

Sézary Syndrome in a Cat

Sézary syndrome is an uncommon leukemic variant of cutaneous lymphoma in cats. This cat had recurrent dermatitis with erythematous, pruritic plaques. Multiple skin imprints and biopsy samples were obtained over a 6-month period, and histopathological findings were consistent initially with eosinophilic miliary dermatitis and later with erythema multiforme. One week before death, Sézary cells were identified in the peripheral blood that expressed cluster of differentiation (CD)3 and CD8 antigens. Massive infiltration of CD3+ lymphocytes was noted in the skin and multiple internal tissues by histopathological examination. This case demonstrates the difficulty in diagnosing cutaneous lymphoma early in the disease course.

J Am Anim Hosp Assoc 2008;44:144-148.

Casey Wood, DVM

Kelli Almes, DVM

Mary Bagladi-Swanson, DVM,
Diplomate ACVD

Brad Debey, DVM, PhD,
Diplomate ACVP

Gordon Andrews, DVM, PhD,
Diplomate ACVP

Jerome Nietfeld, DVM, PhD,
Diplomate ACVP

Melinda Wilkerson, DVM, PhD,
Diplomate ACVP

C

Introduction

Sézary syndrome is a rare, end-stage leukemic variant of cutaneous T cell lymphoma (CTCL) and is characterized by the presence of small to large (8 to 20 μ m) lymphocytes with cerebriform or convoluted nuclei (Sézary cells) in the peripheral blood in addition to erythematous skin lesions and peripheral lymphadenomegaly.¹⁻⁴ Diagnosis of CTCL may be difficult, and the condition may mimic more common pruritic, exfoliative skin lesions. Multiple cutaneous biopsy samples may be necessary to obtain a definitive diagnosis.⁴

The cause of CTCL is unknown in cats. It has been reported, however, that feline leukemia virus (FeLV) could be isolated from tumor deoxyribonucleic acid (DNA) in a cat with cutaneous lymphoma while circulating antigen to FeLV was not detected.⁵ Humans with chronic atopic dermatitis may have an increased risk for developing CTCL, leading to speculation that chronic antigenic stimulation can lead to the development of CTCL, although the antigen in question is unknown.^{4,6}

The purpose of this paper is to describe a feline case of Sézary syndrome that mimicked other clinical conditions, including eosinophilic miliary dermatitis and erythema multiforme, until thoroughly investigated postmortem.

Case Report

A 15-year-old, female spayed, domestic shorthair cat was presented for a recent onset of pruritic, crusty miliary dermatitis that occurred at multiple sites including the neck, dorsum, and inner thighs. Cytological examination of skin imprints revealed many degenerate neutrophils containing bacterial cocci. Additional skin scrapings for mites and a Wood's lamp test for dermatophytes were negative. The cat was discharged on Clavamox (amoxicillin and clavulanate potassium, 62.5 mg per os [PO] *q* 12 hours for 2 weeks) for the bacterial pyoderma.

Two months later, the cat was assessed by a board-certified veterinary dermatologist and was clinically described to have multifocal areas of erythema, alopecia, and crusting on the dorsum along with erythema, erosion, and excoriations on the medial thighs and paronychia. Increased numbers of neutrophils and eosinophils with few round cells were evident

From the Departments of
Diagnostic Medicine/Pathobiology
(Wood, Almes, Debey, Andrews,
Nietfeld, Wilkerson) and
Clinical Sciences (Bagladi-Swanson),
College of Veterinary Medicine,
Kansas State University,
1800 Denison Avenue,
Manhattan, Kansas 66506-5705.

