



Infiltrative lymphocytic mural folliculitis: a histopathological reaction pattern in skin-biopsy specimens from cats with allergic skin disease

Andrew S Rosenberg BS¹, Danny W Scott DVM, Dipl ACVD^{1*}, Hollis N Erb DVM, PhD², Sean P McDonough DVM, PhD, Dipl ACVP³

¹Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA

²Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA

³Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA

This study was conducted to determine the prevalence of infiltrative lymphocytic mural folliculitis (ILMF) in skin-biopsy specimens from 354 cats with various inflammatory dermatoses and from 33 cats with normal skin. Although ILMF was present in 33/47 dermatoses evaluated, the prevalence of ILMF in allergic dermatoses (116/172 cats; 67%) was significantly greater than that in non-allergic dermatoses (61/182 cats; 33%). Cats with allergic dermatoses had a 4.1 times greater odds of having ILMF than cats with non-allergic dermatoses. ILMF was not observed in any of the normal skin specimens.

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Infiltrative lymphocytic mural folliculitis (ILMF) is a histopathological reaction pattern reported to occur in selected feline inflammatory dermatoses (Table 1).^{1,2} 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.^{1,3} 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: (i) the prevalence of ILMF in skin-biopsy specimens from 354 cats with various inflammatory dermatoses; (ii) the prevalence of ILMF in skin-biopsy specimens from 33 cats with normal skin; and (iii) 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 (Table 2).¹ 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* species dermatitis, bacterial cellulitis, bacterial pyogranuloma, cryptococcosis, eumycotic mycetoma, sterile panniculitis and sterile pyogranuloma in our study (Table 2). 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.

*Corresponding author. Tel: +1-607-253-3029; Fax: +1-607-253-3534. E-mail: shb3@cornell.edu

Table 1. Feline inflammatory dermatoses wherein ILMF has previously been reported

Dermatosis	References
Adverse cutaneous drug reaction	Scott et al ¹
Alopecia areata	Scott et al, Gross et al ^{1,2}
Alopecia mucinosa	Scott et al, Gross et al ^{1,2}
Degenerative mucinotic mural folliculitis	Gross et al ²¹
Demodicosis	Scott et al, Gross et al ^{1,2}
Dermatophytosis	Scott et al, Gross et al ^{1,2}
Food allergy	Declercq, Scott et al ^{1,22}
Idiopathy	Declercq, Scott et al, Marignac et al ^{1,22,23}
Pseudopelade	Olivry et al, Scott et al, Gross et al ^{1,2,9}
Sebaceous adenitis	Scott, Scott et al, de Sepibus et al, Noli and Toma, Inukai and Isomura ^{1,10,24–26}
Thymoma-associated exfoliative dermatitis	Rottenberg et al ²⁷

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^{1,2,4}:

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 quantify 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 was recorded. The prevalence of ILMF for each dermatosis was determined.

Immunohistochemistry was performed on six cases (two with atopic dermatitis, two with bacterial folliculitis/furunculosis, two with dermatophytosis) to help determine the immunophenotype of the lymphocytes present in hair follicle epithelium.⁵ Briefly, formalin-fixed, paraffin-embedded tissue was sectioned at 4 μ m, mounted (Probe On Microscope Slides, Fisher Scientific, Pittsburgh, PA, USA) and deparaffinized. The sections were incubated with rabbit anti-human CD3 (CD3, Dako Corporation, 6392 Via Real, Carpinteria, CA, USA) at a 1:200 dilution and stained using a standardized streptavidin-biotin immunoperoxidase technique (Zymed Laboratories, San Francisco, CA, USA) and diaminobenzidine as the chromogen. Additional sections were incubated

with non-immune 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 anti-human CD3 to serve as the positive control.

Statistical analysis

The specimens were divided into two groups: those of allergic origin, and those of non-allergic origin. A Pearson's χ^2 test⁶ was used to determine if there was a statistically significant difference in the prevalence of ILMF in allergic versus non-allergic dermatoses. Significance was set at a P -value of ≤ 0.05 (two-sided).

As anecdotal literature^{1,2} indicates ILMF is a feature of dermatophytosis, a continuity corrected confidence interval analysis⁶ 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 χ^2 analysis).

