cats), back (1 cat), and neck (1 cat). Indolent ulcers were present in 10 cats (38.4%): left or right upper lip (9 cats), and both upper lips (1 cat).

Two or more cutaneous reaction patterns were simultaneously present in 36.2% (70/194) of our cats.

Secondary bacterial infections were present in 30/194 (15.5%) of the cats: bacterial folliculitis and/or furunculosis (30 cats; 15.5%), or bacterial otitis externa (6 cats; 3.1%). All bacterial infections were confirmed cytologically (suppurative or pyogranulomatous inflammation with degenerative neutrophils and phagocytosed cocci). Cultures were not performed. Empirical systemic and topical antibiotic therapy resolved the bacterial infections. The bacterial infections occurred where the allergic reaction patterns were present: face (17 cats), neck (10 cats), ears (6 cats), ventrum (3 cats), back (2 cats), lips (1 cat). One cat with bacterial folliculitis also had yeast otitis externa, and three cats with bacterial folliculitis had concurrent yeast dermatitis.

Secondary yeast infections were present in 13/194 (6.6%) cats: yeast dermatitis (5 cats; 2.5%), or yeast otitis externa (8 cats; 4.1%). All yeast infections were confirmed cytologically (numerous unipolar budding yeasts per high-power [400X] microscopic field). Cultures were not performed. Empirical systemic and topical antifungal therapy resolved the yeast infections. The yeast infections occurred where the allergic patterns were present: ears (8
cats), face (2 cats), paws (2 cats), back (2 cats), and perineum (1 cat). Three cats with yeast dermatitis also had bacterial folliculitis, and one cat with yeast otitis externa had concurrent bacterial folliculitis.

Nine cats (4.6%) with AD had concurrent food allergy. These cats had one or more of the following cutaneous reaction patterns: ILSP (8 cats), SIHL (5 cats), MD (3 cats), and EGC (2 cats). In these cats, their dermatoses were reduced in severity by 50% to 80% with the feeding of a novel diet, and this improvement was lost when their previous diet was fed. The remaining 20% to 50% of their clinical signs were controlled by antihistamines (3 cats), dexamethasone every 7 to 10 days (2 cats), or allergen-specific immunotherapy (1 cat). For the other 4 cats, the remaining level of skin disease was considered tolerable by the owners, and observation without treatment was chosen.

Allergy testing was performed in 48 cats (24.7%). The 59 allergens used are listed. Intradermal, serological, or intradermal and serological testing was performed in 23 (Table 1), 17 (Table 2), and 8 (Table 3) cats, respectively. The most common positive reactions were to house dust/house dust mite mix (Dermatophagoides farinae and D. pteronyssinus) (20 cats; 41.7%), Helminthosporium (20 cats; 41.7%), Pullularia (19 cats; 39.6%), Mucor (17 cats; 35.4%), alfalfa (17 cats; 35.4%), English plantain (16 cats; 33.3%), Timothy (15 cats; 31.3%), firebush (15 cats, 31.3%), and lambs quarter (15 cats; 31.3%). Positive reactions were seen to at least one pollen and one mold in 43/48 (89.6%) and 39/48 (81.3%) tests, respectively. Nine of the 10 most common positive reactions were to molds and pollens.

Medical management was successful in 153/194 (78.9%) cats. Injectable methylprednisolone acetate was administered from once/year to every 3 months. One to three injections/year were required in the 30 cats with seasonal disease. Twenty-five of 66 cats (37.9%) were followed for 3 to 10 years.

Dexamethasone (0.05 to 0.1 mg/kg) was required every 2 to 7 days. Seven (36.9%) of these cats were followed for 3 to 7 years.

Prednisolone (≤0.5 mg/kg/day) was required every 48 hours. Five of these cats (50%) were followed for 2 to 3 years. The 2 cats (16.3%) that did not respond to prednisolone were successfully managed with dexamethasone (1 cat) or demastine (1 cat).

Prednisone (≤0.5 mg/kg/day) was required every 48 hours. Three of these cats (33.3%) were followed for 3 to 7 years. The 7 cats (43.7%) that did not respond to prednisone were successfully managed with dexamethasone (4 cats), methylprednisolone acetate (2 cats), or cyclosporine (1 cat).

Complete physical examination, hemogram, and biochemistry panel were performed annually on all cats treated with glucocorticoids. No significant side effects were reported. A few cats exhibited mild polyphagia and/or weight gain.

Antihistamines were prescribed for 111 cats, and provided satisfactory control in 34 (30.6%). Control was maintained for follow-up periods of 0.5 to 9 years, and for >1 year in 28 (82.4%) cats. Side effects were rarely reported: polyphagia with cyproheptadine; refusal to take chlorpheniramine (bitter tasting tablet).

A commercial omega-6/omega-3-fatty acid supplement was prescribed for 37 cats, and provided satisfactory control in 6 (16.2%) cats with follow-up periods of 2 to 8 years. No side effects were reported.
In 12 cats, neither chlorpheniramine nor the commercial omega-6/omega-3 fatty acid supplements were effective when administered alone. However, when the two medicaments were administered simultaneously, 8 of the 12 cats (66.7%) were satisfactorily controlled for follow-up periods of 0.5 to 3 years.

In 8 cats with the SIHL reaction pattern, owners elected to simply observe their pets. These cats were stable over follow-up periods of 0.5 to 6 years.

Although allergy testing was performed in 48 cats, only 27 cats (56.3%) received ASIT. In 2 cats, the allergy test results did not explain the cats’ allergy seasons, so ASIT was not attempted. In 1 cat with nonseasonal disease and positive reactions to wool and feathers, the animal became normal when contact with feathers was eliminated (follow-up period 1.5 years). In 18 cats, the owners decided that ASIT would not be possible due to their cats’ personalities or concerns over damaging the pet-owner bond. In the 20 cats that actually received ASIT for at least 1 year, the protocol was successful in 18 cats (90%).

ASIT was unsuccessful in 2 cats, and 7 cats were lost to follow-up. Wherein follow-up was possible, ASIT was successful in 2/2 cats with seasonal AD, and 16/18 cats with nonseasonal AD, with maintenance injections required every 2 to 3 weeks. Wherein follow-up was available, ASIT was successful in 10/10 cats (100%), 5/6 cats (83.3), and 3/4 cats (75%) when based on intradermal, serological, and combined intradermal/serological testing, respectively. In 10/18 (55.6%) ASIT successes, house dust/house dust mites were not in the prescription, but all prescriptions contained molds and pollens. Success of ASIT was not associated with cutaneous reaction pattern(s) present.

In 13/18 (72.2%) of the ASIT successes, ASIT was the only treatment required. In the other 5 cats, ASIT was deemed successful for the following reasons:

1. In one cat, ASIT allowed a reduction in frequency of methylprednisolone acetate injections from every 6 weeks to once or twice per year.
2. In three cats, ASIT allowed a reduction in frequency of dexamethasone administration from daily to every 3 to 7 days.
3. In one cat, pruritus was reduced by 75% with ASIT, and the rest of the animal’s pruritus was controlled with the addition of chlorpheniramine.

Adverse reactions to ASIT were not reported.

In our study, 7/194 (40%) and 117/194 (60%) cats were first-opinion and second-opinion cases, respectively. Follow-up was available for 76/77 (98.7%) and 110/117 (94%) of the first-opinion and second-opinion cases, respectively. Follow-up times for both groups varied from 6 months to 12 years, with 84/187 (44.9%) cats having follow-up periods of over 2 years.
Table 1. Prevalence of Positive Reactions with Intradermal Testing Alone (23 Cats)

<table>
<thead>
<tr>
<th>Allergen</th>
<th># Positive Reactions</th>
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<td><strong>Environmental</strong></td>
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<tr>
<td>Cottonseed</td>
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<tr>
<td>Feathers</td>
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<td>Lambs quarter</td>
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<td>Wormwood</td>
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Table 2. Prevalence of Positive Reactions with Serological Testing Alone (17 Cats)

<table>
<thead>
<tr>
<th>Allergen</th>
<th># Positive Reactions</th>
<th>% Positive Reactions</th>
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<tr>
<td><strong>Environmental</strong></td>
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<tr>
<td>Dog dander</td>
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<tr>
<td>House dust/dust mite mix</td>
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<tr>
<td>Human dander</td>
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<tr>
<td>Kapok</td>
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<tr>
<td><strong>Molds</strong></td>
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<td></td>
</tr>
<tr>
<td>Alternaria</td>
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<tr>
<td>Aspergillus</td>
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<td>41.2</td>
</tr>
<tr>
<td>Cladosporium</td>
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<td>11.8</td>
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<tr>
<td>Curvularia</td>
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<td>52.9</td>
</tr>
<tr>
<td>Epicoccum</td>
<td>7</td>
<td>41.2</td>
</tr>
<tr>
<td>Fusarium</td>
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<td>29.4</td>
</tr>
<tr>
<td>Helminthosporium</td>
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<td>58.8</td>
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<td>Mucor</td>
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<td>52.9</td>
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<tr>
<td>Penicillium</td>
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<td>23.5</td>
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<td>Phoma</td>
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<td>Pullularia</td>
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<td>Rhizopus</td>
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<tr>
<td>Stemphylium</td>
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<tr>
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<td>Cedar</td>
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<td>Oak</td>
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<tr>
<td>Pine</td>
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<td>Sycamore</td>
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<td>Walnut</td>
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<tr>
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<td>Dock</td>
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<tr>
<td>English plantain</td>
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<tr>
<td>Firebush</td>
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<td>41.2</td>
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<tr>
<td>Lambs quarter</td>
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<td>47.1</td>
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<tr>
<td>Marsh elder</td>
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<td>5.9</td>
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<tr>
<td>Mugwort</td>
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<tr>
<td>Pigweed</td>
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<td>29.4</td>
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<tr>
<td>Ragweed</td>
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</tr>
<tr>
<td>Wormwood</td>
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</table>
### Table 3. Positive Reactions with Intradermal and Serological Testing Combined (8 Cats)

<table>
<thead>
<tr>
<th>Case #</th>
<th>Intradermal</th>
<th>Serological</th>
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<tbody>
<tr>
<td>1*</td>
<td>Negative</td>
<td>Pigweed, lambs quarter, ragweed, goldenrod, cocklebur, firebush, cedar, birch, elm, walnut, sycamore</td>
</tr>
<tr>
<td>3§</td>
<td>Negative</td>
<td>Ragweed, goldenrod, alfalfa, dandelion, marsh elder, <em>Phoma</em>, <em>Curvularia</em>, <em>Helminthosporium</em>, <em>Epicoccum</em></td>
</tr>
<tr>
<td>5†</td>
<td>Alfalfa, cedar, lambs quarter, ragweed, <em>Stemphylium</em>, firebush, feathers, kapok</td>
<td>Alfalfa, cedar, lambs quarter, mugwort, English plantain, pine, orchard, rye, <em>Phoma</em>, <em>Helminthosporium</em>, house dust</td>
</tr>
<tr>
<td>7§</td>
<td>Negative</td>
<td>Dandelion, dock, English plantain, vernal, orchard, rye, <em>Penicillium</em>, <em>Fusarium</em>, <em>Epicoccum</em>, <em>Mucor</em>, <em>Curvularia</em></td>
</tr>
<tr>
<td>8*</td>
<td>Negative</td>
<td>Marsh elder, fescue, Timothy, brome, orchard, <em>Alternaria</em>, <em>Fusarium</em>, <em>Rhizopus</em>, <em>Aspergillus</em>, <em>Mucor</em>, <em>Helminthosporium</em>, <em>Stemphylium</em>, <em>Curvularia</em>, house dust</td>
</tr>
</tbody>
</table>

*In these cases (1 and 8) no ASIT was attempted.
†In these cases (2 and 5) ASIT was instituted, but no follow-up was available.
§In these cases (3, 4, and 7) ASIT was successful.
‡In this case (6) ASIT was unsuccessful.

**REFERENCE**

FELINE FOOD ALLERGY

Many terms are used when referring to dermatological reactions to foods. “Food allergy” or “food hypersensitivity” result from immunological mechanisms. “Food intolerance” results from nonimmunological mechanisms. “Food sensitivity” and “cutaneous adverse food reaction” include both immunological and nonimmunological phenomena. The clinical findings attributable to these various mechanisms are usually clinically indistinguishable, and no practical laboratory methods of distinguishing between the various mechanisms are currently available. In this article, we will use the common term “food allergy” to refer to our patients.

Cutaneous food allergy (CFA) in cats was probably first reported in detail by Dr. Gus Walton in 1967. Since this original description, feline CFA has been widely reported and reviewed. The immunopathogenesis of feline CFA is poorly understood, with clinical and rare immunological studies suggesting that “immediate (minutes to hours following consumption of the offending food)” and “delayed (several days after consumption of the offending food)” reactions occur (Table 1).

The prevalence of feline CFA is unknown, but the condition is generally believed to be the third most common allergic skin disease of cats in areas of the world where flea-bite hypersensitivity is common. In a recent study, CFA accounted for 2.5% of the dermatologic diagnoses, and 0.22% of the total cat population examined at a university clinic.

The clinical signs of feline CFA are typically nonseasonal. Episodic disease can be seen if the food allergens are fed intermittently. The most common cutaneous reaction patterns associated with feline CFA are papulocrustous dermatitis (“miliary dermatitis”), symmetrical initially nonlesional pruritus leading to excoriation, symmetrical self-induced hair loss with normal-appearing skin, and the eosinophilic granuloma complex (indolent ulcer, eosinophilic plaque, eosinophilic granuloma). These reaction patterns are reportedly seen in various combinations in any given cat.

The diagnosis of feline CFA is based on compatible historical and clinical findings, ruling-out other conditions that can produce similar clinical reaction patterns, resolution of the skin disease with the feeding of a novel protein (elimination) diet, and reproduction of the skin disease by feeding the original diet (rechallenge).

Our purpose was to report the results of a retrospective study of 48 cats with CFA.

MATERIALS AND METHODS

A retrospective study was conducted on 48 cats with CFA examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) from 1988 to 2003. In addition, we reviewed the medical records of all cats with dermatologic disease that had undergone a novel diet trial. Inclusion criteria for CFA were the following:

1. Historical and clinical findings consistent with CFA.
2. The exclusion of other conditions that mimic the clinical aspects of CFA. This was accomplished by skin scrapings, flea combings, trichography, cytology, fungal culture, skin biopsy, and response to therapy as appropriate to each case.
3. Resolution of clinical signs with the feeding of novel protein (elimination) diet for 4 to 6 weeks. The diets were home-cooked or limited ingredient commercial diets.
selected on the basis of a detailed dietary ingredient history. If a reduction in severity of clinical signs was apparent after 4 to 6 weeks on the novel diet, this diet was continued until maximum improvement was seen.

4. Reproduction of clinical signs with the feeding of the original diet (rechallenge).

Medical records were reviewed for the following information:

1. Breed, sex, and age of onset of clinical signs.
2. Dermatological findings.
3. Results of elimination diet and rechallenge protocols.
4. Follow-up period.

Breed, age, and sex data for cats with CFA were compared with those for the general CUHA cat population for the same time period using the relative risk (RR) calculation.

\[
RR = \frac{\text{data for CFA cats}}{\text{data for CUHA cats}}
\]

An RR of 2.0 or greater was considered significant.

RESULTS

CFA was diagnosed in 3.4% (48/1407 cats) of the feline dermatology cases and 0.2% (48/22,135 cats) of all cats examined at the CUHA over a 15-year period. Fourteen of 48 (29.2%) cats were first-opinion consultations, and 34/48 (70.8%) cats had previously been seen by one or more veterinarians. Domestic shorthair cats accounted for 68.8% (33/48) of the cats with CFA, and 79.6% of the CUHA cat population (RR = 0.87). CFA was also diagnosed in domestic longhair (5 cases), Burmese (2 cases), Himalayan (2 cases), Maine coon (2 cases), Siamese (2 cases), and Abyssinian and Rex cats (1 case each). Burmese (RR = 11.35), Maine coon (RR = 4.88), and Himalayan (RR = 3.26) cats were over-represented.

Spayed females, castrated males, intact females, and intact males accounted for 56.3% (RR = 1.47), 29.2% (RR = 0.75), 10.3% (RR = 0.93), and 4.2% (RR = 0.42) of the cats with CFA. Hence, no sex predilection was evident.

The age at onset of clinical signs for clinical signs for CFA cats varied from 3 months to 15 years. The age of 8 cats (16.7%) with CFA was unknown. The age of onset of clinical signs was <3 years, 4 to 6 years, 7 to 9 years, and ≥10 years for 50%, 10.3%, 16.7%, and 6.2%, respectively, of the cats with CFA. By comparison, these same age groups accounted for 46.4% (RR = 1.07), 17% (RR = 0.6), 12.7% (RR = 1.32), and 23.6% (RR = 0.26), respectively, of the total CUHA cat population. Hence, no age group was over-represented.

The most common reaction pattern in cats with CFA was initially lesionless symmetrical pruritus (ILSP) which progressed to excoriations. It was present in 26/48 (54.2%) cats, as the only reaction pattern in 10/48 (20.8%) cats, and in conjunction with one or two other reaction patterns in 13 and 3 cases, respectively. The ILSP reaction pattern affected one or more of the following body regions: face (19 cats; 73.1%), ears (11 cats; 42.3%), neck (10 cats; 38.5%), axillae (4 cats; 15.4%), and paws (4 cats; 15.4%). Ears or paws were the only cutaneous sites affected in 1 cat (3.8%) each.

The second most common cutaneous reaction pattern was self-induced hair loss (SIHL). The skin in affected areas was grossly normal. SIHL was present in 20/48 (41.7%) cats, as the
only reaction pattern in 9/48 (18.8%) cats and in conjunction with one or two other reaction patterns in 9 and 2 cases, respectively. The SIHL reaction pattern affected one or more of the following body regions: abdomen (14 cats; 70%), legs (9 cats; 45%), back (8 cats; 40%), tail (1 cat; 5%), and paws (1 cat; 5%).

The third most common reaction pattern was miliary dermatitis (MD) characterized by multiple crusted papules. It was present in 12/48 (25%) cats, as the only reaction pattern in 4/48 (8.3%) cats, and in conjunction with one or two other reaction patterns in 7 and 1 cases, respectively. The MD reaction pattern affected one or more of the following body regions: back (12 cats; 100%), neck (6 cats; 50%), ears (4 cats; 33.3%), head (4 cats; 33.3%), and tail (4 cats; 33.3%).

The least common reaction pattern was the eosinophilic granuloma complex (EGC). It was present in 11/48 (22.9%) cats, as the only reaction pattern in 3/48 (6.3%) cats, and in conjunction with one or two other reaction patterns in 6 and 2 cats, respectively. Eosinophilic granulomas were present in 5 cats (45.4%): caudal thighs (2 cats), lower lip (2 cats), upper lip, face, and tongue (1 cat each). Indolent ulcers were present in 5 cats (45.4%): both upper lips (3 cats), right upper lip (2 cats).

Two or more cutaneous reaction patterns were simultaneously present in 54.2% (26/48) of our cats.

Secondary bacterial folliculitis, furunculosis, or both of these were present in 9/48 (18.8%) of the cats. All bacterial infections were confirmed cytologically (suppurative or pyogranulomatous inflammation with degenerate neutrophils and phagocytosed cocci). Cultures were not performed. Empirical systemic and topical antibiotic therapy resolved the bacterial infections. The bacterial infections occurred where the allergic reaction patterns were present: face (5 cats), neck (3 cats), back (2 cats), and legs (1 cat).

