Case Report

Clinical response to oclacitinib in canine cutaneous epitheliotropic T-cell lymphoma: A case reports

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Abstract

The chemotherapy for canine cutaneous epitheliotropic T cell lymphoma (CETL) might cause unpleasant side effects or fail to produce positive results. We attempted a different approach with a more tolerable treatment option. We administered a high dose of oclacitinib (1.6 mg/kg/twice daily) to a patient diagnosed with CETL through histopathological examination and immunocytochemical staining. The patient had previously shown a poor response to chemotherapy and severe side effects to steroids. Within one month of starting oclacitinib treatment, we observed significant improvement in clinical symptoms, followed by improved appetite, increased activity, and weight gain after 2.5 months. However, subsequently, the patient's condition worsened. Nevertheless, through repeated dose escalation of oclacitinib, the patient was able to survive for 189 days. In terms of tolerability, we observed mild anemia and a decrease in white blood cells when oclacitinib was administered at 3.3 mg/kg/twice daily. However, no abnormalities were seen in blood tests when oclacitinib was administered at 3.0 mg/kg/twice daily, suggesting good tolerance to oclacitinib treatment. In conclusion, despite the safety concerns of high-dose oclacitinib, it did provide an effective and well-tolerated alternative treatment for CETL in dogs.

Keywords: cutaneous epitheliotropic T cell lymphoma, cutaneous lymphoma, oclacitinib

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Introduction

Canine cutaneous epitheliotropic T cell lymphoma (CETL) is characterized by neoplastic T-cell infiltration of the epidermis and adnexal structures and sometimes involves mucosa as well (Fontaine *et al.,* 2009). Various treatment regimens and protocols have been reported, including lomustine, masitinib, L-asparaginase, doxorubicin, retinoids, prednisolone, and radiation (Aslan *et al.,* 2021; Chan *et al.,* 2018; Laprais and Olivry 2017; Risbon *et al.,* 2006; Williams *et al.,* 2006). Despite the promising efficacy of chemotherapy, potential adverse reactions may affect the patient's quality of life (Heading *et al.,* 2011). Recently, a few studies have confirmed that oclacitinib might suppress T-cell proliferation *in vitro* (Jasiecka-Mikołajczyk *et al.,* 2018). In addition, there was a case report regarding the use of oclacitinib for the treatment of CETL, with 0.7 mg/kg oclacitinib BID showing partial remission. Currently, there is no literature regarding the treatment dosage of oclacitinib in CETL. Herein, we present a case of CETL that was treated using high-dose oclacitinib under careful clinical monitoring.

