Cutaneous epitheliotropic T-cell lymphoma in the cat: a review of the literature and five new cases

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Abstract
Cutaneous epitheliotropic T-cell lymphoma (CETL) is characterized by cutaneous infiltration of neoplastic T lymphocytes with a specific tropism for the epidermis and adnexal epithelium. This disease is reported very rarely in the cat. Clinical data were collected from an informal discussion with veterinary dermatologists through the Vetdermlist (vetderm@lists.ncsu.edu). In parallel, case archives of two European diagnostic histopathology laboratories (Institut de Pathologie et Génétique/Bio.be Gosselies, Belgium and the School of Veterinary Sciences, University of Bristol, UK) were reviewed. Fifteen cases with a good clinical description were selected, and five sets of skin biopsies were available for review. Cutaneous epitheliotropic T-cell lymphoma generally affects older cats with no apparent sex or breed predisposition. Solitary or multiple lesions were reported without predilection for any particular location. The lesions consisted of erythematous plaques or patches, scaly alopecic patches and nonhealing ulcers or nodules, which sometimes mimicked an eosinophilic plaque. Pruritus was rarely reported. No lesions affecting the oral mucosa were observed. Clinical diagnosis of CETL is more challenging in cats than in dogs. Final diagnosis must be based on histopathological examination of skin biopsy samples. The characteristic lesions of feline CETL are similar to those reported in the dog, but involvement of the adnexal glands was not observed in this series (n = 5). The neoplastic T cells were generally small to medium in size. The survival time of cats with CETL seems to be more variable than that of affected dogs. Too few cases have been evaluated to permit clear recommendations to be made with respect to treatment.

Introduction
Cutaneous epitheliotropic T-cell lymphoma (CETL) is well described in dogs, but the disease is rarely reported in the cat. Only seven cases of feline CETL have been documented. Cutaneous epitheliotropic T-cell lymphoma is characterized in all species by cutaneous infiltration of neoplastic T lymphocytes with tropism for the epidermis and adnexal epithelium. By application of the same criteria used for human or canine CETL, the feline tumour may be subclassified as either mycosis fungoides or Sézary syndrome. Cutaneous epitheliotropic T-cell lymphoma must be differentiated from nonepitheliotropic (dermal) lymphoma.

Materials and methods
To collect data on previously unreported cases of feline CETL, an informal discussion was instigated with veterinary dermatologists through the Vetdermlist (vetderm@lists.ncsu.edu) and reviewed the files of two European diagnostic histopathology laboratories.

Results
Twelve cases with a good clinical description and a histopathological diagnosis made by a veterinary pathologist...
were documented from responses made by 10 Vetderm-list dermatologists. A further two cases (investigated clinically by J.F.) were obtained from the archive of the Belgian laboratory and one further case was derived from the archive of the UK laboratory, making a total of 15 cases, from which five sets of skin biopsies were available for review (Table 1).

**Epidemiology**

Informal assessment of the prevalence of feline CETL by discussion with veterinary dermatologists through the Vetderm-list (vetderm@lists.ncsu.edu) and by review of the files of the two diagnostic laboratories confirmed the very low prevalence of this disease. Twelve cases (median age at diagnosis 13.5 years; range 4–18 years) were reported by 10 Vetderm-list dermatologists. In the Belgian laboratory, CETL comprised 0.08% of all feline cutaneous tumours reported between 1992 and 2009. For the UK laboratory, a single well-defined case was retrieved from a database encompassing 1984–2009.

**Clinical signs**

Affected cats were always presented with a chronic history of slowly progressive disease. The lesions were isolated, or in some cases, diffuse to generalized. No particular anatomical distribution was reported, but the face was affected in eight of 15 cases (Figures 1–3). In one case, only the feet were affected (Figure 4). The lesions consisted of erythematous plaques or patches, scaly alopecic patches, nonhealing ulcers or nodules, and sometimes resembled an eosinophilic plaque (Table 2). Pruritus was reported rarely.