Results

The prevalence of ILMF in each dermatosis studied is presented in Table 2. The agreement between the two histological assessments (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 (Figs 1A and 2A). Less commonly, ILMF also involved the isthmus of hair follicles. In 44 cases (six eosinophilic granuloma, 20 eosinophilic plaque, two bacterial cellulitis, five bacterial folliculitis/furunculosis, one cryptococcosis, one phaeohyphomycosis, six sterile panniculitis, two sterile pyogranuloma, one xanthoma), ILMF was a minor histopathological reaction pattern, represented by one or two involved hair follicles at the periphery of a larger histopathological reaction pattern (Table 2).¹

Table 2. Prevalence of ILMF in 354 cats with inflammatory dermatoses and 33 cats with normal skin

Dermatosis	Number of cases	% with ILMF
Allergic dermatoses (n = 172)		
Allergic dermatitis*	83	66
Atopic dermatitis	11	36
Atopic dermatitis and flea allergy	2	100
Contact allergy	1	100
Eosinophilic granuloma*	3	100
Eosinophilic plaque*	24	79
Eosinophilic plaque†	3	33
Flea allergy	19	42
Food allergy	13	85
Indolent ulcer†	11	100
Mosquito allergy	2	50
Non-allergic dermatoses (n = 182)		
Abscess	1	0
Adverse cutaneous drug reaction	3	33
<i>Alternaria</i> species dermatitis	1	0
Bacterial cellulitis	6	33
Bacterial folliculitis and furunculosis	23	22
Bacterial pyogranuloma	2	0
Cheyletiellosis	1	0
Cryptococcosis	2	50
Demodicosis	4	100
Dermatophytosis	8	25
Eosinophilic granuloma‡	18	17
Eosinophilic plaque‡	5	0
Erythema multiforme	5	40
Eumycotic mycetoma	1	0
FeLV dermatitis	2	0
Feline herpesvirus dermatitis	3	33
Hypereosinophilic syndrome	1	0
Indolent ulcer‡	8	0
Indolent ulcer with linear fibrosis	2	0
Lichenoid dermatitis	2	0
Pemphigus erythematosus	3	0
Pemphigus foliaceus	15	53
Pemphigus vulgaris	3	67
Phaeohyphomycosis	1	100
Primary seborrhea	2	0
Pseudopelade	2	100
Sebaceous adenitis	2	100
Solar dermatitis	10	10
Sterile panniculitis	16	38
Sterile pyogranuloma	6	33
Systemic lupus erythematosus	12	50
Thymoma-associated exfoliative dermatitis	5	80
Toxic epidermal necrolysis	2	100
Trombiculosis	1	0
Urticaria pigmentosa	2	50
Xanthoma	2	50
Normal skin	33	0

*These cats had atopic dermatitis, food allergy, or both of these (seasonally or non-seasonally recurrent lesions). Allergy testing was not performed.

†These cats had concurrent atopic dermatitis and flea allergy.

‡These cats had idiopathic lesions that were treated and never recurred (follow-up 2 to 6 years).

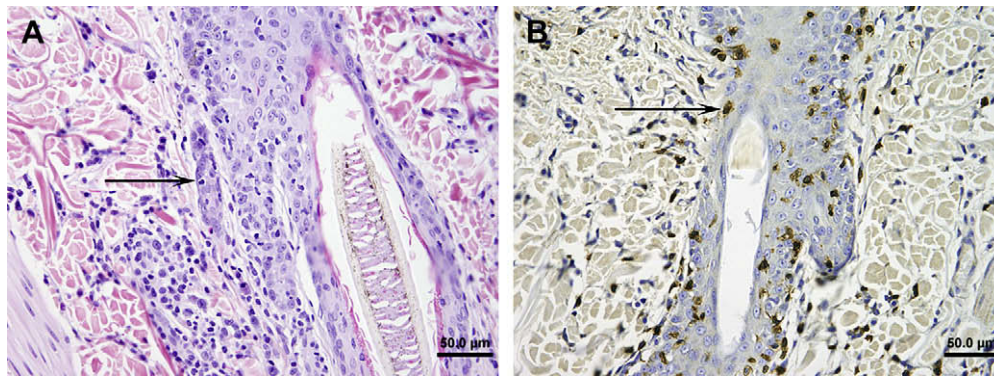


Fig 1. A. Skin-biopsy specimen from a cat with atopic dermatitis. Note the lymphocytic infiltrate in hair follicle epithelium (arrow) (hematoxylin and eosin stain; 200× original). B. Same skin-biopsy specimen as A. Note the CD3+ lymphocytes in the hair follicle epithelium (arrow) (diaminobenzidine; 200× original).

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

Immunohistochemistry revealed that the lymphocytes in hair follicle epithelium were CD3+ T-cells (Figs 1B and 2B).