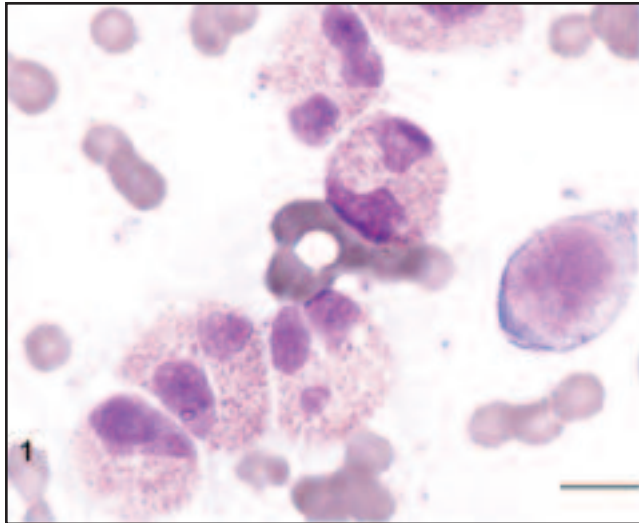


Figure 1—Skin imprint from dorsum; cat. Numerous eosinophils and a round cell resembling a lymphocyte (Dip stain, bar=10 μ m).

on cytological examination of skin imprints, with eosinophils predominating [Figure 1]. Staining the preparations with a modified Wright's stain^a rather than Dip Stain^b more clearly revealed the round cells as a mixture of poorly granulated mast cells and lymphocytes. A combined enzyme-linked immunosorbent assay (ELISA) for FeLV and feline immunodeficiency virus (FIV) was performed on whole blood and determined to be negative.^c The results of a complete blood count (CBC) and serum biochemical panels performed were within reference intervals. A culture on hair samples for dermatophytes was performed and exhibited no growth. *Streptococcus* spp. (beta hemolytic) and *Staphylococcus aureus* were isolated from a skin swab. Because of the antibiotic sensitivity results, the presence of secondary pyoderma, and possible gastrointestinal irritation from Clavamox, the antibiotic was switched to clindamycin (25 mg PO *q* 12 hours). To help with the intense pruritus, clemastine (1.34 mg; half tablet PO *q* 12 hours) was also initiated. Histopathological examinations of skin samples taken from the trunk and thigh revealed multifocal, erosive, suppurative dermatitis with bacterial colonies, epidermal necrosis, and mast cell infiltrate—consistent with hypersensitivity or miliary dermatitis with secondary pyoderma.

One month later, the cat's skin condition had not resolved, despite the continued administration of clindamycin. Concern about the possibility of cutaneous lymphoma as the cat's underlying problem led to the collection of a second set of skin biopsy samples, which revealed a similar histological diagnosis. Complete blood count and serum biochemical panels were repeated with no abnormal results noted. As an adjunctive treatment for the intense pruritus, the cat received an injection of 15 mg of Depo Medrol (methylprednisolone acetate, 20 mg/mL) subcutaneously, which resulted in slight improvement of the skin lesions for about 7 to 10 days. Because food allergies can cause cutaneous manifestations of a hypersensitivity response, the cat

was started on a food trial using Innovative Veterinary Diets,^d which also was believed to result in mild clinical improvement for a short time.

Four months after the initial presentation, and despite being on a food trial, the cat's dermatitis worsened. It involved most of the skin of the dorsum and ventrum, leading to almost complete hair loss over the ventrum, inner thighs, and forelimbs. Patchy alopecia was present over the dorsum. Skin-punch biopsy samples were collected and revealed continued presence of eosinophilic and mastocytic dermatitis. Evidence of individual necrotic keratinocytes within all layers of the epidermis and follicular epidermis was suggestive of erythema multiforme [Figure 2]. Lymphocytic infiltrates were also evident in the epidermis and follicular epidermis [Figure 2]. As a result of this diagnosis and the concern of clindamycin-induced erythema multiforme, the treatment was switched to enrofloxacin

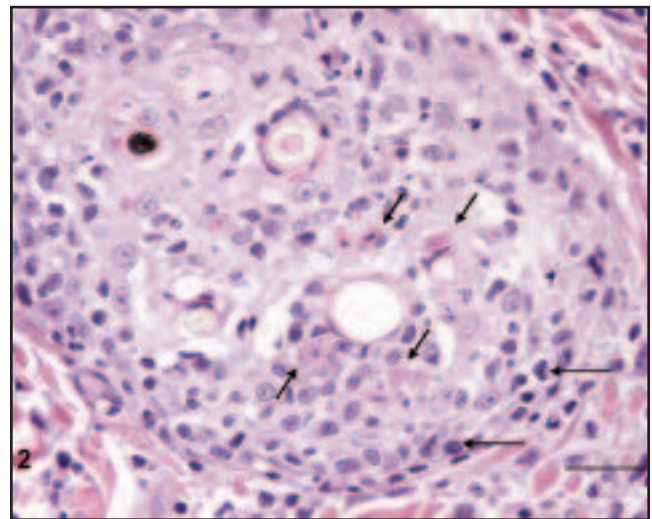


Figure 2—Skin; cat. Apoptotic keratinocytes (short arrows) and lymphocytes (long arrows) within the rete pegs of the epidermis (Hematoxylin and eosin stain, bar=70 μ m).