**Histopathological diagnosis**

A total of five cases were reviewed histopathologically (Table 3). Epitheliotropism was observed in all cases (Figure 5). Pautrier’s microabcession was only observed in one case (Figure 6), but rare small intraepidermal aggregates were observed in all cases. The follicular epithelium was mildly, but consistently affected, but only at the superficial level (ostium). In two cases, there was greater infiltration of the dermis than the epithelium (nodular stage). The intraepithelial lymphocytes were of variable size, ranging from small (<20 μm) to medium (20–30 μm) or large (>30 μm), and were often characterized by having a convoluted nucleus. Secondary changes including spongiosis and apoptosis of individual keratinocytes were sometimes observed. In two cases, a mixed inflammatory reaction, composed of plasma cells, lymphocytes and macrophages, accompanied the tumour, complicating the diagnosis, and in two cases mild to severe mixed ortho- and parakeratosis covered the affected epidermis.
Involvement of follicular epithelium below the level of the ostium or of adnexal glands was not observed. There was no evidence of dermal neoangiogenesis, and mild superficial dermal fibrosis was observed in only one case. On immunohistochemical examination of the five cases, the neoplastic lymphocytes were CD3-positive (Figure 5c), with only sparse infiltration by B lymphocytes expressing CD79a. The presence of these B lymphocytes was correlated mostly with nodular lesions and observed in the dermis.

Discussion

Lymphoma is the most common malignancy in the cat, representing one-third of all tumours, although cutaneous involvement only occurs in 1.78% of cases. Only seven cases of feline CETL have been documented previously. The signalment of those historical cases was consistent with that of the five new cases documented here (Table 1). Cutaneous epitheliotropic T-cell lymphoma generally affects older cats, with no apparent sex or breed predisposition. The median age of cats previously reported was 10 years (range 5–15 years), and this group included four neutered males and three neutered females.

The aetiology of CETL remains undetermined. A viral aetiology has been suggested in cats and humans. The majority of cats with cutaneous lymphoma are negative for feline leukaemia virus (FeLV) on routine blood testing, although it is feasible that FeLV could play a role in individual patients. In one cat with cutaneous (non-epitheliotropic) lymphoma, intracutaneous proviral FeLV DNA was identified by PCR. Of the seven cases reported in the literature, only one cat was positive for FeLV. None of the five cats reported here was positive for FeLV. Sequences of human T-lymphotropic virus (HTLV-1) have been isolated from some cats with CETL. In humans, herpes virus 8 (HHV-8) has also been found in cutaneous lymphoproliferative lesions. Another herpesvirus, the Epstein–Barr virus (HHV-4), has been implicated in the development of Hodgkin’s lymphoma in humans. A possible predisposing factor debated in human CETL is the presence of pre-existing chronic inflammation that transforms into lymphoma. However, this hypothesis is not supported by recent studies. A history of chronic dermatitis before the development of CETL has also been proposed in dogs, but a recent study of 25 cases of canine CETL did not report prior chronic dermatitis in any patient. For the historical feline cases, the median time between the onset of first lesions until the final diagnosis of CETL was 3.5 months (range 2.5–10 months, n = 4). In the cases reported in our study, the owners always described the cats as having a long history of slowly progressive dermatitis, but a relationship with a possible chronic inflammatory process was impossible to verify.

The observed tropism of neoplastic T cells for the epidermis and adnexal epithelium in CETL may be associated with the expression of skin-homing receptors by the neoplastic T cells. Molecules including the cutaneous lymphocyte antigen or CC-chemokine receptor 4 are known to be involved in the migration of lymphocytes into the epidermis and to permit the association of these cells with epidermal keratinocytes and Langerhans’ cells.
express high levels of the β1 integrin intercellular adhesion molecule-1.25–27 Such expression may be important for adhesion to surface receptors and thus for the epitheliotropism observed in the disease.25

As reported in dogs, 1–4 the clinical presentation of feline CETL is highly variable, and the disease may mimic many dermatoses. Solitary or multiple lesions were reported without predilection for any particular body location. Facial lesions were observed in eight of the 15 cases reported. One of the cases of the present series presented only with pododermatitis. The lesions were isolated, or in some cases, diffuse to generalized. The

Table 3. Summary of histopathological lesions in five reviewed cases

<table>
<thead>
<tr>
<th>Epidermis</th>
<th>Dermal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic infiltration: single cell/diffuse</td>
<td>Involvement of apocrine sweat glands</td>
</tr>
<tr>
<td>Lymphocytic aggregation</td>
<td>Involvement of sebaceous glands</td>
</tr>
<tr>
<td>Pautrier’s microabscess*</td>
<td>Dermal fibrosis</td>
</tr>
<tr>
<td>Localization to basal epidermis</td>
<td></td>
</tr>
<tr>
<td>Panepidermal localization</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Size of epidermal lymphocytes (µm)</th>
<th>Size of dermal lymphocytes (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large &gt;30</td>
<td>Large &gt;30</td>
</tr>
<tr>
<td>Medium 20–30</td>
<td>Medium 20–30</td>
</tr>
<tr>
<td>Small &lt;20</td>
<td>Small &lt;20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other epidermal changes</th>
<th>Follicular involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiosis</td>
<td>Focal involvement of isthmus</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Panfollicular (nodular effect)</td>
</tr>
<tr>
<td>Acanthosis</td>
<td></td>
</tr>
<tr>
<td>Orthokeratosis and parakeratosis</td>
<td></td>
</tr>
<tr>
<td>Dermo-epidermal obliteration</td>
<td></td>
</tr>
<tr>
<td>Pigmentary incontinence</td>
<td></td>
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Numbers in parentheses correspond to the case numbers in Table 1.

