KJVR
Korean Journal of Veterinary Research

Case Report

pISSN 2466-1384 · eISSN 2466-1392
Korean J Vet Res 2021;61(1):e1
https://doi.org/10.14405/kjvr.2021.61.e1

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Conflict of Interest:
The authors declare no conflict of interest.

Received: June 23, 2020
Revised: November 04, 2020
Accepted: November 12, 2020

Successful management of systemic lupus erythematosus with levamisole in a Dachshund dog

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A 5-year-old neutered female Dachshund dog presented with a 3-month history of hyperthermia, skin lesions, and shifting lameness. Based on physical examination, blood tests, urinalysis, and radiographs, the dog was diagnosed with systemic lupus erythematosus. Clinical signs improved after administration of prednisolone and cyclosporine but relapsed after the prednisolone was reduced due to side effects. Oral levamisole was commenced and the other immunosuppressants were tapered over a period of 2 months and then stopped. Levamisole was retained as the sole therapy for an additional 2 months. Six months after discontinuation of all treatment, the patient remained in remission.

Keywords: autoimmune disease; levamisole; regulatory T-cells; systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with inflammation and induced by the deposition of circulating immune complexes in multiple tissues and organs [1]. Immune complexes are formed by a reaction that occurs when the immune system recognizes an antigen, such as nuclear, double-stranded or single–stranded DNA, Smith antigen, or phospholipid. Since the 13th century there have been descriptions of SLE in humans, dogs, cats, and mice [1]. Canine SLE most closely mimics the clinical and immunological features of human SLE [2], hence human SLE criteria, which include immunopathologic abnormalities, are used for diagnosing canine SLE [2]. Additionally, a study has suggested that the immunological imbalance seen in SLE may be associated with defective suppressor T cells [2].

Levamisole, the levo-isomer of tetramisole, is an anthelmintic drug with a variety of immunomodulatory effects [3]. Although the underlying mechanism has not been clearly elucidated, it is thought that levamisole is immunomodulatory by facilitating the differentiation, proliferation, and activation of T cells [3-5]. In humans, levamisole has also been used successfully for many years as both a sole and adjuvant therapy for a wide range of T cell-mediated diseases [3].

Here we present a case of SLE in which the patient was administered levamisole to allow for stable immunosuppressant tapering. The patient had a history of relapse during glucocorticoid tapering when previously treated with glucocorticoids and cyclosporine A.

A 5-year-old, 5.7 kg neutered female Dachshund dog was presented to the Konkuk University Veterinary Medical Teaching Hospital with a 3-month history of hyperthermia, skin lesions, and shifting lameness. At the time of presentation, the dog was being managed medically with non-steroidal anti–inflammatory drugs and analgesia without any clinical improvement.

Physical examination revealed pyrexia (40.4°C), heart rate of 140 beats per minute, respiratory rate of 24 breaths per minute, moist and pink mucous membranes, adequate hydration, and positive direct and indirect pupillary light reflexes. Thoracic auscultation was unremarkable. The dog had multiple swollen joints which were painful on palpation, and it became evident that an increased carpal and tarsal articulation volume was causing a plantigrade stance (Fig. 1A). Cutaneous manifestations included trunk rashes (Fig. 1B), erosion of the lateral region of the right metacarpus (Fig. 1C), depigmentation of the ventral region of the thoracic trunk (Fig. 1D), and painful ulcerated wounds on the dog's metatarsal region bilaterally (Fig. 1E). Radiography of the forelimbs and hindlimbs revealed no erosive or proliferative lesions. Stifle joint radiography revealed infrapatellar fat pad signs bilaterally, consistent with joint effusions (Fig. 2A and C).

