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# Cutaneous anaplastic large T-cell lymphoma in a cat – case report

[*Linfoma cutâneo anaplásico de grandes células T em um gato – relato de caso]*

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## ABSTRACT

Lymphoma is the most common lymphoproliferative disorder in cats. However, cutaneous lymphomas are uncommon in this species and can be classified as epitheliotropic or non-epitheliotropic. Epitheliotropic lymphomas are typically of T-cells and have tropism for epidermis and/or adnexal epithelium. Non-epitheliotropic lymphomas can be of either T-cell or B-cell and involve predominantly the dermis. The present study describes a case of multifocal cutaneous anaplastic large T-cell lymphoma. The skin nodules were multiple and variable in size, alopecic and erythematous in appearance and randomly distributed. Immunohistochemistry revealed positivity for the CD3 antigen, consistent with T-lymphocytes. This neoplasm should be remembered whenever multiple cutaneous nodules are observed in cats.

Keywords: cancer, feline, lymphomas, skin

## RESUMO

*Linfoma é o distúrbio linfoproliferativo mais comumente observado em gatos. Contudo, linfomas cutâneos são incomuns nessa espécie e podem ser classificados como epiteliotrópico ou não epiteliotrópico. Linfomas epiteliotrópicos são tipicamente originários de células T e têm tropismo pela epiderme e/ou pelo epitélio anexial. Linfomas não epiteliotrópicos podem ser originários de células T ou B e envolvem predominantemente a derme. No presente trabalho, descreve-se um caso de linfoma cutâneo multifocal anaplásico de grandes células T em um gato. Os nódulos cutâneos eram múltiplos, de dimensões variáveis, alopécicos, eritematosos e aleatoriamente distribuídos. A imuno-histoquímica revelou positividade para CD3, sendo consistente com origem em linfócitos T. Essa neoplasia deve ser lembrada sempre que forem observados nódulos cutâneos múltiplos em gatos.*

*Palavras-chave: câncer, felino, linfomas, pele*

## INTRODUCTION

Lymphoma is the most common lymphoproliferative disorder in cats, representing 41% of all cancers (MacVean *et al.*, 1978). However, cutaneous lymphomas are uncommon, accounting for 0.6% to 3% of all skin tumors diagnosed in this species (Miller *et al.*, 1991; Goldschmidt and Shofer, 1992). Despite the strong relationship between the lymphomas developing in cats and the infection by Feline Leukemia Virus (FeLV), when it arises in the skin, this association is yet to be detected (Moore and Olivry, 1994). However, FeLV infection or proviral DNA have already been detected in cats with cutaneous lymphomas, which could suggest a certain relationship (Gross *et al.*, 2005).

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Cutaneous lymphomas can be classified as epitheliotropic or non-epitheliotropic (Gross *et al.,* 2005; Valli *et al.,* 2016). Epitheliotropic lymphomas are typically of T-cells and have tropism for epidermis and/or adnexal epithelium (Gross *et al.,* 2005; Valli *et al.,* 2016). Non-epitheliotropic lymphomas can be of either T-cell or B-cell and involve predominantly the dermis (Gross *et al.,* 2005; Valli *et al.,* 2016). Based on the few cases reported in the literature on this topic, this paper aims to describe a case of multifocal cutaneous anaplastic large T-cell lymphoma in a cat.

## CASUISTRY

A 11-year-old female mixed breed cat admitted to the University Veterinary Hospital presented multifocal skin nodules. No other abnormalities were noted, and complete blood count (CBC), blood smear examination, and serum biochemical profile were unremarkable. The blood sample was negative for FeLV p27 antigen and IgG antibodies against Feline Immunodeficiency Virus (FIV), which were measured using a commercial enzyme-linked immunosorbent assay (ELISA) (rapid assay kit, SNAP® FIV Antibody/FeLV Antigen Combo Test: IDEXX Laboratories, Westbrook, ME, USA). A fine-needle aspiration cytology (FNAC) of the nodules was consistent with lymphoma. The owner requested euthanasia and a complete post-mortem examination was conducted immediately after death. At necropsy the cutaneous nodules appeared red to purplish, hemispherical, and alopecic, showing partial ulceration, with the diameter ranging from 0.5 to 4.3cm (Fig. 1 and 2). The cutting surface was homogeneously white. No other gross abnormalities were detected. Samples of cutaneous nodules and different organs were fixed in 10% neutral buffered formalin, processed routinely to histopathology and hematoxylin-eosin (HE) staining.

