13-year-old female spayed European shorthaired cat with excessive licking on the left shoulder with focal ulceration. Which of the following is the most likely disease?

1. Cutaneous epitheliotropic lymphoma
2. Food allergy
3. Neuropathic pruritus
4. Cutaneous lymphocytosis CORRECT
5. Cutaneous non epitheliotropic lymphoma

Signalment and history: A 13-year-old, female spayed, European shorthaired cat is examined for a 4-year duration alopecic lesion on the left scapular region with erythema, hyperpigmentation, scaling, erosions, and ulcers (Figure 1 and 2). An apparently self-induced alopecia is also present on the abdomen, on the posterior aspect of thighs and on the forearms. During consultation, the cat is compulsively licking the left shoulder region. Itching is defined as the main dermatological problem of the animal, either as cause of the lesion (self-induced) or secondary to other diseases causing the lesion. Among the differential diagnoses of pruritus as primary cause of the lesion a neuropathic pruritus, a behavioral pruritus and, less likely given the compulsive licking confined to the left shoulder, a dermatological pruritus caused by an allergic dermatitis (flea bite, food, atopy) were considered. Among the possible causes of diseases causing itching neoplasms, i.e. mast cell tumor, cutaneous lymphocytosis and dermatophytosis were considered. Microscopic examination of plucked hairs is unremarkable, cytology (imprints from the ulcers) reveal erythrocytes, macrophages, neutrophils, and numerous lymphocytes. The neurological examination is within normal limits and hematobiochemical exam reveal a peripheral lymphocytosis. During the manual constraint for blood collection, spontaneous laceration of the skin occurs on the left shoulder region. Therefore, in order to evaluate the presence of lesions in internal organs possibly associated with acquired skin fragility, an abdominal ultrasound examination is performed which revealed no abnormalities. Two skin biopsy punches are taken from the left scapular region and one from apparently normal skin from the right scapular region in order to evaluate any changes in the collagen suggestive of skin fragility.

Histopathologic description: All three skin punches are characterized by similar histopathological lesions, with different degree of severity and in different developmental stages. In the dermis there is a superficial to deep (Figure 3), perivascular to diffuse (Figure 4) infiltration with a relatively monomorphic population of discrete, round cells arranged in parallel sheets and embedded in moderate connective stroma. The majority of these cells are well differentiated and small-sized and a minority are medium-sized (Figure 5). The cells have round or oval, occasionally indented nuclei and a scant amount of eosinophilic cytoplasm. Anisocytosis and anisokariosis are low, mitotic count is up to 1 mitosis per 10 HPF. Small foci of necrosis and single cell necrosis are evident. There is occasional epitheliotropism towards hair follicles, sweat glands and epidermis (Figure 5). In the epidermis occasional hydropic degeneration and apoptosis of basal keratinocytes is seen. Scattered within the lymphoid cells, there is a significant number of mast cells, sometimes arranged in multicellular aggregates and a lower number of histiocytes. The epidermis is diffusely and moderately hyperplastic with lamellar orthokeratotic hyperkeratosis. In the biopsy punch from the left shoulder, the infiltration is more densely cellular, often diffuse, reaches the deep dermis and sometimes the muscular layer, while in the biopsy punch from the right shoulder the infiltration is more superficial and rather perivascular to interstitial (Figure 7). Immunohistochemical examination using anti-CD3 and anti-CD20 antibodies reveal a diffuse infiltration with CD3 positive cells, admixed with fewer CD20 positive cells, either scattered as single cells between T lymphocytes or arranged in small groups (Figure 8).

Morphologic diagnosis: Dermal lymphocytic proliferation (lymphocytosis)

Name the condition: Feline cutaneous lymphocytosis (Synonyms: cutaneous lymphocytoma, cutaneous lymphocytic hyperplasia, pseudolymphoma)
Follow up: While waiting for the results of the histopathological examination and for the management of pruritus, the cat is prescribed with the use of a cotton dress and a padded Elizabethan collar; maropitant and oclacitinib are also prescribed, later replaced by gabapentin due to the poor improvement of pruritus. After the result of the histopathological examination, methylprednisolone is given in combination with gabapentin. Currently, about four months after diagnosis, the cat is kept under glucocorticoids and gabapentin. Lesions appear moderately improved: ulcers and scales are no longer present and the erythema is mild (Figure 8); a partial re-growth of the hair is observed, but the cat continues to wear the cotton dress due to persistent licking. Its general conditions continue to be good and the skin on the right shoulder in which histological lesions compatible with lymphocytosis were present is still clinically normal.

