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NOTE

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Lokivetmab improved pruritus in a dog with cutaneous epitheliotropic lymphoma

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ABSTRACT. A 13-year-old spayed female Cavalier King Charles Spaniel presented with chronic swelling and pruritus on the palmar aspect of the left forepaw and on the tail. Cutaneous epitheliotropic lymphoma (CEL) was diagnosed by histopathology and immunocytochemistry. Prednisolone was initially used alone as an alternative treatment for CEL. Despite long-term corticosteroid therapy, the patient's physiological (pruritus) and dermatological signs (alopecia, erythema, erosion, and ulceration with crust) progressed and showed no evidence of improvement. To address the worsening condition of pruritus, lokivetmab was started in combination with prednisolone. Once on lokivetmab, the pruritus steadily improved and was effective in resolving and maintaining remission. Further investigation on the critical role of IL-31 in the pruritus pathway of dogs with CEL is required.

KEY WORDS: cutaneous epitheliotropic lymphoma, interleukin 31 (IL-31), lokivetmab, pruritus

Cutaneous lymphoma in dogs accounts for approximately 3 to 8% of all types of lymphomas. It occurs frequently in middle-aged and elderly dogs, and there is an unknown difference in morbidity depending on the breed or gender [2, 5]. Typically, canine cutaneous lymphoma represents the T-cell immunophenotype and is classified into cutaneous epitheliotropic lymphoma (CEL) and non-epitheliotropic lymphoma based on histopathology [1, 8]. Canine CEL can cause erythema, plaques, erosions, scales, nodules, hypopigmentation, crusts, alopecia and may cause mild to severe pruritus [2].

Interleukin 31 (IL-31) transmits pruritus signals to the brain via the janus kinase/signal transducer and activator of transcription pathway [3]. Lokivetmab is a caninized anti-canine IL-31 monoclonal antibody (mAb) that interferes with the binding of IL-31 to its receptor by forming an antigen-antibody complex and neutralizing it. Thereby, it inhibits IL-31-mediated signal transduction and relieves pruritus associated with canine atopic dermatitis (CAD) [7]. In human medicine, some studies have reported a connection between pruritus in cutaneous lymphoma and IL-31 [10]. However, it has been controversial whether IL-31 is involved in the mechanism of pruritus in CEL in veterinary medicine.

In this case report, we described a unique case of CEL in which pruritus was improved following treatment with lokivetmab. Lokivetmab was used after the patient failed on prednisolone. To the authors' knowledge, this is the first case report in which an anti-IL-31 mAb played a possible role in reducing pruritus in a dog with CEL.

A 13-year-old spayed female Cavalier King Charles Spaniel presented with chronic swelling and mild pruritus over the palmar aspect of the left forepaw and on the tail, defined as Day 1. The patient also sustained a superficial ulceration on the palmar aspect of the left forepaw. There was mild to moderate erythema on the tail. The patient's degree of pruritus was quantitatively assessed using the pruritus visual analogue scale (PVAS) score (Fig. 1) [4]. On skin cytology, impression smears of the ulcerated and erythematic lesion revealed mild to moderate suppurative granulomatous inflammation (i.e., small amounts of cocci, denatured neutrophils, and macrophages). On Day 14, the patient was started on cephalexin (Therios; DS Pharma Animal Health, Osaka, Japan) (20 mg/kg, PO, q12 hr, for 14 days). Despite antibacterial therapy, the lesion showed no marked improvement and additional nasal depigmentation had emerged overtime (Fig. 2). On Day 28 of follow-up, there were progressive ulcerations and worsened erythema on the left forepaw. Multiple biopsies from the muzzle and tail were submitted for histopathology to provide a definitive diagnosis. The erythema on the tail was resected as the lesion was only limited to the tip.

