

Feline cutaneous lymphocytosis: case report and summary of the literature



Marlene S Pariser
DVM¹

Dunbar W Gram
DVM MRCVS DipACVD²

¹Animal Allergy and Dermatology, 1100 Eden Way N, Chesapeake, VA 23320, USA

²University of Florida College of Veterinary Medicine, College of Veterinary Medicine, PO Box 100126, Gainesville, FL 32610, USA

Corresponding author:
Marlene S Pariser
Email: mspariser@gmail.com

Date accepted:
1 May 2014

Practical relevance: Feline cutaneous lymphocytosis is a rare disease characterized by proliferation of T and/or B lymphocytes in the dermis. Although some of the clinical and histopathologic findings of this condition can overlap with cutaneous lymphoma, it is important to distinguish these entities since their treatment and clinical outcomes vary greatly.

Scope: This report presents a summary of the literature on feline cutaneous lymphocytosis and describes a case of this condition which showed some unique clinical features and was successfully controlled with oral glucocorticoids.

Cutaneous lymphocytosis is a disease characterized by a proliferation of T and/or B lymphocytes in the dermis.^{1–3} This rare condition has been documented in humans, horses, dogs and cats.^{1,4–7} This report describes a case of feline cutaneous lymphocytosis and reviews the literature on this condition.

Case history

A 13-year-old, 3.4 kg female spayed domestic shorthair cat presented to the referring veterinarian with purple discoloration and alopecia of the right forelimb near the first digit. It was treated with a long-acting injectable glucocorticoid (Depo-Medrol; Zoetis, 1.9 mg/kg SC) and the clinical signs resolved for 1 month but then recurred. The referring veterinarian administered another injection of the long-acting glucocorticoid, resulting in a 1 month remission, which again was followed by recurrence of the signs together with an ulceration and surrounding moderate erythema at the location of the original lesion. There was also a new alopecic area with erythematous to purple discoloration of the skin cranial to the metacarpal pad on the same extremity. Radiographs of the affected area did not indicate any pathological findings.

The lesions were treated with cefovecin sodium (Convenia; Zoetis, 7.1 mg/kg SC) and enrofloxacin (Baytril; Bayer, 5.4 mg/kg PO q24h) based on bacterial culture and susceptibility testing, and with short-acting

(Dexamethasone sodium phosphate; Butler Schein Animal Health, 0.76 mg/kg SC) and long-acting injectable glucocorticoids (Depo-Medrol; Zoetis, 1.9 mg/kg SC); however, the lesions subsequently worsened. The ulcerated area expanded, and the erythema cranial to the metacarpal pad on the right paw intensified. The ulceration bled when traumatized by normal activity, such as grooming, though there was no evidence that the lesions were pruritic or painful. The affected leg was bandaged to prevent further trauma.

Seven months after the initial clinical signs developed, the patient presented to the dermatology service with severe erythema, an ulceration near the first digit and a patchy, erythematous area of alopecia measuring approximately 3 x 1 cm cranial to the metacarpal pad. Cytology of the ulcerated area consisted of intracellular coccoid bacteria with a mixture of mostly degenerative neutrophils and a few lymphocytes. Beneath the bandage the cat had also developed a superficial pyoderma on the palmar aspect of the right front paw, which was confirmed by cytology. Due to the presence of bacteria, treatment was initiated with oral clindamycin (Lannett, 22 mg/kg PO q12h), with a plan to perform skin biopsies at the next visit. The pyoderma on the right front paw was also treated with chlorhexidine wipes (Douxo Chlorhexidine 3% PS Pads; Sogeval q12–24h).