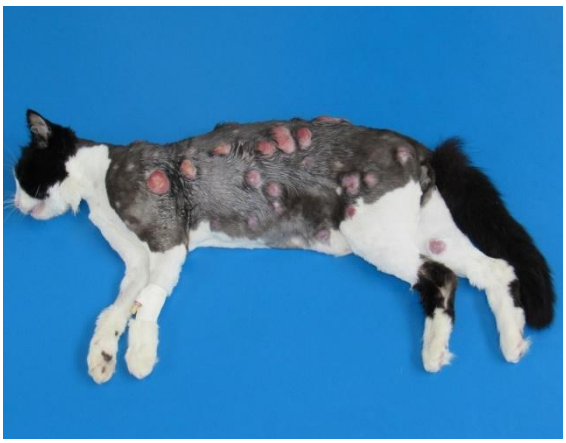

Figure 1. Primary cutaneous lymphoma in a 11-year-old female mixed breed cat. The lymphoma appeared as several nodules, hemispherical, alopecic, red or purplish, showing random distribution over the body surface, and coalescing at times as plaques.

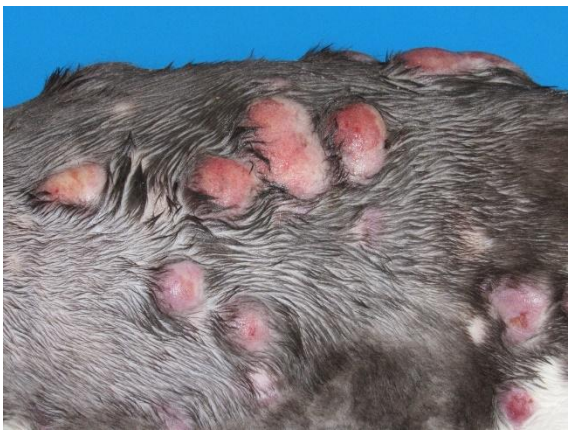

Figure 2. Primary cutaneous lymphoma in a 11-year-old female mixed breed cat. Close-up view. These nodules appear mostly alopecic, although some show some ulceration.

The cutaneous nodules were histologically composed of a dense proliferation of neoplastic cells organized in a mantle. The neoplastic cells replaced the dermis, including the cutaneous adnexal, but they showed no invasion into the adnexal epithelium or epidermis (Fig. 3). In the neoplastic areas, the epidermal layer showed evidence of atrophy, revealing ulcers. The neoplastic cells were round or oval and were composed of a small to moderate amount of homogeneous and eosinophilic cytoplasm (Fig. 4a). The nuclei were round or oval, with slight indentations or irregularity, located in the cell center, and composed of coarsely clumped chromatin. The nucleoli were predominantly single, eosinophilic, and variably evident (the

morphology revealed consistency with the large lymphocytes). Interspersed with these neoplastic lymphocytes, there were large lymphocytes with horseshoe-shaped or reniform eccentric nuclei, termed the hallmark cells (Fig. 4b). Some binucleated neoplastic cells (Fig. 4c) were also observed. Either between the lymphocytes or in the cytoplasm of the macrophages (lymphogranular bodies) large quantities of free cell debris were present, giving this tissue the typical 'starry sky' pattern, under lower magnifications.

