Case Report

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Oral Fluralaner Treatment in a Dog with Desperate Demodicosis: A Case Report

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Abstract A 10-year-old castrated male Shih-tzu dog presented with a history of generalized demodicosis, refractory to conventional therapy with ivermectin and amitraz for a year. The patient was also diagnosed with concurrent deep pyoderma, *Malassezia* dermatitis, and otitis externa. Treatment with amoxicillin-clavulanate, antifungal drugs (itraconazole, miconazole), and milbemycin oxime resulted in a good response for 90 days. Approximately 4 months later, the first relapse of demodicosis occurred and the miticidal therapy was changed to ivermectin. Additional diagnostic tests were performed to investigate an underlying cause for the recurrence of demodicosis, and endocrinopathies and allergic dermatitis were excluded based on the results. Although ivermectin therapy was sustained for 440 days, a second relapse occurred and amitraz baths were added to the therapy. Despite this therapy, the demodicosis persisted, and the miticidal therapy was changed to oral fluralaner, which led to rapid resolution. Demodicosis did not recur again before death approximately 920 days after administration of oral fluralaner. This case report describes the complete resolution of refractory demodicosis using oral fluralaner in a dog.

Key words canine, demodicosis, fluralaner, refractory infection.

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Introduction

Canine demodicosis, caused by the proliferation of *Demodex* spp. mites, is a common disease encountered in small animal practice. Skin lesions usually manifest as patchy, regional, multifocal, or diffuse alopecia with varying degrees of erythema, scaling, papules, or pruritus (14).

Desperate demodicosis is defined as being unresponsive to conventional therapy or with the occurrence of frequent relapses (3). Cases of desperate canine demodicosis are treated with various macrocyclic lactones such as ivermectin, milbemycin, and doramectin, and/or with fluralaner, fipronil, and amitraz baths (3).

Prior to the development of isoxazolines, the most common conventional treatments prescribed by veterinarians for generalized demodicosis were oral milbemycin oxime and/or ivermectin and/or amitraz baths at various concentrations (14).

Fluralaner (Bravecto® Chew for Dogs, Merck Animal Health, Madison, NJ, USA), a new class of isoxazoline, is a long-acting systemic insecticide/acaricide that selectively inhibits γ-aminobutyric acid and L-glutamate-gated chloride channels (5). Fluralaner has demonstrated a high efficacy and safety in treating dogs with generalized demodicosis when orally administered at a dose of 25-50 mg/kg every 12 weeks (4,12,17). In the present case, we describe complete resolution of refractory demodicosis using oral fluralaner in a dog.

Case Report

A 10-year-old castrated male Shih-tzu dog presented with a history of generalized demodicosis refractory to conventional therapy with antibiotics, ivermectin, and amitraz baths for a year at a local animal hospital. In addition to a concurrent severe pruritus, physical examination revealed cutaneous lesions with erosion, ulceration, erythema, scaling, and crusting on the face, tail, and all foot pads (Fig. 1A-C). Skin cytology revealed numerous degenerated neutrophils and mixed infections of moderately infective cocci and *Malassezia*. No ectoparasites were observed in skin scrapings. Laboratory examinations revealed neutrophilic leukocytosis (white blood

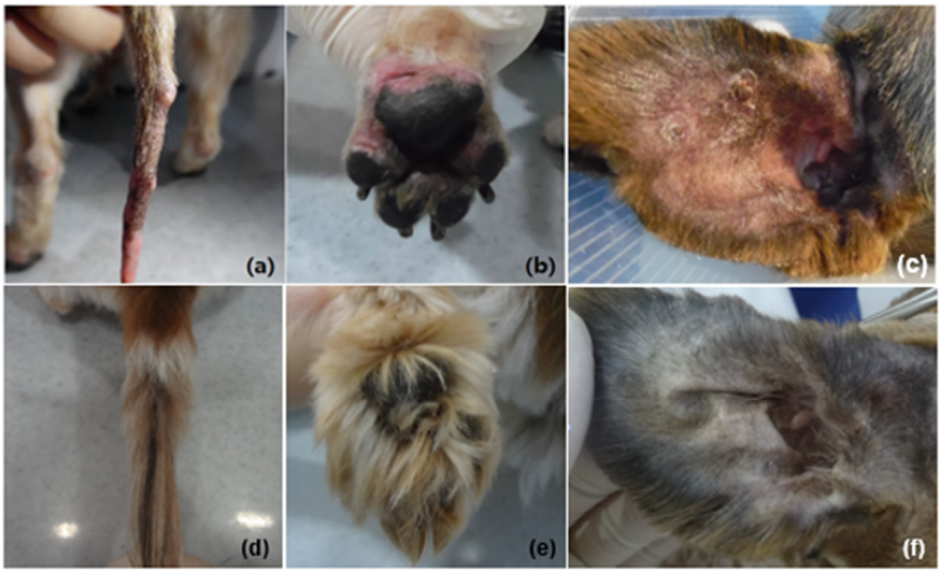

Fig. 1. Photographs of the physical examination at the first visit (A-C) and at 441 days after oral fluralaner administration (D-F). Erythema, alopecia, and erosion on the tail (A). Edema, erythema, and alopecia with fissures on the foot pad (B). Erythema, scales, and crusting on the ear pinna (C).