Nine cats (18.8%) with CFA had concurrent atopic dermatitis. These cats had one or more of the following cutaneous reaction patterns: ILSP (8 cats), SIHL (5 cats), MD (3 cats), and EGC (2 cats). In these cats, their dermatoses were reduced in severity by 50% to 80% with the feeding of a novel diet, and this improvement was lost when their previous diet was fed. The remaining 20% to 50% of their clinical signs were controlled by antihistamines (3 cats), dexamethasone every 7 to 10 days (2 cats), or allergen-specific immunotherapy (1 cat). For the other 4 cats, the remaining skin disease was deemed tolerable by the owners, and observation without treatment was chosen.

Only 1/48 (2.1%) cats was reported to have gastrointestinal disease (episodic vomiting and diarrhea). This cat’s gastrointestinal abnormalities resolved when the novel diet was fed, and recurred when the cat’s original diet was fed.

During the 15-year study period, 179 cats received a novel diet. Of these cats, 131 (73.2%) did not respond and were ultimately determined to have atopic dermatitis. Of the 48 cats with confirmed CFA, all showed initial reduction in severity of their clinical signs after consuming their novel diet for 3 to 6 weeks. The cats that required 6 weeks to show improvement had the SIHL reaction pattern (9 cats) or the EGC reaction pattern (3 cats). Maximum improvement was achieved after 6 to 10 weeks. All 48 cats had a recurrence of their dermatoses within 1 to 7 days after reintroduction of their original diets. Only 4 cats were fed single items from their previous diets: 2 cats reacted to milk, 1 cat to fish, and 1 cat to fish and beef. The other 44 cats were satisfactorily managed with carefully selected limited ingredient commercial foods. The commercial diets used contained duck and green pea,
venison and green pea, or lamb and green pea. Dietary management was successful for follow-up periods of 6 months to 11 years. Follow-up periods were >1 year to 11 years in 28/48 (58.4%) cats.

Medical treatment had been previously attempted in 21 of the 48 cats.

1. Methylprednisolone acetate, 20 mg/cat subcutaneously in 10 cats, satisfactory control in 3 (30%) of cats.
2. Dexamethasone, 0.2 mg/kg every 24 hours by mouth in 7 cats, satisfactory control in 5 (71.4%) cats.
3. Prednisolone, 2 mg/kg every 24 hours by mouth in 6 cats, satisfactory control in 1 (16.7%) cat.
4. Chlorpheniramine, 2 mg/cat every 12 hours by mouth in 2 cats, neither responded.
5. Clemastine, 0.67 mg/cat every 12 hours by mouth in 2 cats, neither responded.

Table 1. Substances Reported to Have Caused Cutaneous Food Allergy in the Cat

<table>
<thead>
<tr>
<th>Substance</th>
</tr>
</thead>
<tbody>
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<td>Dairy products (milk, cheese)</td>
</tr>
<tr>
<td>Fish</td>
</tr>
<tr>
<td>Beef</td>
</tr>
<tr>
<td>Chicken</td>
</tr>
<tr>
<td>Eggs</td>
</tr>
<tr>
<td>Commercial food (dry or canned)</td>
</tr>
<tr>
<td>Pork</td>
</tr>
<tr>
<td>Lamb and mutton</td>
</tr>
<tr>
<td>Horse meat</td>
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<tr>
<td>Whale meat</td>
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<tr>
<td>Rabbit</td>
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<tr>
<td>Clams</td>
</tr>
<tr>
<td>Cod liver oil</td>
</tr>
<tr>
<td>Mice</td>
</tr>
<tr>
<td>Benzoic acid</td>
</tr>
<tr>
<td>Gluten</td>
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<td>Corn</td>
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REFERENCE

Just as the macroscopic lesions associated with feline allergic dermatoses are quite variable, so are the microscopic findings. The classic microscopic patterns include: (1) superficial and deep perivascular-to-interstitial eosinophilic and lymphocytic dermatitis (the “miliary dermatitis” and “initial lesionless symmetrical pruritus” cutaneous reaction patterns), (2) mild pure superficial perivascular lymphocytic and mastocytic dermatitis (the “fur mowing” cutaneous reaction pattern), and (3) the eosinophilic granuloma complex (eosinophilic granuloma, eosinophilic plaque, indolent ulcer).

REFERENCES


SUPERFICIAL AND DEEP EOSINOPHILIC INFLAMMATION

Atopic dermatitis (AD), food hypersensitivity (FH), and flea-bite hypersensitivity (FBH) are the three most common allergic skin diseases in cats. The most common cutaneous reaction patterns in cats with these allergies are: miliary dermatitis (bilaterally symmetric crusted papules, especially prominent over the rump and around the neck), nonlesional pruritus (bilaterally symmetric pruritus, which initially involves clinically normal skin but leads to excoriations and dermatitis, especially on the face, neck, and pinnae), eosinophilic granuloma complex (eosinophilic plaques, eosinophilic granulomas, indolent ulcers), self-induced alopecia (bilaterally symmetric, self-induced hair loss, especially on the ventral surface of the abdomen and medial thighs, wherein the underlying skin appears normal), or combinations of these.

Histopathologic findings in skin-biopsy specimens from allergic cats are somewhat controversial. It is agreed that cats with eosinophilic plaques and eosinophilic granulomas have superficial and deep dermal-to-subcutaneous inflammation. Cats with self-induced alopecia have superficial dermal inflammation. However, descriptions of the histopathologic findings in skin-biopsy specimens from allergic cats with the miliary dermatitis reaction pattern are not consistent. Some authors indicate that the inflammation in this reaction pattern can be superficial and/or deep in AD, FH, and FBH, and attach no diagnostic significance to the depth of inflammation. Other authors indicate that deep inflammation is very suggestive of FH.

There are a limited number of published studies documenting the histopathologic findings in skin-biopsy specimens from cats with AD, FH, and FBH. Six cats with FH were reported to have superficial dermal inflammation. Five cats with AD were reported to have superficial and deep dermal inflammation, while one had only superficial dermal inflammation thirteen cats with FBH were reported to have superficial dermal inflammation, while two had superficial and deep inflammation.

Our purpose was to determine the depth of dermal eosinophilic inflammation in skin-biopsy specimens from cats with AD, FH, and FBH that presented with the miliary dermatitis or nonlesional pruritus cutaneous reaction patterns.

MATERIALS AND METHODS

A retrospective light-microscopic study of skin-biopsy specimens from 43 cats with allergic skin disease was performed. All biopsy specimens had been procured with a 6 mm biopsy punch, submitted to the Diagnostic Laboratory at the College of Veterinary Medicine at Cornell University, processed routinely for histopathological evaluation, and stained with hematoxylin and eosin. All cats were examined, diagnosed, and treated by dermatologists at the College of Veterinary Medicine at Cornell University.

Inclusion criteria included:

1. A diagnosis of AD, FH, or FBH had been established by standard clinical, laboratory, and therapeutic criteria. In brief, cats with AD had seasonal or nonseasonal disease, failed to respond to novel protein diets and flea control, and responded completely to systemic glucocorticoid therapy. Cats with FH had nonseasonal disease, failed to respond to flea control, responded completely to novel protein diets (4 to 6 weeks duration), and relapsed when their original diets were re-instituted (within 1 to 7
days). Cats with FBH had seasonal disease (spring through fall) and responded completely to flea control.

2. Affected cats had either miliary dermatitis or nonlesional pruritus as cutaneous reaction patterns.

3. No cat had received systemic glucocorticoid treatment for at least 3 weeks prior to skin biopsy.

4. Biopsy specimens were characterized by perivascular-to-interstitial inflammation. Superficial perivascular-to-interstitial inflammation is confined to the superficial dermis, while deep perivascular-to-interstitial inflammation also involves the deep dermis.

5. Eosinophils were a prominent inflammatory cell.

6. No confounding histopathological patterns (e.g., suppurative epidermitis or folliculitis indicating concurrent infection) or ulcers were present.

One section of tissue per cat was examined. If multiple specimens were present on a slide, the section with the least amount of artifact was chosen for evaluation.

RESULTS

Of the 43 cats that met the inclusion criteria, 14 had AD, 15 had FH, and 14 had FBH. Miliary dermatitis was the cutaneous reaction pattern in 7/14 cats with AD, 8/15 cats with FH, and 14/14 cats with FBH. Nonlesional pruritus was the cutaneous reaction pattern in 7/14 cats with AD, 7/15 cats with FH, and 0/14 cats with FBH. All cats with the nonlesional pruritus reaction pattern had self-induced excoriations when biopsies were performed. Thirty-nine of the 43 cats were domestic shorthair or domestic longhair. Cats ranged from 1.5 to 11 years old, and included 22 females and 21 males.

In 41/43 cats, the histopathological reaction pattern was both superficial and deep. In 40 of these 41 cats, superficial dermal inflammation was perivascular-to-interstitial, and deep dermal and superficial subcutaneous inflammation was perivascular and less intense (fewer inflammatory cells). In one of the 41 cats, the deep inflammation was more intense than the superficial inflammation. Two of the 43 cats had only superficial perivascular-to-interstitial inflammation.

As 41/43 cats had the same histopathological reaction pattern, no statistics were run; there was too little variation because almost all cats were the same.

There was no difference in histopathologic reaction pattern between cats with AD, FH, or FBH. Neither was there a difference in histopathologic reaction pattern between cats with clinical cutaneous reaction patterns of miliary dermatitis or nonlesional pruritus.

REFERENCE

INfiltrative lymphocytic mural folliculitis (ILMF) is a histopathological reaction pattern reported to occur in selected feline inflammatory dermatoses (Table 1). One of the authors (DWS) has long believed that ILMF is a common histopathological reaction pattern in inflammatory skin disorders of the cat, especially allergic dermatoses (eg, atopic dermatitis, flea allergy, food allergy).

The skin biopsy – when appropriately performed and interpreted – is an invaluable diagnostic aid in feline dermatology. A more complete understanding of the interpretation of the ILMF reaction pattern in cats could be of great benefit to veterinarians and their feline patients.

Our purposes were to determine (1) the prevalence of ILMF in skin-biopsy specimens from 354 cats with various inflammatory dermatoses, (2) the prevalence of ILMF in skin-biopsy specimens from 33 cats with normal skin, and (3) if ILMF was a common reaction pattern in cats with allergic dermatoses.

MATERIALS AND METHODS

A retrospective study of skin-biopsy specimens from 354 cats with inflammatory dermatoses was performed. All biopsy specimens had been submitted to the Section of Anatomic Pathology at the College of Veterinary Medicine at Cornell University, processed routinely for histopathological evaluation, and stained with hematoxylin and eosin. All diagnoses were confirmed by standard clinical, laboratory, histopathological, and therapeutic criteria. In addition, skin-biopsy specimens were taken from 33 cats with normal skin that had been submitted to our necropsy service.

Because we wanted to follow routine procedures in diagnostic pathology, serial sections were not routinely examined. Generally, serial sections are only done when infectious agents are suspected and special stains are required, as was the case in the cats with Alternaria dermatitis, bacterial cellulitis, bacterial pyogranuloma, cryptococcosis, eumycotic mycetoma, sterile panniculitis, and sterile pyogranuloma in our study. One section of tissue was examined per slide. If multiple specimens were present on a slide, the section with the least amount of artifact and numerous hair follicles was chosen for evaluation. One author (ASR), who was blinded to the diagnoses, examined all specimens for the presence of ILMF. For 33% of the cases with inflammatory skin disease and 100% of the normal cats, a second author (DWS) also examined the specimens to insure reproducibility of the findings. A histopathological diagnosis of ILMF was based on the following criteria:

1. Only lymphocytes were present in the wall of hair follicles (no neutrophils, eosinophils, or macrophages).
2. Inflammatory cells were not present in the hair follicle lumen.
3. Mural lymphocytes were accompanied by other signs of inflammation in various combinations (intercellular edema of the hair follicle wall; intracellular edema of follicular keratinocytes; perifollicular inflammation).

No attempt was made to quantitate the number of lymphocytes per hair follicle or the percentage of hair follicles affected per specimen. In cases wherein ILMF was a minor histopathological reaction pattern, the specimens were re-examined and the number of hair follicles with ILMF were recorded. The prevalence of ILMF for each dermatosis was determined.
Immunohistochemistry was performed on 6 cases (2 with atopic dermatitis, 2 with bacterial folliculitis/furunculosis, 2 with dermatophytosis) to help determine the immunophenotype of the lymphocytes present in hair follicle epithelium. Briefly, formalin-fixed, paraffin-embedded tissue was sectioned at 4 µm, mounted (Probe On Microscope Slides, Fisher Scientific, Pittsburgh, PA, USA) and deparaffinized. The sections were incubated with rabbit antihuman CD3 (CD3, Dako Corporation, 6392 Via Real, Carpinteria, CA, USA) at a 1:200 dilution and stained using a standardized strepavidin-biotin immunoperoxidase technique (Zymed Laboratories, Inc., San Francisco, CA, USA) and diaminobenzodine as the chromogen. Additional sections were incubated with nonimmune rabbit serum at a 1:200 dilution and processed in identical fashion to serve as negative controls. Normal feline lymph node was processed in identical fashion and incubated with the rabbit antihuman CD3 to serve as the positive control.

STATISTICAL ANALYSIS

The specimens were divided into two groups: those of allergic origin, and those of nonallergic origin. A Pearson’s chi-square test was used to determine if there was a statistically significant difference in the prevalence of ILMF in allergic versus nonallergic dermatoses. Significance was set at a P-value of ≤ 0.05 (2-sided).

Because anecdotal literature indicates ILMF is a feature of dermatophytosis, a continuity corrected confidence interval analysis was calculated to suggest the range of prevalences of ILMF among dermatophytosis cases (the sample size in our study [n = 8] was not large enough to allow a chi-square analysis).

RESULTS

The agreement between the two histopathological assessment (ASR and DWS) was 100%. Thirty-three of the 47 dermatoses evaluated had ILMF, with a prevalence (among the 33) varying from 10 to 100% if observed at all. ILMF was consistently present in the infundibular region of the hair follicles. Less commonly, ILMF also involved the isthmus of hair follicles. In 44 cases (6 eosinophilic granuloma, 20 eosinophilic plaque, 2 bacterial cellulitis, 5 bacterial folliculitis/furunculosis, 1 cryptococcosis, 1 phaeohyphomycosis, 6 sterile panniculitis, 2 sterile pyogranuloma, 1 xanthoma), ILMF was a minor histopathological reaction pattern, represented by 1 or 2 involved hair follicles at the periphery of a larger histopathological reaction pattern.

The prevalence of ILMF in allergic dermatoses (116 of 172 cats; 67%) was significantly greater (P <0.0001) than that in nonallergic dermatoses (61 of 182 cats; 33%). Cats with allergic dermatoses had a 4.1 times greater odds of having ILMF than cats with nonallergic dermatoses (95% confidence interval is 2.6 to 6.4). ILMF was present in 25% (2 of 8 cats) of the cases of dermatophytosis. The continuity corrected 95% confidence interval was 0% to 61%. ILMF was not observed in any of the normal skin specimens.

Immunohistochemistry revealed that the lymphocytes in hair follicle epithelium were CD3+ T-cells.
Table 1. Feline Inflammatory Dermatoses Wherein Infiltrative Lymphocytic Mural Folliculitis Has Previously Been Reported

<table>
<thead>
<tr>
<th>Dermatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse cutaneous drug reaction</td>
</tr>
<tr>
<td>Alopecia areata</td>
</tr>
<tr>
<td>Alopecia mucinosa</td>
</tr>
<tr>
<td>Degenerative mucinotic mural folliculitis</td>
</tr>
<tr>
<td>Demodiosis</td>
</tr>
<tr>
<td>Dermatophytosis</td>
</tr>
<tr>
<td>Food allergy</td>
</tr>
<tr>
<td>Idiopathy</td>
</tr>
<tr>
<td>Pseudopelade</td>
</tr>
<tr>
<td>Sebaceous adenitis</td>
</tr>
<tr>
<td>Thymoma-associated exfoliative dermatitis</td>
</tr>
</tbody>
</table>

REFERENCE

APOPTOTIC EPIDERMAL KERATINOCYTES

Apoptosis is cell death that occurs in a programmed fashion in physiological and pathological processes. Apoptosis is an active process that requires energy and protein synthesis and is comprised of two distinct phases: nuclear condensation and phagocytosis and clearance of fragments by adjacent cells. Apoptosis is under genetic control and occurs via an extrinsic or death receptor pathway and an intrinsic or mitochondrial pathway. It can be initiated by several extracellular factors such as hormones, cytokines, chemical, physical and infectious agents, or cytotoxic T lymphocytes. Apoptosis differs from oncosis (oncotic necrosis), or accidental cell death that occurs after cellular injury, and does not result in the release of inflammatory mediators into the surrounding tissues. Apoptosis can be recognized by light microscopy and is characterized by cell shrinkage, margination of nuclear chromatin, and nuclear pyknosis and karyorrhexis. Terminal uridyl transferase nick and labeling (TUNEL) and immunohistochemistry can be used to validate morphological criteria by detecting DNA fragmentation, but the specificity of these methodologies has been questioned.

Anecdotal information indicates that (1) apoptotic keratinocytes (AKs) are rarely seen (one or two in a section through a 6-mm skin-biopsy specimen) in normal epidermis, and (2) AKs may be seen in small numbers in virtually any hyperplastic epidermis. However, more recent studies indicate that AKs are rarely seen in 6-mm skin biopsy specimens of normal skin from horses (a single AK seen in two of 45 [4%] horses) and cats (a single apoptotic keratinocyte seen in one of 33 [4%] cats). In addition, there was no correlation between the number of AKs and the extent of epidermal hyperplasia.

Apoptotic keratinocytes are a key histopathologic feature in certain immune-mediated dermatoses, solar-induced dermatitis, and certain viral dermatopathies in dogs, horses, cats, and humans, though they are occasionally found in smaller numbers in other inflammatory dermatoses. A recent light-microscopic study looking at the frequency of AKs in various inflammatory dermatoses of the cat reported that – in dermatoses not expected to have high numbers of AKs – ectoparasitic diseases had a higher number of AKs than other inflammatory dermatoses. When examining these cases further, eosinophils were occasionally seen directly adjacent to AKs in flea-bite hypersensitivity, cheyletiellosis, and mosquito-bite hypersensitivity.

Epidermal AKs are most commonly reported in association with dermatoses characterized by an interface histopathologic pattern. These dermatoses are typically characterized by an exocytosis of lymphocytes, some of which may be seen adjacent to AKs (so-called “satellite cell apoptosis”). It has also been reported that neutrophils can be found adjacent to AKs in cases of pemphigus foliaceus and toxic shock-like syndrome in dogs. Whether or not these activated neutrophils release granule contents and cytotoxic substances that trigger apoptosis is unknown.

To our knowledge, the prevalence of eosinophils in dose proximity to AKs in eosinophilic dermatoses of any species has not been previously reported. The role of eosinophils in causing apoptosis of epidermal keratinocytes has been called into question by findings. Because apoptotic cells do not release their cellular components into the surrounding interstitial tissue and are quickly phagocytosed, virtually no inflammatory reaction is incited, making it unlikely that the apoptotic epidermal cells are inducing eosinophil migration.

Our purposes were to determine: (1) the prevalence of AKs in eosinophilic inflammatory dermatoses of the cat, (2) the prevalence of eosinophils in dose proximity to AKs, and (3)
the association – if any – between the prevalence of AKs and eosinophils in proximity to AKs based on histopathologic reaction pattern.