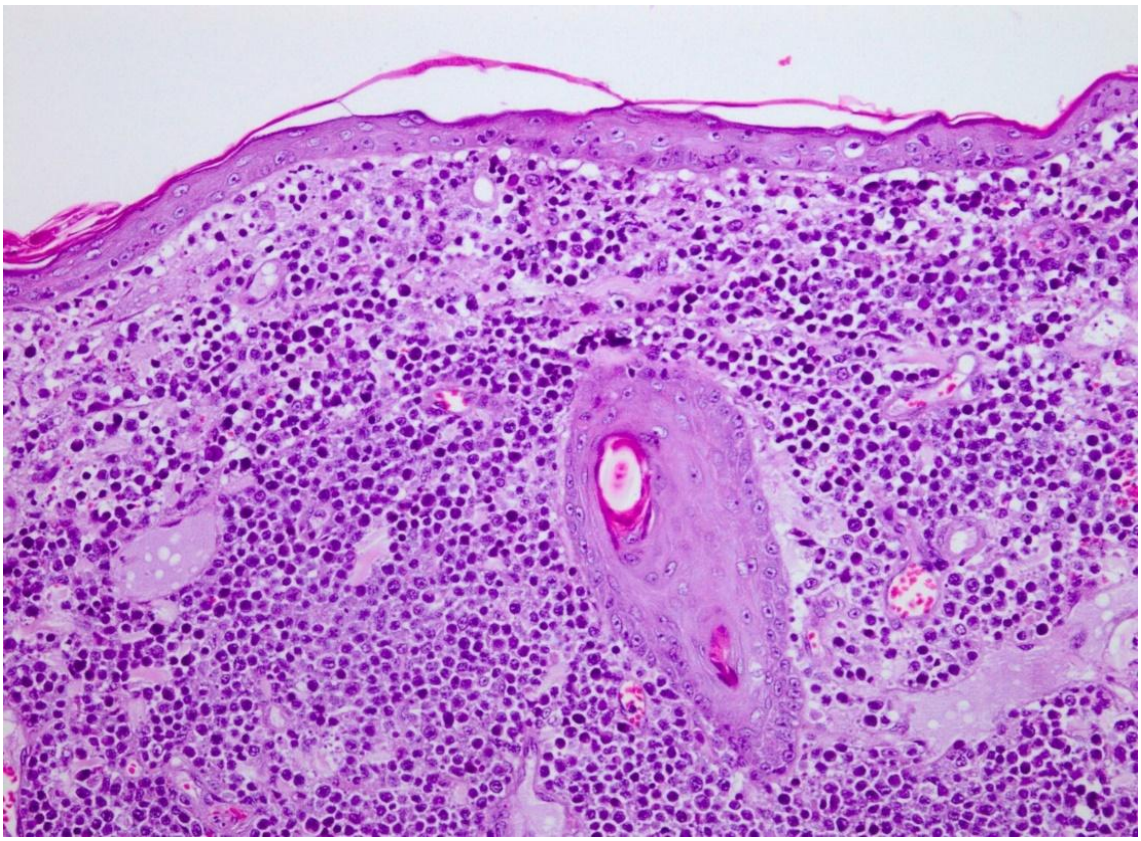

Figure 3. Primary cutaneous anaplastic large T-cell lymphoma in a female cat. Histopathological examination revealed a densely cellular proliferation, obliterating the dermis quite diffusely, but not extending to the epidermis and adnexal epithelium. Hematoxylin and Eosin (HE). Obj.20x.

To determine the origin of the neoplastic lymphocytes and for classification purposes, samples of tumor were analyzed by immunohistochemistry (IHC). The technique employed was B-lymphocyte immunostaining using CD20 antibody (polyclonal, RB9013-P, Thermo Scientific, rabbit-produced) and T-lymphocyte immunostaining CD3 antibody (monoclonal, Clone F7.2.38, Dako Cytomation, mouse-produced). Additionally, IHC was conducted for the CD204 (monoclonal, SRA-C6, Trans Genic Inc, mouse-produced) and KIT (polyclonal, A4502, Dako Cytomation, rabbit-produced), aimed at a differential with tumor of histiocytes and mast cells, respectively.

