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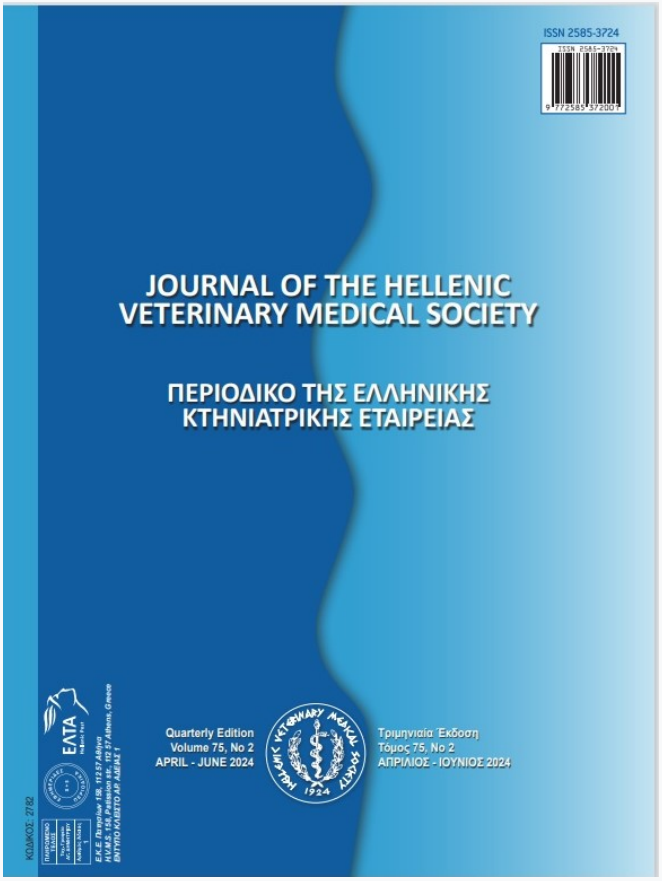

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Research article
Ερευνητικό άρθρο

Epitheliotropic T-cell lymphoma in Syrian Hamster (*Mesocricetus auratus*)

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ABSTRACT: Lymphomas are neoplasms characterized by the clonal proliferation of malignant lymphocytes, and are considered one of the most common tumors recognized in hamsters. The objective of the present work is to describe a case of epitheliotropic T-cell lymphoma (ETCL) in a Syrian hamster kept as a pet in Paraguay, diagnosed by histopathological and immunohistochemical techniques. We report the case of a 1-year-old, male, pet Syrian Hamster (*Mesocricetus auratus*), that presented scabs, ulcers, erythema, crusting, and hyperkeratosis, with a case evolution of approximately 20 days. Days after the inspection the animal is found dead, and the body is subjected to post-mortem examinations. Histopathologic analysis with hematoxylin-eosin and immunohistochemic assays for CD3 and CD79 lymphoid markers and ki-67 cell proliferation are performed on skin sections, confirming the diagnosis for epitheliotropic T-cell lymphoma. Clinical signs and skin lesions coincide with cited literature, and confirmation through immunohistochemical assays offer a better diagnosis. To date, there is no known cause nor treatment for epitheliotropic T-cell lymphoma in hamsters, and euthanasia is considered for animal welfare.

Keywords: Cricetidae; cutaneous tumor; oncology; pet; rodentia

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CASE HISTORY

Lymphomas are neoplasms characterized by the clonal proliferation of malignant lymphocytes, and originate mainly in lymphoid organs such as the bone marrow, spleen and lymph nodes. However, lymphomas can develop in practically any organ due to the continuous migration of lymphocytes through the different tissues of the organism (Gouveia et al, 2016). These neoplasms are considered one of the most common tumors recognized in hamsters (Table 1), and three different forms of lymphoma have been described in the species: (1) hamster polyomavirus-induced lymphoma; (2) multicentric form lymphoma; and (3) epitheliotropic T-cell lymphoma (Hocker, 2017). Lymphomas in the skin may be a primary cutaneous neoplasm or be part of a multicentric lymphocytic neoplasm. Cutaneous lymphomas have been reported in most domestic animals and in many wildlife species; however, the tumor has been studied most closely in dogs, cats, horses, and cattle (Mauldin, 2016).