MATERIALS AND METHODS

A retrospective light-microscopic study of skin-biopsy specimens from 145 cats with eosinophilic inflammatory dermatoses was performed. All biopsy specimens had been submitted to the Pathology Service at the Cornell University College of Veterinary Medicine, processed routinely for histopathological evaluation, and stained with hematoxylin and eosin (H&E). All diagnoses had been established previously via standard clinical, laboratory, and histopathological criteria (Table 1). One author (JSG), who was blinded to the diagnoses, examined all specimens for epidermal AKs, and the presence of eosinophils or lymphocytes in close proximity to the AKs.

One 6-mm section was examined at 400X magnification from each of the 145 specimens. In order to duplicate routine procedures in diagnostic dermatopathology, only one section of tissue from each specimen was examined. If multiple specimens were present on a slide, the section fulfilling the inclusion criteria and containing the least amount of artifact was chosen for evaluation. Specimens were excluded if no epidermis was present, if the epidermis was <6 mm in length, or if eosinophilic dermatitis was not present. Eosinophilic dermatitis was defined as an inflammatory reaction wherein eosinophils were prominent in the cellular infiltrate. Each specimen was examined for the presence, number, and location of AKs within the epidermis. An AK was defined as a keratinocyte with the following characteristics: cell shrinkage, dense eosinophilic cytoplasm, nuclear pyknosis and/or karyorrhexis, and margination of nuclear chromatin. Specimens which contained AKs were then examined for any eosinophils in close proximity to the AK. Close proximity was defined as eosinophils directly adherent to or within 100 µm of the AK. Lymphocytic exocytosis within that field at 400X magnification was also noted.

STATISTICAL ANALYSIS

All statistical methods were performed using Statistix 9.0. The prevalence of AKs in eosinophilic dermatoses of the cat and its 95% Wilson score continuity-corrected confidence interval (CI) was calculated. From the cases which had AKs present, the prevalence of eosinophils in close proximity to those AKs was calculated along with the 95% CI. The prevalence of lymphocytes (seen in only 4/145 specimens) in close proximity to the AKs was so low that this was seen as insignificant and excluded from further analysis.

The specimens were separated into 3 groups based on their histologic reaction pattern – perivascular-to-interstitial, diffuse, and nodular – in order to determine whether the presence of AKs or eosinophils in close proximity to AKs was associated with histologic pattern. The association between AKs and the 3 histologic patterns was determined based on chi-square test. When analyzing the data containing eosinophils in close proximity to AKs, the sample size was too small to fulfill the assumptions of the chi-square test. The data were dichotomized by comparing the nodular pattern to the other two patterns and tested by Fisher’s exact test. Whether or not the presence of eosinophils in close proximity to AKs was associated with the nodular or non-nodular pattern also was tested using the one-sided Fisher’s exact test.
The Wilcoxon rank-sum test was used to determine whether the number of AKs was associated with the presence of eosinophils in close proximity. Alpha equals 5% was used for our tests.

RESULTS

One or more AKs were present in 43% (62 of 145; 95% CI = 35%, 51%) of cats with eosinophilic dermatoses (Table 1). Of the 62 cases that had AKs present, 18% (11 of 62; 95% CI = 10%, 30%) had eosinophils in close proximity (Table 1). We found no association between the prevalence of AKs and the 3 histologic patterns (chi-square = 1.74, df = 2, P = 0.42). Eosinophils being in close proximity to AKs was, likewise, not associated with the nodular or non-nodular histologic patterns (P = 0.21, two-sided). A higher number of AKs was associated with having eosinophils in close proximity (the minimum, median [P = 0.03, one-sided], and maximum AKs were 1, 2, 9 if eosinophils were in close proximity, and 0, 0, 7 otherwise).

Table 1. Prevalence of Apoptotic Epidermal Keratinocytes (AKs) in Eosinophilic Inflammatory Dermatoses in 145 Cats

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># Cases</th>
<th># Cases with AKs</th>
<th>Total AKs</th>
<th># Cases with eosinophils in proximity to AKs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food hypersensitivity</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>57</td>
<td>17</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Flea-bite hypersensitivity</td>
<td>12</td>
<td>8</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Cheyletiellosis</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Trombiculosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mosquito-bite hypersensitivity</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>23</td>
<td>9</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilic plaque</td>
<td>30</td>
<td>15</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Indolent ulcer</td>
<td>11</td>
<td>6</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

REFERENCE

EPITHELIAL MAST CELLS

Dermal mast cells have been extensively studied and voluminously described in the literature. In humans, cutaneous mast cells have been mapped and quantitated, and their close association with dermal blood vessels emphasized. Remarkably, such studies make no mention of epidermal mast cells. In addition, modern textbooks devoted to the anatomy, physiology, histopathology, and diseases of human skin do not acknowledge the existence of epidermal mast cells.

However, there is ample reason to suspect that mast cells occur with some frequency in the normal and abnormal human epidermis. Zelickson states that examination of the normal human epidermis by electron microscopy often reveals mast cells. Others have reported epidermal mast cells in a wide variety of human dermatoses.

In the cat, numerous studies have commented on the dermal mast cells. However, neither in these studies nor in standard textbooks of veterinary dermatology and veterinary pathology, can one find the mention of an epidermal mast cell in cats (nor any other domestic species). Recently, epidermal mast cells were observed in one of 14 cats with cutaneous mast cell neoplasms.

The purpose of this paper is to report the results of a retrospective study of 338 cats with non-neoplastic skin disease, as well as 4 normal cats, which was directed at determining the frequency of occurrence of epidermal mast cells in cat skin biopsies.

MATERIALS AND METHODS

A retrospective histopathological study was performed on skin biopsies from 338 cats with non-neoplastic skin disorders. Skin biopsies from 4 normal cats were similarly studied. All biopsies had been routinely processed for histopathological examination and stained with hematoxylin and eosin and acid orcein-Giemsa.

RESULTS

The diagnoses were established by standard clinicopathological and therapeutic criteria. Thirty-seven (11.6%) of these cases had demonstrable mast cells within the epidermis (Table 1). Epidermal mast cells were not observed in the biopsies from the 4 normal cats.

Mast cells were present diffusely and, occasionally, focally within the surface epidermis, and often within the outer root sheath of hair follicles. Mast cells occurred singly and were usually confined to the intercellular spaces of the basal and immediately suprabasal layers of the epithelium. Occasionally, isolated mast cells were found in the middle and upper layers of the epidermis. Thirty-three (89.2%) of the dermatoses wherein epidermal mast cells were found were characterized by significant tissue eosinophilia.
Table 1. Dermatoses in 37 Cats Wherein Epidermal Mast Cells Were Found

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic plaque</td>
<td>16</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>6</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>3</td>
</tr>
<tr>
<td>Allergy</td>
<td>2</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>2</td>
</tr>
<tr>
<td>Idiopathic lichenoid dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Sterile eosinophilic folliculitis</td>
<td>2</td>
</tr>
<tr>
<td>Atopy</td>
<td>1</td>
</tr>
<tr>
<td>Flea-bite hypersensitivity</td>
<td>1</td>
</tr>
<tr>
<td>Indolent ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>1</td>
</tr>
</tbody>
</table>

REFERENCE

LYMPHOID NODULES

Lymphoid nodules are defined as well-circumscribed, rounded, dense, usually perivascular accumulations of predominantly mature lymphocytes. Lymphoid nodules are found with varying frequency in a number of benign and malignant skin diseases of humans. In veterinary medicine, cutaneous lymphoid nodules are reported to occur uncommonly, usually in association with dermatoses of presumed immune-mediated origin.

The present report details the results of a retrospective histopathologic study of non-neoplastic skin diseases of dogs, cats, and horses, wherein the occurrence of lymphoid nodules was recorded.

MATERIALS AND METHODS

A retrospective histopathologic study was performed on skin biopsies from 3,408 dogs, 469 cats, and 325 horses with non-neoplastic skin disorders. All biopsies had been routinely processed for histopathologic examination and stained with hematoxylin and eosin.

All biopsies were read blindly (without prior knowledge of the diagnosis), given a pathologic diagnosis, and examined closely for the presence of lymphoid nodules. The final diagnoses in all cases had been established by standard clinicopathologic and therapeutic criteria.

RESULTS

Lymphoid nodules were found in 11 of 3,408 (0.3%) canine, 24 of 469 (5.1%) feline, and 15 of 325 (4.6%) equine skin biopsies (Table 1). In the dog, the majority of cases wherein lymphoid nodules were found were panniculitides and immunologic disorders. In the cat, the majority of cases were the eosinophilic granuloma complex and panniculitides. In the horse, the majority of cases were diseases characterized by tissue eosinophilia and presumed immune-mediated nature.

In the specimens examined, lymphoid nodules were always multiple, and occurred in the deep dermis and subcutis. Lymphoid nodules were characterized discrete, dense, nodular, perivascular accumulations of primary lymphocytes. Plasmas cells and histiocytes were present in small numbers. Neutrophils and eosinophils were found within the lymphoid nodules in only 2 biopsies, and only in small numbers. In general, lymphoid nodules occurred peripheral to, and often appeared to surround, the primary pathologic process. There was no apparent correlation between the number, size, or position of lymphoid nodules and any particular disease or prognosis.
Table 1. Lymphoid Nodules in Feline Skin Biopsies

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Total number of biopsies</td>
<td>469</td>
</tr>
<tr>
<td>Total number of biopsies positive for lymphoid nodules</td>
<td>24</td>
</tr>
<tr>
<td>Percentage of biopsies positive for lymphoid nodules</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Number of specific diseases positive for lymphoid nodules:

- 11 Eosinophilic plaque
- 7 Idiopathic sterile panniculitis
- 3 Eosinophilic granuloma
- 1 Indolent ulcer
- 1 Allergy*
- 1 Bacterial pseudomyxoma (botryomycosis)

*Seasonal allergic dermatitis, presumably atopy and/or flea-bite hypersensitivity.

REFERENCE

MAST CELL NUMBERS

The role of mast cells in the cutaneous immune system of cats has been reviewed. Mast cells are normal residents of connective tissue, and are found in highest numbers in regions of the body that interface with the environment: skin, lung, and gastrointestinal tract. In addition to their antigen-specific role in the development of allergic inflammation in the skin, mast cells are important in the innate defense against bacteria, and in wound healing.

Small studies of hematoxylin and eosin (H&E)-stained biopsy specimens taken from normal cat skin have indicated that mast cell numbers vary from 4 to 20 per 400X microscopic field in the superficial dermis. For the most part, no consistent regional variation in the number of mast cells has been found in the normal skin of cats. Only Foster—evaluating toluidine blue (TB)-stained biopsy specimens—reported a significantly higher number of mast cells in the normal skin of the pinnae of cats.

A number of special stains are used to accentuate the cytoplasmic granules of mast cells, thus making the cells more easily identified: TB, Giemsa, acid-orcein Giemsa, periodic acid-Schiff, and Alcian blue. Of these special stains, TB is probably the most commonly used. Although several investigators have simultaneously used H&E and a special stain to evaluate mast cell numbers in normal cat skin, only the data for the special stains were reported. Hence, it is not known how mast cell numbers in H&E-stained specimens compared with those in the same specimens colored with special stains.

The numbers of mast cells in biopsy specimens from cats with inflammatory and allergic skin diseases are often higher than those in normal cat skin. In routine diagnostic dermatopathology, large numbers of mast cells are often reported to be “consistent with allergic skin disease”. However, one of us (DWS) has long believed that the numbers of mast cells in biopsy specimens from cats with inflammatory dermatoses are of no diagnostic value, being in normal or increased numbers in numerous conditions.

The purpose of this article is to report the results of a retrospective study of mast cell numbers in biopsy specimens from 371 cats with various inflammatory dermatoses and 31 cats with normal skin. We wanted to assess differences in mast cell numbers in (1) allergic versus nonallergic versus normal cats, (2) superficial dermis versus deep dermis, and (3) H&E- versus TB-stained sections of normal skin.

MATERIALS AND METHODS

A retrospective study of skin-biopsy specimens from 371 cats with inflammatory dermatoses was performed. All biopsy specimens had been submitted to the Section of Anatomic Pathology at the College of Veterinary Medicine at Cornell University between 1978 and 2010, processed routinely for histopathological evaluation, and stained with hematoxylin and eosin (H&E). All diagnoses were confirmed by standard clinical, laboratory, histopathological, and therapeutic criteria. In addition, skin-biopsy specimens were taken from the dorsolateral thorax of 31 cats with normal skin that had been submitted to our necropsy service.

Because we wanted to follow routine procedures in diagnostic pathology, serial sections were not routinely performed. One section of tissue was examined per slide. If multiple specimens were present on a slide, the section with the least amount of artifact was chosen for evaluation. Because special stains for mast cells are rarely, if ever, applied to feline...
inflammatory dermatoses in routine diagnostic pathology, only H&E-stained specimens were examined.

One author (MT), who was blinded to the diagnoses, examined all specimens for the presence of mast cells. For 25% of the cases with inflammatory skin disease and 33% of the normal cats, a second author (DWS) also examined the specimens to ensure reproducibility of the findings.

Mast cells were counted in six 400X microscopic fields (HPF) – 3 in the superficial dermis, 3 in the deep dermis – in all specimens. Each microscopic field contained at least one vascular plexus. The superficial dermis was defined as the region superficial to the sebaceous glands. The deep dermis was defined as the region deep to the sebaceous glands. Three HPF – one from each end of the specimen and one in the center – were evaluated for the number of mast cells. This was performed in the superficial and deep dermis. We also wanted to describe the variation in the numbers of mast cells counted in each set of 3 HPF, to indicate the need (or not) to examine multiple HPF rather than only a single HPF.

Mast cells were only counted in areas of perivascular or interstitial inflammation. Areas of nodular or diffuse inflammation – wherein individual mast cells are more difficult to visualize and count – were not evaluated.

For the specimens of normal skin, additional slides were prepared and stained with toluidine blue (TB). Mast cells were counted in six HPF – 3 in the superficial dermis and 3 in the deep dermis – as described above. Author MT examined the TB-stained sections at a separate time from the H&E evaluations, and was blinded to the mast cell counts she had recorded for the sections stained with H&E.

STATISTICAL ANALYSIS

We separately calculated the median number of mast cells in the superficial and deep dermis of each cat. The data were analyzed using standard software, the Statistix® 10 program (2013, Analytical Software, Tallahassee, Florida, USA). Shapiro-Wilk normality tests showed that at least some of the data were not normally distributed. Bonferroni-type corrections were imposed to adjust for the multiplicity of formal hypothesis tests. Two Kruskal-Wallis tests (rank-based 1-way ANOVAs) were used for comparison of the mast cell numbers (separately in superficial and deep dermis; followed if needed by a Dunn’s all-pairwise comparison) between cats with normal skin, allergic diagnoses, and nonallergic diagnoses.

The cut-off $P$-value was 0.025 (0.05/2) because the comparison between the diagnostic groups was the primary hypothesis. To assess the variation in the numbers of mast cells counted in each set of 3 HPF, we calculated the difference (i.e., range) between the highest and lowest count of mast cells within each set of 3 HPF in the H&E-stained slides (there were 2 such ranges for each cat: 1 for the superficial dermis, and 1 for the deep dermis). If the range by inspection were a small, trivial number (especially if zero, meaning that all 3 counts were identical), then the need to count multiple HPF would not be demonstrated.

However, if the range were by inspection clinically nontrivial, then that would confirm the need to take the time to count multiple HPF in each stratum, for each patient. To examine the difference in mast cell numbers between the superficial and deep dermis of each diagnostic group, the Wilcoxon signed-rank test was used. The cut-off $P$-value was 0.0033 (a lower alpha of 0.01, divided by 3 tests). Furthermore, the test was also carried out in the comparison of the mast cell numbers between H&E-stained and TB-stained normal cat skin.
The cut-off $P$-value was 0.005 ($=0.01/2$); this was done separately for the superficial and deep dermis.

RESULTS

The median mast cell count in the superficial dermis did not differ significantly between groups ($P=0.030$). However, the median number of mast cells in the deep dermis differed significantly between normal skin and inflammatory dermatoses. The median count for the deep dermis of normal skin was lower ($P<0.0001$) than the medians of the other two diagnostic groups (which themselves did not differ).

In normal skin, mast cells were never more abundant in the deep dermis than in the superficial dermis in the same cat, and were often more abundant in the superficial dermis ($P<0.0001$). Similarly (but without the same exclusivity), there were significantly more mast cells ($P<0.0001$) in the superficial than in the deep dermis from skin biopsies of both the allergic and nonallergic skin-disease groups.

Significantly more mast cells were detected in the superficial dermis of normal skin when stained with TB than with H&E ($P=0.0005$): 21 of 31 cats had 1 to 7 more mast cells counted with TB than with H&E. However, there was no significant difference in the mast cells count in the deep dermis between TB-stained and H&E-stained specimens ($P=0.58$).

REFERENCE

Tunhikorn M, Scott DW and Erb HN. The significance of the numbers of mast cells in the evaluation of skin-biopsy specimens from cats with inflammatory dermatoses. (Submitted for publication 2015).
EOSINOPHILIC FOLLICULITIS AND FURUNCULOSIS

Eosinophilic folliculitis and furunculosis may be seen as minor, focal histologic changes in cats with atopic dermatitis, food allergy, and flea allergy. The follicular inflammation that characterizes mosquito allergy is eosinophilic, infiltrative, and necrotizing.

REFERENCES


EPITHELIAL MUCINOSIS

Epithelial mucinosis (epidermal and/or follicular) is seen in cats with allergic dermatoses.

REFERENCES


THE “TWANG” SIGN

Dr. Bob Dunstan (then at Michigan State University, 1990s) was the first person to use the term “twang sign” in a lecture on dermatopathology. He was describing the coiled, corkscrewed, sometimes dysplastic hair shafts in the hair follicle of hair-pulling cats.
EOSINOPHILIC GRANULOMAS AND STAPHYLOCOCCAL INFECTION

Granulomatous-to-pyogranulomatous dermatitis with marked accumulation of eosinophils (eosinophilic granuloma) is a common cutaneous reaction pattern in horses. Several equine dermatoses are characterized by eosinophilic granulomatous inflammation (Table 1).

CASE REPORTS

Case 1

A 5-year-old crossbred stallion was presented to the Cornell University Hospital for Animals (CUHA) with a several week history of an “abscess” on the ventral surface of the left mandibular area, which was followed by the appearance of similar lesions on the right pectoral area and dorsal neck. There was no history of trauma, vaccination, deworming, or medication preceding the onset of lesions. Previous skin-biopsy specimens sent to a commercial veterinary diagnostic laboratory were interpreted to represent the equine eosinophilic granuloma. Therapy with dexamethasone (0.1 mg/kg given orally, once daily) for 7 days produced minimal improvement.

On presentation to the CUHA, the stallion was in good health except for the skin lesions. The lesions were raised, deep-seated, poorly circumscribed, firm nodules and plaques. Alopecia, crusting, and hyperkeratosis were present on the surface of the lesions. The mandibular skin lesion had focal areas of purulent discharge. The lesions seemed to be mildly pruritic.

Routine hemogram and serum biochemistry results were unremarkable. Cytological findings in a direct smear included numerous eosinophils, macrophages, and degenerate-to-nondegenerate neutrophils. Some neutrophils contained phagocytosed cocci. Routine radiographs of the mandibular area revealed no involvement of underlying bone.

Skin-biopsy specimens were taken for bacterial and fungal culture, as well as histopathological examination. A coagulase-positive Staphylococcus sp. (not speciated) was isolated in pure culture. It was susceptible to a number of antibiotics, including trimethoprim-sulfamethazole. Histopathological examination revealed diffuse eosinophilic granulomatous dermatitis with multifocal areas of collagen flame figures and necrosis. Throughout the inflammation were small, multifocal areas of neutrophil accumulation. Special stains (Gram, Gomori methenamine silver) were negative for fungi and bacteria.