Skin biopsies were performed by an attending veterinarian (KI) and the samples were read by a board-certified pathologist. The diagnosis of CEL was made based on the histological findings and metastatic lesions. Histopathological findings from the skin

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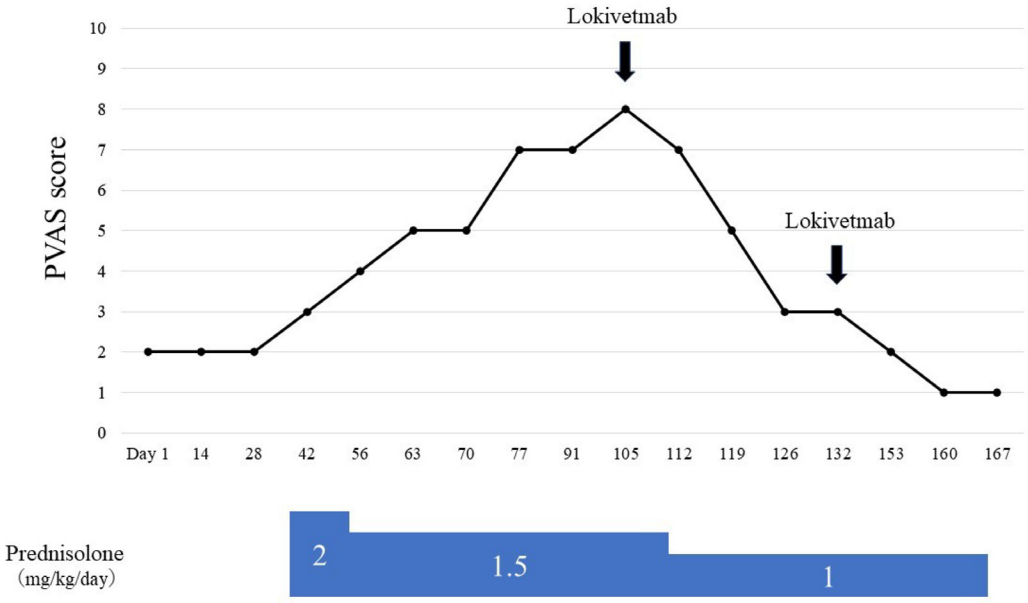

Fig. 1. The change in the pruritus visual analogue scale (PVAS) score over time. The change of PVAS score is drawn in a black line, decreasing at the time when lokivetmab was administered. Lokivetmab was administered on Day 105 and Day 132 (black arrow). The blue bar below the graph shows the dosage of prednisolone prescribed.

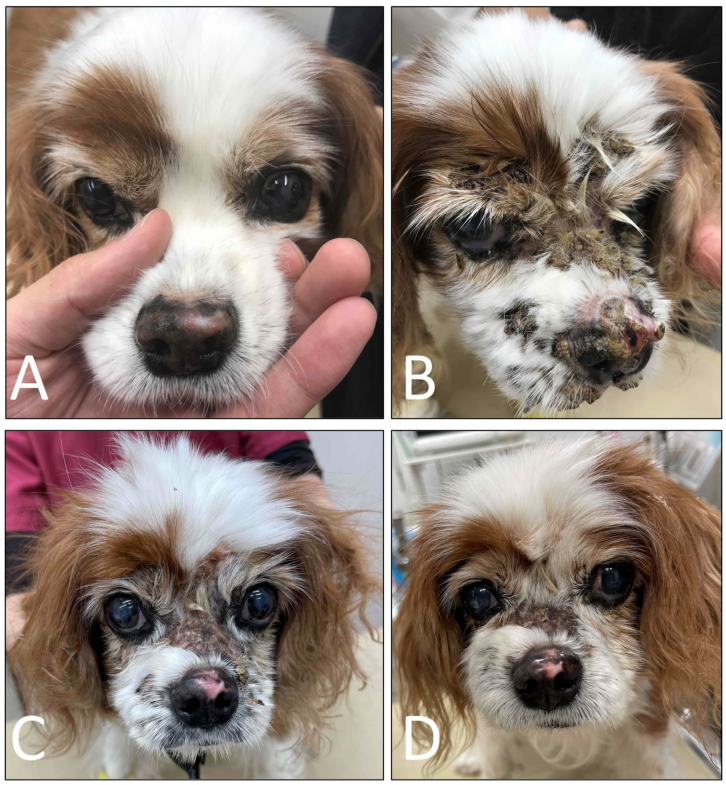

Fig. 2. (**A**) On Day 14, nasal depigmentation had emerged. (**B**) On Day 105, progression of facial alopecia with crusting was found. (**C**) On Day 132, facial alopecia with crusting was still present. (**D**) On Day 160, hair regrew on the face where alopecia was present.