Case description

A 7-year-old neutered male Pomeranian presented with generalized scaling, crusted, and moderated pruritus for the past six months. Concurrently, the dog exhibited lethargy, inappetence, and depression. On the first day of presentation (D1), a skin biopsy was performed under generalized anesthesia owing to progressive nodular ulcerative lesions, severe erythema, and generalized accumulating scaling. Multiple biopsies revealed neoplastic lymphocytes infiltrating the epidermal layer. Diffuse lymphocytes also invaded the epithelium of hair follicles and sebaceous glands. The infiltrating cells were medium to large and showed irregular morphology, clear nucleoli, irregular nuclear morphology, and mitotic images (Fig.1). No lymphatic or venous invasion was observed. In addition, immunohistochemistry was positive for CD3 (rabbit monoclonal) and negative for CD79a (rabbit polyclonal) and CD20 (rabbit polyclonal), consistent with the diagnosis of CETL. Initially, L-asparaginase (Loinase, Kyowa Kirin, Tokyo) was administered at 400 U/kg SC combined with prednisolone (prednisolone tablets 5 mg, Kyorin, Kanazawa, Japan; 2 mg/kg once a day) and etretinate (Tigason capsule, Taiyo Pharma, Tokyo, Japan; 2.0 mg/kg/once a day). In the following 10 weeks, a total of three L-asparaginase injections were administered; nevertheless, the clinical lesions did not show any signs of alleviation despite continued chemotherapy. The haematology and blood chemistries of the dog were in the normal range (Table 1, D70). Moreover, the dog suffered from severe diarrhea since etretinate was prescribed. After etretinate was withdrawn, the intestinal symptoms spontaneously resolved. Additionally, the pruritus level gradually increased, and a trial of a single dose of lokivetmab (Cytopint; Zoetis, Tokyo, Japan) was injected (2.2 mg/kg). No significant relief from pruritus was observed within 1 month. At D97, the dog shown significant exercitation in clinical presentation and it exhibited with generalized severe erythema with multiple erosion and ulceration (Fig.2-A). The reticulocytes and ALP were slightly increased (Table, D97). However, the owners did not wish to accept any other chemotherapy regimen, such as CCNU, owing to concerns about side effects. After consultation with the owner, the owner agreed with new protocol of withdrawing the current therapy and switching to oclacitinib (1.6 mg/kg, BID). The patient was carefully monitored using blood chemistry and complete blood count. Before the treatment, the reticulocytes and ALP were slightly increased (Table, D97), but no abnormalities in radiographs and abdominal ultrasound. No Sézary cells were found in the peripheral blood smear, and no neoplastic lesions were found in other organs on radiographs and ultrasound. A Within 1 month (D126), a complete remission to a high dosage of oclacitinib was observed. Good appetite, energy, and increased body weight were noted at 2 months (Fig.2-B). A monthly recheck shown that the CBC results were within the normal range, despite the high-dose oclacitinib (1.6mg/kg, BID) was continued (table 1, D126 and D161). The skin lesion was deemed to have completely resolved as the erythematous nodules disappeared and there was a significant reduction in pruritus. Yet, at D188, the skin lesion once again gradually deteriorated while the same dosage of oclacitinib (1.6mg/kg, BID) was continued. The dog presented with mild pruritus, patch of erythematous lesions, mild scaling on trunk and abdomen region. In addition, acute diarrhea was reported despite a good appetite. No significant abnormality in routine blood works (Table 1, D188). With proper symptomatic treatment, diarrhea recovered within a few days. On D216, a few nodular lesions and erosions were reported around the eyelids, mandible, and perianal area. After consultation with the owner, the dosage of oclacitinib was elevated to 2.2 mg/kg BID. A few erythematous nodules disappeared or were alleviated, corresponding to higher dose of oclacitinib, but the pruritus persisted. No abnormality was observed on frequent blood examinations during the high dose oclacitinib therapy (Table 1, D244). However, pruritus continued to deteriorate even when the dose of oclacitinib was temporary increased to 3 mg/kg at D244. The dog suffered from moderate to severe pruritus, to prevent further self-induced excoriation, the E-collar was added. In the final stage, the skin lesion waxed and waned, and the pruritus was poorly manageable, despite further increased dose of oclacitinib to 3.3 mg/kg BID since D279. The CBC results shown mild abnormality (Table 1, D279). By D286, the dog was euthanized because of severe erosion on the tail and progressive painful lesions (Fig.2-C). During the treatment period, the patient had mild skin symptoms and good quality of life. Mild anemia (HCT 32.9%), leukopenia (WBC 4.46 K/μL), and hypoalbuminemia (1.7 g/dL) were found since the dosage was elevated to 3.3 mg/kg BID, but no further abnormality was noticed (table 1, D286). In the current report, the patient maintained a good quality of life and good clinical response to an elevated dosage of oclacitinib.