The final clinicopathological diagnosis was eosinophilic granuloma associated with staphylococcal infection. The stallion was treated with dexamethasone (0.1 mg/kg given orally, once daily) for 5 days, and trimethoprim-sulfamethazole (15 mg/kg given orally, twice daily) until 7 days beyond clinical resolution. Total duration of antibiotic treatment was 4 weeks. There was no relapse during a 9-month follow-up period.
Case 2

A 10-year-old Warmblood mare was presented to the CUHA with a 6-week history of skin lesions beginning below the left eye. The lesions enlarged but did not appear to be painful or pruritic. There was no history of trauma, vaccination, deworming, or medication preceding the onset of lesions. The mare was treated with flunixin meglumine (1 mg/kg given intramuscularly, once daily) and trimethoprim-sulfadiazine (70 mg/kg given orally, once daily) for 2 days, during which time the lesions failed to improve. The local veterinarian then administered ceftriaxone (2.2 mg/kg given intravenously, once daily) for 6 days, during which time more lesions appeared. A skin-biopsy specimen sent to a commercial veterinary diagnostic laboratory was interpreted to be consistent with the equine eosinophilic granuloma. Treatment with dexamethasone (0.1 mg/kg given orally, once daily) for 7 days was unsuccessful.

On presentation to the CUHA, the mare was in good health except for the skin lesions. Firm papules, nodules, and plaques were present on the face, brisket, shoulder, and right side of the neck. Many lesions were alopecic and crusted, some had a purulent discharge, and some were covered by a normal-appearing integument. Larger lesions were warm and somewhat painful.

Routine hemogram and serum biochemistry findings were unremarkable. Cytological findings in a direct smear included numerous eosinophils, macrophages, and degenerate-to-nondegenerate neutrophils. Some neutrophils contained phagocytosed cocci. Skin-biopsy specimens were procured for bacterial and fungal culture, as well as histopathological examination. Staphylococcus aureus was isolated in pure culture, and was susceptible to several antibiotics, including trimethoprim-sulfamethazole. Histopathological findings were as described for case 1.

The final clinicopathological diagnosis was eosinophilic granuloma associated with \textit{S. aureus} infection. The mare was treated with dexamethasone (0.1 mg/kg given orally, once daily) for 5 days and trimethoprim-sulfamethazole (15 mg/kg given orally, twice daily) until 7 days beyond clinical resolution. Total duration of treatment was 4 weeks. There was no relapse during a 6-month follow-up period.
Table 1. Causes of Eosinophilic Granulomatous Dermatitis in Horses

<table>
<thead>
<tr>
<th>Fungal Infections</th>
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<tbody>
<tr>
<td>Pythiosis (Pythium sp)</td>
<td>Zygomycesis (Basidiobolus sp., Conidiobolus sp., Absidia sp.)</td>
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<td>Parasitic Infections</td>
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<tr>
<td>Habronemiasis (Habronema sp., Draschia sp.)</td>
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<td>Parafilariasis (Parafilaria sp.)</td>
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<td></td>
<td>Insect- and tick-bite granulomas</td>
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<tr>
<td>Miscellaneous Conditions</td>
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<tr>
<td>Eosinophilic granuloma (idiopathic; silicone needles; free hair shafts; allergic reactions)</td>
<td></td>
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<tr>
<td>Axillary nodular necrosis</td>
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<tr>
<td>Sterile eosinophilic furunculosis</td>
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REFERENCE

MULTINUCLEATED HISTIOCYTIC GIANT CELLS

Multinucleated histiocytic giant cells (MHGC) are commonly seen in cutaneous granulomas produced by a wide variety of known and unknown agents. It is widely accepted that MHGC formation results from the fusion of macrophages, which appears to be the incidental result of macrophages ingesting material in close apposition to other macrophages.

MHGC assume 3 classical morphological forms in skin-biopsy specimens: (1) Langhans’-type (nuclei form a circle or semi-circle at the periphery of the cell); (2) foreign body-type (nuclei scattered throughout the cell cytoplasm); and (3) Touton-type (a central core of homogeneous cytoplasm is surrounded by a wreath of nuclei, which is in turn surrounded by abundant foamy cytoplasm. Touton-type MHGC are usually seen in response to lipids (e.g., xanthomas). The importance of the Langhans’-type and foreign body-type of MHGC is unclear. Both types are present in most skin lesions in humans, and MHGC that show a nuclear arrangement intermediate between the two are often seen. The elegant experiments of Mariano and Spector (1974) indicated that the Langhans’-type and foreign body-type of MHGC represent not distinct cell types but different degrees of nucleocytoplasmic organization or activation. In fact, both types of MHGC are simultaneously produced from peripheral blood monocytes treated with supernatants of concanavalin A-stimulated mononuclear cells, suggesting that the two types of MHGC are identical except for the arrangement of their nuclei. Recent studies have shown that the surface markers for monocyte-macrophages lineage cells were the same for Langhans’-type and foreign body-type MHGC.

Granulomatous inflammation – which often contains MHGC – is seen in a number of infectious, noninfectious, immune-mediated, and idiopathic skin conditions in humans. MHGC have also been observed in various granulomatous and nongranulomatous equine dermatoses. In those reports, the prevalence, number, and morphological type of MHGC typically were not indicated.

The skin biopsy – when appropriately performed and interpreted – is an informative and invaluable diagnostic aid in equine dermatology. However, we found no published studies wherein the light-microscopic prevalence and number of MHGC and their morphological types were evaluated in equine inflammatory dermatoses.

Our aims in this study were: (1) to determine the prevalence and number of MHGC in equine inflammatory dermatoses; (2) to determine the morphological types of MHGC found in equine inflammatory dermatoses; and (3) to determine if there was an association between the prevalence, number, and morphological type of MHGC and particular categories of dermatoses.
MATERIALS AND METHODS

A retrospective study of skin-biopsy specimens from 335 horses with inflammatory dermatoses was performed. All biopsy specimens had been submitted to the Pathology Service at the College of Veterinary Medicine at Cornell University, processed routinely for histopathologic evaluation, and stained with hematoxylin and eosin. All diagnoses were confirmed by standard clinical and histopathologic criteria. In addition, 27 skin-biopsy specimens were taken from horses with normal skin that had been submitted to our necropsy service. The specimens of normal skin and 265 of the diseased skin specimens were procured from the dorsolateral trunk.

Because we wanted to follow routine procedures in diagnostic pathology, serial sections were not examined. One section of tissue was examined per slide. If multiple specimens were present on a slide, the section with the least amount of artifact and the most MHGC in a 6 mm-long segment was chosen for evaluation. One author (RDC), who was blinded to the diagnoses, examined all specimens for MHGC. If many MHGC were immediately apparent, the specimen was scanned for the area with the greatest density of MHGC. The number of MHGC in that one 100X magnification microscopic field was counted, and the MHGC were classified as to morphological type (Langhans’, foreign-body, Touton). If a specimen did not contain an area with at least 10 MHGC per 100X magnification microscopic field, the MHGC in the entire 6 mm segment were counted and classified as to morphological type.

After the individual specimens were evaluated, they were divided into 5 groups (Table 2): normal skin (n=27), infectious granulomatous dermatoses (n=43), noninfectious granulomatous dermatoses (n=59), infectious nongranulomatous dermatoses (n=60), and noninfectious nongranulomatous dermatoses (n=173).

STATISTICAL ANALYSIS

The analysis was stratified based on whether one 100X field or an entire 6 mm segment was evaluated for number and morphological type of MHGC. The Fisher’s exact test was used to distinguish a difference between granulomatous and nongranulomatous dermatoses and category (single versus all) microscopic field evaluated. Once this distinction was made, the Kruskal-Wallis test was performed to compare the 5 groups based on numbers of MHGC. The Wilcoxon’s signed-rank test for paired data was performed to evaluate which morphological type of MHGC was most numerous. The statistical program used was Statistix™ 9.0. For all analyses, a P-value of <0.05 was considered significant.

RESULTS

The prevalence of MHGC varied from 0 to 100% in granulomatous dermatoses (although most dermatoses had ≥57% prevalence), and from 0 to 50% in nongranulomatous dermatoses (most dermatoses had ≤36% prevalence). There were significantly more MHGC associated with infectious and noninfectious granulomatous dermatoses than with infectious and noninfectious nongranulomatous dermatoses (P <0.0001). The number of MHGC in granulomatous dermatoses of infectious and noninfectious origins were not significantly different (P ≥0.21) if only a single 100X magnification microscopic field was evaluated. Foreign-body-type MHGC were consistently more numerous than Langhans’-type MHGC in all diseases except exuberant granulation tissue (P <0.0001). Touton-type MHGC were not seen. MHGC were not found in normal skin.
INFILTRATIVE LYMPHOCYTIC MURAL FOLLICULITIS

Infiltrative lymphocytic mural folliculitis (ILMF) is a histopathological reaction pattern characterized by the infiltration of lymphocytes into the outer root sheath epithelium of hair follicles. It has been reported to occur in a small number of mostly uncommon-to-rare equine inflammatory dermatoses: dermatophytosis, demodicosis, lupus erythematosus, erythema multiforme, adverse cutaneous drug reaction and alopecia areata. One of the authors (DWS) has long believed that ILMF is a common histopathological reaction pattern in inflammatory skin disorders of the horse, especially allergic skin diseases (e.g., atopic dermatitis, insect-bite hypersensitivity).

The skin biopsy – when appropriately performed and interpreted – is an invaluable diagnostic aid in equine dermatology. A more complete understanding of the interpretation of the ILMF reaction pattern in horses could be of benefit to veterinarians and their equine patients.

The aims in this study were to determine: (1) the prevalence of ILMF in skin-biopsy specimens from 250 horses with various inflammatory dermatoses; (2) the prevalence of ILMF in skin-biopsy specimens from 27 horses with physically healthy skin; and (3) whether ILMF was a common reaction pattern in horses with allergic dermatoses.

MATERIALS AND METHODS

A retrospective study of skin-biopsy specimens from 250 horses with inflammatory dermatoses was performed. All biopsy specimens had been submitted to the Pathology Service at the College of Veterinary Medicine at Cornell University, processed routinely for histopathology and stained with haematoxylin and eosin. All diagnoses were confirmed by standard clinical, laboratory, histopathological and therapeutic criteria. In addition, skin-biopsy specimens were taken from 27 horses with physically healthy skin that had been submitted to the necropsy service. The specimens of physically healthy skin and 201 of the diseased skin specimens were procured from the dorsolateral trunk.

Because routine procedures in diagnostic pathology were to be followed in this study, serial sections were not examined. One section of tissue was examined per slide. If multiple specimens were present on a slide, the section with the least amount of artifact was chosen for evaluation. One author (KY), who was blinded to the diagnoses, examined all specimens for ILMF. For 31% of the cases with inflammatory skin disease and 100% of the normal horses, a second author (DWS) also examined the specimens to insure reproducibility of the findings. A histopathological diagnosis of ILMF was based on the following criteria:

1. Only lymphocytes were present in the wall of hair follicles (no neutrophils, eosinophils or macrophages).
2. Inflammatory cells were not present in the hair follicle lumen.
3. Mural lymphocytes were accompanied by other signs of inflammation in various combinations (intercellular edema of the hair follicle wall; intracellular edema of follicular keratinocytes; perifollicular inflammation).

No attempt was made to quantitate the number of lymphocytes per hair follicle or the percentage of hair follicles affected per specimen. In cases wherein ILMF was a minor
histopathological reaction pattern – present at the periphery of a larger histopathological reaction pattern – the specimens were re-examined and the number of hair follicles with ILMF were recorded. The prevalence of ILMF for each dermatosis was determined.

Immunohistochemistry was performed on 6 cases (3 with dermatophytosis, 2 with insect-bite hypersensitivity, 1 with atopic dermatitis) to help determine the immunophenotype of the lymphocytes present in hair follicle epithelium. Briefly, formalin-fixed, paraffin-embedded tissue was sectioned at 4 µm, mounted and deparaffinized. The sections were incubated with rabbit antihuman CD3 at a 1:200 solution and stained using a standardized strepavidin-biotin immunoperoxidase technique and diaminobenzidine as the chromogen. Additional sections were incubated with nonimmune rabbit globulin at a 1:200 dilution and processed in identical fashion to serve as negative controls. Normal equine lymph node was processed in identical fashion and incubated with the rabbit antihuman CD3 to serve as the positive control.

STATISTICAL ANALYSIS

The skin-biopsy specimens from horses with skin disease were divided into 2 groups: those of allergic and nonallergic origins. A Pearson’s chi-square test was used to determine if there was a statistically significant difference in the prevalence of ILMF in allergic versus nonallergic dermatoses. Wilson score method was used to determine 95% confidence interval (CI) of allergic and nonallergic skin dermatoses and healthy skin. Significance was set at a P-value of ≤0.05. The statistical programme used was Statistix 9.0.

RESULTS

The agreement between the 2 histopathological assessments (KY and DWS) was 100%. ILMF was consistently present in the infundibular region of the hair follicles. Less commonly, ILMF also involved the isthmus of hair follicles. In 55 cases (29 eosinophilic granuloma; 5 bacterial cellulitis; 5 bacterial pseudomyxoma; 4 sterile granuloma, 3 sterile panniculitis; 1 case each of Alternaria granuloma, calcinosis circumscripta, xanthoma, exuberant granulation tissue, habronemiasis, eumycotic mycetoma, phaeohyphomycosis, protothecosis, pseudolymphoma) ILMF was a minor histopathological reaction pattern, represented by 1 or 2 involved hair follicles at the periphery of a larger histopathological reaction pattern.

The prevalence of ILMF in allergic dermatoses (30 of 41; 73%) was not significantly different (P = 0.11, chi-square = 2.59, df = 1) from that in nonallergic dermatoses (175 of 209; 84%). The 95% CIs on the allergic dermatoses, nonallergic dermatoses and physically healthy skin were 57% - 85%, 78% - 88% and 0 – 16%, respectively. ILMF was not observed in any of the physically healthy skin specimens.

Immunohistochemistry revealed that the lymphocytes in the hair follicle epithelium were CD3+ T-cells.

DISCUSSION

The histological reaction pattern of ILMF has been reported to be associated with a few mostly uncommon-to-rare equine inflammatory dermatoses. We were able to confirm the presence of ILMF in these previously reported dermatoses. In addition, to the best of our
knowledge, we report for the first time the occurrence of ILMF in several other dermatoses. This is the first study to determine the prevalence of ILMF in a large number of inflammatory dermatoses in horses. We found that ILMF is a common reaction pattern in horses, occurring in 82% of the skin-diseased horses studied. ILMF was often a focal, minor reaction pattern in many of the dermatoses examined (for example, 1 or 2 follicles with ILMF peripheral to a nodule of eosinophilic granuloma or bacterial pseudomycetoma). There was no significant difference in the prevalence of ILMF between the group with an allergic origin (73%) and those with a nonallergic origin (84%). ILMF was not present in physically healthy skin. Hence, the presence of lymphocytes in hair follicle epithelium should always be considered abnormal.

Immunohistochemistry performed on skin-biopsy specimens from 6 horses with ILMF showed the lymphocytes to be CD3+ T-cells. This would be expected because, in humans, lymphocytes in inflammatory dermatoses are predominantly of the T-cell immunophenotype. T lymphocytes are characterized by expression of the antigen-specific T-cell receptor (TCR)-CD3 complex. T lymphocytes expressing a TCR consisting of gamma and delta chains predominate in the skin and are important in the immune response to various antigens (microbial, chemical, etc.). To our knowledge, immunophenotyping of lymphocytes has not been conducted on a large number of horses with various inflammatory dermatoses.

In conclusion, ILMF is a common histopathological reaction pattern in equine skin-biopsy specimens, and occurs in a wide variety of inflammatory dermatoses. As such, ILMF has little diagnostic specificity in equine dermatopathology.

REFERENCE

HYDROPIC DEGENERATION OF EPIDERMAL BASAL CELLS

Hydropic degeneration of epidermal basal cells (HD) is defined as intracellular edema restricted to keratinocytes of the basal cell layer (stratum basale). Synonyms for HD include “liquefaction degeneration”, “vacuolar degeneration”, “vacuolar alteration”, and “cloudy swelling”. HD is a common histopathological finding in a cutaneous reaction pattern termed interface dermatitis. The interface dermatitis reaction pattern is uncommon and, if seen, is usually associated with various immune-mediated disorders.

Some authors have suggested that HD is encountered in a variety of superficial inflammatory dermatoses in the horse and seems to lack the specificity it has in humans and other species of domestic animals. Other authors do not agree. In addition, we are not aware of any published studies that address the prevalence and specificity of HD in the dermatopathology of any host species.

Our purpose in this study was to document the prevalence of HD in skin-biopsy specimens from horses with normal skin or various inflammatory dermatoses. We were particularly interested to learn if there was a statistically significant association between the prevalence of HD and a group of specific dermatoses associated with an increased frequency of HD in the anecdotal equine literature.

MATERIALS AND METHODS

A retrospective study of skin-biopsy specimens from 299 horses with inflammatory skin disease was performed. These were all of the equine inflammatory skin-biopsy specimens that had been procured with a 6-mm biopsy punch and submitted to the Pathology Service at the College of Veterinary Medicine at Cornell University from 1975 to 2007, processed routinely for histopathological evaluation, and stained with hematoxylin and eosin, and for which the Dermatology Service had follow-up information. All diagnoses were confirmed by standard clinical, clinicopathological, and histopathological criteria. In addition, skin-biopsy specimens were taken from the dorsolateral thorax of 27 horses with normal skin that had been submitted to our Necropsy Service in 2004.

Because we wanted to follow routine procedures in diagnostic pathology, serial sections were not examined. One section of tissue was examined per slide. If multiple specimens were present on a slide, the section with the least amount of artifact was chosen for evaluation. One author (CBE), who was blinded to the diagnoses, examined all specimens for HD. For two-thirds of the cases with inflammatory skin disease and 100% of the normal horses, the second author (DWS) also examined the specimens to ensure reproducibility of the findings.

For this study, HD was defined as intracellular edema of keratinocytes restricted to the stratum basale. Intraacellular edema of keratinocytes in multiple epidermal layers (stratum basale, stratum spinosum, stratum granulosum) (IE) was separately recorded and was not included in this study among the cases listed as “HD”.

STATISTICAL ANALYSIS

The 299 inflammatory dermatosis specimens were divided into two mutually exclusive groups: those conditions wherein HD is not frequently reported in the literature.
One or more areas of HD were seen in 13 of 299 horses with inflammatory dermatoses, for a prevalence of 4%.

The prevalence of HD was significantly greater ($P < 0.0001$; Fisher’s exact tests) in SuspHDIfl horses than it was in group NonSuspHDIfl and group Normal (consistent with the non-overlap of the confidence intervals between the SuspHDIfl group and the other two groups). The prevalence of HD was not significantly different ($P > 0.99$) between groups NonSuspHDIfl and Normal (as shown also in their greatly overlapping confidence intervals).

The prevalence of IE was 16% for group NonSuspHDIfl, 12% for group SuspHDIfl, and 0% for group Normal. There was no significant difference ($P = 0.78$) in the prevalence of IE between groups NonSuspHDIfl and SuspHDIfl. The prevalence of IE was significantly greater ($P = 0.02$) in both groups NonSuspHDIfl and SuspHDIfl than it was in group Normal.