*Pautrier’s microabscess is defined as at least four atypical lymphocytes in a single intraepidermal space.

Figure 5. Skin biopsy from an 8-year-old neutered male domestic short-haired cat. (a) Epidermal acanthosis crowned by hyperkeratosis, with the lymphocytic infiltrate within the epidermis mostly limited to the basal layer and interface area (H&E; scale bar represents 175 µm). (b) The lymphocytes are mainly distributed singly within the epidermis and only sparsely scattered within the dermis (white arrows). Numerous dyskeratotic cells occupy the spinous layers (white asterisks; H&E; scale bar represents 75 µm). (c) The neoplastic T lymphocytes infiltrate the superficial dermis and the epidermis as demonstrated by the CD3 immunolabelling (H&E; scale bar represents 400 µm).

Figure 6. Same skin biopsy as shown in Figure 5 (H&E; scale bar represents 100 µm). The neoplastic cells form a small Pautrier’s abscess (white arrows) at the level of the follicular ostia.

As reported in dogs,1–4 the clinical presentation of feline CETL is highly variable, and the disease may mimic many dermatoses. Solitary or multiple lesions were reported without predilection for any particular body location. Facial lesions were observed in eight of the 15 cases reported. One of the cases of the present series presented only with pododermatitis. The lesions were isolated, or in some cases, diffuse to generalized. The
lesions consisted of erythematous plaques or patches, scale alopecic patches, nonhealing ulcers or nodules, and sometimes resembled an eosinophilic plaque. One cat reported in the literature had a crusting milary multicentric dermatitis. The clinical features of CETL in cats closely resemble the description of the entity in dogs, summarized as exfoliative erythroderma, plaques and/or nodules. Ulceration of the oral mucosa appears to be very uncommon in cats. None of the five cats reported here had oral lesions. Only one cat from the historical cases reviewed presented with a plaque on the hard palate. The mucocutaneous form of the disease and focal hypopigmentation (common lesions reported in up to 50% of dogs with CETL) have never been reported previously in feline CETL, but four cats in our series presented with mild focal nasal or lip hypopigmentation. Pruritus is rarely reported in feline CETL, whereas in dogs 40% of cases have moderate to severe pruritus.

For two cases previously reported, the cutaneous symptoms were associated with the presence of neoplastic lymphocytes in lymph nodes and peripheral blood (leukaemia). This combination of clinical findings is classically described as Sézary syndrome. The pattern of cutaneous involvement in those two cases was similar. None of the cats in the present series had such a presentation. Sézary syndrome is rare in dogs, with only a single case clearly documented in the literature. In dogs, the clinical appearance of CETL may be very suggestive of the disease, but in cats the clinical diagnosis is more challenging. Cytological examination, performed with a direct imprint smear of an eroded or ulcerated lesion or by a fine-needle aspiration of a nodule, may reveal the presence of round cells, suggesting a haemolymphopoietic tumour. However, the final diagnosis must be based on histopathological examination of skin biopsy specimens. The characteristic lesion of CETL, as reported in dogs or humans, is tropism of neoplastic cells for the epidermis and adnexal structures.

In cats, the low number of reported cases limits the description of the different possible histological lesions of CETL. The typical lesions reported in the literature were diffuse superficial or follicular epitheliotropism or the formation of Pautrier’s microabscesses. As reported in dogs, the formation of Pautrier’s microabscesses must not be considered an inevitable feature of feline CETL. Pautrier’s microabscesses were observed in only one of five cats in our case series. The follicular ostial epithelium was mildly, but consistently affected in cats. Dermal lymphocytic infiltration was reported in three of the seven historical feline cases reported and in four of our five new cases. In two of these new cases, there was greater infiltration of the dermis than the epithelium (nodular stage).