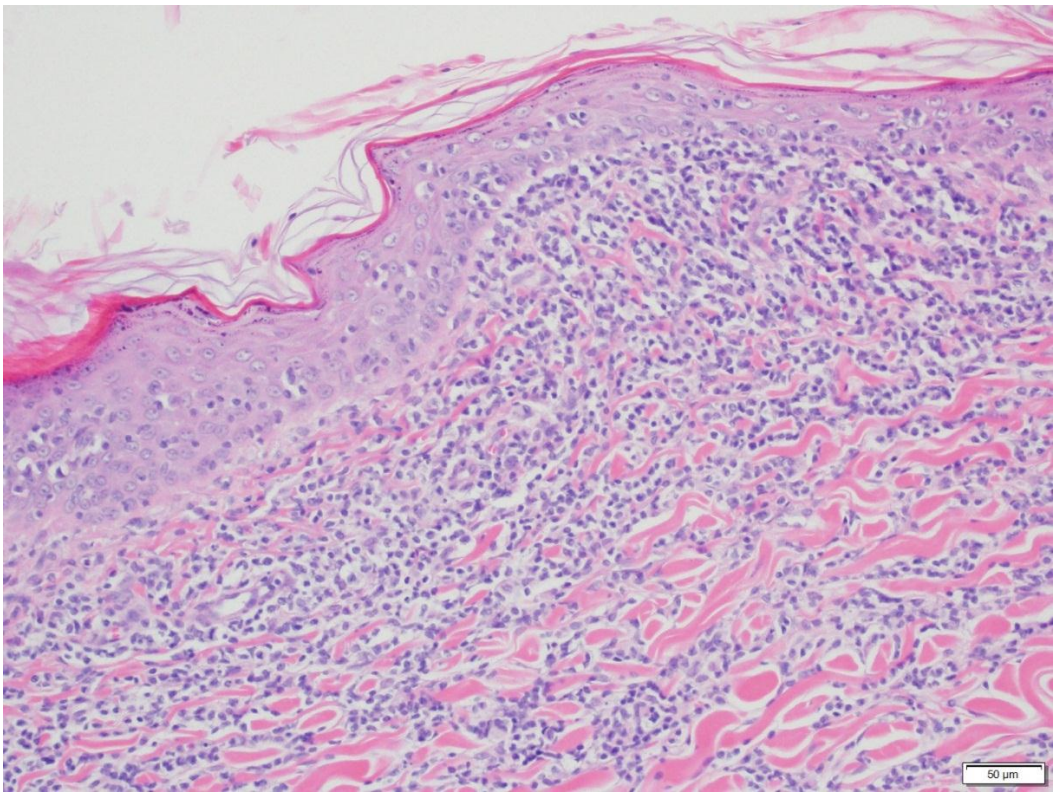


Figure 1 (A) Classical form with intense dermal and partially intraepidermal lymphoid infiltrates. Haematoxylin and eosin, 200x; scale bar represents 50 µm.

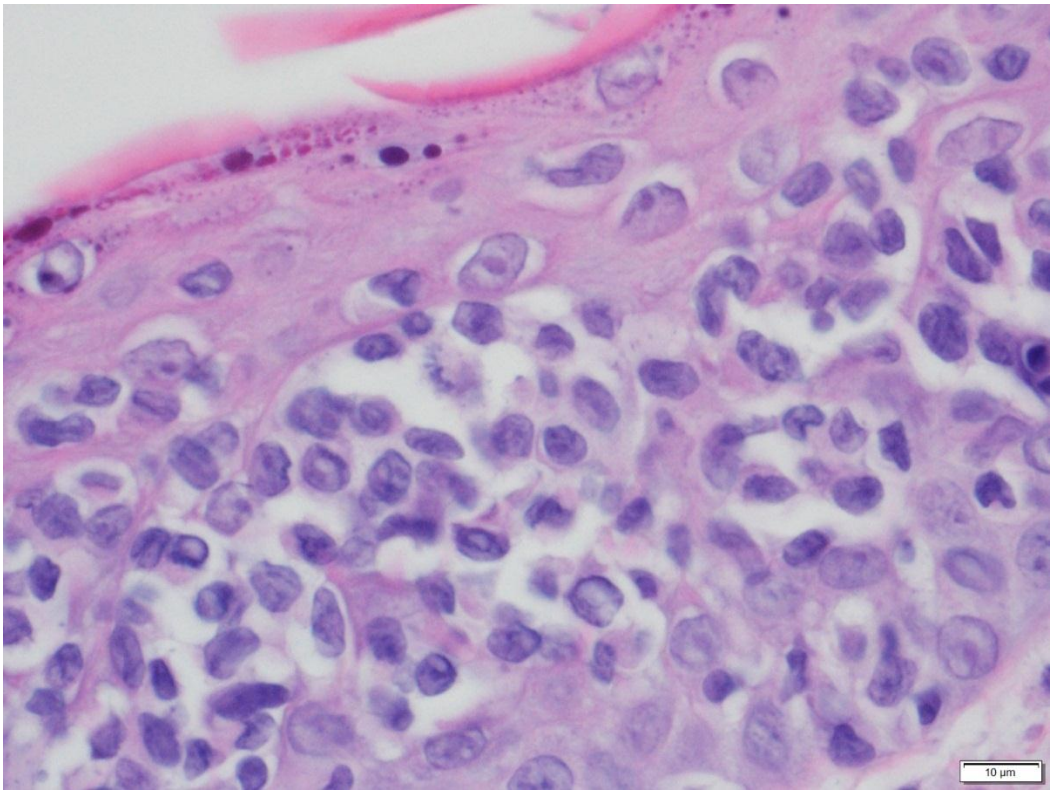


Figure 2 (B) The epidermal proliferation of small to medium to large-sized neoplastic lymphoid cells with formation of Pautrier's microabscess (arrow). Haematoxylin and eosin, 1000x; scale bar represents 10 µm.



Figure 2 (A) On day 110, the patient presented with diffuse erythroderma, large scales in the whole body, and a papule and crusted plaque from the abdomen to the inguinal region.
(B) On day 174, skin lesions and pruritus showed improvement and remission was achieved.
(C) On day 292, relapse of cutaneous epitheliotropic T-cell lymphoma was observed, and recurrence of skin lesions and pruritus was noted.