The objective of the present work is to describe a case of epitheliotropic T-cell lymphoma (ETCL) in a Syrian hamster kept as a pet in Paraguay, diagnosed through histopathological and immunohistochemical techniques.

A Syrian hamster (*Mesocricetus auratus*), male, 1-year-old, 150g body weight, body condition 3/5 (good), was presented to the Wildlife and Exotics Clinic. Dermatological inspection of the facial region showed erythema, crusting, and hyperkeratosis (Fig. 1). In the ventral mandibular region, scabs, ulcers and erythema were observed with an evolution of approximately 20 days (Fig. 2). The owner stated that initially it was treated with an undisclosed antifungal cream, with a slight remission, but later presenting a relapse. No other specific clinical signs were identified, and the owner did not allow blood samples to be taken. The presumptive diagnosis suggested cutaneous lymphoma, indicating a poor prognosis for the animal. One week after the diagnosis, the owner reported the death of the individual and the body was sent to the Department of Pathological Sciences of the Faculty of Veterinary Sciences, National University of Asuncion, for post-mortem studies.

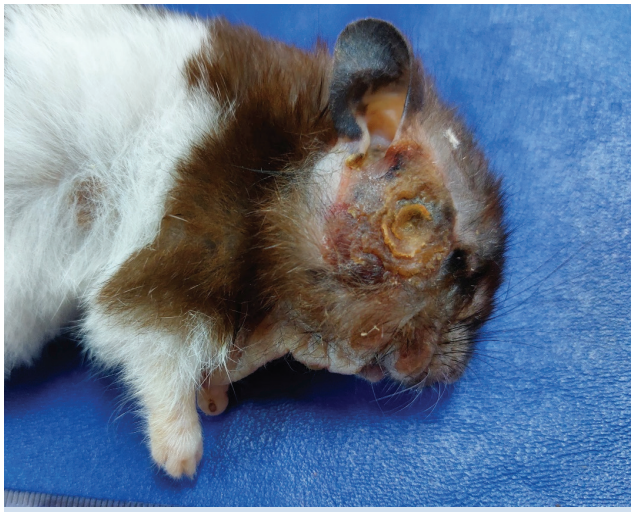

Figure 1. Lesions on the patient's face

Table 1. Previous reports of epitheliotropic T-cell lymphoma in Syrian hamster

Age (months)	Sex	Anatomic region	Diagnostic methods	Country	Reference
18	Male	Tail	Skin histopathology, immuno-histochemistry	Poland	(Otrocka-Domagala et al., 2022)
24	Male	Flank / Dorsolumbar	Skin histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
18	Male	Flank / Dorsolumbar	Skin histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
20	Male	Flank / Dorsolumbar	Skin histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
18	Female	Flank / Dorsolumbar	Skin and organ histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
24	Female	Flank / Dorsolumbar	Skin histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
18	Female	Flank / Dorsolumbar	Skin histopathology, immuno-histochemistry	United Kingdom	(Harvey, 1992)
Unknown	Female	Thorax / Abdomen	Skin histopathology, immuno-histochemistry	Canada	(Turner et al., 2017)

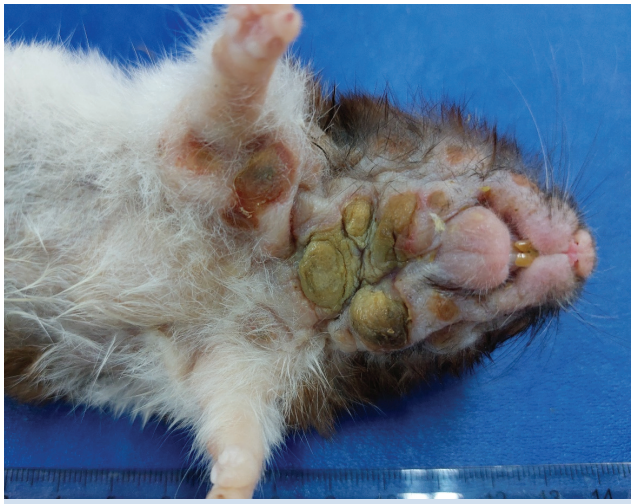

Figure 2. Lesions in the ventral mandibular and axillary regions of the patient.