IHC was performed according to the following protocol: after tissue deparaffinization and rehydration, antigen recovery using Tris-EDTA solution (pH 9.0) was performed in microwave oven at high power for 10 min. Endogenous peroxidase blockade was performed using 3% hydrogen peroxide for 20 min. Nonspecific reactions were blocked using Protein Block at room temperature for 10 min. The primary antibodies were incubated in an oven at 37°C for 60 min or in a refrigerator at 7°C for 16h (overnight). Secondary antibody and Horseradish peroxidase (HRP) polymer were used consecutively incubated at 25°C for 30min and developed by adding 3-3'diaminobenzidine (DAB) tetrachloride chromogen for 5min.

Counterstaining was performed using Harris Hematoxylin. Cat lymph nodes were used as positive and negative controls, respectively. Negative control was obtained by omitting the primary antibody using only the antibody diluent. Immunohistochemical staining with CD3 antibody revealed diffuse cytoplasmic staining of the population of neoplastic cells (Fig. 4d), whereas staining with CD20, CD204 and KIT antibodies was not observed. The diagnosis of primary cutaneous anaplastic large T-cell lymphoma was made based on macroscopic, histopathological, and immunohistochemical findings.

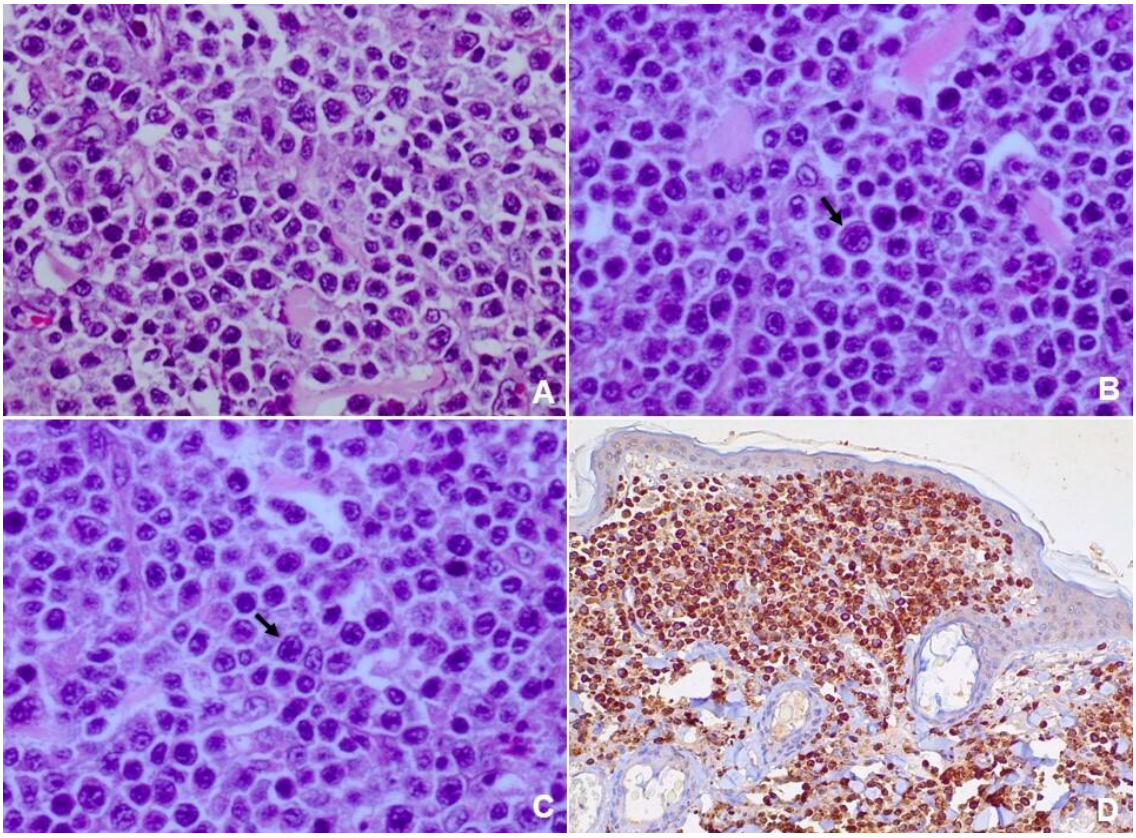


Figure 4. Primary cutaneous anaplastic large T-cell lymphoma in a female cat. Skin. (A) Large lymphocytes composed of small to moderate quantities of cytoplasm that was homogeneous and eosinophilic, with nuclei that appeared either rounded or irregular in shape and made up of loose chromatin; the nucleoli were variably evident, single, and eosinophilic in character. Hematoxylin and Eosin (HE). Obj.40x. (B) Large lymphocyte revealing an indented nucleus with loose chromatin as the main constituent and possessing only one unmistakably distinct nucleolus (arrow), typical of a hallmark cell, that is, a cell classically characteristic of anaplastic lymphomas. HE. Obj.40x. (C) Binucleated lymphocytes (arrow) exhibit cellular atypia, which is one of the distinguishing features of anaplastic lymphomas. Hematoxylin and Eosin (HE). Obj.40x. (D) Confirming the T-lymphocyte origin, the cytoplasmic immunostaining was positive for CD3. Immunohistochemistry technique. Obj.20x.

## DISCUSSION

From the histological perspective, the differential diagnoses for Anaplastic Large T-Cell Lymphoma (ALTCL) included Mycosis Fungoides (MF), Subcutaneous Lymphomas (SL), Feline Progressive Histiocytosis (FPH), the histiocytic form of Mast Cell Tumor (MCT), and Cutaneous Lymphocytosis (CL). In MF, rapid proliferation is noticed in the lymphocytes from the upper dermal region, either making an invasion into the epidermal layer and adnexal epithelium or creating intraepithelial aggregates (Darier-Pautrier microabscesses) (Goldschmidt and Shofer, 1992; Moore and Olivry, 1994; Gross *et al.*, 2005). The exclusion criterion for