Table 1

CBC	D1	D70	D97	D126	D161	D188	D216	D244	D279	D286	Ref range
RBC (M/µL)	8.42	6.98	6.68	7.11	7.56	8.73	7.81	7.4	5.42	4.66	5.65-8.87
HCT (%)	54.6	47.1	45.4	47.2	48.8	56.2	49.5	47.1	32.9	29.1	37.3-61.7
Hgb (g/dL)	19	16.3	15.7	16.1	16.6	18.9	16.8	16.1	11.5	10	13.1-20.5
MCV (fL)	64.8	67.5	68	66.4	64.6	64.4	63.4	63.6	60.7	62.4	61.6-73.5
MCH (pg)	22.6	23.4	23.5	22.6	22	21.6	21.5	21.8	21.2	21.5	21.2-25.9
MCHC (g/dL)	34.8	34.6	34.6	34.1	34	33.6	33.9	34.2	35	34.4	32.0-37.9
RDW (%)	18.3	16	17.5	17.5	18.2	19.8	19.1	18.9	17.7	18.2	13.6-21.7
RETIC (K/µL)	79.1	34.2	118.2	44.1	56.7	70.7	53.9	70.3	22.2	15.8	10.0-110.0
WBC (K/µL)	6.6	8.01	12.59	7.04	6.9	6.44	6.84	7.54	4.46	6.87	5.05-16.76
Neu (K/µL)	4.6	5.57	9.86	5.4	4.89	4.9	5.22	5.83	2.69	4.34	2.95-11.64
Lym (K/µL)	1.41	1.4	1.19	1.03	1.32	1.01	1.01	0.89	1.37	1.66	1.05-5.10
Mono (K/µL)	0.23	0.69	1.08	0.3	0.25	0.26	0.34	0.34	0.29	0.57	0.16-1.12
Eos (K/µL)	0.35	0.29	0.44	0.3	0.42	0.27	0.27	0.46	0.11	0.28	0.06-1.23
Baso (K/µL)	0.01	0.06	0.02	0.01	0.02	0	0	0.02	0	0.02	0.00-0.10
PLT (K/µL)	268	290	411	313	288	284	263	191	351	516	148-484
MPV (fL)	11.7	12.3	11	12.7	13.1	13.2	13.1	14.1	12.3	11.6	8.7-13.2
PDW (fL)	11.9	13.6	10.7	14	15.7	17.3	17.5		14.9	13.7	9.1-19.4
PCT (%)	0.31	0.36	0.45	0.4	0.38	0.37	0.34	0.28	0.43	0.6	0.14-0.46
BIOCHEMISTRY											**Ref range**
TP (g/dL)	7.2		6.5			5.6	6.6	6.2	4.2		5.2-8.2
Alb (g/dL)	3.4		2.9			3.2	3.4	3.1	1.7		2.2-3.9
Glob (g/dL)	3.7		3.6			2.4	3.2	3.1	2.5		2.5-4.5
ALT (U/L)	45		50			51	110	45	177		10-125
ALKP (U/L)	87		427			86	155	121	198		23-212
GGT (U/L)	1					0	10.4	5			0-11
TBIL (mg/dL)	0.3					0.2		0.2			0.0-0.9
CHOL(mg/dL)	191					226		156			110-320
Glu (mg/dL)	129					109		113	104		70-143
AMYL(U/L)	513					556		726			500-1500
LIPA(U/L)	500					969		561			200-1800
Bun (mg/dL)	13					15	20	16	13		7.0-27
Crea (mg/dL)	0.8					0.8	1	0.9	1.6		0.5-1.8
Phos (mg/dL)	2.8					2.4		1.9	2.9		2.5-6.8
Ca (mg/dL)	9.9		9.8			9.8		9.8	8.7		7.9-12.0
Na (mmol/L)	149					154			150		144-160
K (mmol/L)	4.2					3.8			4.5		3.5-5.8
Cl (mmol/L)	112					117			116		109-122
CRP(mg/dL)									8.7		

Discussion

Cutaneous epitheliotropic lymphoma is a rare type of lymphoma in dogs, accounting for approximately 3-8% of all canine lymphoma cases and less than 1% of canine cutaneous tumors. Typically, this disease is observed in older dogs, with a mean age of onset reported as 10.4 years (Dettwiler *et al.,* 2023). However, our case presented at the age of 7, which is slightly earlier compared to previous research findings (Dettwiler *et al.,* 2023). Previous research has indicated that dogs with multiple cutaneous lesions generally have a poorer prognosis. However, the use of chemotherapy or retinoid therapy in these cases has shown a significant positive effect on survival (Chan *et al.,* 2018) . Nevertheless, in our case, the patient experienced difficulties tolerating the potential side effects of L-asparaginase and retinoids, leading to a switch to oclacitinib treatment. The high-dose (1.6–3.3 mg/kg, BID) of oclacitinib was continued for 189 days, which is much longer than the previous survival time of patients treated with traditional chemotherapy (Chan *et al.,* 2018; Dettwiler *et al.,* 2023).