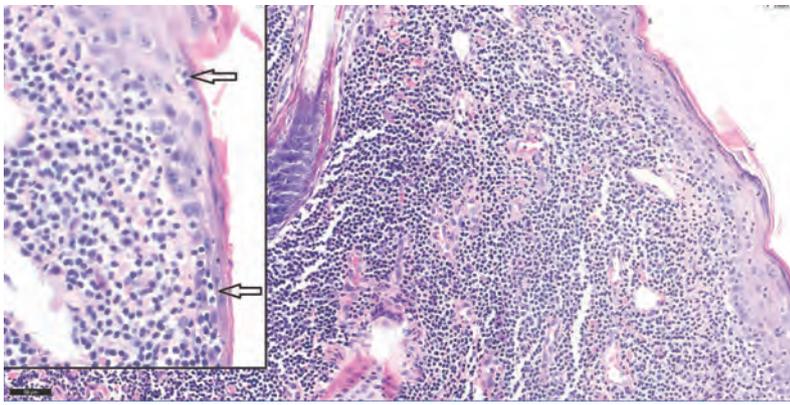


Figure 1 A diffuse infiltrate of small, monomorphic lymphocytes occupies the entire dermis. Hematoxylin and eosin stain, x 20. Inset: Arrows indicate epitheliotropic lymphocytes

At the 2 week re-evaluation the bacterial dermatitis appeared to be responding to treatment as significantly fewer coccoid bacteria were noted on cytology. However, inflammatory cells were still present, and the patient's lesions had worsened. The first area of ulceration remained unchanged, but there was a second ulceration, approximately 1 x 2 cm, lateral to the first digit. Between these ulcerations was a well-defined area of moderate erythema and alopecia. The patchy alopecia and erythema cranial to the metacarpal pad remained unchanged. A 6 mm punch biopsy of the erythematous area of alopecia between the ulcerations was performed, but due to the highly vascular nature of this lesion only one sample could be obtained for histopathology, and for this reason tissue culture could not be performed.

The histopathologic findings consisted of a monomorphic population of small lymphocytes forming a diffuse infiltrate in the superficial and deep dermis. Small numbers of similar lymphocytes were detected in the epidermis and occasionally within the follicular epithelium (Figure 1). The lymphocytes had sparse to mildly expanded pale cytoplasm surrounding ovoid nuclei. Mitotic figures were not seen. Small numbers of mast cells, large lymphocytes, plasma cells and macrophages were present in the infiltrate. The pattern of dermal infiltration accompanied by minor epitheliotropism, the cellular

morphology and the low mitotic index were supportive of cutaneous lymphocytosis (Figure 1). Immunohistochemistry revealed a predominance of CD3-positive T cells with small randomly scattered clusters of CD79a-reactive B cells (Figures 2 and 3).⁸ An archived formalin-fixed, paraffin-embedded skin biopsy was submitted to the Leukocyte Antigen Biology Laboratory at UC Davis for molecular clonality analysis, which revealed T cell receptor gene rearrangement (TCRg).⁹ Based on these findings a diagnosis of feline cutaneous lymphocytosis was made.

The patient was started on oral dexamethasone (Decadron; Par Pharmaceutical, 0.15 mg/kg PO q24h for 14 days) and cefovecin sodium injection (0.4 ml SC once). After 2 weeks of treatment a slight improvement was noted; there was one remaining ulceration adjacent to the first digit and mild erythema cranial to the metacarpal pad. The cat was continued on the same dosage of dexamethasone and an additional cefovecin sodium injection was administered (0.4 ml SC once).

After a further 4 weeks there was significant improvement in the lesions. The ulceration had resolved completely and was replaced by mildly erythematous intact skin and alopecia. The mild erythema cranial to the metacarpal pad was reduced in size by about 50%. Complete blood count (CBC) and chemistry profile were within normal limits. At this

The pattern of dermal infiltration accompanied by minor epitheliotropism, the cellular morphology and the low mitotic index were supportive of cutaneous lymphocytosis.