Comment: Cutaneous lymphocytosis is a disease of human beings, cats and less commonly dogs, characterized by a proliferation of well-differentiated lymphocytes, with a relatively benign clinical behavior (slow progression, lack of metastasis, waxing and waning). The proliferation of lymphocytes is thought to be driven by a chronic, persistent antigenic stimulus, due to different antigens such as drugs, vaccines, arthropod bites, contactants, infections. Some cases are idiopathic. In cats, the disease is often seen in older animals (12–13 years); there is no breed predisposition, and female cats are usually overrepresented. Lesions can be solitary or multiple, and are usually associated with alopecia, erythema, and scaling, with or without crusting. Lesions are often pruritic. Predilection site is the thorax, followed by legs, pinnae, flank, and neck. Lesions generally have a benign clinical behaviour although spontaneous regression in cats has not been reported, different from humans. In few cases, spread to internal organs was described with systemic signs. Histologically, there is a proliferation of well-differentiated lymphocytes, extending from superficial to deep dermis. Scattered lymphocytes can infiltrate the epidermis or the follicular walls but epitheliotropism is usually not pronounced. Lymphocytes have dark nuclei with compact chromatin and a small to moderate amount of cytoplasm. Mitotic figures are rare or absent. Different from lymphocytosis in humans, where proliferating lymphocytes can be of T- or B-cell origin, lymphocytosis in cats and dogs is usually of T cell origin. In the cat, B cells can be found either as single cells or in small aggregated between T-cells. Admixed with lymphocytes are inflammatory cells such as histiocytes, mast cells and eosinophils. Clonality testing for rearrangement of the T cell receptor genes in lesions of feline lymphocytosis has shown a clonal rearrangement, suggesting that feline clonal cutaneous lymphocytosis may represent a low-grade, indolent lymphoma.

Most of the features of the current case of the month were consistent with those of previous cases, as this was an older female cat with alopecic and erythematous lesions. However, in this case, the compulsive licking localized to such a circumscribed region of the body, as well as the duration of the problem (4 years) were more suggestive of neuropathic or behavioral problem, while the presence of self-induced alopecia on the abdomen was more suggestive of allergic or possibly behavioral dermatological pruritus. On the other hand, the scaling and the irregular and jagged contour of the ulcers, as well as the presence of numerous lymphocytes on cytological examination of the lesions, were not compatible with self-induced lesions. Furthermore, the skin fragility noted during manipulation of the animal was suggestive of a metabolic or neoplastic problem. Worthy of note in this particular case is the presence of histological lesions in clinically normal skin and the skin fragility associated with lymphocytosis. Regarding this last point, we hypothesize that the cutaneous lymphocytosis is the cause of the fragility.

References:

Contributors:
Clinical case: Dr. Alessandra Fondati and Alessandra Cucco, Dermatologists, Lido di Camaiore (LU), Italy;
Histopathology: Dr. Chiara Brachelente, Department of Veterinary Medicine, University of Perugia (PG), Italy.
Figure legend:

**Figure 1**: 13-year-old, female spayed, European shorthaired cat. Left shoulder: partial alopecia with erythema and hyperpigmentation, scales, ulcers, scarring focal thickening of skin.

**Figure 2**: 13-year-old, female spayed, European shorthaired cat. Particular of the previous figure.
Figure 3. 13-year-old, female spayed, European shorthaired cat. The superficial, mid and deep dermis are diffusely infiltrated by a dense cellular infiltration.

Figure 4. 13-year-old, female spayed, European shorthaired cat. The cellular infiltration usually spares the epithelial layers of the epidermis and of the follicular walls.
Infiltrating lymphocytes are small-sized, have a scant amount of eosinophilic cytoplasm, with low anisocytosis and anisokaryosis and rare mitoses.

Clinically normal skin from the right shoulder shows that same type of cellular infiltration, although of a lower severity and with a more superficial distribution.
Figure 7. 13-year-old, female spayed, European shorthaired cat. Immunohistochemistry shows a predominance of infiltrating T-lymphocytes with fewer B-lymphocytes scattered within the main cell population.

Figure 8. 13-year-old, female spayed, European shorthaired cat. Currently, about four months after diagnosis, the cat is kept under glucocorticoids and gabapentin. Lesions appear moderately improved: ulcers and scales are no longer present and the erythema is mild; partial hair re-growth is present.