The neoplastic T cells in CETL are usually described as small to medium (8–20 μm) or medium to large (more than 20 μm) in size and are often characterized as having a convoluted nucleus. This was consistently observed in our case series. Secondary changes including spongiosis (two of five) and keratinocyte apoptosis (two of five) were sometimes observed. In two of our cases, a mixed inflammatory reaction accompanied the tumour, complicating the diagnosis, and in three cases mild to severe ortho- and parakeratosis covered the affected epidermis, one with associated inflammation, the other without. The involvement of adnexal glands is common in canine CETL (in 70% of cases), but does not appear to be a feature of the disease in cats. There was no evidence of dermal neoangiogenesis, and mild dermal fibrosis was only observed in one case.

With two exceptions of cases of Sézary syndrome reported in the literature, all of the new and historical cases described here were of the classical mycosis fungoides type. Pagetoid reticulosis has not been described in cats. Pagetoid reticulosis is defined as a lymphocytic infiltration mainly confined to the epidermis and dermal adnexa (which was not affected in these cases). Pagetoid reticulosis has been described in dogs (seven cases of 30 in a recent study).

As only formalin-fixed and paraffin wax-embedded skin biopsy samples were available from the five new cases described herein, we were not able to investigate the subtype of the neoplastic T lymphocytes. This aspect has only been studied in one case of feline CETL, and in that animal the tumour cells were CD8 positive. However, V. Affolter (personal communication) suggested that the subtype of neoplastic lymphocytes involved in feline CETL might be more similar to human cases, in which most cells are CD4 positive, CD8 negative. In canine CETL, the classic immunohistochemical findings, in 80% of cases, are that the neoplastic cells are CD4 negative, CD8 positive.

Some inflammatory reactions characterized by dermal infiltration of reactive lymphocytes must be differentiated from feline CETL. In reactive feline lymphocytic dermatitis, lymphocytes usually migrate through all layers of the epidermis, while in CETL the neoplastic cells may initially be concentrated in the lower half of the epidermis. Feline CETL must also be distinguished from feline cutaneous lymphocytosis. This disease has sometimes been considered to be a variant of CETL or a preneoplastic condition. Clonal rearrangement of the γ-chain of the T-cell receptor in cats with cutaneous lymphocytosis indicates that the disease may be considered to be a reactive process that has the potential to evolve into a low-grade indolent T-cell lymphoma.

The prognosis of canine CETL is generally considered to be poor, although some subtypes (e.g. localized pagetoid reticulosis) may be less aggressive than mycosis fungoides. In man, the 5 year survival time depends on the type of CETL. Sézary syndrome has a poor prognosis, with a 33% 5 year survival rate. In contrast, with mycosis fungoides, the estimated survival rate after 5 years is 89–93%. The prognosis for pagetoid reticulosis is often considered good. The mean survival time after diagnosis of canine CETL, as reported in the literature, ranges from a few months to 2 years and was 6.3 months in a recent study. In cats, the survival time appears to be more variable. The median survival time reported in the literature was 10.25 months (range 2.5 months to 4 years, n = 6); in our series of five cats, the survival time was impossible to determine with precision (but was estimated to be between 1 and 6 months).

Many protocols for the treatment of canine CETL have been reported. Currently, the most promising include...
the use of lomustine or CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosoure)
In cats, the same dosage of CCNU (60–70 mg/m² orally given once every 3 weeks) is recommended.
Other reported treatments, with variable efficacy, include the following: surgery, electronbeam irradiation, vincristine/cyclophosphamide chemotherapy, and intravenous and local administration of fibronectin. Fibronectin, a circulating glycoprotein dimer, has an antineoplastic effect due to its ability to opsonize target cells for destruction by macrophages and monocytes.
In conclusion, the prevalence of CETL appears to be lower in cats than in dogs. The mucosal form of CETL is unusual in cats, but exfoliative dermatitis and focal hypopigmentation of the nose or the lips may be more common. In feline CETL, histopathological examination does not reveal involvement of adnexal glands. Immunohistochemical studies confirm this to be a T-cell tumour, but the T-cell phenotype has only been described in a single historical case (CD8 positive). The prognosis in feline CETL seems to be more variable than in dogs, and no specific treatment regime has been determined to be optimum.