this differential diagnosis was the absence of epitheliotropism. In the case of SL, proliferation of the lymphocytes is observed in the subcutaneous tissue, as well as an invasion right into the deep dermis, however, most often, the superficial dermis is not reached (Gross *et al.*, 2005; Miller *et al.*, 2013; Valli *et al.*, 2016), thus revealing a different cell distribution pattern from the one described in this case.

The FPH characteristically reveals dense multiplication of cells, which are principally dermal, without extending into the subcutaneous tissue ("top-heavy") (Goldschmidt and Shofer, 1992; Gross *et al.*, 2005; Valli *et al.*, 2016), like those found in this study. However, due to the lack of reactive lymphocytes, as is common in histiocytic diseases (Goldschmidt and Shofer, 1992; Gross *et al.*, 2005), as well as the morphological characteristics of the neoplastic cells, specifically the presence of the anaplastic nuclei and, manly, the positive immunostaining of these cells for CD3, but not for CD204, allowed the exclusion of this differential. Dissimilar to the lymphocytes evident in this study, the mast cells are abundant in the cytoplasm (Miller *et al.*, 1991; Goldschmidt and Shofer, 1992; Moore and Olivry, 1994; Gross *et al.*, 2005). Besides, the lack of eosinophil infiltrate was another feature that enabled a diagnosis of exclusion, which was decisively ruled out due to the negative immunostaining for KIT.

The characteristic feature of the CL is the rapid T-lymphocyte proliferation, small but well differentiated, surrounding the vessels or diffusely distributed right through the dermis (Moore and Olivry, 1994; Gross *et al.*, 2005). Further, small well-differentiated B-lymphocytes form small aggregates or random distribution among a large percentage of the T-lymphocytes (Gross *et al.*, 2005; Valli *et al.*, 2016). According to the specific cell morphology, as well as the lack of a mixed lymphoid population, verified by the negative CD20, a diagnosis of ALTCL was reached, nullifying the diagnosis of CL.

## CONCLUSION

In this study, a report is given on multiple cutaneous lymphoma in a cat, a presentation not usually described for this species, particularly when a comparison is made to the subcutaneous form. Furthermore, the significance of including the lymphomas as a differential diagnosis for the tumors that arise as multiple cutaneous nodules in cats is emphasized.

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