(22.7 mg; one tablet PO *q* 24 hours for 14 days) and a daily injection of dexamethasone sodium phosphate (1 mg) subcutaneously for 1 week, followed by tapered doses at every 3-day intervals. The cat responded well to the treatment within 2 weeks. By 5 months after the initial visit, the majority of the skin lesions had resolved, hair had regrown, and pruritus had decreased. A few crusty lesions remained, principally around the neck and head. Over the next several months, the cat was treated periodically with antibiotics previously mentioned for recurrent pyoderma. Oral dexamethasone (1 mg *q* 3 days) was administered for intermittent pruritus.

Ten months following the initial examination, the cat's general condition deteriorated markedly. Physical examination revealed severe, generalized, moist erythematous dermatitis; dehydration; and slight bilateral, popliteal

lymphadenomegaly. Cytological assessment of skin imprints revealed numerous round cells that resembled medium-sized lymphocytes containing abundant, azurophilic, cytoplasmic granules.

A CBC^e showed a leukocytosis (27,700/ μ L, reference interval 5500 to 19,500/ μ L) characterized by a neutrophilia with a left shift (segmented neutrophils 11,400/ μ L, reference interval 2500 to 12,500/ μ L; band neutrophils 5000/ μ L, reference interval 0 to 300/ μ L); lymphocytosis (9700/ μ L, reference interval 2000 to 7000/ μ L); basophilia (300/ μ L, reference interval 0 to 100/ μ L); and normocytic, normochromic anemia (packed cell volume 28%, reference interval 30% to 45%). Examination of the peripheral blood film demonstrated toxic changes in neutrophils and increased numbers of lymphocytes with oval to lobulated nuclei and azurophilic, cytoplasmic granules [Figure 3A]. Occasional cells had cerebriform nuclei resembling Sézary

The lack of finding CD4+ T lymphocytes in an inflammatory leukogram was unusual and suggested a clonal proliferation of CD8+ T cells, which was confirmed 2 weeks later with a polymerase chain reaction (PCR) assay for T cell antigen-receptor gene rearrangement of the peripheral blood. However, this information was not known at the time the CBC results were reported. The presence of a neutrophilia with a left shift could be explained by chronic inflammation of the skin. Lymphocytosis with abnormal granular lymphocytes seen in this cat was consistent with a lymphoproliferative disorder or reactive lymphocytosis.

A serum biochemical profile^h was performed and revealed the following abnormalities: increased urea nitrogen (64 mg/dL, reference interval 17 to 35 mg/dL), hyperglobulinemia (5.9 g/dL, reference interval 2.6 to 4.8 g/dL), increased alanine transaminase (ALT) activity (184 U/L, reference interval 27 to 127 U/L), and hyperbilirubinemia