REFERENCE

CUTANEOUS LUPUS ERYTHEMATOSUS

Cutaneous lupus erythematosus is a rare immune-mediated dermatitis of the horse, and accounted for only 0.33% of the equine skin disease seen at the CUHA.

CAUSE AND PATHOGENESIS

Cutaneous lupus erythematosus is a relatively benign cutaneous disease with no systemic involvement. Sun exposure often aggravates the disease, suggesting that photosensitivity plays a role in the pathogenesis. Anecdotal reports indicate that, in many cases, there appears to be a triggering of disease onset by various incidents, including excessive sun exposure, extremes in environmental temperature (hot or cold), drug administration, or “stressful situations”. In humans, it has been demonstrated that the lymphocytes infiltrating skin lesions are predominantly T cells.

CLINICAL FEATURES

Cutaneous lupus erythematosus is a rare dermatosis in which there is no systemic involvement. No breed or sex predilections are apparent, and affected horses range from 1 to 14 years. The onset of lesions may be gradual or rapid. Skin lesions begin on the face—especially the lips, nostrils, and periocular region—and include more or less symmetric areas of erythema, scaling, and alopecia. These lesions are annular to oval, variably well circumscribed, and manifest variable degrees of leukoderma. Crusts, erosions, and leukotrichia are occasionally present. Pruritus and pain are typically mild to absent. Some horses develop lesions on the pinnae, neck, and shoulders and on the perianal, perineal, and genital areas. The disease is often exacerbated in warm, sunny weather.

DIAGNOSIS

The differential diagnosis includes photodermatitis, dermatophilosis, dermatophytosis, demodicosis, onchocerciasis, and in the absence of gross signs of inflammation, vitiligo. The definitive diagnosis is based on history, physical examination, skin biopsy, and immunofluorescence or immunohistochemical testing. Skin biopsy reveals an interface dermatitis (hydropic, lichenoid, or both). Focal hydropic degeneration and apoptosis of basal epidermal and follicular outer root sheath cells, pigmentary incontinence, focal thickening of the basement membrane zone, subepidermal vacuolar alteration, accumulations of lymphocytes, plasma cells, and histiocytes around dermal vessels and appendages, and variable degrees of dermal mucinosis are common features. Rarely, an occasional multinucleated histiocytic giant cell may be present. “Fibrinoid material” may be seen in the superficial dermis, near the basement membrane zone and/or perivascularly.

It must be emphasized, here, that the basement membrane zone in normal horse skin is thick and prominent, and caution is warranted in assessing pathologic thickening. It has also been suggested that hydropic degeneration of basal cells is encountered in a variety of superficial inflammatory processes in horse skin, and that this pathologic change seems to lack the specificity it has in other species. The authors do not agree.
Immunopathologic tests reveal immunoglobulin or complement or both at the basement membrane zone of affected skin. Indirect immunofluorescence testing, ANA tests, and LE cell tests are negative.

CLINICAL MANAGEMENT

The prognosis for cutaneous lupus erythematosus is usually good. Therapy will probably need to be continued for life, and marked depigmentation predisposes to sunburn.

Therapy of discoid lupus erythematosus must be appropriate to the individual. Mild cases may be controlled by, and all cases benefit from, avoidance of exposure to intense sunlight (from 8 am to 5 pm), the use of topical sunscreens, and the use of topical glucocorticoids. Initially, topical glucocorticoid therapy is most successful when potent agents, such as betamethasone valerate, fluocinolone DMSO (Synotic), or triamcinolone spray (Genesis) are applied q12h. After the dermatosis is in remission, topical glucocorticoids are applied as needed (once daily, q48h, and so forth), and less potent agents (e.g., 1% to 2% hydrocortisone) may be sufficient for maintenance. In some cases, a 1-month course of systemic prednisolone or prednisone (2.2 mg/kg orally q24h until remission is achieved, then q48h) is helpful. The topical agents may then be sufficient to maintain the remission. Tacrolimus ointment is useful in dogs and humans with cutaneous lupus erythematosus, and could be useful in horses, especially if local glucocorticoid-induced cutaneous atrophy is a problem.

Omega-3/omega-6 fatty acid-containing products have been used in dogs and cats in order to reduce glucocorticoid dose requirements and may be useful in horses as well. Anecdotal reports indicate that flaxseed oil (200 ml/500 kg q24h PO) and/or vitamin E (13 mg/kg q24h PO) may be beneficial.

REFERENCES

RESIDENT LYMPHOCYTES IN ALPACA SKIN

Alpacas, like other South American camelids, have become increasingly popular in recent years. This has created the need for more knowledge about the microanatomy of healthy and unhealthy skin in such animals. Recent in-depth publications have characterized clinical, histopathological, and therapeutic aspects of skin diseases in alpacas and the microanatomy of normal skin from alpacas.

Resident lymphocytes in human epidermis were likely first described by Kondo in 1922. Studies have demonstrated that resident epidermal lymphocytes in humans are CD3+ (pan T-cell marker) T-lymphocytes and occur rarely in the epidermis and adnexal epithelia. Resident epidermal CD3+ T-lymphocytes have also been described in the mouse, sheep, and cow, and are found in very small numbers. To the authors’ knowledge, the occurrence of resident lymphocytes in the epidermis and adnexal epithelia of normal alpaca skin has not been investigated.

B-lymphocytes have not been found in the epidermis and adnexal epithelia of normal human and murine skin. To the authors’ knowledge, the occurrence of B-lymphocytes has not been previously investigated in normal alpaca skin.

Previous publications have documented the reliability of immunophenotyping alpaca lymphocytes utilizing anti-human CD3 (T-lymphocytes) and CD79a (B-lymphocytes and plasma cells). The purpose of this study was to determine the prevalence of CD3+ and CD79a+ cells in the epidermis and adnexal epithelia in skin biopsy specimens from 31 alpacas with normal skin.

MATERIALS AND METHODS

Sample Collection

Archival samples of normal skin from 31 alpacas submitted to the Section of Anatomic Pathology for necropsy from 2007-2011 were used in this study. The 31 alpacas ranged in age from <1 month to 16 years old (median age 2 years), and included 15 males and 16 females. All skin samples were taken from the dorsolateral thorax using a 6-mm biopsy punch. Samples were then formalin-fixed and paraffin-embedded. Serial sections (4 µm thick) from each block were stained with hematoxylin and eosin (H&E) and with antibodies against CD3 and CD79a.

Histological Evaluation

Sections stained with H&E (1 section per alpaca) were examined by 2 of the authors (MDC & JPK). Epidermis and epithelia of all hair follicles, sebaceous glands, and epidermal sweat glands were examined for the presence of lymphocytes. The number of pilosebaceous units per section was recorded.
Immunohistochemical Investigation

Immunohistochemistry for CD3 and CD79a was performed as previously described. Briefly, sections were mounted and deparaffinized. The sections were incubated with rabbit anti-human polyclonal CD3 antibody (Dako Corporation, Carpinteria, California, USA) at a 1:100 dilution, and mouse anti-human monoclonal CD79a antibody (Dako Corporation, Carpinteria, California, USA) at a dilution of 1:20, and stained using a standardized streptavidin-biotin immunoperoxidase technique. The chromagen was 3,3-diaminobenzidine-tetra hydrochloride (DAB from Dakocytomation).

Normal alpaca lymph node and alpaca brain served as positive and negative tissue controls, respectively. Additionally, diseased alpaca skin (bacterial folliculitis with numerous epidermal and dermal lymphocytes and dermal plasma cells present on H&E) was processed in an identical fashion to the samples in question to serve as a positive tissue control. Diseased alpaca skin also served as a negative tissue control, when processed by substituting the primary antibody with nonimmune rabbit serum.

RESULTS

The number of pilosebaceous units per H&E-stained section ranged from 7-20 (total number examined = 374). Lymphocytes were rarely seen in the H&E-stained sections. CD3+ lymphocytes were found in all specimens. The total number of lymphocytes in all areas examined varied from 1-53 per sample. They were found in the epidermis in 27/31 (87%) samples, in the follicular epithelia in 30/31 (97%) samples, in sebaceous gland epithelia in 19/31 (61%) samples and in epithelial sweat gland epithelia in 10/31 (32%) samples. The numbers of CD3+ lymphocytes were larger in epidermis and hair follicle epithelia than in sebaceous gland or epithelial sweat gland epithelia. CD79a cells were not present in epidermis or adnexal epithelia. The authors agreed on the total numbers of lymphocytes present. Positive and negative controls reacted appropriately. The lymphocytes and plasma cells in the sections of bacterial folliculitis were CD3+ and CD79a+, respectively.

CD3+ lymphocytes were also found in the superficial and deep dermis – primarily in a perivascular location – in 31/31 samples (100%) and 27/31 samples (87%), respectively. CD79+ lymphocytes were found in the superficial and deep dermis – also in a perivascular location – in 21/31 samples (68%) and 19/31 samples (61%), respectively. The total number of CD3+ lymphocytes (1,426) counted in all samples was larger than the total number of CD79a+ lymphocytes (261).

The total number of superficial perivascular CD3+ lymphocytes (1,161) in all samples was larger than the total number of deep perivascular CD3+ lymphocytes (265). The total number of superficial and deep perivascular CD3+ lymphocytes counted per sample varied from 1 to 106 (median 22) and 0 to 41 (median 5), respectively.

The total number of superficial perivascular CD79a+ lymphocytes (175) in all samples was larger than the total number of deep perivascular CD79a+ lymphocytes (86). The total number of superficial and deep perivascular CD79a+ lymphocytes counted per sample varied from 0 to 39 (median 1) and 0 to 17 (median 1), respectively. Because alpaca B-lymphocytes and plasma cells are both CD79a+, the H&E samples were scrutinized, and plasma cells were rarely seen. CD79a+ cells did not have the appearance of plasma cells.
REFERENCES


CYTOLOGY AND RESIDENT FLORA OF THE INTERDIGITAL SKIN OF ALPACAS

Alpacas (*Vicugna pacos*), like other South American camelids, have been growing in popularity in North America. With this growth, has come the need for better knowledge of normal and abnormal skin states. A review article and retrospective analysis published in 2010 by Scott et al. in *Veterinary Dermatology* describes 68 alpacas with skin disease seen at a university veterinary hospital from 1997-2006. In that paper, common skin diseases of the alpaca were reported as: bacterial infections (22% of the cases); neoplasms, cysts and hamartomas (19%); presumed immunologic disorders (12%); and ectoparasitisms (10%). Normal microanatomy of alpaca skin has also been reported.

As with general dermatoses, specific dermatoses of the feet of alpacas are important. Diseases involving the feet included bacterial folliculitis, *Sarcoptes* infestation, *Chorioptes* infestation, contact dermatitis, presumed insect-bite hypersensitivity and zinc-responsive dermatoses Ulcerative pododermatitis associated with *Staphylococcus*, *Corynebacterium* and *Fusobacterium* species of bacteria occurs in alpacas. To date, no studies have been conducted to evaluate the cytology found on the interdigital skin from healthy alpacas. This study addresses this gap in knowledge. Based on the observed behavior of camelids to back into a communal defecation area, we also evaluated differences in cytology between front and rear feet; we also considered that weight-bearing might differ between front and rear feet, and might also influence cytology.

CYTOLOGY

Sample Collection

Thirty alpacas were included in this study from one farm located in central New York State. The alpacas were part of two separate groups (15 animals sampled from each group). Written consent was obtained from the farm’s owner and all animals were handled in accordance with the approval of the Cornell University Institutional Animal Care and Use Committee. The 30 alpacas included 15 males (ages 14 months to 9 years) and 15 females (ages 10 months to 19 months). Sample collection took place in May 2011.

The farm staff manually restrained alpacas. Wearing exam gloves and using sterile cotton swabs, samples were collected from interdigital material from one front and one rear foot from each alpaca. Each swab was rolled onto two separate glass microscope slides. The slides were stored for transport and subsequent staining. An attempt was made to insure that all smears were of the same length and thickness.

Slide Staining

The slides for cytological analysis were transported back to the Cornell University Hospital for Animals that same day and stained using Diff-Quik® on one slide per swab and Gram stain on the other slide by the same investigator (MDC) to ensure consistency.
Cytological Evaluation

All microscope slides were examined by the same investigator (MDC) with independent verification by a second investigator (WHM). Each slide was scanned at 10X magnification to check for quality of staining and homogeneity of sample. Efforts were made to select 10 oil-immersion fields (OIFs; 1000X magnification) that were representative of the entire slide for both the Diff-Quik® and Gram-stained slides. The numbers of non-nucleated and nucleated epithelial cells were counted in each of the 10 OIFs on the Diff-Quik® slides. We also searched for polymorphonuclear and mononuclear inflammatory cells. The numbers of yeasts, bacterial cocci, and rods were counted on the Gram-stained slides (also for 10 OIFs). Microorganisms were counted and then categorized using the following scale per OIF: 0 = 0; 1 = 1-10; 2 = 11-20; 3 = 21-30; 4 = 31-40; 5 = >40. This type of numbering system for cytological findings is often used by clinicians when assessing ear and skin diseases.

Statistics

For each foot, we separately calculated the median number (category) of microorganisms across the 10 OIF for each type of cell. Because we expected to find some non-nucleated epithelial cells on normal alpaca feet, these results were only described (not tested).

Microorganism counts from one front and one rear foot for each animal constituted sets of paired data; we also had data that were ordinal because of the categorization of microorganism counts. Consequently, we used Wilcoxon signed-rank tests to evaluate whether being from the front versus rear foot was related to the numbers of microorganisms. We did this separately for the males and females. Our overall P-value for significance was 0.05, but we ran eight signed-rank tests. We intended to impose a Bonferroni adjustment for the multiplicity, and the cut-off P-value was therefore 0.05/8 = 0.00625 (2-sided). All statistical work was performed using standard software, Statistix® 9e.

Results

The minima, medians, and maxima for the non-nucleated epithelial cells and the microorganisms are in Table 1. Nucleated epithelial cells were so scarce that the medians across 10 OIFs were always zero and we neither show that in the table nor attempted the futile exercise of trying to correlate the “constant” value of zero to the counts of the microorganisms (as had been our original intention). Additionally, no inflammatory cells (polymorphonuclear or mononuclear) or Gram-negative cocci were observed, so these also were not tested or displayed in Table 1.

CULTURE

Sample Collection

Samples were collected on one day in May of 2011 from two separate groups of animals (15 from each group; total 30) from one alpaca farm located in central New York State. Written consent was obtained from the alpaca farm’s owner and approval of the Cornell University Institutional Animal Care and Use Committee was obtained. Each alpaca group differed in housing location, management and sex of animals. The 30 alpacas included 15 males (ages 14 months to 9 years) and 15 females (ages 10 months to 19 months).
The farm staff manually restrained alpacas. Wearing exam gloves (Synguard Vinyl Examination Gloves, Basic Medical Industries, Inc, Chino, California USA) and using sterile cotton swabs (Puritan Medical Products Company LLC, Guilford, Maine USA), one investigator (MDC) collected samples from interdigital material from one front and one rear foot from each alpaca. The swabs were vigorously rubbed on the dorsal surface of the interdigital skin for 5 seconds. The swabs were then passed to a second investigator (WHM) who placed each swab aseptically into culture transport media (BBL Port-A-Cul Tubes, Beckton, Dickinson and Co., Sparks, Maryland USA). The collected samples were delivered within a few hours to the Animal Health Diagnostic Center at Cornell University. Aerobic and anaerobic bacterial cultures and fungal cultures were performed in standard fashion. For the most part, isolated organisms were only identified to the genus level.

RESULTS

The following organisms were isolated from at least 25% of samples: *Enterococcus* spp. (96.7% of samples), nonhemolytic *Staphylococcus* spp. (85.0%), *Pantoea* spp. (71.7%), *Bacillus* spp. (70.0%), *Escherichia coli* (65.0%), *Klebsiella* spp. (55.0%), α-hemolytic *Streptococcus* spp. (31.7%), and *Proteus* spp. (26.7%). A total of 21 species of aerobic bacteria were isolated.

For the anaerobic bacterial cultures, five species of bacteria were isolated. The most commonly isolated anaerobic bacterium was *Bacteroides* spp. and it was found only in 5/60 (8.3%) samples collected. Other isolates included *Porphyromonas* spp. (5% of samples), *Clostridium* spp. (3.3%), *Peptostreptococcus* spp. (3.3%) and *Fusobacterium* spp. (1.7%).

Fungal culture results and a total of 12 fungi or categories of fungi were isolated. The following organisms were isolated from at least 25% of samples: *Mucor* spp. (66.7% of samples), yeast (45.0%), *Geomyces* spp. (40.0%), and *Penicillium* spp. (28.3%).

Table 1. Cell-counts and Categories, Across 10 High-Powered Fields per Foot (N = 15 Healthy Alpacas for Each Statistic)

<table>
<thead>
<tr>
<th>Cell or micro-organism</th>
<th>Statistic</th>
<th>Group and Foot</th>
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<th></th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Male, Front</td>
<td>Male, Rear</td>
<td>Female, Front</td>
<td>Female, Rear</td>
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<td>Non-nucleated epithelial</td>
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<tr>
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<td>5</td>
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<tr>
<td>Gram+ cocci</td>
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<td></td>
<td>Maximum</td>
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</table>

Categories of cell counts and microorganism counts per oil-immersion field: 0 = 0; 1 = 1-10; 2 = 11-20; 3 = 21-30; 4 = 31-40; 5 = >40.
REFERENCES


ICHTHYOSIS IN A GOAT

Ichthyosis (Greek: “fishy condition”; “fish scale disease”) consists of a heterogeneous group of hereditary and usually congenital disorders of keratinization (cornification) of the skin. Humans are affected by over 21 ichthyosiform dermatoses diagnosed on the basis of clinical, histopathological, ultrastructural, and genetic criteria.

Ichthyoses have been uncommonly diagnosed in various breeds of dogs and cattle, and rarely-to-extremely rarely diagnosed in alpacas, cats, llamas, and swine. Although the vast majority of ichthyoses in animals are assumed or proven to be of autosomal recessive inheritance, the precise genetic abnormality has only been determined in three dog breeds: Golden retrievers (insertion-deletion mutation in patatin-like phospholipase domain-containing protein), Norfolk terriers (donor splice-site mutation in keratin 10), and Parson (Jack) Russell terriers (insertion of a long interspersed nucleotide element in transglutaminase 1). To our knowledge, ichthyosis has not been previously reported in goats. Our purpose is to report a case of ichthyosis in a Nigerian dwarf goat.

CASE REPORT

A 4-year-old, 40 kg male castrated Nigerian dwarf goat presented to the Equine and Farm Animal Hospital’s Internal Medicine Service with a long history of nonpruritic, scaly skin noticed since it was acquired at 3 weeks of age. None of the other five goats in the herd were affected. The diet consisted of free choice hay and a salad consisting of cabbage, apples, and carrots along with access to a mineral and salt block. Additional supplementation included Capri-Min® (Caprine Supply, De Sota, Kansas, USA) (calcium 6-8% and phosphorus 12.0%/pound), Herbal Weekly Worm Formula and Tonic® (Molly’s Herbals, Okemos, Michigan, USA) (garlic, cucurbita pepo, mugwort, fennel, hyssop, thyme, stevia), and a 400 mg vitamin E (d-α tocopherol acetate) tablet once daily. He had also received a Bo-Se® (Intervet/Merck Animal Health, Summit, New Jersey, USA; 50 mg vitamin E, 1 mg selenium/ml) injection (3 ml subcutaneously) three months prior to examination. Other previous therapy for the dermatosis included chlorhexidine shampoo, ivermectin, and permethrin powder with minimal improvement.