biopsy of the muzzle revealed that the lymphoblastic-like tumor cells were infiltrating the epidermis, the hair follicle epithelium, and the sweat glands. The cytoplasm of the tumor cells was scant to moderate in amount. The nuclei were round but sometimes irregular with stippled chromatin and distinct nucleoli. These findings were also obtained in the tail lesion. These tumor cells were positive for CD3, but negative for CD79α and CD20 on immunohistochemistry (Fig. 3).

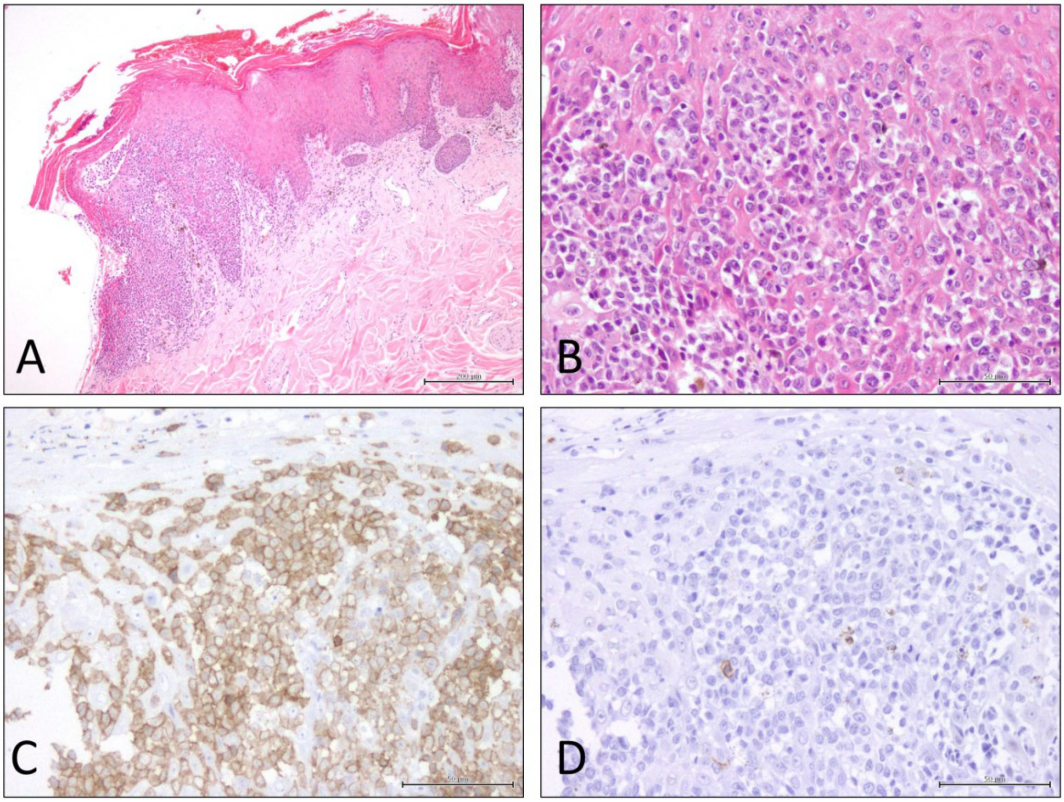

Fig. 3. Histopathological and immunohistochemical images of the muzzle sample. The epithelium was thickened and markedly infiltrated by the tumor cells (**A**, **B**). The tumor cells in the epithelium were strongly positive for CD3 (**C**), but negative for CD20 (**D**). Bar=200 µm (A), Bar=50 µm (B, C, D).