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References


Résumé Le lymphome cutané éphémitrope à cellule T (CETL) est caractérisé par un infiltrat cutané de lymphocytes T néoplasiques avec un tropisme spécifique pour l’épiderme et les annexes épithéliales. Cette maladie est très rarement rapportée chez le chat. Des données cliniques ont été collectées à partir de la Vetdermlist, forum de discussion de dermatologues vétérinaires (vetderm@lists.ncsu.edu). En parallèle, les archives des cas de deux laboratoires de diagnostic histopathologique (Institut de Pathologie et Génétique/Bio.be Gosselies, Belgique et School of Veterinary Sciences, University of Bristol, United Kingdom) ont été étudiées. Quinze cas avec une bonne description clinique ont été retenus et cinq séries de biopsies cutanées étaient disponibles pour relecture. Le CETL atteint généralement les chats âgés sans prédilection de genre ou de race. Les lésions uniques ou multiples ont été rapportées sans prédilection pour une quelconque localisation. Les lésions consistaient en plaques ou patches érythroïdes, patches alopeciques et squameux et des nodules ou ulcères ne cicatrisant pas, mimant parfois une plaque éosinophile. Le prurit était rarement rapporté. Aucune lésion de la muqueuse orale n’a été observée. Le diagnostic clinique de CETL est plus difficile chez les chats que chez les chiens. Le diagnostic définitif doit reposer sur l’examen histopathologique de biopsies cutanées. Les lésions caractéristiques de CETL félin sont identiques à celles rapportées chez le chien mais l’invasion des glandes annexes n’a pas été rapportée dans cette série (n=5). Les cellules T néoplasiques étaient généralement de taille petite à moyenne. La durée de survie des chats avec CETL semble plus variable que celui des chiens atteints. Trop peu de cas ont été évalué pour permettre d’établir des recommandations claires sur les traitements à suivre.

Resumen El linfoma epiteliotrópico cutáneo de linfocitos T (CETL) se caracteriza por la infiltración cutánea de linfocitos T neoplásicos con un tropismo específico para la epidermis y el epitelio adnexal. Esta enfermedad se describe muy raramente en el gato. Los datos clínicos fueron recogidos en una discusión informal con los dermatólogos veterinarios en el Vetdermlist (vetderm@lists.ncsu.edu). En paralelo, se revisaron los archivos de casos de dos laboratorios de diagnóstico europeos de histopatología (Institut de Pathologie et Génétique/Bio.be Gosselies, Bélgica y la escuela veterinaria de la universidad de Bristol, Reino Unido). Se seleccionaron quince casos con una buena descripción clínica y se revisaron cinco grupos de biopsias de piel. CETL afecta generalmente gatos de edad avanzada sin predisposición evidente de sexo o de raza. Las lesiones solitarias o múltiples fueron descritas sin predilección por una localización particular. Las lesiones consistieron en placas eritematosas, áreas alopecicas escamosas y úlceras o nódulos no cicatrizantes, que simulaban a veces una placa eosinofílica. Prurito fue raramente observado. No se vieron ninguna lesiones en la mucosa oral. El diagnóstico clínico de CETL es más difícil en gatos que en perros. El diagnóstico final se debe basar en el examen histopatológico de las muestras de la biopsia de la piel. Las características lesiones de CETL felino son similares a las descritas en el perro, pero no se observó extensión a las anejos pilosos en esta serie (n=5). Los linfocitos T neoplásicos eran generalmente de tamaño pequeño a mediano. La supervivencia media de gatos con CETL parece ser más variable que la de perros afectados. Se han descrito pocos casos para permitir realizar recomendaciones con respecto al tratamiento.


要約 皮膚上皮向性 T 細胞リンパ腫（CETL）は表皮と付属器上皮に特異的に親和性を示す腫瘍性 T 細胞リンパ腫が皮膚に浸潤する特徴を示す。この疾患は猫において非常に稀であるが報告されている。臨床データは Vet Derm List (VetDermLists.ncsu.edu) を通じて皮膚科獣医師の非公式な話し合いによって集められた。同時に、2 つのヨーロッパの病理診断研究所 (Institut de Pathologie et Génétique/Bio.be Gosselies, Belgium and the School of Veterinary Sciences, University of Bristol, United Kingdom) の症例の資料を再検討した。臨床的な詳細な記載がある 15 例が選出でき、5 例の皮膚生検標本が再検討に使用可能であった。CETL は一般的に老齢の猫が罹患し、性別や品種の好発は認められなかった。病変は単発性または多発性であり、特定の部位に発症傾向がないことが報告された。病変は紅斑性局所または斑、鱗屑を伴った脱毛斑、難治性潰瘍やしばしば好酸球性ブラークに似た結節で構成されていた。そうした症例であった。口唇粘膜の病変は認められなかった。猫の CETL の臨床診断は犬と比べて困難である。最終診断は皮膚生検材料の病理組織学的な検査により行う。猫 CETL の病変の特徴は犬で報告されているものと似ているが、今回の中の症例（n = 5）において付属器へ浸潤は認められなかった。腫瘍性 T 細胞はほとんどが小型から中程度の大きさであった。CETL の猫の生存期間は犬と比べて多様のようなである。治療に関しての明確な提案をするには、評価できる症例が過少すぎた。