Discussion

The histological reaction pattern of ILMF has previously been reported to be associated with a variety of mostly uncommon to rare feline inflammatory dermatoses (Table 1). We were able to confirm the presence of ILMF in many of these previously reported

dermatoses (Table 2). In addition, to the best of our knowledge, we report for the first time the occurrence of ILMF in several other dermatoses. We especially point out that for seven dermatoses (atopic dermatitis, eosinophilic plaque, flea allergy, indolent ulcer, bacterial folliculitis and furunculosis, sterile panniculitis, systemic lupus erythematosus) we had both ≥ 10 total cats and multiple cases with ILMF. We also noted at least one cat with ILMF in several less common dermatoses (contact allergy, eosinophilic granuloma, mosquito allergy, cryptococcosis, erythema multiforme, herpesvirus dermatitis, pemphigus foliaceus, pemphigus vulgaris, phaeohyphomycosis, solar dermatitis, toxic epidermal necrolysis, urticaria pigmentosa, xanthoma).

This is the first study to determine the prevalence of ILMF in a large number of inflammatory dermatoses in cats. We found that ILMF is a common reaction pattern in cats, occurring in 70% of the dermatoses studied. ILMF was often a focal, minor reaction pattern in many of the dermatoses examined (for example, one

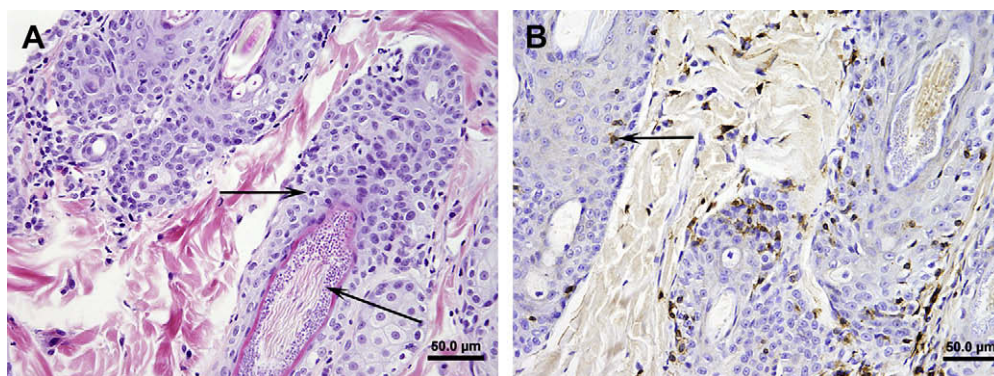


Fig 2. A. Skin-biopsy specimen from a cat with dermatophytosis. Note the lymphocytic infiltrate in hair follicle epithelium (upper arrow) and the intraluminal arthroconidia (lower arrow) (hematoxylin and eosin stain; 200× original). B. Same skin-biopsy specimen as A. Note the CD3+ lymphocytes in the hair follicle epithelium (arrow) (diaminobenzidine; 200× original).

or two follicles with ILMF peripheral to a nodule of eosinophilic granuloma or cryptococcal pyogranuloma). When the dermatoses were separated into those with an allergic origin ($n = 172$) and those with a non-allergic origin ($n = 182$), we found that the prevalence of ILMF was significantly higher in allergic dermatoses (67% versus 33%). ILMF was not present in clinically normal skin.

Immunohistochemistry performed on skin-biopsy specimens from six cats with ILMF showed the lymphocytes to be CD3 + T-cells. This would be expected because in cats,^{7–10} dogs,^{11–17} and humans,¹⁸ 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.^{19,20} T lymphocytes expressing a TCR consisting of gamma (γ) and delta (δ) chains predominate in the skin and are important in the immune response to various antigens (microbial, chemical, etc). As the majority of our cats had cutaneous allergies and infections, a T lymphocyte response would be expected.

Contrary to previous anecdotal reports,^{1,2} the presence of ILMF might not be an accurate indicator of the presence of dermatophytosis. In our study, ILMF was present in only 25% of cases in which dermatophytosis was the diagnosis. However, as was the case in our study, dermatophytes are usually readily seen in hair shafts in the follicular lumen on examination of skin-biopsy specimens from cats with dermatophytosis.¹

Conclusion

ILMF is common histopathological reaction pattern in feline skin-biopsy specimens, and occurs in a wide variety of inflammatory dermatoses. However, the prevalence of ILMF is significantly higher in cats with allergic dermatoses. Thus, the presence of ILMF in feline skin-biopsy specimens – even when it is present as a focal, minor reaction pattern – should always be interpreted as possible evidence for a concurrent allergic skin disease.

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