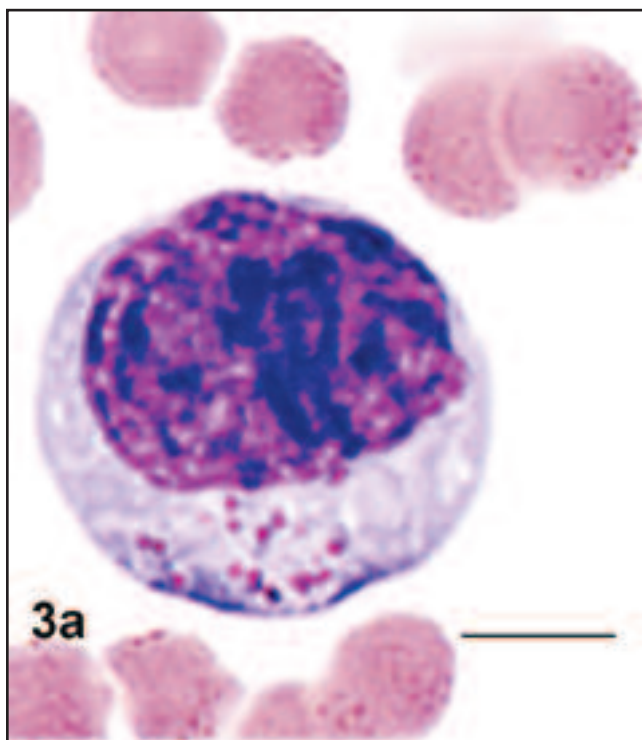


Figure 3A—Venous blood; cat. Granular lymphocyte (Modified-Wright's stain, bar=6 μ m).

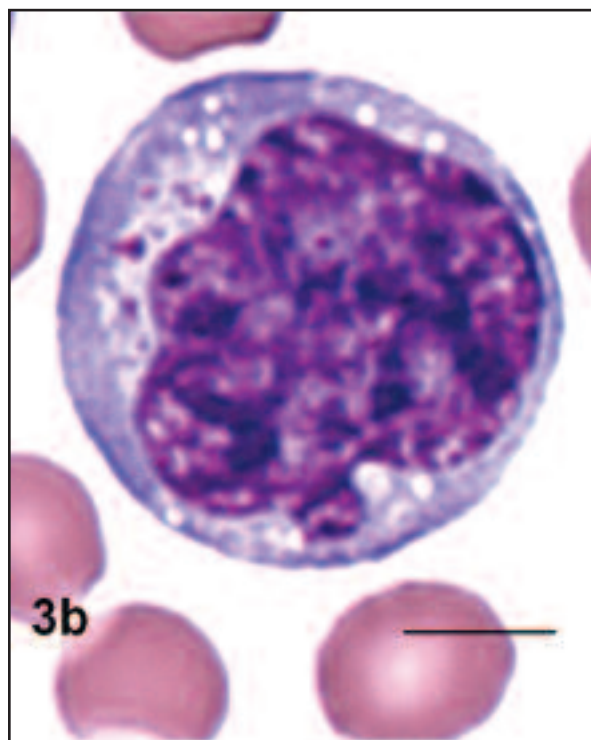


Figure 3B—Venous blood; cat. Sézary cell with a cerebriform nucleus (Modified-Wright's stain, bar=5 μ m).

cells [Figure 3B]. Toxic changes in the neutrophil series included diffuse cytoplasmic basophilia, Döhle bodies, and occasional asynchronous nuclear maturation.

Leukocytes in the peripheral blood were immunophenotyped using a previously described method and a panel of monoclonal antibodies to T lymphocyte subsets (i.e., CD4, CD8),^f B lymphocytes (i.e., CD21),^g and monocytes (i.e., CD14).^{g,7} The percentages of leukocytes that expressed CD4, CD8, CD21, and CD14 of the total population were 1%, 85%, 10%, and 4%, respectively. These findings indicated that CD8+ T cells contributed to the peripheral lymphocytosis.

(total 2.1 mg/dL, reference interval 0.0 to 0.4 mg/dL). The azotemia was attributed to decreased glomerular filtration rate secondary to dehydration. The increased ALT activity indicated hepatocellular damage, and hyperbilirubinemia was thought to indicate cholestasis. Hyperglobulinemia was likely caused by chronic inflammation of the skin.

The cat died 3 days later, before any further clinical assessment or diagnostics could be completed.

A necropsy was performed, and gross examination revealed diffuse, 2- to 3-mm, cutaneous papules located over the dorsum, with a normal distribution of hair.

However, on the ventrum and medial surfaces of all four limbs, hair loss was almost complete and accompanied by a uniform, thick, serous exudate that varied in appearance from bright red to yellow. The left prescapular lymph node was enlarged (1.5 by 1.0 by 1.0 cm). All other organs appeared grossly normal, including the liver, kidney, and spleen. Histopathological examination of affected skin revealed diffuse infiltration of the dermis, adnexa, and epidermis, with a population of neoplastic round cells. The neoplastic round cells ranged in size from 10 to 20 μm , with indistinct cell borders and scant, pale, eosinophilic cytoplasm. Nuclei were round, centrally located, and measured 10 to 15 μm with hyperchromatic, coarsely stippled chromatin. Mitotic figures averaged 1 per high-power field (40 $\times$ objective). Moderate numbers of mast cells were intermixed with neoplastic cells in the dermis. Neoplastic cells in the skin stained positively for CD3ⁱ [Figure 4A] and negatively for CD79a^j (not shown). Multifocal areas of epidermal ulceration, neutrophilic crusting with moderate numbers of cocci, and follicular casts were also present.