Oclacitinib is a relatively innovative oral medication used for the treatment of canine atopic dermatitis by inhibiting Janus kinase 1 (JAK1), JAK2, JAK3, and TYK2. Oclacitinib suppresses T-cell proliferation and cytokine production in the body, leading to the alleviation of pruritus and inflammation. Several studies have demonstrated the effectiveness of oclacitinib in improving pruritus in dogs by modulating various immune mechanisms (Aslan *et al.,* 2021; Banovic *et al.,* 2019; Inai *et al.,* 2022; Jasiecka-Mikołajczyk *et al.,* 2018). However, when it comes to conditions other than atopic dermatitis, there is still limited data and lacking of clinical trials regarding the appropriate dosage of oclacitinib. In an *in vitro* study, lymphocyte-enriched cells were incubated with different concentrations of oclacitinib. When the cells were incubated with a low concentration (1 µM), which corresponded to an oral dosage of 0.4–0.6 mg/kg, T-cell proliferation was not affected. However, immune suppression was significant at 10 µM oclacitinib, which corresponded to an oral dosage of 3–4 mg/kg (Banovic *et al.,* 2019).

That echoes a study that demonstrated that regular oral dosage of 0.4–0.6 mg/kg oclacitinib failed to inhibit T cell proliferation *in vitro* (Jasiecka-Mikołajczyk *et al.,* 2018). The research indicates that oclacitinib has demonstrated T cell suppression in a dose-dependent manner. In the safety assessment of oclacitinib, the group receiving a five times higher dosage (administered twice a day for 42 days, followed by same dosage once a day for another 42 days) exhibited a significant decrease in reticulocyte count compared to the normal dosage group (Zoetis 2018) . Similar results have been observed in human medicine with JAK1 inhibitors, showing a correlation between

the dosage and the development of dose-dependent anemia and thrombocytopenia. (Mascarenhas *et al.*, 2017). Despite several large-scale retrospective studies have shown long-term safety and good tolerability in most cases (Cosgrove *et al.*, 2015; Gonzales *et al.*, 2014), there is still a serious concern about using such high doses. However, when treating conditions with a poor prognosis, such as cutaneous lymphoma, the benefits and risks should be carefully discussed with pet owners, and the pet's condition should be closely monitored while on off-label dosage.

In this case, based on clinical symptoms and histopathological findings, the patient had mycosis fungoides (erythematous stage) CETL at the start of oclacitinib treatment. Subsequently, as the disease progressed to the tumor stage, it appeared to be refractory to oclacitinib. Therefore, it is hypothesized that oclacitinib-treated CETL responds well to treatment with regard to mycosis fungoides (erythematous stage), whereas patients who have progressed to the tumor stage will be refractory to even high-dose oclacitinib. Further studies are warranted to determine the therapeutic effect of oclacitinib on the disease type and stage of CETL. In addition, the mechanism of action remains unclear, and further research is needed to elucidate the mechanism. Regarding the concentration of IL-31 and its actual mechanism of action in canine CETL, which have not been elucidated, although previous reports have shown good efficacy in cutaneous injection of lokivetmab (anti-IL31 antibody) that combinate with prednisolone (Inai *et al.*, 2022). According to previous researches, the concentration of IL-31 showed no significant difference compared to a small group of healthy dogs with non-pruritic cutaneous lymphoma and mast cell tumors (Gonzales *et al.*, 2014; Ignatenko *et al.*, 2020). Nevertheless, the concentration of IL-31 and its actual mechanism of action in canine CETL have not been elucidated. In current case, a single injection of lokivetmab was not beneficial in the treatment of pruritus. The further research is needed to elucidated the mechanism of Il-31 in CETL patients.

In conclusion, oclacitinib may offer benefits for cutaneous epitheliotropic T-cell lymphoma cases that have not responded to previous chemotherapy. However, given the potential safety considerations, close monitoring is highly advised.

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