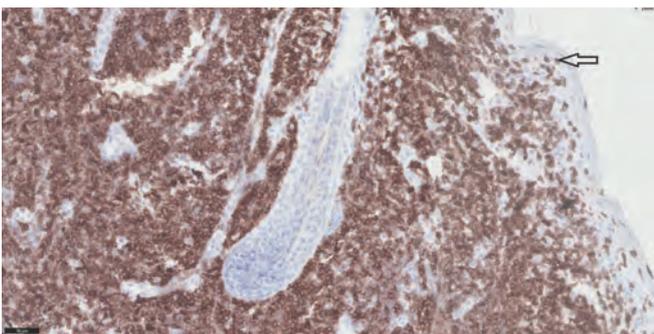


Figure 2 Virtually all of the lymphocytes express CD3. One such lymphocyte in the epidermis is indicated by the arrow. Immunohistochemistry CD3, x 20

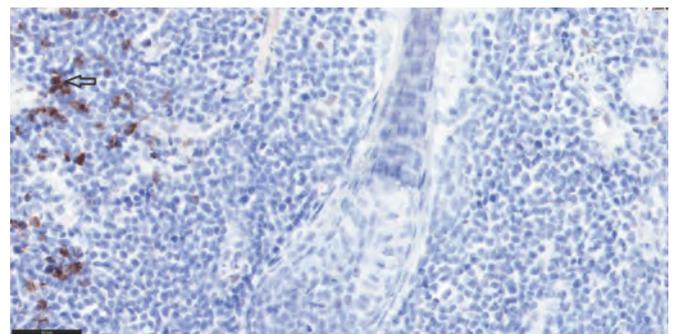


Figure 3 A few of the lymphocytes were CD79a-positive B cells (arrow). Immunohistochemistry CD79a, x 40



Figure 4 Palmar aspect of the right front paw with severe alopecia, erythema and depigmentation of the paw pads and surrounding skin



Figure 5 Right front paw with partial alopecia and severe erythema



Figure 6 Left front paw with erythema

point the patient's dexamethasone was tapered to 0.15 mg/kg PO q48h for 2 weeks, then 0.07 mg/kg PO q48h, and the cefovecin sodium injections were discontinued.

For the next 6 months the erythema and alopecia continued to improve slightly. Treatment with dexamethasone (0.07 mg/kg PO q48h) was maintained. The dexamethasone dose was not reduced further because the affected areas were not completely controlled, but the disease was considered stable at this point.

After another 6 month period of stability, there was slow progression of clinical signs over 3–4 months. The alopecic, erythematous skin area cranial to the metacarpal pad began to increase in size to encompass the whole palmar aspect of the right paw. There was also depigmentation and erythema of the paw pads (Figure 4). The cranial aspect of the right front paw had moderate to severe erythema and patchy alopecia extending from the distal phalanges to the first digit (Figure 5). A new lesion appeared on the cranial aspect of the right forelimb at the elbow, and developed into an alopecic, erythematous patch measuring 2 x 3 cm. The patient also started to develop moderate erythema on the cranial aspect of the carpal region of the left front paw pad (Figure 6). At this point the dexamethasone dose was increased, initially to 0.15 mg/kg PO q48h and subsequently to 0.15 mg/kg PO q24h, after which the lesions stabilized but did not regress. The skin lesions remained stable over the following 4 months. Repeat CBC and chemistry profile were within normal limits.

The typical clinical presentation of feline cutaneous lymphocytosis is a solitary lesion showing alopecia, erythema and scaling, with or without crusting – most commonly on the thorax. Most cats do not become systemically ill.