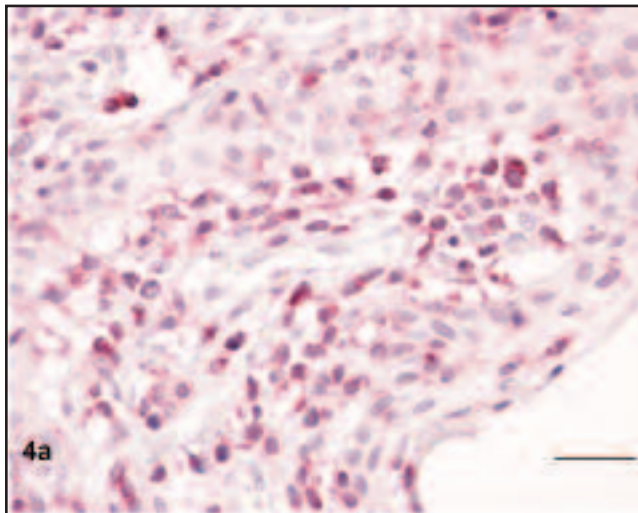


Figure 4A—Skin of ventrum; cat. Immunohistochemical staining for CD3 expression on lymphocytes that infiltrate the dermis and epidermis (Ventana Red detection kit, Mayer's hematoxylin counterstain, bar=60 μm).

The left prescapular lymph node architecture was effaced by similar neoplastic round cells. Neoplastic round cells and moderate numbers of eosinophils and plasma cells were also present within portal areas and surrounding sinusoids of the liver [Figure 4B]. Neoplastic cells were also found in renal tubular epithelial cells. The white pulp of the spleen was diffusely infiltrated with similar cell populations. Due to the positive staining of these neoplastic cells with CD3 and the negative staining for CD79a, the cat was diagnosed with disseminated epitheliotropic CTCL (also known as mycosis fungoides). These findings, together with identification of Sézary cells in the blood, supported a diagnosis of Sézary syndrome.

Discussion

Identifying the neoplastic lymphocytes in the skin, left prescapular lymph node, kidney, liver, and spleen as positive for CD3 (a mature T cell surface marker) and the presence of these neoplastic lymphocytes within the epidermis led to a diagnosis of epitheliotropic CTCL. Furthermore, immunophenotyping and PCR assay for antigen-receptor gene rearrangement of the lymphocytes in the blood subclassified the T cells as a clonal population of CD8⁺ cells. To the authors' knowledge, this is the first case of Sézary syndrome in a cat in which the Sézary cells were identified as CD8⁺ T cells with a clonal rearrangement of the T cell antigen receptor.

Cutaneous T cell lymphoma in humans is usually characterized by an elevated dermal CD4⁺/CD8⁻ ratio and the presence of a T cell clone detected by PCR in tissues and peripheral blood.^{8,9} In humans with Sézary syndrome, the cells are most commonly reported as CD4⁺ T cells, whereas cases that express CD8 are less common.⁸ It is possible that this cat had an unusual form of Sézary syndrome in

