**Progressive Histiocytosis of Non-Epitheliotropic Dendritic Cells in a Feline**

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**ABSTRACT**

**Background:** Histiocytic tumors in felines are nodules that commonly develop on limbs and head extremities. They can be divided into many subtypes including cutaneous histiocytoma, histiocytic sarcoma, reactive fibrohistiocytic nodule, Langerhans cell histiocytosis, and progressive feline dendritic cell. Despite the same origin, they have behaviors that differ from each other, thus it is important to confirm diagnosis with histopathological and immunohistochemical tests, because early identification can facilitate prognosis and treatment. In this study, we describe the pathological and immunohistochemical characteristics, enabling differentiation feline neoplasms derived from histiocytes.

**Case:** A 5-year-old, crossbreed, male, feline presented with a nodulation at the base of the left ear. The mass was slow growing, partially alopecic, with no other changes associated with tumor development. The nodule was round and circumscribed, movable, with an elevated surface. He was referred for surgery and an elliptical sample around the tumor was carefully dissected. Routine histopathological evaluation was performed with hematoxylin and eosin (HE), as well as immunohistochemistry. Histopathology showed circumscribed proliferation of histiocytic cells, with abundant and eosinophilic cytoplasm. The proliferative cells were large and rounded, extending from the superficial dermis and base membrane to the deep dermis. At the extremities, some cells had visible vacuoles. Mitotic activity ranged from 3 to 4 mitoses per field in 40x magnification. Immunohistochemistry showed positive staining for histocompatibility complex MCII and lysozyme antibodies, marking histiocytic cells. Labeling was positive for CD20 in cells of lymphoid lineage B and negative for E-cadherin. Histiocytic cells did not invade the epidermis; hence, proliferation was classified as non-epitheliotropic. These methods contribute to the literature regarding the diagnosis of this rare tumor. Therefore, histological as well as immunohistochemical evaluation are important for confirming clinical diagnosis of histiocytic proliferation non-epitheliotropic.

**Discussion:** Progressive histiocytosis of feline dendritic cells, in both epitheliotropic and non-epitheliotropic forms, is considered a clinically progressive and rare disorder. There are reports which include cytological, clinical, histological and immunohistochemical examinations, but the diagnostic characteristics regarding the non-epitheliotropic classification have not yet been properly identified. Nodulations are predominantly observed in head and limb regions, usually non-ulcerated, which can both increase and decrease in size, and are typically painless. The tumor in the present case was restricted to the base of the ear and no evidence of infiltration or metastasis was found. Progressive histiocytosis may spread and reach the lymphatic system through the lymph nodes, subsequently becoming systemic. The non-aggressive behavior observed in this case is possibly related to the non-epitheliotropic pattern. In the present case, MHC II histocompatibility complex markers, a phenotype compatible with dendritic cells, were used. Lysozyme antibodies marked histiocytic cells and the reactive lymphoid infiltrate was composed of CD20-positive B lymphoid lineage cells. Staining for E-cadherin was negative, negative results in labeling experiments is common, it is dependent upon the cellular origin of the leukocytes present in the sample. Staining for these molecules is recommended for differentiating feline progressive histiocytosis from Langerhans cells. Langerhans cells can be characterized by E-cadherin expression in about 10% of cases and marked T lymphocyte and neutrophil expression in the affected tissue. In this case, the histopathological exam along with immunohistochemistry was essential for differentiating them.

**Keywords:** tumor, histopathological, histocompatibility, histiocytic.
INTRODUCTION

Histiocytic tumors in felines are nodules that commonly develop on limbs and head extremities. They can be divided into many subtypes including cutaneous histiocytoma [2,7], histiocytic sarcoma [5], reactive fibrohistiocytic nodule, Langerhans cell histiocytosis, and progressive feline dendritic cell histiocytosis [1,4,6,8]. Despite the same origin, they have behaviors that differ from each other, thus it is important to confirm diagnosis with histopathological and immunohistochemical tests, which can allow vets to differentiate between the different types, and early identification can facilitate prognosis and treatment [9].

In this study, we describe the pathological and immunohistochemical characteristics that can allow accurate diagnosis; enabling differentiation between non epitheliotropic progressive, histiocytosis of epitheliotropic and others feline neoplasms derived from histiocytes, such as histiocytes as well as common skin tumors, mastocytomas, and sarcomas.

CASE

A 5-year-old male, crossbreed, feline presented with a nodule at the base of the left auricle that was characterized by slow and progressive growth. Blood count and biochemistry were within the standards ranges considered normal for this species. The neoplasm of the ear region was circumscribed, and 1 cm in diameter and could be further described as a single, nodular, unattached, non-ulcerated, gelatinous mass, which was limited to the dermis layer (Figure 1). When an incision was made, the interior was soft and greasy in consistency. He was referred for histological processing performed with HE1.