Histopathological analysis of the skin obtained from the ventral mandibular and axillary regions, in serial sections stained with hematoxylin-eosin, showed epidermis with intra-epidermal cluster of lymphocytes, superficial and deep dermis a marked monomorphic proliferation of round cells, with prominent hyperchromatic central nucleus, with lax chromatin and basophilic cytoplasm, with marked anisocytosis and anisokaryosis, supported by connective tissue (Fig. 3). There was also scattered evidence of a neutrophilic polymorphonuclear infiltrate.

Immunohistochemistry (IHC) assays were performed on skin sections for CD3 and CD79 lymphoid markers and ki-67 cell proliferation. Selected formalin-fixed paraffin embedded tissues sections were prepared on silanized slides with 0.1% poly-L-lysine (Sigma-Aldrich, St. Louis, MO, USA). The steps of IHC protocol are shown in Table 2.

Both solutions for antigen retrieval were utilized with the pressure cooker system (Electrolux Pressure Cooker PCC10, São Paulo, Brazil) for 5 min. Endogenous peroxidase was blocked with distilled water and hydrogen peroxide (6%) for 30 min in a dark chamber. The primary incubation was achieved with the monoclonal antibodies shown in Table 2 during 24 hr at 4°C. Incubation with the secondary antibody was done in a humid chamber for 30 min at 25°C, after which the chromogen 3,3′-diaminobenzidine (DAB, Invitrogen® Life Technologies, Frederick, MD, USA) was added for 2 min. The slides were counterstained with Harris' haematoxylin. Negative control consisted of using the same tissue, with substitution of the primary antibody by its diluent. Positive and negative controls were included in each IHC assay. All antibodies used in the panel are mouse monoclonal, anti-CD3 (F7.2.38; Santa Cruz Biotechnology) to identify T lymphocytes, anti-CD79 (JCB117; Sigma-Aldrich) to identify B lymphocytes, and ki67 (MIB; Dako) for cell proliferation index (Table 2).

The samples stained positive for CD3 (Fig. 4) and negative for CD79 (Fig. 5), confirming the diagnosis of epitheliotropic T-cell lymphoma (ETCL). Also, 70% labeling to Ki-67 was reported (Fig. 6).

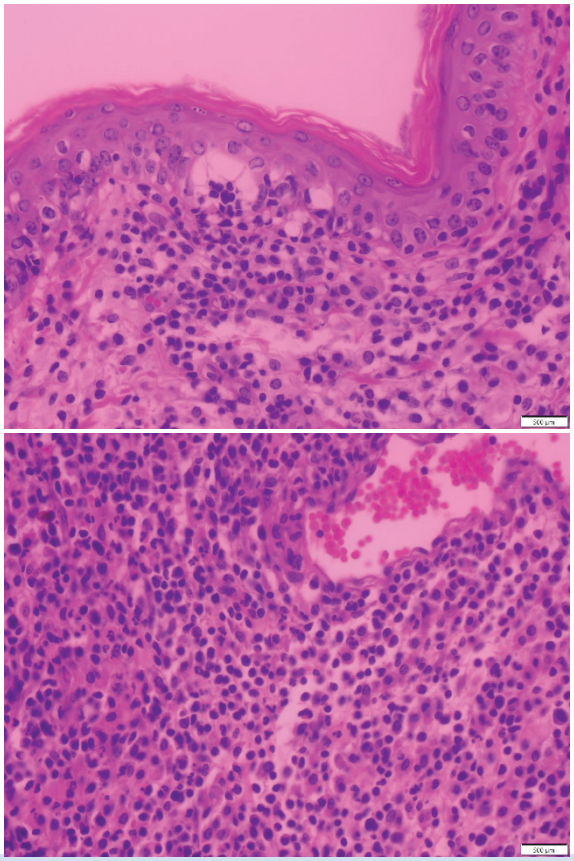

Figure 3. Epidermis with lymphocyte invasion (A). Dermis with monomorphic proliferation of neoplastic lymphocyte with diffuse distribution, not encapsulated (B) (20x, H-E). Bar = 500μm.