A complete blood count revealed mild leukocytosis (19,650/μL; reference interval, 5,050-16,760/μL) and mild thrombocytosis (520 × 10^3/μL; reference interval, 148-484 × 10^3/μL). A serum chemistry profile revealed hyperglobulinemia (5.9 g/dL; reference interval, 2.5-4.5 g/dL), hyperproteinemia (9.2 g/dL; reference interval, 5.2-8.2 g/dL), and markedly elevated creatine kinase (1,177 U/L; reference interval, 10-20 U/L), lactate dehydrogenase (1,557 U/L; reference interval, 40-400 U/L), and C-reactive protein (128.89 mg/L; reference interval, 0–10 mg/L) concentrations. D-dimer levels were mildly elevated (0.8 mg/dL; reference interval, 0-0.3 mg/dL). A rheumatoid factor test (ANTECH Diagnostics, USA) was negative. An anti-nuclear antibody (ANA) test via indirect fluorescence antibody testing (ANTECH Diagnostics) was positive with a serum dilution titer of 256:1 (normal range < 32:1). Serum protein electrophoresis revealed a broad-based polyclonal band (IDEXX Korea, Korea). Urinalysis revealed proteinuria (UPC = 1.05; reference interval, 0-0.2) with no growth on microbial culture. Arthrocentesis and skin biopsy were recommended but not performed due to owner refusal. However, the cutaneous manifestations were revealed as sterile erythematous lesions over the whole body by skin scraping test and negative culture result.

The patient had the positive result for ANA test and 2 major signs compatible with SLE (skin lesions and polymyositis); therefore, this patient was diagnosed with SLE [6]. In addition, hyperthermia of unknown origin, polyarthritis and proteinuria that could be suspected of symptoms of SLE were shown concurrently. Treatment was initiated with a combination of an immunosuppressive dose of prednisolone (1 mg/kg, PO q 12 h; Solondo Tab; Yuhan Co., Ltd., Korea) and cyclosporine (13 mg/kg, PO q 24 h; Sandimmune Neoral Soft Cap.; Novartis Co., Ltd., Switzerland). Additionally, clopidogrel (4 mg/kg, PO q 24 h; clopidogrel hydrogen sulphate; Jin Yang Pharm Co., Ltd., Korea) and famotidine (0.5 mg/kg, PO q 12 h; Famotidine Nelson, Nelson Pharm Co., Ltd., Korea) were administered. After 1 week of treatment, the clinical signs of SLE (hyperthermia, skin lesions, and shifting lameness) were disappeared with the improvement of nonerosive arthritis on radiography (Fig. 2B and D). And serum abnormalities including hyperglobulinemia resolved but hyperglycemia (149 mg/dL; reference interval, 74–143 mg/dL) and elevated hepatic enzymes (ALT = 105 U/L; reference interval, 10-100 U/L, ALP = 694 U/L; reference interval, 23-121 U/L, GGT = 10 U/L; reference interval, 0-7 U/L) were detected, most likely as a side effect of prednisolone therapy. The hepatic abnormally was sustained despite administering a hepatic protectant such as ursodeoxycholic acid (7.5 mg/kg, PO q 12 h; Urusa Tab; Daewoong Pharmaceutical Co., Ltd., Korea), Samylin (1 pack/dog, PO q 24 h; Vet–plus Co., Ltd., China) and Lefotil (1 tablet/dog, PO q 24 h; Lefotil Tab; CMG Pharm Co., Ltd., Korea). Other side effects (panting, polyphagia and polyuria/polydipsia) were also consistently found, so the decision was made to reduce the dose of prednisolone after

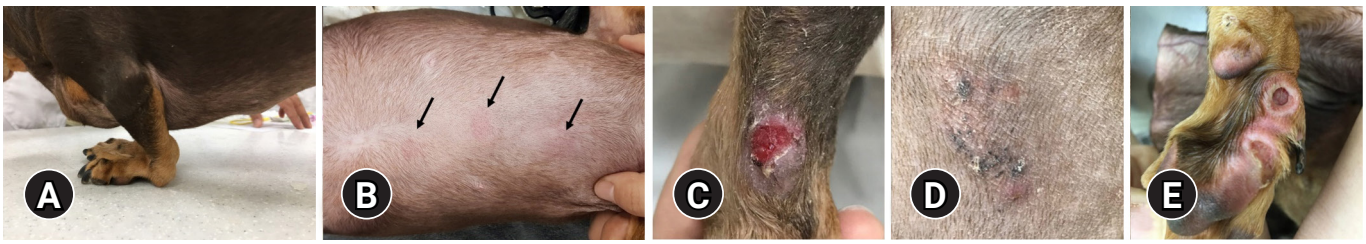

Fig. 1. (A) Forelimb with plantigrade stance. Cutaneous lesions including erythema (B, arrows), erosions (C), depigmentation (D), ulcerations (E), and crusting and/or scaling are proposed criteria for the diagnosis of systemic lupus erythematosus.