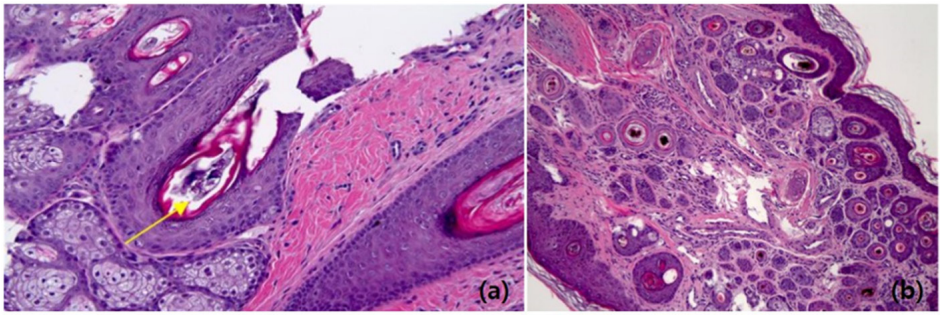

Fig. 2. Photomicrographs of the skin biopsy. Accumulated *Demodex canis* (Yellow arrow) in a hair follicle of the left metatarsophalangeal region (A). Inflammatory cell infiltration in the dermis of the left ear tip (B).

cells: 30,790, reference range: 5,050-16,760/μL; neutrophils: 19,159, reference range: 2,950-11,640/μL) and an increase in alkaline phosphatase (406 IU/L; reference range: 29-97 IU/L). Punch biopsy samples were collected from the skin of the ear pinnae and the right metatarsophalangeal region. Histopathology of the biopsy samples demonstrated *Demodex canis* in a hair follicle (Fig. 2A) and inflammatory cell infiltration in the dermis (Fig. 2B). Based on these findings, the dog was diagnosed with generalized demodicosis with concurrent otitis externa, deep pyoderma, and *Malassezia* dermatitis.

It was initially treated with amoxicillin-clavulanate (25 mg/kg, per oral [PO], twice daily; Lactamox Tab., Aprogen Pharmaceuticals, South Korea), itraconazole (5 mg/kg, PO, once daily; Sponazol Tab., Nelson Korea, Republic of Korea), and miticidal therapy with milbemycin oxime (1 mg/kg, PO, once daily; Milbemycin A, Elanco, USA). Milbemycin oxime was administered for 30 days until multiple two-consecutive deep skin scrapings tested negative, and then for an additional 60 days. Continual improvement was observed for 4 months but after that time the demodicosis recurred, and the miticidal therapy was changed to ivermectin (0.3-0.4 mg/kg, PO, once daily; Ivomecm, 1 mg/mL [1%] in 100 mL, Merial Saude Animal Ltd., Brazil) and benzoyl peroxide shampoo (SB Vetcare Benzoyl Shampoo, 12.5 mg/mL [2.5%] in 500 mL, 1-5 times per week, SUNGBO Pet Healthcare Ltd., South Korea). To investigate other possible underlying causes for the continuing *D. canis* infection, such as hypothyroidism and hyperadrenocorticism (HAC), a thyroid panel (Free T4: 0.317 μg/dL, reference range: 0.6-3.7 μg/dL; Total T4: 0.373 μg/dL, reference range: 1.0-4.0 μg/dL; thyroid stimulating hormone (TSH): 0.231 μg/dL, reference range: 0.1-0.6 μg/dL) and adrenocorticotropic hormone stimulation test (0 hours: 6 μg/dL, reference range: 0.5-4 μg/dL; 1 hour: 22 μg/dL, reference range: 8-20 μg/dL) and ultrasonography and radiography were performed. All results were equivocal. Cutaneous adverse food reactions were also ruled-out by an elimination diet trial. Canine atopic dermatitis (CAD) was considered unlikely because the current case failed to satisfy Favrot's criteria (6). The dog's clinical signs improved with treatment, and *Demodex* was not found on dermatological or histopathological examinations for 210 days after the first relapse. Thus, maintenance miticidal therapy was instituted with ivermectin (0.3 mg/kg, PO, once per 1 or 2 weeks). Even though a maintenance dose of ivermectin was sustained for an additional 309 days, a second relapse occurred. Accordingly, the ivermectin dosage was increased (0.3-0.4 mg/kg, PO, once daily), and amitraz baths were added to the medical therapy. In view of persistent relapses of the demodicosis, to definitively exclude hypothyroidism and HAC, a TSH stimulation test (0.5, 1.5, 1.9, and 1.7 μg/dL at 0, 4, 6, and 8 hours, respectively) and a low-dose dexamethasone suppression test (6.35, 1.31, and 1.26 μg/dL at 0, 4, and 8 hours, respectively) were performed. HAC was excluded as an underlying cause, and although the TSH stimulation test results were equivocal, hypothyroidism was considered unlikely due to the absence of associated clinical signs.