Table 2. List of antibodies, dilutions, method of antigen retrieval and source manufactures of the immunohistochemical assays

Primary Antibody	Clone	Dilution	Source	Antigen retrieval	pH	Secundary Antibody
CD3	F7.2.38	1:300	Santa Cruz Biotechnology	Citrate	5.6	Ervision Flex / HRP
CD79	JCB117	1:200	Sigma-Aldrich	EDTA	8.9	Dako Agilent
Ki67	MIB-1	1:400	Dako	EDTA	8.9	

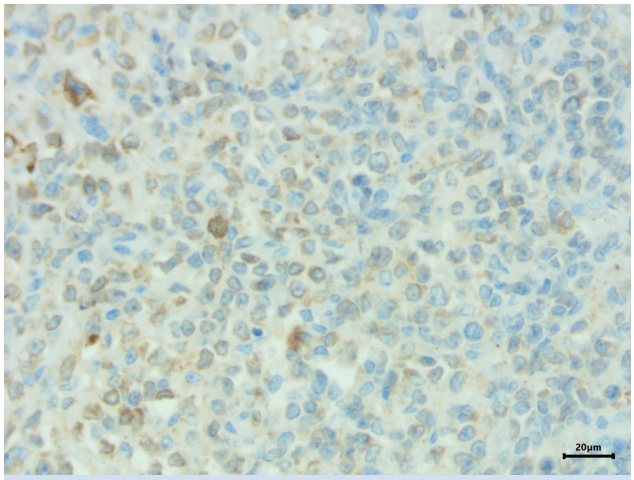

Figure 4. Immunohistochemical findings observed in Syrian hamster with epitheliotropic lymphoma. There is diffuse, strong, membranous immunoreactivity of the neoplastic round cells CD3 positive in epitheliotropic T-cell lymphoma. F7.2.38, DAB, 40×. Immunoperoxidase counterstained with haematoxylin. Bar = 20µm.

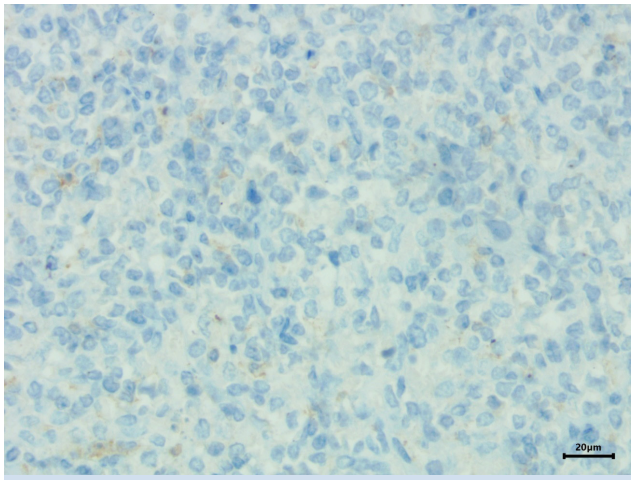

Figure 5. Immunohistochemical findings observed in Syrian hamster with epitheliotropic lymphoma. Photomicrograph of CD79 negative stained in the skin of a Syrian hamster diagnosed with epitheliotropic T-cell lymphoma. JCB117, DAB, 40×. Bar = 20µm.