Discussion and literature review

Cutaneous pseudolymphoma is a broad term used to describe a clinical or histopathologic lesion that resembles lymphoma.¹ In human medicine it can be further broken down into Spiegler-Fendt sarroid, lymphocytoma cutis, lymphadenosis benigna cutis and cutaneous lymphoid hyperplasia.¹ The last, cutaneous lymphoid hyperplasia, is the preferred term as it most directly describes the pathophysiology.¹ Most human cases of cutaneous lymphoid hyperplasia are idiopathic, but these lesions have also been linked to bites and stings by arthropods, infections, tattoos, acupuncture, trauma, gold jewelry, vaccinations, and hypersensitization injections or medications.¹

In veterinary medicine, cutaneous lymphocytosis has been the preferred terminology,⁵ but it has been suggested that the term cutaneous lymphoid hyperplasia may be more accurate.⁸ As described by Gilbert et al, cutaneous lymphocytosis 'implies neither a specific disease, nor a causation, but simply designates a process of accumulation of lymphocytes in the skin'.⁵

Feline cutaneous lymphocytosis is a rare disease characterized by proliferation of small, mostly T lymphocytes in the superficial and deep dermis.^{4,5} The disease is most often seen in older cats, averaging 12–13 years; there is no breed predisposition, but there may be a slight predominance of females.^{4,6} The duration of disease at the time of diagnosis varies from 2 weeks to 48 months. The disease is generally characterized by acute onset with slow progression.^{4,5} Although generally considered a benign condition, malignant transformation has been observed (see later).^{4,5,10} The etiology is unknown;^{4,6} however, the presence of clonal gene rearrangement suggests that this is a low-grade or indolent lymphoma.^{4,10}

The typical clinical presentation is a solitary lesion showing alopecia, erythema and scaling, with or without crusting, most commonly on the thorax.^{4,6} In some cases there are multiple lesions on various body sites (thorax, leg, pinna, flank, neck, abdomen, paw pad, between the scapulae, elbow, caudal thigh, hip, digit and planum nasale).^{4,6} Other clinical presentations include alopecic erythematous plaques, single or multiple nodular lesions, solitary ulcers, milium papules, proliferation of the paw pad and ulcerations of the planum nasale.^{4,6} Pruritus and sometimes excoriation and ulceration can be seen in about half of cases.^{4,6} Lesion size is variable (1.5–12 cm diameter).⁵

Blood studies are generally unrewarding.⁵ Most cats are feline leukemia virus and feline immunodeficiency virus negative.⁵

Histopathologic findings in an early lesion consist of a perivascular to diffuse infiltrate of small lymphocytes in the superficial dermis, but as the disease progresses the infiltrate can extend into the deep dermis.^{4,6} The lymphocytes have dark nuclei with compact chromatin and a small to moderate amount of cytoplasm.^{4,5} Mitotic figures are absent to rare.^{4,5} The majority of the lymphocytes are CD3 ϵ + T cells which express CD18, CD3 and CD5.^{4,5}

In approximately half of all cases there are small, tightly packed aggregates of smaller B lymphocytes (CD79a+, CD21+) with minimal cytoplasm.^{4,5} Some cases show epitheliotropism of lymphocytes into the epidermis or follicular epithelium.⁵ Moderate epidermal hyperplasia, erosion and ulceration may be present.⁵

Treatment results are variable. In one case surgical excision of a solitary lesion was initially successful, but a new lesion returned after 18 months, prompting additional surgery, the outcome of which is unclear.⁵ Response to systemic or topical glucocorticoid treatment is also variable: 14/18 cats reportedly showed some response to these interventions.^{5,6} When this approach failed, the

Most of the features in this case were consistent with previous cases – this was an older female cat, the etiology was unknown, and the process developed acutely with slow progression. Less common features were the multiple lesions on both front limbs.



addition of chlorambucil or lomustine led to an additional response in 4/5 cats.^{5,6}

In general the disease runs an indolent but benign course with treatment.^{4,5} Most cats do not become systemically ill. However, in some cases weight loss and anorexia have progressed to the point of euthanasia.^{4,5}

On necropsy gross lesions were noted in four cats.⁵ Cytology or histology of these lesions showed a monomorphic infiltrate of lymphocytes similar to that seen in the skin.⁵ It is not known whether these lesions preceded or followed the development of cutaneous lesions.^{4,5}