Microscopy showed a dense, unencapsulated mass with circumscribed proliferation of histiocytic cells, which had abundant and eosinophilic cytoplasm (Figure 2A). The proliferative cells were enlarged and rounded, with centrally located nuclei ranging from round to oval in shape. These cells had broad cytoplasms, but sometimes in regions near the center of the nodule, the cytoplasm was scarce and with poorly defined edges. The cells infiltrated the tissues to the superficial dermis, and some cells, which had vacuoles were located at the extremities of the lesion. Some of these invading cells were associated with an inflammatory infiltrate consisting of lymphoplasmacytoid cells which intermingled with the neoplastic cells and limited cell proliferation (Figure 2B).

The neoplasm developed at the basement membrane without invasion of the underlying epidermis. Mitotic activity ranged from 3 to 4 mitoses per field in 40x magnification. CD202, E-cadherin2, MHCII2, and lysozyme2 (Figure 2C), antibodies were used for immunohistochemistry analysis.

DISCUSSION

The diagnosis of feline progressive histiocytosis in the present case was determined by histopathological and immunohistochemical evaluation. The histological type of the tumor was confirmed by observing that a proliferative lesion with a diffuse infiltration pattern of histiocytes, which did not reach the underlying dermis, was characteristic of the nonepitheliotropic type [6].

Progressive histiocytosis of feline dendritic cells, in both epitheliotropic and non-epitheliotropic forms, is considered a clinically progressive and rare disorder. There are reports which include cytological, clinical, histological and immunohistochemical examinations, but the diagnostic characteristics regarding the non-epitheliotropic classification have not yet been explored. These characteristics are essential for a correct diagnosis and appropriate treatment.
been properly identified [1]. Nodulations are predo-
minantly observed in head and limb regions, usually
non-ulcerated, which can both increase and decrease
in size, and are typically painless [6,9,11]. There is
no predisposition regarding age or breed, but a study
involving 30 cases points to a greater predisposition
among females [1].

The tumor in the present case was restricted
to the base of the ear and no evidence of infiltration
or metastasis was found. According to literature, pro-
gressive histiocytosis may spread and reach the lym-
phatic system through the lymph nodes, subsequently
becoming systemic. When systemic, multiple nodules
extend from the initial nodule and may become ulce-
rated and plaque-shaped [6-8,10]. The non-aggressive
behavior observed in this case is possibly related to the
non-epitheliotropic pattern.

In this study, the histological characteristics
and immunohistochemistry both suggested the same
diagnosis and were distinctly different to the charac-
teristics typically seen in progressive histiocytosis
types. In the microscopic examination, it was possible
to observe that the tumor was restricted to the dermis
layer, differing from the epitheliotropic type that often
adhered to reaches epidermis and subcutaneous, but
macroscopy could also become ulcerated and even
form multiple masses or multinodular masses as the
disease progressed [8].

This type of tumor is clinically indistinguisha-
ble from other neoplastic, allergic and inflammatory
diseases, such as granulomas and tumor metastases
[10], as well as other primary neoplasms, xanthomas,
sarcomas and mastocytomas [5,6]. These conditions
are important differentials within the histological
examination and should be addressed initially by mor-
phology and when possible, through specific markers
in immunohistochemistry, as they commonly change
over time [9].

For tumors of histiocytic origin antibodies
should be applied, such as CD18, CD1, MHC II
(major histocompatibility complex) that mark cells
of histiocytic origin, while lysozyme antibodies can

Figure 2. A- HPD microscopy showing circumscribed round cell proliferation, infiltration of randomly distributed plasma cells and lymphocytes, some-
times forming cords [HE; Magnification: 20x]. B- The histiocytes had proliferative and eosinophilic cytoplasm, proliferative, enlarged and rounded, with
nucleus ranging from round to oval, centrally located [HE; Magnification: 40x]. C- HLA-DR antibody, highlighting cells of histiocytic origin densely
labeled by the MHCII Histocompatibility complex. D- Intense brown marking of cells of histiocytic origin by the lysozyme antibody.
mark myeloid granulocytes and histiocytes [3,6]. In
the present case, MHC II² histocompatibility complex
markers, a phenotype compatible with dendritic cells,
were used. Lysozyme² antibodies marked histiocytic
cells and the reactive lymphoid infiltrate was composed
of CD20²-positive B lymphoid lineage cells. Staining
for E-cadherin² was negative, negative results in la-
beling experiments is common, it is dependent upon
the cellular origin of the leukocytes present in the
sample. Staining for these molecules is recommended
for differentiating feline progressive histiocytosis from
Langerhans cells [4].

Langerhans cells can be characterized by
E-cadherin expression in about 10% of cases and
marked T lymphocyte and neutrophil expression in
the affected tissue. Approximately 30% of cases are
cutaneous, while 10% of diagnosed cases are systemic.
Importantly, the tumor can be successfully treated by
corticosteroid, cyclosporine, and leflunomide-based
medicines [6,11]. In this case, the histopathological
exam along with immunohistochemistry was essential
for differentiating them.

Improvements to the diagnosis of rare tumors
are required. This study demonstrated the utility of
various diagnostic methods, including clinical and
histological characterization as well as immunohis-
tochemical analysis, to confirm tentative diagnosis.
Based on this report, it is possible to assist clinicians
and pathologists regarding the diagnostic conduct.

MANUFACTURERS

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