At presentation, the goat was alert and responsive with nonpruritic widespread scaly skin. A Dermatology Service consultation was obtained. Physical examination revealed widespread large, white nonadherent scales covering the entire skin, including both the convex and concave aspect of the pinnae. A complete blood count, biochemistry profile, Salmonella culture, caprine arthritis enteritis virus ELISA, serum vitamin E, whole blood selenium, and serum zinc concentration were performed.

Complete blood count and biochemistry profile were unremarkable with the exception of a mild mature neutrophilia (12.5 thou/µL; reference range 1.9-9.5 thou/L), attributed to the stress of being in the hospital. Serum zinc was markedly low (0.23 ppm; reference range 0.65-2.7 ppm). All other laboratory tests were unremarkable. Dermatologic testing included impression smears, trichography, and skin scrapings - all of which were unremarkable.

Differential diagnoses at this time included ichthyosis, nutritional deficiency, and a topical drug reaction. Three 6-mm-punch biopsies were obtained from the truncal skin. Histopathologic analysis revealed mild to moderate diffuse compact orthokeratosis of the epidermis and follicular infundibula. These changes were consistent with ichthyosis.
Although the dermatosis was not typical of a zinc-responsive dermatitis, it was decided to firstly correct the low serum zinc concentration with zinc gluconate therapy (50 mg [1 mg/kg] orally once daily). After 6 weeks on this therapy, no improvement in the skin was noted. The zinc was then discontinued for four weeks with no change in the dermatosis. Additional impression smears, trichography, and skin scrapings were again unremarkable. Serum zinc concentration was again measured and was within normal limits (1.59 ppm; reference range 0.65-2.7 ppm). Vitamin A therapy (8000 IU [200 IU/kg] orally once daily) was prescribed for treatment of the previously diagnosed ichthyosis. After three months of vitamin A 8000 IU (200 IU/kg) therapy, an approximate 85% reduction in the widespread scaling was noted. The scaling previously noted along the concave and convex aspects of the pinnae was no longer present. Although scaling was persistent in all other regions, the severity was greatly decreased.

REFERENCE

Suppurative otitis is well-documented in swine. In most instances, the infection is confined to the middle (otitis media) and inner (otitis interna) ear. Isolated bacteria include streptococci, staphylococci, Pasteurella multocida, Arcanobacterium (Corynebacterium) pyogenes, coryneforms, Actinobacillus (Haemophilus) pleuropneumoniae, and Mycoplasma hyorhinis. Swine with atrophic rhinitis and post-weaning multisystemic wasting syndrome (porcine circovirus 2 infection) may be predisposed. Otitis externa is less commonly reported, and has been associated with the above bacteria as well as with Malassezia pachydermatis, Sarcoptes scabiei, and foreign material (e.g., meal) in the ear canals.

The diagnosis of otitis externa is achieved through clinical history, examination of the ears, and cytological examination of stained samples from the external ear canal. By visualizing the presence and number of organisms and cells, the process helps in determining the presence of infectious agents and their role in the disease. This information, in turn, allows the clinician to rapidly institute appropriate treatment. The diagnosis of a diseased external ear canal via cytology requires knowledge of the cytology of the normal external ear canal. To our knowledge, there have been no published studies on the cytology of the external ear canal in healthy pigs.

The purposes of this study were to examine the cytology of clinically normal pig ears and to quantify the numbers of organisms and cells present.

Thirty-six healthy pigs of various ages were included in this study. The pigs were housed indoors in the Cornell University swine barn and fed a soy/corn-based diet if not nursing their dams. The adult sows were Yorkshire/Landrace crosses. All other pigs were of mixed (Yorkshire/Landrace/ Hampshire) breeding. The external ear canals and pinnae of all animals were examined for clinical signs of otitis externa such as erythema, swelling, scaling, crusting, excessive otic discharge, and pain upon palpation of the auricular cartilage. The animal caretakers were questioned to determine if the pigs exhibited any of the common indicators of otitis externa such as otic pruritus or head shaking. No animal had received treatment for ear disease. All pigs were free of systemic or dermatological disease.

One ear per pig was sampled. The left or right ear of the pigs was chosen by convenience for sample collection. The color and consistency of cerumen was recorded. A nonsterile cotton swab was inserted into the lumen of the ear canal and rotated against the surface of the vertical ear canal. No attempt was made to introduce the cotton swab into the horizontal portion of the external ear canal. The cotton swab was rolled onto two glass microscope slides. All rolled samples were of similar length, width, and thickness visually. The slides were not heat-fixed. One slide per subject was stained with a modified Wright’s stain (Diff-Quik®, Baxter Health Care Co, McGraw Park, IL, USA), and one slide per subject was stained with a Gram’s stain. Each slide was mounted with a coverslip.

The following were counted in 10 different high-power microscopic fields (HPF, 600 X magnification) on each slide stained with Diff-Quik: yeasts and epithelial cells. The Gram-stained slide of each subject was used to count bacteria in 10 different HPFs, and to characterize the bacteria as either cocci or rods, and as either Gram-positive or Gram-negative.

The cerumen was brown in color and waxy in consistency in all pigs. Bacteria were found in 10 of 36 (28%) samples. In 4 of these 10 positive samples, the bacteria were present concurrently with yeasts. Gram-positive cocci were the predominant bacteria in all samples. Small numbers of Gram-positive rods (case 11) and Gram-negative rods (case 35) were
present in only one sample each. Seventeen of 36 (47%) samples contained neither bacteria nor yeasts. There was no apparent effect of age on bacterial counts. Yeasts were found in 14 of 36 (39%) samples. In 4 of these 14 positive samples, the yeasts were present concurrently with bacteria. Yeast counts appeared to often be higher in adult pigs. Epithelial cells were present in all samples. The cells were mostly angular, anuclear corneocytes present individually or in clumps. Occasional epithelial cells were more rounded and contained a single nucleus. There was no apparent effect of age on epithelial cell counts. Erythrocytes and leukocytes (neutrophil, lymphocyte, eosinophil, macrophage, plasma cell) were not seen.

We only examined the cytology of the vertical portion of the external ear canal. No attempt was made to examine the horizontal portion of the external ear canal as this would have required sedation or anesthetization of the pigs, and passing the swab via an otoscope cone so as to not contact the vertical canal. We wanted to mimic what is carried out in a typical clinical situation, which means sampling the vertical ear canal. It is possible that the cytology of the horizontal ear canal is different from that of the vertical ear canal.

We did not perform bacterial and fungal cultures. Hence, we cannot speculate on the identity of the bacteria observed cytologically. We assume that the yeasts seen in our pig ear study were *Malassezia* spp. In two previous reports, *Malassezia* spp. were cultured from the external ear canals of 22.5% to 73% of the normal pigs sampled. The following *Malassezia* spp. were isolated: *M. pachydermatis*, *M. sympodialis*, *M. sloofiae*, and *M. furfur*.

In conclusion, epithelial cells (predominantly anuclear corneocytes), bacterial cocci (Gram-positive), and yeasts are commonly found in cytological preparations of normal pig ears. Leukocytes, erythrocytes, and large numbers of bacterial rods should be considered abnormal.

REFERENCE

DERMATOSES OF POTBELLIED PIGS

Information on skin disorders of domestic pigs is present in many textbooks and review articles. However, potbellied pigs are not specifically mentioned in these sources. In fact, all sources of information on skin diseases of potbellied pigs are anecdotal.

We will discuss the results of a retrospective survey of potbellied pig dermatoses as seen at Cornell University.

REFERENCE

Boldrick L. Veterinary Care of Pot-bellied Pet Pigs. All Publishing Company, Orange, California, 1993.


JUVENILE IMPETIGO IN DOGS

Impetigo is one of the classical canine skin disorders. The “father” of veterinary dermatology – Dr. Frank Král – described canine impetigo in his early textbooks on veterinary dermatology. From its Latin roots, impetigo implies “an attack,” “a scabby eruption.” In modern veterinary dermatology, impetigo implies a superficial bacterial infection that does not involve hair follicles. We recognize two forms of impetigo in veterinary dermatology: juvenile and bullous. Juvenile impetigo is a benign, spontaneously resolving infection of young dogs. Bullous impetigo is a more severe infection seen in adult-to-older dogs that have concurrent metabolic and/or immunologic disorders. Juvenile impetigo has also been called “puppy pyoderma”, “milk rash”, and “juvenile pustular dermatitis.” These nonspecific and confusing terms should not be used.

Although canine juvenile impetigo is discussed in a number of continuing education articles and textbooks, we are not aware of any case reports or published case series concerning this classic dermatosis. Hence, to a large extent, all available information on canine juvenile impetigo is anecdotal. There is even disagreement over the prevalence of canine juvenile impetigo, with some authors stating that the disease is common, while others say that it is uncommon.

Canine juvenile impetigo is a benign, noncontagious, nonzoonotic, superficial, pustular, bacterial infection of the glabrous areas of the skin, particularly axillae, groin, and ventral abdomen. The eruption tends to be more-or-less symmetrical. Annular nonfollicular whitish-to-yellow pustules rupture to leave erosions, collarettes, yellowish-to-brownish crusts, and crusted erythematous papules. The rash is typically neither pruritic nor painful.

Whereas all authors agree that there are no sex or breed predilections for canine juvenile impetigo, there is disagreement on the ages of affected dogs: pubescent and prepubescent, <1 year of age, 3 months to 1 year of age, 3 to 9 months of age, 1 to 8 months of age, 6 to 14 weeks of age, 2 to 16 weeks of age, and “young”. Early literature indicated that canine juvenile impetigo was usually secondary to various debilitating conditions: canine distemper, other infectious diseases, ectoparasites, endoparasites, poor nutrition, poor hygiene, and immunologic abnormalities. However, more recent literature suggests that predisposing or underlying causes are rarely documented, and that the vast majority of affected puppies are otherwise healthy.

In fact, juvenile impetigo is often diagnosed when puppies are presented to veterinarians for other reasons (e.g., vaccination), and many cases may go undiagnosed because owners are not aware of the skin lesions.

Older literature states that the bacteria most commonly isolated from juvenile impetigo are coagulase-positive staphylococci, *Staphylococcus aureus*, or streptococci. More recent sources indicate that *S. intermedius* or *S. pseudintermedius* is the primary pathogen. Literature on cultural findings is anecdotal.
In most cases, canine juvenile impetigo is visually distinctive, and a good history and physical examination are sufficient for diagnosis. Cytological examination of exudate reveals degenerate and nondegenerate neutrophils, and intracellular and extracellular Gram-positive cocci. Culture and susceptibility and skin biopsies are rarely performed. Skin biopsy findings are characterized by subcorneal pustules that: (1) are elevated above the epidermal surface, (2) contain pus and Gram-positive cocci, and (3) do not involve hair follicles.

The duration of untreated canine juvenile impetigo is unclear. Most authors agree that the majority of dogs experience spontaneous resolution, but only a few authors state a specific time interval of one to four weeks. Some authors indicate that topical and/or systemic antibacterial therapy will hasten recovery. However, the suggested courses of topical (1 to 4 weeks) or systemic (1 to 3 weeks) therapy are identical to the aforementioned 1 to 4 weeks for spontaneous resolution! Most authors agree that systemic antibiotics are rarely needed.

Clearly, certain aspects of canine juvenile impetigo remain confusing and controversial. The purpose of our study was to clarify some of these issues.

MATERIALS AND METHODS

A retrospective study was conducted on 65 dogs with juvenile impetigo seen by the Dermatology Service of the Cornell University College of Veterinary Medicine from 1976 to 2005. Medical records were reviewed for the following information:

1. Signalment (breed, age, sex).
2. Duration of disease prior to examination.
3. Evidence of contagion or zoonosis.
4. Dermatological findings.
5. Concurrent disorders (e.g., infectious, parasitic, nutritional, hygienic).
6. Laboratory findings.
7. Therapeutic protocols
8. Total duration of disease, with or without treatment.

RESULTS

There were 38 purebred and 27 mongrel dogs in our study with no apparent breed predilections. There were 43 females and 23 males. The age at which the condition was first noticed varied from 5 weeks to 10 months, with 59 of the dogs (91%) being <6 months old. For 20 dogs, the duration of disease prior to examination by the Dermatology Service was 0.5 to 4 weeks. None of these dogs had received treatment for their juvenile impetigo. For 45 dogs (70%), the disease had not been noticed by the owners, and was identified during routine physical examination (initial puppy examination, vaccination). Only 8 dogs had concurrent diseases: 4 puppies had fleas, 1 had sarcoptic mange, 1 had hookworms, 1 had ascarids, and 1 had both hookworms and whipworms. Hygiene and nutrition were excellent for all puppies. There was no history of contagion or zoonosis. Twenty-eight dogs developed their disease in summer (June to August), 17 in fall (September to November), 11 in spring (March to May), and 9 in winter (December to February).
Skin lesions were present on the abdomen, medial thighs, and axillae in 64 (98%), 22 (34%) and 14 (22%), respectively, of the dogs. Only the dog with concurrent sarcoptic mange was pruritic. All dogs were otherwise healthy.

Skin cytology was performed on 12 dogs, and revealed suppurative inflammation (degenerate neutrophils, nuclear streaming, intracellular cocci). Skin scrapings were only performed on the dog with sarcoptic mange. Cultures, skin biopsies, and blood work were not performed.

Forty-seven dogs (72%) received no treatment for their juvenile impetigo. The total duration of disease was 1 to 6 weeks for those dogs (16) for which the owners had previously recognized the condition, and 0.5 to 4 weeks for those dogs (31) for which the condition was initially discovered during the veterinary examination.

Eighteen dogs (28%) received treatment for their juvenile impetigo. In 17 of these dogs, treatment was given according to the owners’ wishes. The other dog had concurrent sarcoptic mange. Ten dogs received antibiotics by mouth (amoxicillin clavulanate, cephalixin, chloramphenicol, dindamycin, or lincomycin) for 10 days, and the other 8 dogs received topical chlorhexidine 2 or 3 times per week for 2 weeks. Total duration of disease was 2 to 4 weeks for those dogs (7) for which the owners had previously recognized the condition, and 1 to 4 weeks for those dogs (11) for which the condition was initially discovered during the veterinary examination.

Post-cure follow-up information was available for 54 dogs. Thirty-two of the dogs had no relapse during a 1- to 14-year period. Twenty-two of the dogs had no relapse during a 1- to 10-month period.

REFERENCE

IDIOPATHIC EOSINOPHILIC GRANULOMA IN CATS

Lesions of the feline eosinophilic granuloma complex were probably described in the 1930s through the 1950s as “syphiloid”, “rodent ulcer”, “lip ulcer”, and “chin edema”. In 1975, based on clinical and histopathological criteria, the complex was divided into 3 different lesions: the indolent (“eosinophilic”) ulcer, the eosinophilic plaque, and the eosinophilic (“collagenolytic”, “linear”) granuloma.

The eosinophilic granuloma is characterized by firm, usually well-circumscribed, papules and nodules. Papular lesions are intradermal, and nodular lesions involve the dermis and subcutis. The overlying skin and, where normally present, hair coat are initially normal in appearance. As lesions enlarge, the overlying pelage is often lost, and the lesions often take on an erythematous-to-yellow/orange hue. Lesions may become scaly or eroded-to-ulcerated and crusted. Oral and mucocutaneous lesions may develop multiple annular and coalescing small areas (1 to 2 mm diameter) of white discoloration. Lesions on the legs, neck, and trunk often assume a distinctive linear appearance. Chin lesions typically retain a normal overlying integument, and may be firm or soft.

In most instances, feline eosinophilic granulomas are associated with allergies, especially atopic dermatitis, food allergy, flea-bite allergy, and mosquito-bite allergy. Small numbers of cases have been attributed to ectoparasites (Cheyletiella, Notoedres, Otodectes), staphylococcal infection, foreign bodies (cactus tines, insect parts), allergic contact dermatitis, and idiopathy.

Idiopathic eosinophilic granuloma (IEG) has been frequently mentioned in the literature, but has not been extensively studied or reported. Our purpose was to report the results of a retrospective study of 55 cats with IEG.

MATERIALS AND METHODS

A retrospective study was conducted on 55 cats with IEG examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) from 1988 to 2003. Medical records were reviewed for the following information:

1. Signalment (breed, age, sex).
2. Duration of disease prior to examination at the CUHA.
3. Dermatological findings.
5. Laboratory findings.
6. Therapeutic protocols.
7. Total duration of disease, with or without treatment.
8. Follow-up period.

Various data for the cats with IEG were compared with those for the general CUHA cat population for the same time period using the relative risk (RR) calculation.

\[
RR = \frac{\text{data for IEG cats}}{\text{data for CUHA cats}}
\]

An RR of 2.0 or greater was considered significant.
RESULTS

IEG was diagnosed in 4% (55/1407 cats) of the feline dermatology cases and 0.2% (55/22,135 cats) of all cats examined at the CUHA over a 15-year period. Domestic shorthair cats accounted for 85% (47/55) of the cats with IEG, and 80% of the CUHA cat population (RR = 1.1). IEG was also diagnosed in domestic longhair (4 cases), Siamese (1 case), Manx (1 case), Himalayan (1 case), and Maine coon (1 case) cats.

Castrated males, spayed females, intact males, and intact females accounted for 38%, 24%, 20%, and 16%, respectively, of the cats with IEG. These same sexes accounted for 38% (RR = 1), 38% (RR = 0.6), 10% (RR = 2), and 11% (RR = 1.4), respectively, of the total CUHA cat population. The sex was not recorded for a small percentage of the IEG and CUHA cats.

The age at onset of disease of IEG cats varied from 0.2 years to 13 years. Ninety-three percent (51 of 55 cats) of the IEG cats had an age of onset of ≤ 4 years old; 55% (30 of 55 cats) had an age of onset of ≤ 2 years old; and 40% (22 of 55 cats) had an age of onset of ≤ 1 year old.

All cats were presented for the initial examination of the lesion(s), and had received no previous therapy. An associated cause was not found for any of the cats with IEG. All cats were reported to be otherwise healthy.

Lesions occurred most commonly on the lips (23 cases; 42%), caudal thighs (12 cases; 22%), and chin (10 cases; 18%). Forty-five of 55 (82%) cats had lesions in one location (e.g., chin, lips, thighs). Seventeen of 55 (30%) cats had linear lesions, and 39 of 55 (70%) cats had papular or nodular lesions. Only 1 cat had both morphological types of lesions. Lesions were reported to be symptomatic in only 3 cats, in which paw or pawpad lesions were believed to be painful or pruritic. The distribution and morphological types of lesions did not appear to be related to the age or sex of the cats.

Diagnosis was primarily based on the results of history and physical examination. Cytological examination (by fine-needle aspirate) was performed on 34 of 55 (62%) cats, and revealed eosinophils, macrophages, lymphocytes, and occasional neutrophils in all cases. Microbes (bacteria, fungi) were not seen. Skin biopsies were performed on only 5 of 55 (9%) cats. These 5 cats had ulcerated papular-to-nodular lesions in unusual locations: paw, pawpads, nasal plane, bridge of nose. Histopathological findings in all 5 cats were characterized by nodular-to-diffuse, eosinophilic granulomatous dermatitis with collagen flame figures. These histopathological findings are typical for the feline eosinophilic granuloma.

In 25 of 55 (45%) cats the duration of lesion(s) prior to examination at the CUHA was described by the owners as “recently noticed”, “just noticed”, or “days”. In the remaining cats, duration of lesion(s) varied from 2 weeks to 4 years.