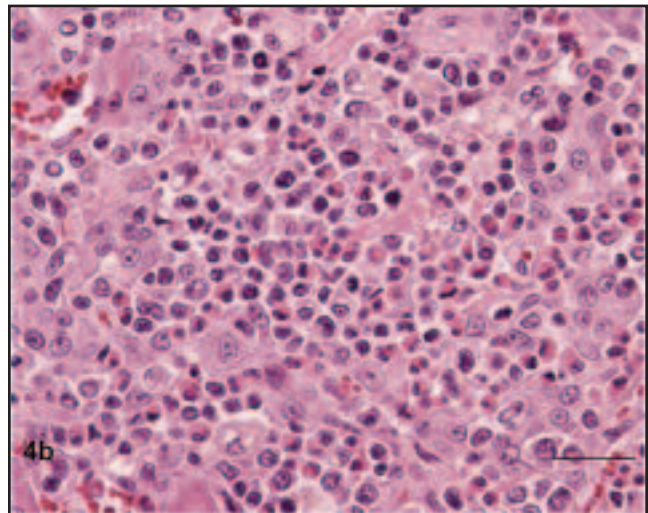


Figure 4B—Liver; cat. Eosinophils comprise the majority of infiltrating cells in the sinusoids (Hematoxylin and eosin stain, bar=70 μm).

which a proliferation of CD8⁺ rather than CD4⁺ lymphocytes was present. However, more cases of Sézary syndrome in cats will need to be immunophenotyped to determine if the cell type is more commonly CD4⁺, as it is in humans.

In this cat, frequent lymphocytes were noticed in the mixed inflammatory cell population of the skin imprints and in the epidermis upon histopathological examination of some skin biopsy samples. However, hypersensitivities to various antigens can cause nonmalignant accumulation of lymphocytes in the skin, and early in the course of CTCL, the infiltrative lymphocytes are usually reactive T cells.^{10,11}

Histologically, it can be nearly impossible to differentiate benign inflammatory skin diseases from early CTCL.¹² Erythema multiforme, diagnosed earlier in the disease course by histopathological examinations of skin biopsy samples, is also characterized by invasion of the epidermis by T cells (usually CD8+), leading to keratinocyte apoptosis.¹³ The earlier diagnosis of erythema multiforme was also supported by the administration of various antibiotics (clindamycin) that have been associated with the development of erythema multiforme, and by apparent partial resolution of most of the skin lesions for a few months after removal of the suspected offending drug.^{13,14} It is possible that the slow progression of disease seen in this case contributed to the lack of an earlier, more specific diagnosis.

The prominence of eosinophils may be explained by the presence of T helper 2 (Th2) lymphocyte cytokines (e.g., interleukin [IL]-3, IL-4, or IL-5) that stimulate growth and differentiation of eosinophils.¹⁵⁻¹⁷ In humans, Sézary syndrome and hypereosinophilia are associated with increased Th2 cytokines and are related to the progression of the lymphoma malignancy.¹⁶ Rare, paraneoplastic, hypereosinophilic syndromes have been described in horses and dogs that have concurrent lymphoma; however, cytokine production in these disorders has not been defined.^{18,19}

The cause of sudden death in this cat is unknown. Death in cats and dogs with CTCL is reported to be most commonly caused by septicemia or metastatic lymphoma.³ Humans with CTCL frequently succumb to fatal opportunistic infections.²⁰

Conclusion

This case report is an example of Sézary syndrome, a rare, end-stage leukemic form of CTCL. This report is unique in that it demonstrates CD8+ Sézary cells in a cat.

Footnotes

^a Richard Allen Scientific, Kalamazoo, MI 49008

^b Volu-Sol, Inc., Salt Lake City, UT 84121

^c IDEXX Laboratories, Westbrook, ME 04092

^d Royal Canin USA, Inc., St. Charles, MO 63301

^e Cell-Dyn 3700; Abbott Laboratories, Abbott Park, IL 60064-3500

^f Southern Biotechnology, Birmingham, AL 35260

^g Serotec, Raleigh, NC 27604-1699

^h Boehringer Mannheim/Hitachi 911, Indianapolis, IN 46250

ⁱ Rabbit antihuman; DAKO, Carpinteria, CA 93013

Ventana Red detection kit; Ventana Medical Systems, Inc., Tucson, AZ 85755

^j HM57; DAKO, Carpinteria, CA 93013

Acknowledgments

The authors acknowledge Drs. Marjorie Arzter, Susan Nelson, and Laura Garrett for their care of the animal and their contributions to this case; Dr. Mehrdad Ameri for immunophenotyping the peripheral blood; Dr. Anne Avery for the PCR testing; and Cindy Chard-Bergstrom for the immunohistochemical testing.

