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Canine Cutaneous Epitheliotropic T-Cell Lymphoma

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Introduction
Cutaneous epitheliotropic T-cell lymphoma in the dog (CETL) is a rare neoplastic condition with unknown aetiology. A possible cause discussed in man is chronic inflammation. However, this hypothesis is controversial. In the dog, the relationship between chronic dermatitis and CETL is poorly documented. Recently, Santoro et al. suggested a possible association between atopic dermatitis and MF in dogs based on a retrospective study. The dermatosis is characterized by infiltration of neoplastic T-lymphocytes with a specific tropism for the epidermis and adnexal structures. When there is a dysregulation in the lymphocyte division, malignant T cells express skin-homing receptors which are crucial for the exocytosis of lymphocytes into the skin, binding to epidermal keratinocytes and Langerhans cells and thus epitheliotropism.

CETL is an uncommon skin tumor. At the veterinary faculty at the university of Liège the prevalence is 2 cases per 1000 dermatologic consultations.

Reviewing the literature it appears that English Cocker Spaniels and Boxers may be predisposed to this disease. The mean age at the time of diagnostic is around 8 years. There is no sexual predisposition.

The clinical presentation of CETL is very pleomorphic. Sometimes muco-cutaneous junctions or oral mucosa can be affected. Involvement of other organs can be observed in late stages of disease.

Using criteria described in humans, CETL in the dog can be subclassified in three forms: Mycosis fungoides (MF), pagetoid reticulosis (PR), and Sézary syndrome. In the dog, it is impossible to characterize the CETL subtype based on cutaneous signs. The classification used by Scott et al. is a good approach to describe the clinical presentation of CETL: exfoliative erythroderma, plaque(s)/ nodule(s) (This form is the most frequently reported in the dog, possibly due to the fact that the initial erythroderma is not recognised by owners and the dog not presented before plaques or nodules occur), ulcerative disease of the oral mucosa and a mucocutaneous form. In humans, the three forms (patch, plaque and nodule) are quite distinct, but in dogs these forms usually overlap.

Clinical Appearance and Histopathology
For the experienced clinician, clinical appearance may be suggestive of the disease but the final diagnosis is always based on histopathologic examination. Biopsy samples should be taken from the most representative lesions. Erythroderma and infiltrative lesions that are neither infected nor ulcerated, depigmented patches, plaques or intact nodules are most suitable. During early stages of the disease, histologic differentiation from non-neoplastic lymphocytic dermatitides such as atopic dermatitis can be very difficult.

The most characteristic histologic lesion, common to all forms of CETL, is the tropism of neoplastic cells for the epidermis and the adnexal structures (hair follicles, apocrine sweat and sebaceous glands). T lymphocytes may be distributed diffusely in the epithelium or may form significant aggregates (Pautrier’s microabcesses). In more advanced cases, ulceration is observed and the reactive infiltration becomes more severe. The epithelial infiltration also affects hair follicles inducing a secondary alopecia. Some authors consider epitheliotropism a feature of all stages of canine CETL, whereas others suggest reduced epitheliotropism with progressive dermal invasion, as observed in humans.

Pagetoid Reticulosis
In pagetoid reticulosis, the lymphocytic infiltrate is mainly confined to the epidermis and its adnexae. The superficial dermis may contain a mild to moderate reactive infiltrate composed of non neoplastic lymphocytes, plasma cells, histiocytes and occasionally granulocytes. Dermal neoplastic infiltration occurs only in the Ketron-Goodman type of the disease (disseminated form). The histological features of this terminal stage cannot be distinguished from the nodular stage of classic mycosis fungoides thus this form is considered a manifestation of MF. Canine Pagetoid reticulosis is rarely documented in veterinary literature, but is similar to the human variant disseminated pagetoid reticulosis or Ketron-Goodman Pagetoid reticulosis. Only one case with a single isolated slowly progressing plaque has been described in the dog. This could be the canine equivalent of human Woringer-Kolopp disease (localized form).

Sézary Syndrome
Sézary syndrome is a form of CETL associated with the presence of neoplastic lymphocytes in lymph nodes and peripheral blood (leukemia). Clinically and histologically, the lesions resemble those observed in the classic mycosis fungoides but lymph nodes are also affected and small lymphocytes with a hyperchromatic convoluted nucleus (“Sézary cells”) can be observed in the skin, the lymph nodes, the blood and sometimes in organs such as spleen, liver, lungs, heart, and kidneys. This syndrome must be differentiated from lymphocytic lymphoma with secondary cutaneous involvement.
Dermatology

Cellular phenotype
The classic neoplastic cells in canine CETL are CD3+ (a common marker of all T-lymphocytes) and in 80% of the cases CD4-/CD8+ cytotoxic T cells. In 20% of the cases, CD4-/CD8- lymphocytes (natural killer cells) are found. In man, 90% of CETL cases are due to clonal expansion of T-helper lymphocytes (CD4+/CD8-).

Gene rearrangement analysis
Because clonal proliferation in humans typically occurs from a single lymphocyte, the population of neoplastic lymphocytes contains the same signature gene rearrangement. In contrast, reactive lymphocytes contain a mixture of gene rearrangements. This can be detected using DNA analysis from a skin biopsy to confirm the diagnosis of neoplasia in borderline cases. DNA can be extracted from fresh, frozen or formalin-fixed tissue. The technique showed a very good sensitivity (91%) and specificity (95%) in 77 dogs with lymphoid neoplasia.

The prognosis for dogs with canine CETL is poor. The mean survival time after diagnosis is a few months to 2 years. Euthanasia is often requested by the owners because of the severe skin condition.

Many treatment protocols for CETL have been reported, the large number attesting to the fact that none of them have good efficacy. Currently the most promising protocols include the use of Lomustine or CCNU. In dogs, the recommended dosage is 60 to 70 mg/m² orally every 3 weeks with a mean of 4 treatments. Recently retrospective studies of dogs with CETL cases showed an overall response rate of 78 to 83%. However, survival times were not listed. Although the disease cannot be cured, treatment frequently increases the quality of life.

References