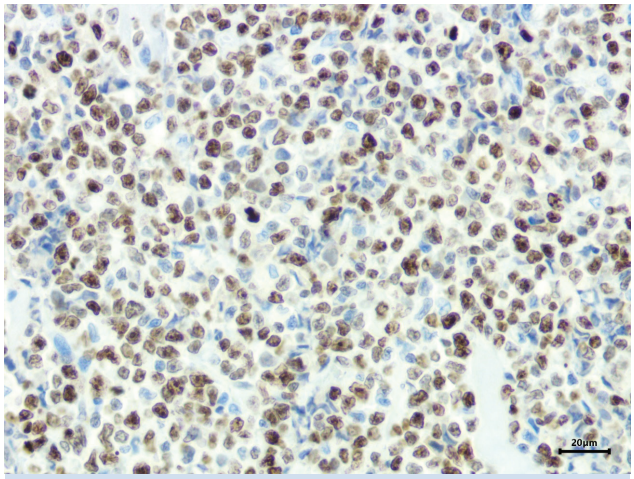

Figure 6. Immunohistochemical findings observed in Syrian hamster with epitheliotropic lymphoma. Photomicrograph of Ki67 nuclear staining in the skin of a Syrian hamster diagnosed with epitheliotropic T-cell lymphoma. Positive cells were counted in 1 cm^2 using a 10 × 10 mm grid reticle (70%). MIB-1, DAB, 40×. Bar = 20µm.

DISCUSSION

Cutaneous lymphomas in pets are usually divided into 2 groups: epitheliotropic cutaneous lymphomas, in which neoplastic lymphocytes invade the epidermis and/or adnexal epithelium, and non-epitheliotropic lymphomas, which affect the dermis and subcutaneous tissue (Mauldin, 2016). Epitheliotrophic neoplasms are divided into the classic nodular form or cutaneous T-cell lymphoma (also called mycosis fungoides), and pagetoid reticulosis (Martorell, 2011).

Epitheliotropic T-cell lymphoma (ETCL) is a rare neoplasm arising in the skin as a consequence of malignant transformation of a T-cell clone and its subsequent hematogenous spread to the skin and oral cavity where the cells show epitheliotropism (Harvey, 1992). Unlike what has been observed in human cases (van der Putte et al, 1989) and in dogs (Fontaine, 2010), where B-cell population is present as single cells within the tumor or as a linear band at the base of the neoplastic T-cell infiltrate within the dermis. Sometimes follicular formation and a variable number of plasma cells associated with the infiltrating B cells are also observed. This reaction is thought to be due to the production of cytokines such as interleukin-4 and B-cell stimulating factor-2 by the neoplastic T cells (van der Putte et al, 1989).

Clinical signs and physical examination findings that have been associated with ETCL in hamsters include anorexia, lethargy, ataxia, dyspnea, palpably enlarged peripheral lymph nodes, and palpable abdominal masses, if the patient is in an advanced stage of the disease, but these patients may present with only skin lesions that have not responded to conservative treatment of other skin conditions (Hocker, 2017). The primary skin lesions seen with this form are patchy or generalized alopecia, pruritus, generalized exfoliative erythroderma, and skin plaques or nodules that may be ulcerated (Hocker, 2017).

Fine needle aspiration and cytology of a lymph node may aid in the diagnosis of lymphoma, as the cytologic appearance is similar to that seen in other mammals (Hocker, 2017). Histologically, early plaque-like lesions show band-like perivascular infil-

trates in the upper dermis containing atypical T cells with cerebriform nuclei, which have a tendency to infiltrate the epidermis (Willemze, 2003). Incisional biopsy and histopathology are necessary to confirm the diagnosis of ETCL (Hocker, 2017).

The use of monoclonal antibodies has greatly facilitated the investigation and classification of lymphocyte populations and has allowed the identification of infiltrating cells (Harvey et al, 1992). The CD3 antigen is located on the T-cell surface membrane and is closely associated with the T-cell antigen receptor where it is believed to function as a transmembrane signal transducer (Harvey et al, 1992). CD3 antigen is used as a T-cell marker because it is unique to the T-cell lineage, so the presence of CD3 antigen in the infiltrating cell population confirms the T-cell lineage of the neoplastic cells (Campana et al, 1987). CD3 antigen has already been described as a diagnostic tool for epitheliotrophic lymphoma by immunohistochemistry in Syrian hamsters (Harvey et al, 1992; Otrocka-Domagala et al, 2022), rat (Prats et al, 1994; Barthold et al, 2016), guinea pig (Martorell et al, 2011), dogs (Machicote & Gonzalez, 2008; Choueri et al, 2010), Degu (Otrocka-Domagala et al, 2022), and a report in a squirrel (*Sciurus* sp.) (Honnold et al, 2007). Neoplastic T-cells have the phenotype of cutaneous localized mature T-cells (CLA-positive) CD3-positive, CD4-positive, CD45RO-positive, CD8-negative (Willemze, 2003).