References

1. Thrall MA, Macy DW, Snyder SP, *et al.* Cutaneous lymphosarcoma and leukemia in a dog resembling Sezary syndrome in man. *Vet Pathol* 1984;21:182-186.
2. DeBoer DJ, Turrel JW, Moore PF. Mycosis fungoides in a dog: demonstration of T cell specificity and response to radiotherapy. *J Am Anim Hosp Assoc* 1990;26:566-572.
3. Moriello KA. Cutaneous lymphoma and variants. In: Feldman B, Zinkl J, Jain N, eds. *Schalm's Veterinary Hematology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:648-653.
4. Kotz EA, Anderson D, Thiers BH. Cutaneous T cell lymphoma. *J Eur Acad Dermatol Venereol* 2003;17:131-137.
5. Tobey JC, Houston DM, Breur GJ, *et al.* Cutaneous T cell lymphoma in a cat. *J Am Vet Med Assoc* 1994;204:606-609.
6. Foon KA, Ghobrial I, Geskin LJ, *et al.* The non-Hodgkin lymphomas. In: Lichtman MA, Beutler E, Kipps TJ, *et al.*, eds. *Williams Hematology*. 7th ed. New York: The McGraw-Hill Companies, Inc., 2006:1407-1459.
7. Wilkerson MJ, Dolce K, Koopman T, *et al.* Lineage differentiation of canine lymphoma/leukemias and aberrant expression of CD molecules. *Vet Immunol Immunopathol* 2005;106:179-196.
8. Papadavid E, Economidou J, Psarra A, *et al.* The relevance of peripheral blood T-helper 1 and 2 cytokine pattern in the evaluation of patients with mycosis fungoides and Sezary syndrome. *Br J Dermatol* 2003;148:709-718.
9. Laetsch B, Haffner AC, Dobbeling U, *et al.* CD4 + /CD7- T cell frequency and polymerase chain reaction-based clonality assay correlate with stage in cutaneous T cell lymphomas. *J Invest Dermatol* 2000;114:107-111.
10. Duvic M, Edelson R. Cutaneous T cell lymphoma. *J Am Acad Dermatol* 2004;51:S43-S45.
11. Gilbert S, Affolter VK, Gross TL, *et al.* Clinical, morphological and immunohistochemical characterization of cutaneous lymphocytosis in 23 cats. *Vet Dermatol* 2004;15:3-12.
12. Vonderheid EC. On the diagnosis of erythrodermic cutaneous T-cell lymphoma. *J Cutan Pathol* 2006;33(Suppl 1):27-42.
13. Scott DW, Miller W. Erythema multiforme in dogs and cats: literature review and case material from the Cornell University College of Veterinary Medicine (1988-1996). *Vet Dermatol* 1999;10:297-309.
14. Affolter VK, Von Tscharn C. Cutaneous drug reactions: a retrospective study of histopathological changes and their correlation with the clinical disease. *Vet Dermatol* 1993;4:79-86.
15. Borish L, Dishuck J, Cox L, *et al.* Sezary syndrome with elevated serum IgE and hypereosinophilia: role of dysregulated cytokine production. *J Allergy Clin Immunol* 1993;92:123-131.
16. Saed G, Fivenson DP, Naidu Y, *et al.* Mycosis fungoides exhibits a Th1-type cell-mediated cytokine profile whereas Sezary syndrome expresses a Th2-type profile. *J Invest Dermatol* 1994;103:29-33.
17. Suchin KR, Cassin M, Gottlieb SL, *et al.* Increased interleukin 5 production in eosinophilic Sezary syndrome: regulation by interferon alpha and interleukin 12. *J Am Acad Dermatol* 2001;44:28-32.
18. La Perle KM, Piercy RJ, Long JF, *et al.* Multisystemic, eosinophilic, epitheliotropic disease with intestinal lymphosarcoma in a horse. *Vet Pathol* 1998;35:144-146.
19. Marchetti V, Benetti C, Citi S, *et al.* Paraneoplastic hypereosinophilia in a dog with intestinal T cell lymphoma. *Vet Clin Pathol* 2005;34:259-263.
20. Lorincz AL. Cutaneous T-cell lymphoma (mycosis fungoides). *Lancet* 1996;347:871-876.

Copyright of Journal of the American Animal Hospital Association is the property of American Animal Hospital Association and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.