After consultation with the owners, they did not wish to accept chemotherapy such as the CHOP protocol or L-asparaginase, due to concern about the side effects. Instead, treatment with prednisolone alone was chosen (PREDNISOLONE Tablets 5 mg "Mita"; KYORIN Rimedio, Kanazawa, Japan) (2 mg/kg, PO, q24 hr on Day 42). At this point, the pruritus was mild and the PVAS score was 3. On Day 56, in addition to the lesion previously monitored on the palmar aspect of the left forepaw, similar lesions had emerged on the other paws. Moreover, the pruritus worsened, and the patient had a PVAS score of 4. The prednisolone dose was tapered to 1.5 mg/kg, PO, q24 hr. On Day 63, exacerbation of the erythema on the muzzle was found, whereas the ulcer on the palmar aspect of all four paws did not significantly worsen. The patient's PVAS score of 5 showed worsening conditions. On Day 77, the patient was continued on the same dose of prednisolone. There was a progressive worsening ulcer on the paws and alopecia with crusting was found on the face and upper back. The patient had a PVAS score of 7, in line with exacerbation of pruritus. On Day 91, the patient continued to develop multifocal areas of facial alopecia with crusting, along with concurrent pruritus. On Day 105, as the dose of prednisolone remained the same, the patient's clinical signs, including facial alopecia and ulcerative lesions continued to progress despite treatment. By then, the patient had a PVAS score of 8.

In the hope of mitigating this ongoing pruritus, lokivetmab (Cytopoint; Zoetis, Tokyo, Japan) (1.25 mg/kg, SC, once) was initiated in combination with prednisolone (1.5 mg/kg, PO, q24 hr). On Day 112, facial alopecia with crusting was still present. The ulcerative lesions remained unchanged with no remarkable improvement. Despite the patient's minimal clinical response, the PVAS score was found to be 7. A decision was made to further taper the dose of prednisolone to 1 mg/kg, PO, q24 hr. The PVAS score fell from 5 to 3 in two weeks. On Day 132, one month after starting lokivetmab, the pruritus subsided. To prevent the possibility of relapse, lokivetmab (1.25 mg/kg, SC, once) was re-administered. On Day 153, despite the persistence of the facial alopecia with crusting, the PVAS score had dropped to 2, suggesting the pruritus was now well-controlled. On Day 160, the pruritus was controlled with a PVAS score of 1. Since the pruritus was negligible, active monitoring was initiated without further treatment of lokivetmab. Hair started to regrow on the face where alopecia was previously reported. On Day 167, the pruritus remained stable with a PVAS score of 1. Since the last visit, the patient sustained an excellent quality of life and eventually passed away due to progressive lymphoma on Day 183.

In this dog, there was no history of CAD or cutaneous adverse food reactions before the age of 8, and the patient's pruritus worsened as skin lesions progressed over time despite the use of prednisolone. Therefore, in this case the pruritus was considered to be related to CEL. IL-31 is produced mainly by activated T cells, and it is a critical pruritogenic cytokine associated with atopic dermatitis in humans and dogs [7]. It has been reported that the serum concentrations of IL-31 were not statistically different between non-pruritic dogs with CEL and healthy controls [6]. However, the contribution of IL-31 to pruritus in dogs

with cutaneous lymphoma has not been fully understood in veterinary medicine. In human medicine, it has been reported that the expression of serum IL-31 in cutaneous T-cell lymphoma (CTCL) patients is upregulated [9]. Decreasing serum IL-31 levels are correlated with the resolution of pruritus in CTCL patients [10]. Lokivetmab, a monoclonal antibody used to treat CAD, is reported to neutralize IL-31 and mitigate canine pruritus. Although lokivetmab is not indicated for the treatment of CEL, it was used in the hope of reducing pruritus. In this case of CEL, lokivetmab decreased pruritus. Thus, anti-IL-31 therapy appears to be a potential treatment option in controlling pruritus associated with CEL in dogs.

In this case, the IL-31 concentration before and after lokivetmab treatment was not quantified, and the correlation between the clinical improvement of pruritus in CEL and the IL-31 concentration was not specifically reported. Further studies are needed to determine whether IL-31 plays a critical role in the pruritus pathway in dogs diagnosed with CEL.

CONFLICT OF INTEREST. No authors have any conflicts of interest.

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