There is some evidence that feline cutaneous lymphocytosis may undergo malignant transformation, as is occasionally seen in analogous human cases.^{1,2,4,5,11} Notably, some cases have exhibited systemic lymphoid involvement – such as ascites, enlarged mesenteric lymph nodes and peripheral lymphadenopathy, infiltration of liver, pancreas, stomach, kidney and heart by T cell lymphocytes, and B cell infiltration of the small intestine.⁵

Most of the features of the current case were consistent with those of previous cases, as this was an older female cat, the etiology of the condition was unknown, and the process developed acutely with slow progression and typical histopathologic findings and epitheliotropism.^{4,6}

Immunohistochemistry results agreed with the published data in showing a predominance of CD3-positive T cells and small clusters of CD79a-positive B cells.^{4,5} Clonality analysis also showed T cell clonal rearrangement, which has been seen in some cases.^{4,10} The clonal rearrangement suggests a neoplastic process; cutaneous lymphocytosis may actually be a form of indolent T cell lymphoma.^{4,10}

A different form of lymphoma, cutaneous T cell lymphoma, is a common differential for cutaneous lymphocytosis. However, the treatment, response rate and clinical outcomes differ (Table 1). Both forms show proliferation of small to medium-sized lymphocytes in the dermis, but some features, such as significant involvement of the epidermis or the follicular epithelium, nuclear atypia and Pautrier's microabscesses, are found in cutaneous T cell lymphoma.¹²

Exfoliative erythroderma, alopecic patches or ulcerations, which are clinical presentations of cutaneous T cell lymphoma, can overlap with the clinical lesions of cutaneous lymphocytosis; however, the treatment response is very different.¹² There are a number of chemotherapeutic options for cutaneous T cell lymphoma, but such therapy is not as effective in cutaneous lymphocytosis.^{12,13} In a recent case report of a feline patient with cutaneous lymphocytosis that was originally misdiag-

Table 1 Comparison of cutaneous lymphocytosis and cutaneous T cell lymphoma in feline patients

	Cutaneous lymphocytosis	Cutaneous T cell lymphoma
Age of onset	12–13 years	10 years
Sex predilection	Slightly toward female	None
Breed predilection	None	Not reported
Duration of disease at time of diagnosis	2 weeks to 48 months	Most cases have chronic skin disease before diagnosis
Clinical signs	<ul style="list-style-type: none"> ❖ Solitary lesion showing alopecia, erythema and scaling, with or without crusting ❖ Less common presentations include alopecia and scaling, with or without crusting, alopecic erythematous plaques, single or multiple nodular lesions, solitary ulcers, miliary papules, proliferation of the paw pad and ulcerations of the planum nasale ❖ Pruritus, excoriation and ulceration are present in half of cases 	<ul style="list-style-type: none"> ❖ Highly variable ❖ Solitary or multiple lesions without any predilection for body sites, although the face is commonly affected ❖ Erythematous plaques or patches, scaly alopecic patches, non-healing ulcers or nodules, crusting miliary multicentric dermatitis, exfoliative erythroderma and focal hypopigmentation have been seen. Regional lymphadenopathy is common ❖ Variable pruritus
Location of clinical signs	Thorax, leg, pinna, flank, neck, abdomen, paw pad, between the scapulae, elbow, caudal thigh, hip, digit and planum nasale	Face, eyelid, mucocutaneous junction, elbow, trunk
Lesion size	1.5–12 cm diameter	Not reported
Disease progression	Acute onset but slow progression	History of chronic skin disease with slow progression
Disease outcome	Disease considered benign	Disease considered malignant
Laboratory results	Unrewarding	Not reported
Histopathologic signs	<ul style="list-style-type: none"> ❖ Lesion consists of a perivascular to diffuse infiltrate of small lymphocytes in the superficial dermis, but as the disease progresses the infiltrate can extend into the deep dermis ❖ Lymphocytes have dark nuclei with compact chromatin and a small to moderate amount of cytoplasm ❖ Mitotic figures are absent to rare and slight epitheliotropism can be present 	<ul style="list-style-type: none"> ❖ Epitheliotropic lymphoma: diffuse superficial or follicular epitheliotropism of small to medium or medium to large lymphocytes of the epithelium and adnexal structures. The lymphocytes have a convoluted nucleus. Pautrier's microabscess can be present. Dermal lymphocytic infiltration has been reported ❖ Spongiosis and keratinocyte apoptosis are noted as secondary changes ❖ Non-epitheliotropic lymphoma: deep dermal and subcutaneous non-encapsulated masses of small cell, large cell or immunoblastic lymphocytic infiltrate which gives it a 'bottom heavy' configuration. Adnexal structures are not affected. Mitotic activity variable
Immunohistochemistry	<ul style="list-style-type: none"> ❖ Majority of lymphocytes are CD3ε+ T cells which express CD18, CD3 and CD5 ❖ Rarely small tightly packed aggregates of smaller B lymphocytes (CD79a+, CD21+) with minimal cytoplasm are present 	One case of CD8-positive T cell lymphocytes reported
Treatment	Surgical removal, systemic or topical glucocorticoids, chlorambucil or lomustine	Glucocorticoids, lomustine, CCNU, surgery, electron beam irradiation, vincristine/cyclophosphamide and intravenous and local administration of fibronectin
Treatment outcome	Variable, but in most cases lesions continue to progress in an indolent but benign form despite treatment	Variable depending on the agent used, but in most cases remission can be achieved for up to 15 months
Survival time	Up to 49 months, with median survival time of 11 months	Variable – median survival 10.25 months, but as low as 1–6 months reported