Follow-up information was available for 41 of 55 (74%) cats, and varied from 2 months to 11 years. Length of follow-up was ≥ 1 year, ≥ 2 years, and ≥ 4 years in 83% (34 of 41 cats), 44% (18 of 41 cats), and 20% (8 of 55 cats) of the patients, respectively. No relapses were recorded.
Twelve of 55 (22%) cats received treatment (Table 1). All cats went into remission with follow-up periods ranging from 2 months to 5 years. No side effects of treatment were recorded. The other 43 (78%) cats received no treatment. Follow-up information was available for 29 of these 43 cats (67%). All 29 cats had spontaneous regression of their lesion(s), with follow-up periods varying from 2 months to 11 years. The total disease duration was recorded for 15 of the 29 cats (52%) that underwent spontaneous resolution without treatment. This disease duration varied from 1 month to 9 months.

Table 1. Response to treatment in 12 cats with IEG

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up period (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone acetate*</td>
<td>2.0</td>
</tr>
<tr>
<td>Prednisolone†</td>
<td>0.2</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>3.5</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>0.6</td>
</tr>
<tr>
<td>Dexamethasone‡</td>
<td>1.0</td>
</tr>
<tr>
<td>Dexamethasone‡</td>
<td>2.0</td>
</tr>
<tr>
<td>Omega-6/omega-3 fatty acids§</td>
<td>5.0</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>1.0</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>4.0</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>2.0</td>
</tr>
<tr>
<td>Methylprednisolone acetate*</td>
<td>1.0</td>
</tr>
<tr>
<td>Prednisolone†</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*20 mg/cat, subcutaneously, given twice at a 2-week interval.
†2.2 mg/kg, orally, once-daily until lesion(s) gone.
‡0.2 mg/kg, orally, once-daily until lesion(s) gone.
§DermCaps™ liquid, orally per manufacturer’s instructions, once-daily until lesion(s) gone.

REFERENCE

LOCALIZED DEMODICOSIS IN DOGS

Localized demodicosis (demodectic mange) is a classic skin disorder of dogs. Dr. George Muller was the first to separate the localized disease from generalized demodicosis on the basis of clinical appearance, prognosis, and therapeutic intervention. To this day, however, there are few uniformly accepted criteria for differentiating localized from generalized demodicosis.

It is generally agreed that localized demodicosis typically occurs in dogs less than 1 year of age (especially 3 to 6 months of age), with no known breed or sex predilection. However, there is inconsistency in the number of skin lesions allowed (1 to 4; 1 to 5; 1 to 6; 1 to “several”; 1 to “multiple”), and the extent of the lesions (e.g., dogs that have many lesions, or involvement of an entire body region, or complete involvement of 2 or more paws, have generalized demodicosis).

Most authors agree that skin lesions are most commonly present on the face (especially periocular and perioral regions) and head, followed by the forelegs. Rarely, lesions are present on the trunk or anywhere on the body. Authors also agree that most (85 to 90%) young dogs with localized demodicosis, who are otherwise healthy, recover spontaneously after a course of several (especially 3 to 8) weeks and rarely relapse.

The cause of localized demodicosis is unknown, but it is not associated with the immunologic abnormalities present in generalized demodicosis. Dogs with localized demodicosis have normal serum protein (total protein, albumin, total globulin, α-globulin, β-globulin, γ-globulin) levels, normal in vitro lymphocytic blastogenic relapses to mitogens (phytohemagglutinin, concanavalin A, pokeweed), and normal responses to the intradermal injection of mitogens and crude Demodex antigen.

It is interesting to note that the current understanding of localized demodicosis in dogs is based entirely on anecdotes. Schwartzman and Orkin reported that 5 dogs with localized demodicosis received no treatment and were free of lesions within 3 months. However, no details were provided. Similarly, in 1979 Scott reported that 61 dogs with localized demodicosis had completely recovered without treatment. Again, no details were provided.

Our purpose was to report the results of a retrospective study of 46 dogs with localized demodicosis.

MATERIALS AND METHODS

A retrospective study was conducted on 46 dogs with localized demodicosis examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) from 1988 through 1998. Medical records were reviewed for the following information:

1. Signalment (breed, age, sex).
2. Duration of disease prior to examination.
3. Dermatological findings.
5. Laboratory findings.
Breed and sex data for the dogs with localized demodicosis were compared to those for the general CUHA dog population for the same time period using the relative risk (RR) calculation.

$$RR = \frac{\text{data for localized demodicosis dogs}}{\text{data for CUHA dogs}}$$

An RR of 2.0 or greater was considered significant.

RESULTS

Localized demodicosis was diagnosed in 0.6% (46/8,207 dogs) of the canine dermatology cases and 0.1% (46/37,775 dogs) of all dogs examined at the CUHA over an 11-year period (Table 1). Twenty different breeds and mongrels were represented. Only 5 breed categories had 3 or more individuals represented: mongrel (9), Labrador retriever (6), German shepherd (5), rottweiler (4), and collie (3). Rottweilers (RR = 3.9), collies (RR = 2.5), and German shepherds (RR = 2.0) were over-represented. Females (54% of cases) and males (46% of cases) were about equally represented. Females and males accounted for 51% (RR = 1.1) and 48% (RR = 0.9), respectively, of the CUHA canine population. Age at disease onset varied from 2 to 25 months. Thirteen of 46 (28%) dogs were over 12 months of age when examined at the CUHA. All dogs were otherwise healthy. Relatives of the dogs were not known to be affected.

Lesions were most commonly seen on the periocular region (17 dogs, 37%), face (11 dogs, 24%), muzzle (8 dogs, 17%), chin (4 dogs, 9%), and lips (4 dogs, 9%), but occurred in a variety of body sites. The actual number of lesions present was rarely recorded. Only 1 dog had lesions in different body regions. Eight of 46 dogs (17%) had lesions on both sides of a body region. No dog was reported to be pruritic. Skin scrapings were positive for live mites in all cases. Hemograms and serum biochemistry panels were performed on the 13 dogs that were over 12 months of age; results were within normal limits.

No dog received treatment. Seven dogs (15%) were lost to follow-up. Thirty-nine (85%) dogs were known to recover completely. Total duration of disease for these 39 dogs was 2 to 11 months, with only one dog being diseased for over 5 months. Post-recovery follow-up information was available for 31 of 39 (79%) dogs. No dog was known to relapse with follow-up periods of 1 to 120 months. Nineteen of 31 (61%) dogs were followed for 1 or more years.

REFERENCE

IDIOPATHIC NASODIGITAL HYPERKERATOSIS IN DOGS

Idiopathic nasodigital hyperkeratosis (INH) is a classic canine skin disorder first described by Dr. George Muller and Dr. Robert Kirk in 1969. It is most often described in older dogs, with no sex predilection, wherein it is presumed to be a senile change. Some authors believe that no breed predilections exist, while other authors believe that the condition is much more common in cocker spaniels, beagles, and basset hounds. INH produces varying degrees of dry hyperkeratosis – from ridged, to grooved, to feathered in appearance – on the nasal plane, pawpads, or both of these. Typically, the nasal hyperkeratosis affects the dorsal aspect of the nasal plane, sparing the rostral portion and the nostrils. The condition is typically asymptomatic – unless fissured or secondarily infected by bacteria or yeasts – and affected dogs are otherwise healthy. Remarkably, in spite of INH being a universally well-recognized condition, we are not aware of a single detailed publication concerning this entity.

A retrospective study was conducted on 35 dogs with INH examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) over an 11-year period (1988 through 1998). Breed and sex data for the dogs with INH were compared to those for the general CUHA dog population for the same period using the relative risk (RR) calculation.

$$RR = \frac{\text{data for INH dogs}}{\text{data for CUHA dogs}}$$

An RR of 2.0 or greater was considered significant.

INH was diagnosed in 0.4% (35/8,207 dogs) of the canine dermatology cases and 0.1% (35/37,775 dogs) of all dogs examined at the CUHA. Fifteen different breeds and mongrels were represented. Only 7 breed categories had 2 or more individuals represented: American cocker spaniel (10), mongrel (4), English bulldog (3), miniature schnauzer (3), German shepherd (2), Doberman pinscher (2), and miniature poodle (2). English bulldogs (RR = 14.3), miniature poodle (RR = 9.5), miniature schnauzer (RR = 9.5), American cocker spaniel (RR = 7.5), and Doberman pinschers (RR = 2.6) were over-represented. Males and females accounted for 57.1% (RR = 1.2) and 42.9% (RR = 0.8), respectively, of the INH cases, showing no sex predilection.

Age at disease onset was known for only 9/35 (25.7%) of the dogs, and varied from 4 to 9 years. The other owners could only say that the condition had been present for “some time” or “years”. Age at examination at the CUHA varied from 3.5 to 15 years. Most dogs (25/35, 71.4%) had only nasal involvement, with the rest (10/35, 28.6%) having both nasal and pawpad involvement. No dog had only pawpad involvement. As all dogs were otherwise healthy, no laboratory tests were performed. Follow-up information was available for 25/35 (71.4%) dogs. In these patients, INH was stable for 1 month to 8 years after initial presentation.

REFERENCE

CANINE EAR MARGIN DERMATOSIS

Ear margin dermatosis (EMD; ear margin seborrhea) is a classic canine skin disorder probably first described by Dr. George Muller and Dr. Robert Kirk in 1976. Because of the marked breed predilection for the dachshund, EMD is hypothesized to be a genetic abnormality of keratinization. No age or sex predilections have been described.

EMD has been reported to be “rare” to “relatively common”. It is characterized by an asymptomatic, bilaterally symmetrical keratinization disorder confined to the pinnal margins. Whitish-to-brownish-to-yellowish, dry-to-greasy-to-waxy accumulations adhere to the skin and hairs of the lateral and medial pinnal margin. Hair casts may be prominent. The underlying skin appears noninflamed. Heavy accumulations of keratinous debris may make the pinnal margins look and feel thickened. In advanced cases, removal of the keratinous deposits results in alopecia. Remarkably, in spite of EMD being a universally well-recognized condition, we are not aware of a single detailed publication concerning this entity.

A retrospective study was conducted on 10 dogs with EMD examined by the Dermatology Service of the Cornell University Hospital for Animals over a 24-year period (1988 through 2012). EMD was diagnosed when dogs presented with (1) a bilaterally symmetrical, asymptomatic, keratinization disorder confined to the pinnal margins, and (2) no other signs of endocrine or seborrheic disease. Diagnostic tests were not performed. EMD was diagnosed in 0.05% (10/20,415 dogs of the canine dermatology cases, and in 3.5% (9/258 dogs) of the dachshunds seen by the Dermatology Service.

Age at disease onset was known for only 20% (2/10) of the dogs (cases 7 and 10): 7 months and 8 months of age. The other owners could only say that the condition had been present for “years” or “since the dog was young”. None of the dogs were presented for the EMD. The dogs had not received any treatment for the EMD, and the dermatosis had remained stable or had slowly worsened over time (usually many years). The lesions were not reported to worsen at certain times of the year nor were these reported to have worsened with the onset of the other dermatologic conditions the dogs were presented for. None of the dogs received treatment from us for their EMD.

Because EMD is typically asymptomatic, treatment is not necessary. If desired, the scale and hair casts can be removed and kept at a minimum with topical applications of mild keratomodulatory agents (e.g., sulfur, salicylic acid) or moisturizing agents (e.g., fatty acids, lactic acid, urea, propylene glycol) as needed.

EMD is asymptomatic, stable-to-slowly progressive over time, and not reported to be cured by treatment nor to spontaneously resolve. In dogs with a typical history that are otherwise healthy, EMD is a visually distinctive disorder that requires no laboratory testing.

REFERENCE

FLY-BITE DERMATITIS IN DOGS

Although flies have presumably been biting dogs for thousands of years, reports of fly-bite dermatitis are of rather recent and anecdotal origin. Drs. George Muller and Robert Kirk were the first to report a form of fly-bite dermatitis involving the pinnae of dogs. Later, the same authors described a form of fly-bite dermatitis that affected the relatively hairless ventrum of dogs. Fly-bite dermatitis in dogs is now routinely mentioned in textbooks and articles. However, to the authors’ knowledge, no detailed case studies have been published.

Fly-bite dermatitis has been reported to be “common” to “uncommon” in dogs spending time outdoors during fly season. No age, breed, or sex predilections have been established. In one form of fly-bite dermatitis, ulcers and hemorrhagic crusts are seen at or near the tips of the pinnae of dogs with erect pinnae, or on the dorsal fold of the pinnae of dogs with pinnae that are folded over. Pruritus is variable. This form of fly-bite dermatitis has been circumstantially attributed to the bites of *Stomoxys calcitrans* (stable fly) and *Chrysops* spp. (deer fly).

A second form of fly-bite dermatitis is characterized by annular lesions featuring a central erythematous punctum, an inner zone of normal-appearing or edematous skin, and an outer rim of erythema (“target” or “bull’s eye” lesions). These lesions occur on the glabrous areas of the ventrum and lateral pinnal surfaces, are usually nonpruritic, and have been circumstantially attributed to *Simulium* spp. (black fly, buffalo gnat) bites.

Our purpose was to report the results of a retrospective study of 35 dogs with fly-bite dermatitis.

MATERIALS AND METHODS

A retrospective study was conducted on 35 dogs with fly-bite dermatitis examined by the Dermatology Service of the Cornell University Hospital for Animals (CUHA) from 1988 through 1998. Medical records were reviewed for the following information:

1. **Signalment (breed, age, sex).**
2. **Lifestyle of dog (indoor, outdoor, both).**
3. **Month of the year when the dog was examined.**
4. **Dermatological findings.**
5. **Therapeutic recommendations.**
6. **Month of the year when the skin lesions resolved.**
7. **Post-recovery follow-up period.**

Breed and sex data for the dogs with fly-bite dermatitis were compared to those for the general CUHA dog population for the same time period using the relative risk (RR) calculation.

\[
RR = \frac{\text{data for fly-bite dermatitis dogs}}{\text{data for CUHA dogs}}
\]

An RR of 2.0 or greater was considered significant.

Inclusion criteria included (1) the presence of typical dermatological presentations, (2) the
occurrence of dermatological presentations in dogs that were allowed to go outdoors from spring to late fall, and (3) the spontaneous resolution of lesions with the onset of sustained freezing weather.

RESULTS

Fly-bite dermatitis was diagnosed in 0.4% (35/8,207 dogs) of the canine dermatology cases and 0.1% (35/37,775 dogs) of all dogs examined at the CUHA over an 11-year period. Fourteen different breeds and mongrels were represented. Only 2 breed categories had over 2 individuals represented: mongrel (9) and Labrador retriever (9). Labrador retrievers were over-represented (RR = 2.9), but mongrels were not (RR = 1.1). Neither females (51% of cases) nor males (49% of cases) were over-represented, with RR = 1.0 for both sexes. Affected dogs ranged from 0.2 to 11 years of age. All dogs lived within an 80 km radius of the CUHA, and spent variable amounts of time outdoors.

Three types of dermatological presentations were recognized. Type 1 presentation was seen in 22/35 (62.9%) of the dogs. Skin lesions were annular, macular, and 1 to 3 cm in diameter. A central erythematous punctum was surrounded by an inner zone of normal-appearing or edematous skin, and an outer rim of erythema (targetoid lesions). Affected skin was not scaly, crusted, or oozing. No dog was reported to be pruritic. Lesions occurred on the abdomen, axillae, lateral surfaces of the pinnae, or combinations of these.

Type 2 presentation was seen in 6/35 (17.1%) of the dogs. Skin lesions were small, 2 to 4 mm in diameter, erythematous crusted papules. Crusts were often red-to-black in color (hemorrhagic). Small, pin-point erythematous-to-hemorrhagic puncta were usually present. No dog was reported to be pruritic. Lesions occurred on the abdomen or lateral surfaces of the pinnae.

Type 3 presentation was seen in 7/35 (20%) of the dogs. Skin lesions were ulcers covered with thick red-to-black (hemorrhagic) crusts. Owners of 4 of these dogs indicated that the dogs seemed to shake their heads more often than normal. No excessive scratching at the ears was reported.

All dogs with Type 1 presentation were examined between April and June, and all lesions had spontaneously resolved by mid-July. No treatments were administered. Ten of the 22 dogs (45.4%) were followed for 1 to 3 years post-recovery, and continued to have seasonal recurrence of the lesions.

All dogs with Type 2 presentation were examined between June and November, and all lesions had spontaneously resolved by the first sustained freezing weather (late October to early November). No treatments were administered. Three of these 6 dogs (50%) were followed for 2 to 3 years post-recovery, and continued to have seasonal recurrence of the lesions.

All dogs with Type 3 presentation were examined between July and September, and all lesions had resolved by the first sustained freezing weather (late October to early November). Because of head-shaking, 4 of the 7 dogs received the topical application of an antimicrobial-glucocorticoid-containing ointment twice daily until lesions were healed, then topical applications of fly repellents (permethrin or N,N-diethyl-meta-toluamide [DEET]-
containing sprays or ointments) as needed until sustained freezing weather. The other 3 dogs received no treatment. Three of these 7 dogs (43%) were followed for 1 year post-recovery and had seasonal recurrence of the dermatitis.

As we consider fly-bite dermatitis to be historically and visually distinctive, no laboratory tests were performed.

REFERENCE

ADDITIONAL PURSUITS OF ANECDOTES FOR YOUR VIEWING PLEASURE


CASE 1

Akita mix, neutered male, 4 years old.
CASE 2

Domestic shorthair cat, spayed female, 5 years old.
ALOPECIA IN CURLY COATED RETRIEVERS

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INTRODUCTION

The Curly-coated retriever (CCR), originally bred in England for bird-hunting, has a tight, curly coat that is considered highly protective. Breeders refer to a hair coat disorder as “patterned baldness”, “coat patterning” or “the curly coat problem”; the breed club states that few veterinarians know about this presentation and that it is often misdiagnosed as hypothyroidism. Standard textbooks contain brief sections wherein a hair loss disorder of CCR is grouped with ‘follicular dysplasia’ of Irish water spaniels / Portugese water dogs but detailed reports have not been published. We aimed to determine the prevalence of skin disease amongst CCR in the UK by questionnaires and to more fully define the clinico-pathological features in dogs with hair coat abnormalities.

MATERIALS AND METHODS

The study was approved by Royal Veterinary College’s Ethics and Welfare committee (UK dogs), the Ethical Committee on Animal Experiments, Uppsala, and the Swedish Board of Agriculture (Swedish dogs). Questionnaires on skin and general health were sent to members of the UK Curly Coated Retriever Club and returned to the authors. Dogs were physically examined with written informed consent of owner and local VS in both UK (n=6, RB±KV) and Sweden (n=8, KV) and further assessed by routine tests (skin scrapings, hair plucks, dermatophyte culture, haematology, blood biochemistry, serum total T4 / fT4 and cTSH, ACTH stimulation test [cortisol, 17-hydroxyprogesterone], and skin biopsies [vertical, transverse sections]).