Ki67 antibody expression in skin biopsies by immunohistochemistry reproduces the role of cell proliferation in differential diagnosis and prognosis, and can be used to differentiate most CTCL from non-neoplastic dermatoses (with the exception of psoriasis), expressing higher levels in aggressive CTCL than compared to indolent CTCL (Zohdy et al, 2020). Ki67 expression is an absolute requirement for cell proliferation and its index is indispensable for classifying neoplasms and predicting their prognosis, with Ki67 immunohistochemistry being the most popular consistent method for assessing proliferation in tissues (Maj et al, 2015). For statistical analysis, the Ki67 index can be classified into low (less than 20%) and high (equal to or greater than 20%) categories (Zohdy et al, 2020). When comparing the Ki67 proliferation index in human patients, it was observed to be significantly higher in advanced CTCL compared to early CTCL and parapsoriasis (Maj et al, 2015). Ki67 proliferation index was also associated with lower survival and metastasis (Maj et al, 2015), reporting a significant correlation between it and prognostic parameters with respect to advanced patient age, male sex, extensive erythrodermic skin or tumor involvement, abnormal peripheral lymph nodes, blood tumor burden, and late-stage disease (Zohdy et al, 2020). A canine study reports that there was no correlation between the ki67 index and time to diagnosis and it was not predictive of survival time (Fontaine et al, 2010).

The clinical course of this disease from the time of diagnosis is rapid and generally carries a grave prognosis, treatment is rarely successful, and euthanasia is most often recommended for welfare reasons (Paterson, 2006; Hoppman et al, 2007; Hocker, 2017). Interferon alpha can be used at a dose of 1,500,000 to 2,000,000 U/m2 twice or three times a week (Hoppman et al, 2007), and there are anecdotal reports of chemotherapeutic treatment using cyclophosphamide, vincristine and prednisolone, with or without the combination with doxorubicin and L-asparaginase (Huston et al, 2012). In canines, several treatments for lymphoma are available, according to the stage of the lymphoma (Gouveia et al, 2016). Due to the lack of available information on the benefits of chemotherapy in the species, potential risks should be considered prior to treatment (Huston et al, 2012).

In human patients, local treatments and systemic therapies are described, aimed at achieving and maintaining remission and preventing disease progression, although there are no studies demonstrating increased survival associated with a particular treatment (Valencia et al, 2010). Skin-directed therapies remain the most appropriate early-stage option, and most human patients can expect a normal life expectancy; but for patients with advanced disease, the prognosis remains bleak, and for only a very select subset of patients, prolonged survival can be achieved with allogeneic stem cell transplantation (alloSCT), but toxicity is a serious limiting factor for this treatment (Trautinger et al, 2017; Cerroni, 2018). Conventional systemic chemotherapy and single-agent chemotherapy (gemcitabine) generally give good results in advanced disease, but recurrences are the rule (Cerroni, 2018). Monoclonal antibodies directed against cluster of differentiation CD52 (alemtuzumab), CD30 (brentuximab vedotin) and chemokine receptor 4 (CCR4; mogamulizumab), as well as several other experimental therapies, have shown promising results and represent a valid alternative (Cerroni, 2018).

Although the etiology of epitheliotrophic lymphoma in hamsters is not yet known, Hamster polyoma-

virus (HaPyV) has been associated with the development of lymphomas in Syrian hamsters (Ito et al, 2022).

The data obtained from the observable signs and physical examination, as well as necropsy findings, histopathological and immunohistochemical results, confirmed the diagnosis of epitheliotropic T-cell lymphoma. To the authors' best knowledge, this is the first report of ETCL in a Syrian Hamster in Paraguay.

CONFLICT OF INTEREST

There is no conflict of interest, including financial, personal or other relationships with other persons or organizations that could inappropriately influence the work.

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