nosed as lymphoma there was no clinical response to the commonly used chemotherapies.¹³ In cutaneous T cell lymphoma it is reasonable to expect remission or at least improved quality of life for up to 15 months with treatment, but cutaneous lymphocytosis generally shows slow progression of clinical signs with stable quality of life despite treatment.^{4–6} Feline cutaneous T cell lymphoma and cutaneous lymphocytosis do have a similar median survival time, but patients with cutaneous lymphocytosis have survived for up to 49 months while cutaneous T cell lym-

phoma survival, in some studies, has been as low as 1–6 months.^{5,12} Thus, although cutaneous lymphocytosis may be an indolent form of T cell lymphoma, it has a very different disease progression, outcome and response to treatment – as such, it is an important distinction in feline patients.

The current case showed some less commonly noted features, namely multiple lesions which developed slowly on both front limbs. Lesions initially had a purplish color, which has not previously been reported, and the uncommon feature of ulcerations. Initially

complete remission was seen with injectable glucocorticoids, but eventually the disorder recurred. As is true in about half of reported cases, the lesions in the current case were asymptomatic and non-pruritic.⁴⁻⁶

In previously reported cases response to treatment was variable.^{5,6} In the current case dexamethasone therapy resulted in lesion stabilization which was maintained, albeit with dose adjustment. Complete remission with dexamethasone was never achieved.

As of the last clinical encounter, the patient's lesions remained stable with the adjusted dosage of dexamethasone, and there was no evidence of malignant transformation.

Conclusions

The literature on feline cutaneous lymphocytosis is limited, consisting of case reports and small case series.^{4-6,13-16} More information is needed to aid in diagnosis of this rare condition and to completely understand the etiology, full range of clinical expression, and treatment options. It is also important that clinicians recognize the difference between cutaneous T cell lymphoma and cutaneous lymphocytosis as the treatment response, prognosis and outcomes are very different.

Acknowledgements

Thank you to Patrick Hensel and William Brewer for their editorial service and Tammy Johnson for her assistance with histopathology.

Funding

The authors received no specific grant from any funding agency in the public, commercial or not-for-profit sectors for the preparation of this case report.

Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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Cutaneous lymphocytosis may be an indolent form of T cell lymphoma, but has a very different disease progression, outcome and response to treatment, which are important distinctions in feline patients.



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