RESULTS

QUESTIONNAIRES

Completed questionnaires were received regarding 56 black and 14 liver-coloured dogs, aged 7 months -13 years (median 4), of which 31 were female (16 neutered) and 39 were male ( 15 neutered). Twenty-four (19 black, 5 liver) had current / previous episodes of symmetrical, non-pruritic alopecia / hypotrichosis without skin inflammation. Eight had coat abnormalities when acquired (median age 5.5 months, range 2-12). In dogs that developed coat abnormalities after acquisition, age at onset reportedly (10/16) ranged from 4-15 months (median 10.5). Twenty had been affected in the preceding 12 months, with 18 currently affected. Fifteen had a waxing and waning course, 2 had become progressively
worse, 2 progressively better, and 1 had been unchanged. Alopecia affected one or more regions, including caudal thighs (n=14), axillae (n=12), dorsum (n=12), neck (n=10), sternum (n=7), tail (n=6), skin overlying the scapula (n=4), and flanks (n=3). Focal abnormalities of hair texture/quality (“frizzy”, “dry”) were reported by 11 owners. Increased skin pigmentation in alopecic areas was reported by only 5 owners. Four cases waxed and waned in association with oestrus, two with whelping, two with season of year and a further three perennially affected dogs were less-severely affected in the summer months. One dog affected for 2 years recovered for unknown reasons. The remaining owners did not specify a pattern. Other skin abnormalities reported included pruritus (atopic dermatitis [n=1], cutaneous adverse food reaction [n=1], unspecified [n=3]), onychodystrophy (n=2), tail gland hyperplasia (n=2), and mast cell tumour (n=1).

DOGS

Fourteen alopecic CCR (11 black, 3 liver, three male [two neutered, one entire], eleven female [four neutered, seven entire]) had an age at onset from 4 months to 6 years (median 13 months); in nine cases, signs developed in the first 14 months, although in one case the owner could be no more precise than ‘young’. Initial signs comprised focal areas of frequently symmetrical alopecia (dorsum, n=12; neck, n=10; caudal thigh, n=8; sternum, n=7; axillae, n=4; tail, n=3; shoulder, n=2; flank, n=2) without pruritus and inflammation, often accompanied by poor coat condition (“frizzy”, “dry”, n=9). In the male entire dog, the alopecia was reportedly slowly progressive, whereas in the two neutered male dogs, a waxing and waning course was described without full hair regrowth. A waxing and waning course was described in six of the seven entire female dogs (whelping, n=1; oestrus, n=3, no pattern, n=2).

CLINICAL PATHOLOGY

Ectoparasites and dermatophytes were not identified. All dogs were considered euthyroid. Serum cortisol concentrations before / after ACTH stimulation were normal. Concentrations of 17-hydroxyprogesterone were normal in ten dogs but mildly elevated post-ACTH simulation in one entire female and one neutered female, and elevated before and after stimulation in two dogs sampled during oestrus.

HISTOPATHOLOGY

Specimens obtained from normal skin (n=6) showed follicular keratosis (n=3) and pigment clumping in the inferior follicle (n=3). Sections from affected areas (n=32) showed infundibular hyperkeratosis (n=28) which often extended into secondary follicles (“witches feet”, n=21). Mild pigment clumping in the hair shaft or follicular epithelium was accompanied by pigmentary incontinence around follicles in 15 transverse and 17 vertical sections. Telogen hairs were more numerous in biopsies from alopecic sites.

CONCLUSIONS

Young adult CCRs that are otherwise healthy not infrequently present with alopecia and “frizzy” coat quality changes that may wax and wane, often in association with reproductive cycles. These changes are characterised histologically by infundibular hyperkeratosis, telogenisation of hair follicles and low-grade pigment dumping. The genetic basis of this disorder requires assessment.
REPEATED ORAL DOSE TOLERANCE IN DOGS TREATED CONCOMITANTLY WITH CICLOSPORIN (ATOPICA®) AND OCLACITINIB (APOQUEL®) FOR THREE WEEKS

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INTRODUCTION

Ciclosporin A (Atopica®) has been successfully used for the management of immune-mediated and inflammatory skin conditions in dogs for over 10 years with few long term safety concerns (Palmeiro, 2013; Forsythe and Paterson, 2014). Due to the relatively slow onset of clinical effect, concomitant use of another anti-inflammatory and/or anti-pruritic medication, such as glucocorticoids, during initial treatment with ciclosporin A is justified (Dip et al., 2013). Once effective, the dosing frequency for ciclosporin A can be reduced in most dogs to every other day or even once a week. Recently oclacitinib (Apoquel®) has been approved for the control of pruritus and clinical signs due to allergic or atopic dermatitis in dogs. Oclacitinib offers a very rapid onset of clinical effect (Cosgrove et al., 2013), but long term treatment with ciclosporin may be preferred. The objective of this study was therefore to evaluate the safety of ciclosporin A and oclacitinib used concomitantly at the approved dose rates.

MATERIALS AND METHODS

Sixteen beagle dogs received oclacitinib every 12 hours for two weeks then every 24 hours for one week (dose range of 0.41 – 0.60mg/kg). Eight of these dogs were randomised to receive concomitant ciclosporin A once daily for three weeks (dose range of 3.91-5.79mg/kg). Physical, clinical and general health assessments were conducted daily before dosing and 3 hours after the morning dose (i.e. ciclosporin A and first oclacitinib dose). Haematology, coagulation and clinical chemistry parameters were evaluated in all animals at Day -6 and then on Days 3, 10, 17 and 21. The data were analysed using a Repeated Measures Analysis of Covariance (RMANCOVA) ‘PROC_MIXED’ model (SAS; SAS Institute Inc., Cary, NC).

RESULTS

All the dogs remained clinically well during the study. There were no statistically significant changes in bodyweight or food consumption within or between the treatment groups during the study. No adverse events were reported apart from loose stools in two dogs in the ciclosporin/oclacitinib group that occurred 3 hours after dosing on Day 2 in one and on Day 17 in the other.
There were no statistically significant changes in haematology or coagulation parameters within or between groups during the study and all parameters remained within the reference ranges. There was a significant increase in blood urea nitrogen (BUN) in the ciclosporin/oclacitinib group compared to the oclacitinib alone group ($p=0.03$), but the levels remained within the reference range.

**CONCLUSIONS AND CLINICAL IMPORTANCE**

Concomitant administration of oclacitinib with ciclosporin A for three weeks appeared to be safe in this group of beagle dogs. No clinically significant adverse events were noted in either treatment group. The observed changes in clinical pathological parameters were minor and not clinically significant. This study utilised healthy beagle dogs rather than dogs suffering from atopic dermatitis, which can affect a variety of breeds. However, canine atopic dermatitis is not associated with any specific systemic metabolic changes and, with the exception of a possible association between long-term ciclosporin treatment and insulin antagonism in West Highland white terriers in Europe (Nuttall et al, 2014), no breed specific adverse effects are reported for either ciclosporin or oclacitinib.

Specific adverse effects associated with short term concomitant oclacitinib and ciclosporin A treatment in dogs with atopic dermatitis are not therefore anticipated. Nevertheless, in the absence of further data and given the potential for broad spectrum immunomodulation and immunosuppression long-term concomitant treatment with these drugs is not recommended.

This study used healthy dogs and, therefore, could not assess clinical outcomes. Concomitant administration of ciclosporin A with oral prednisolone for three weeks significantly decreased the time to clinical remission in canine atopic dermatitis, although the final clinical outcome at six weeks was not affected (Dip et al, 2013). A similar effect is expected following concomitant administration of ciclosporin A with oclacitinib, although this needs to be clinically proven.

In conclusion, this study provides evidence that it is safe to administer oclacitinib during initial treatment with ciclosporin A. This gives clinicians an option to more rapidly manage the pruritus in dogs with atopic dermatitis.

**CONFLICT OF INTEREST**

Tim Nuttall has received lecture fees, consultancy fees and research funding from Elanco (previously Novartis Animal Health) and Zoetis. Alessandro Panteri, Rainer Helbig, Guenther Strehlau, and Kelly Doucette are employees of Elanco Animal Health.

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EFFICACY AND SAFETY OF A NOVEL LONG-ACTING OTIC GEL (OSURNIA®) FOR THE TREATMENT OF OTITIS EXTERNA IN DOGS

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Based on data by Elanco Animal Health as part of submitted dossier
¹Elanco Animal Health, Greenfield, Indiana, USA

INTRODUCTION

Canine otitis externa in dogs is very common in veterinary practice. Current approved treatments are licensed for topical application from once daily for 5 days up to twice daily for 14 days. Treatment challenges include owner compliance and ease of application. Osurnia® is a novel otic gel approved in the US, Europe and Japan for the treatment of canine otitis externa associated with susceptible bacteria and yeast. The active ingredients are florfenicol, terbinafine and betamethasone acetate compounded in a high-viscosity gel packaged in a single use disposable tube. The approved dosage regimen is two doses one week apart per affected ear. This simplified dosing regime should result in better owner compliance and clinical outcomes. The aims of these studies were to demonstrate efficacy and safety in client-owned dogs with otitis externa.

MATERIALS AND METHODS

Two studies were performed to evaluate the efficacy of Osurnia® in dogs with otitis externa. A US study used a randomized, double-masked, placebo-controlled multi-centre trial; the European study was a randomized, single-masked, multi-centre trial using a product approved for the treatment of canine otitis externa as an active control (Easotic®; Virbac Animal Health, Carros, France).

Clinical efficacy was evaluated using a clinical scoring system (range 0-12) that assessed erythema, oedema/swelling, erosion/ulceration and exudate (Nuttall and Bensignor, 2014). For regulatory reasons pain, pruritus, odour and overall efficacy scores were included in the US study.

Dogs with otitis externa with a minimum score of 5 (Europe) or 6 (US) were recruited. There also had to be cytological evidence of infection at inclusion in the European study. Other inclusion criteria included a minimum age of 8 weeks and intact tympanic membranes. Exclusion criteria included: treatment with systemic, topical or otic antimicrobials within 14 days; treatment with topical or systemic anti-inflammatories within 14 days; treatment with ciclosporin within 14 days; pregnant or lactating dogs; and other factors that could have compromised the response to treatment.

Ear swabs were collected at day 0 and cultured for bacteria and yeast according to standard protocols. Microbial identification was performed using standard culture and biochemical methods. The dogs were randomized to receive either Osurnia® or the placebo or active control according to a predetermined allocation schedule. The formulation and packaging of Osurnia® and the placebo were identical. These were administered at a dose of one 1ml tube per affected ear at day 0 and day 7. The active control was administered according to
the approved dosing regimen of once daily for five consecutive days. The investigator was masked to treatment allocation and a separate dispenser undertook all treatment-related contact.

Clinical scores were evaluated at various time points from days 0-56 with efficacy assessed on Day 28 for the EU study. In the US study, the primary clinical endpoint was based on the total otitis externa score on Day 45 with success defined as a score ≤2.

RESULTS
CLINICAL TRIALS
In the US study 235 dogs were recruited among 15 veterinary clinics; in the European study 286 dogs were included in 30 veterinary clinics in France, Germany and Great Britain. The most common presentation was bilateral (US 72%; Europe 92%) erythroceruminous otitis (US 72%; Europe 83%). Acute clinical signs were present in approximately 25% of cases, with chronic otitis in 13% (US) and 36% (European) of cases. The majority of cases were non-recurrent (US 68%; Europe 89%). No adverse effects attributable to the trial products were noted.

In the US study treatment with Osurnia® resulted in a significantly better (p=0.0094) outcome at day 45 than the placebo, with clinical success rates (i.e. total scores of ≤2) in 63.7% and 41.7% of cases, respectively. In the EU study the primary outcome was the percentage reduction in score at D28. The total clinical score decreased similarly between the groups and the percentage of reduction over baseline at Day 28 were 62.5% for Osurnia® and 63.4% for the control product. Non-inferiority could be established (95% confidence interval of 57.7 to 67.4% for Osurnia® compared to 58.3 to 68.4% in the control group, P=0.80).

There were no statistical differences in outcomes scored by veterinarians between the Osurnia® and control groups (day 7: 54% v. 61%; day 28 74% v. 72%; and day 56: 72% v. 66%; p-value 0.23, 0.69 and 0.37 respectively). Further analysis showed no significant difference in efficacy between cases that were acute, subchronic or chronic, recurrent or non-recurrent, mild, moderate or severe, or erythematous or purulent, or the type of infection (staphylocoocal, Malassezia or mixed).

CONCLUSIONS
Osurnia® is safe and effective when administered at 1 ml per affected ear for two applications seven days apart to treat canine otitis externa. The high viscosity gel formulation facilitates rapid spread and retention of the active ingredients within cerumen. This permits precise within-clinic dosing without the necessity for the owner to treat at home.

CONFLICTS OF INTEREST:
Kelly Doucette, DVM is an employee of Elanco Animal Health.

REFERENCES
TERBINAFINE AND FLORFENICOL CONCENTRATIONS IN THE CANINE EAR CANAL EXCEED MINIMUM INHIBITORY CONCENTRATIONS FOR COMMON OTIC PATHOGENS AFTER TREATMENT WITH OSURNA® (ELANCO ANIMAL HEALTH)

Tim Nuttall1 and Sophie Forster 2
Based on data by Elanco Animal Health as part of submitted dossier
1The Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush Campus, Roslin, UK. 2Elanco Animal Health, UK.

INTRODUCTION

Most cases of otitis externa are treated with polyvalent topical preparations that contain at least one antibiotic, an antifungal and a glucocorticoid (Morris, 2004). Topical therapy delivers high concentrations of antimicrobials to the ear canal, which enhances efficacy.

Cytology can be used to determine the likely micro-organisms in cases of otitis. Knowledge of their likely antimicrobial susceptibility can be used to select appropriate antimicrobials (Beco et al., 2013). In contrast, the results of in vitro antimicrobial susceptibility tests may be misleading. In vitro tests usually employ µg/ml concentrations relevant for systemic therapy rather than the mg/ml concentrations achieved following topical therapy. This may underestimate efficacy, leading clinicians to ignore effective treatment options (Nuttall 2013). Moreover, susceptibility and resistance breakpoints may not be available for topical antimicrobials. It is therefore important that antimicrobial concentrations following application of topical products are available to clinicians.

A topical preparation containing 10mg/ml florfenicol, 10mg/ml terbinafine and 1mg/ml betamethasone acetate (Osurnia®; Elanco Animal Health) has recently been licensed for the treatment of otitis externa in dogs at a dose of 1ml into the ear canal repeated after 7 days. The aim of this study was to determine whether the florfenicol and terbinafine concentrations in the ear canal of treated dogs exceeded the MICs for common otic pathogens over the treatment interval.

METHODS

51 healthy beagle dogs received an otic gel containing 10mg/ml florfenicol, 10mg/ml terbinafine and 1mg/ml betamethasone acetate. Two doses of 1ml were administered into the left and right ears of each dog seven days apart. Pre-treatment ear swab samples were collected from all dogs. Ear-swab samples were then collected twice (at two different occasions) in each dog, once in the right ear and once in the left ear. Samples were collected at standard intervals from days 1 to 7 (before the second dose administration) and then from days 8 to 35 after the first administration. The collected material was weighed and stored at -20°C before analysis by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS).
Bacteria and _Malassezia_ strains were isolated from clinical cases of canine otitis, and identified using standard morphological and biochemical tests. The MIC of florfenicol against each bacterial isolate was determined using standardized broth microdilution MIC methodology (Clinical and Laboratory Standards Institute [CLSI] guidelines M31-A3 and M7-A80) using 128 to 0.062 µg/mL. The MIC of terbinafine against each _Malassezia_ isolate was determined using standardized broth microdilution MIC methodology (CLSI document M27-A2) with 64 to 0.062 µg/ml. Appropriate reference strains were used throughout.

**RESULTS**

Estimates of the mean terminal half-life were florfenicol 15 days (SEM 7.4) and terbinafine 5 days (SEM 0.8).

Table 1 Mean (SD) concentrations of florfenicol, terbinafine and betamethasone acetate (µg/ml)

<table>
<thead>
<tr>
<th>Sample time</th>
<th>Florfenicol</th>
<th>Terbinafine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 hours</td>
<td>10500 (1600)</td>
<td>11600 (1400)</td>
</tr>
<tr>
<td>1 day</td>
<td>13400 (4300)</td>
<td>15400 (9600)</td>
</tr>
<tr>
<td>2 days</td>
<td>12100 (6900)</td>
<td>16900 (5000)</td>
</tr>
<tr>
<td>4 days</td>
<td>16100 (9100)</td>
<td>15800 (5100)</td>
</tr>
<tr>
<td>5 days</td>
<td>6100 (4300)</td>
<td>4600 (4600)</td>
</tr>
<tr>
<td>7 days</td>
<td>8000 (1030)</td>
<td>4300 (3800)</td>
</tr>
<tr>
<td>8 days</td>
<td>16200 (3600)</td>
<td>15100 (4400)</td>
</tr>
<tr>
<td>9 days</td>
<td>22000 (5400)</td>
<td>16400 (4200)</td>
</tr>
<tr>
<td>11 days</td>
<td>19800 (4900)</td>
<td>18700 (5700)</td>
</tr>
<tr>
<td>12 days</td>
<td>17900 (15400)</td>
<td>9500 (5300)</td>
</tr>
<tr>
<td>14 days</td>
<td>7500 (7600)</td>
<td>4400 (4500)</td>
</tr>
<tr>
<td>18 days</td>
<td>11800 (8600)</td>
<td>6000 (3400)</td>
</tr>
<tr>
<td>24 days</td>
<td>3900 (2300)</td>
<td>1800 (1100)</td>
</tr>
<tr>
<td>35 days</td>
<td>1400 (1100)</td>
<td>500 (300)</td>
</tr>
</tbody>
</table>
Table 2 – MICs for the clinical isolates

<table>
<thead>
<tr>
<th></th>
<th>E. coli (n=61)</th>
<th>S. pseudintermedius (n=481)</th>
<th>Other staphylococci(^2) (n=28)</th>
<th>Streptococcus canis (n=76)</th>
<th>Other streptococci spp. (n=24)</th>
<th>Enterococcus spp. (n=11)</th>
<th>Proteus spp. (n=165)</th>
<th>Pseudomonas(^1) (n=165)</th>
<th>Malassezia (n=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>4 - 128</td>
<td>0.5 - 32</td>
<td>2 - 32</td>
<td>0.5 to &gt;128</td>
<td>0.5 to &gt;128</td>
<td>1 - 8</td>
<td>4 - 16</td>
<td>16 to &gt;128</td>
<td>0.125 to &gt;64</td>
</tr>
<tr>
<td>MIC(_{50})</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>&gt;128</td>
<td>0.5</td>
</tr>
<tr>
<td>MIC(_{90})</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td>&gt;128</td>
<td>8</td>
<td>8</td>
<td>&gt;128</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>11.3</td>
<td>5.7</td>
<td>7.2</td>
<td>4.9</td>
<td>17.2</td>
<td>3.8</td>
<td>6.5</td>
<td>&gt;128</td>
<td>0.9</td>
</tr>
</tbody>
</table>

\(^1\)A further 52 *Pseudomonas* isolates were tested against higher concentrations of florfenicol, yielding an MIC range of 64-2048 µg/mL, MIC\(_{50}\) 512 µg/mL, MIC\(_{90}\) 1024 µg/mL and mean MIC 386 µg/mL.

\(^2\)Two *S. pseudintermedius* and two *S. aureus* isolates were considered meticillin resistant on the basis of resistance to disc diffusion tests with 1 µg oxacillin and 30 µg cefoxitin discs respectively. All four isolates had an MIC to florfenicol of 8 µg/mL.

DISCUSSION

Florfenicol was active against all bacterial groups, although activity against *Pseudomonas* was more limited. Terbinafine was highly active against the *Malassezia* strains. Concentrations 2-3 orders of magnitude above the MIC90s for *Staphylococcus pseudintermedius* and *Malassezia pachydermatis* were maintained for up to 35 days following two doses of Osurnia® administered 7 days apart. Therapeutic concentrations in the ear canals are therefore achieved and maintained.
CONFLICTS OF INTEREST

Tim Nuttall has received lecture fees, consultancy fees and research funding from Elanco Animal Health (previously Novartis Animal Health).

Sophie Forster is an employee of Elanco Animal Health.

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