Due to the release of Bravecto® in South Korea at the time of this case, the isoxazoline fluralaner (25-26 mg/kg, PO, once per 12 weeks) was prescribed on the 44th day after the second relapse. This led to rapid resolution of the demodicosis (Fig. 1D-F) without adverse effects. This case could be considered as resolved, as *Demodex* infection and associated clinical signs were not identified for more than 1 year after oral fluralaner treatment. The dog lived in good health until it died approximately 2 years and 6 months after treatment.

Discussion

This is the first case in South Korea where desperate canine demodicosis, which is not responsive to conventional treatment, was treated with oral fluralaner.

Until recently, weekly amitraz bathing and oral macrocyclic lactones, especially ivermectin, have been referred to as the gold standard for canine generalized demodicosis (CGD) treatment (3,9). In a meta-analysis reviewing the efficacy of amitraz, a success rate of 74-80% among 693 CGD patients was reported (9). Macrocyclic lactones have a high affinity for glutamate-gated chloride channels and selectively bind to them to increase cell permeability for chloride ions, causing paralysis and death in parasites (1). In addition, these drugs also interact with γ-aminobutyric acid sites (1). In a meta-analysis, ivermectin showed an average success rate of 68% (9). A meta-analysis of the data from eight reports evaluating the efficacy and safety of milbemycin oxime described a higher success rate of 60% with higher doses (>1,500 μg/kg daily) (9). One study evaluating moxidectin exhibited a success rate of 72% (16). Doramectin treatment was evaluated in another study (7) and exhibited a success rate of 43%.

Isoxazolines are pesticides of a new chemical class, which appeared in the 2000s. They were introduced to the veterinary market in 2013 and were directed at the prevention and treatment of flea and tick infestations in dogs (3,8). Recently, fluralaner (and potentially afoxolaner and sarolaner) have been suggested to be very effective for the treatment of CGD (4,12). Cure rates of 63%, 85%, and 100% for adult-onset demodicosis in 46 dogs were observed after two, three, and four months of treatment, respectively (2). In an open study, the effect of a single dose of oral fluralaner was compared

with Advocate® treatment (applied every 4 weeks) in 16 dogs with generalized demodicosis (4). Dogs treated with a single oral dose of fluralaner (25 mg/kg) were parasitologically negative at days 54 and 84 after administration. In comparison, dogs treated with moxidectin-imidacloprid (Advocate®) had a higher "mean mite number" after treatment (98% on day 28, 96.5% on day 56). It has been demonstrated that treatment with fluralaner rarely produces adverse effects and can be safely administered to dogs 8 weeks of age of older and weighing at least 2 kg (17). When the present case was treated with medications commonly prescribed for CGD, the disease relapsed. However, after treatment with oral fluralaner, there were no adverse effects and no recurrence of the disease for over 12 months. Thus, fluralaner can be expected to increase the treatment success rate for dogs with desperate demodicosis, which requires life-long treatment.

Hypothyroidism, HAC, leishmaniosis, neoplasia, babesiosis, ehrlichiosis, and glucocorticoid treatment or chemotherapy leading to a compromised immune system have been reported as potential underlying causes of adult-onset demodicosis (10). The dog in the present case had not been administered glucocorticoid treatment or chemotherapy. In addition, its TSH levels were equivocal in both the thyroid panel and TSH stimulation tests. However, thyroid function was considered to be normal since the relevant associated clinical signs were not identified after fluralaner treatment despite the absence of levothyroxine therapy. HAC was definitively excluded as a potential underlying cause. Leishmaniosis is generally characterized by skin lesions such as exfoliative dermatitis, papules and small nodules, ulcerations, crusting, and partial alopecia (11), but was not identified after fluralaner treatment in this case and therefore excluded. The clinical signs of babesiosis are diverse, such as epistaxis, petechiae, fever, lethargy, anorexia, pale mucous membranes, weakness, bounding pulse, and jaundice (15), but there was no evidence of these clinical signs in our patient. Similarly, our case exhibited no evidence of ehrlichiosis, which can present with nonspecific clinical signs such as fever, lethargy, weakness, and anorexia (13). Neoplasia was considered unlikely because of no associated clinical signs and because no associated abnormalities were observed in blood tests or diagnostic imaging. CAD was excluded due to the initial-onset age of 8 years, and the fact that pruritus and CAD-related clinical signs such as erythema, papules, excoriations, alopecia, and lichenification (6) were not observed after fluralaner treatment.

This case has limitations. First, we reviewed a single case, thereby limiting the generalizability of our findings. Further case studies are required to confirm and verify our results. Second, there was a lack of definitive diagnostic exclusion for potential underlying causes such as leishmaniosis, neoplasia, babesiosis, and ehrlichiosis, but these were considered unlikely based on the response to therapy.

This report demonstrated successful therapy with oral fluralaner in a desperate case of adult-onset canine demodicosis. No adverse effects were observed secondary to fluralaner treatment.

Conclusions

This case report describes the complete resolution of refractory canine demodicosis using oral fluralaner. Fluralaner can be considered an effective therapy for non-responsive or desperate demodicosis in dogs and as an alternative to other treatments.

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Conflicts of Interest

The authors have no conflicting interests.

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