https://doi.org/10.14405/kjvr.2021.61.e1

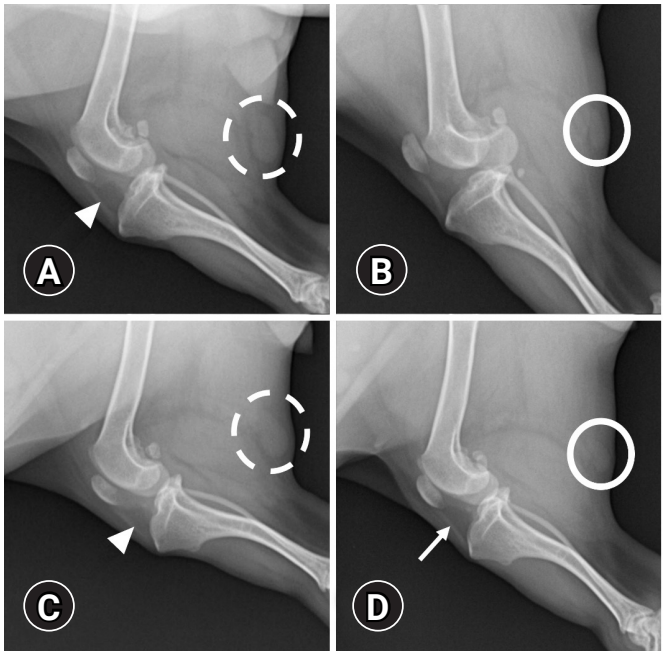

Fig. 2. Lateral radiograph of the left (A, B) and right (C, D) stifle joints. (A, C) Before treatment, the radiolucent area behind patella ligament has been reduced without erosive change, showing increased joint effusion (arrowhead). Note the lymphadenopathy in the bilateral popliteal lymph nodes (dashed circle). (B, D) After treatment, the radiolucent area behind patella ligament has been normalized (arrow). And the lymphadenopathy have resolved (circle).

a therapeutic blood concentration of cyclosporine was achieved (therapeutic range 100-500 ng/ mL). Two months later, prednisolone began gradually tapered to 0.75 mg/kg once a day (blood concentration of cyclosporine 377 ng/mL). Five days after reducing the dose of prednisolone, anorexia and hyperthermia (39.9°C) occurred, and the serum C-reactive protein concentration (36.87 mg/L; reference interval, 0-10 mg/L) was elevated. At this time, prednisolone was increased to 1 mg/kg once daily, and within 3 days the dog's clinical signs had resolved. At this time, however, the owner asked to stop prednisolone and cyclosporine because of side effects and financial cause, respectively. Therefore, we changed those medications to levamisole to reduce the dose of prednisolone and cost. Before attempting to reduce the dose of prednisolone, oral levamisole (3.5 mg/kg, PO; Levamic Powder; DaeSung Microbiological Labs Co., Ltd., Korea) [1] was administered every other day. Two weeks after commencing levamisole treatment, cyclosporine was discontinued; and prednisolone was tapered progressively and eventually stopped after 2 months. Finally, levamisole was administered as a sole therapy for an additional 2 months. During that time, the dog did not experience any adverse effects. Six months after discontinuing levamisole therapy, the patient remained in complete remission.

In one study that included 75 cases of canine SLE show that 68% of male and 32% of female were diagnosed [1]. The mean age of the diagnosed animals was 5 years with a range of 6 months to 13 years [1]. Breeds that are predisposed include the Beagle, Collie, German shepherd dog, Shetland sheepdog, and Poodle. Among them, the prevalence of German shepherd was the highest (46.7%) [1]. Miniature and giant breed were rarely affected [1].

SLE is an autoimmune disease that causes organ dysfunction via multiple abnormal immune processes [1]. Most autoimmune diseases, such as SLE, require lifelong treatment with immunosuppressants [7], which results in unavoidable serious side effects, the most common of these being an increased vulnerability to life-threatening infections. A further issue with prolonged use of immunosuppressants is the associated economic cost. To minimize the side effects and costs associated with prolonged use, immunosuppressants should be administered at the minimum effective dose. However, to establish the optimal dose the disease must recur, and the patient's condition may worsen. Discontinuing use of immunosuppressants is then warranted to achieve a more successful outcome.

Traditionally, SLE was thought to be a disease progressed by B cells. Recent convincing evidence has demonstrated that T cells are decisive players in SLE pathogenesis because they increase the production of autoimmune antibodies [8]. This is accomplished by facilitating and stimulating B cell proliferation, differentiation, and maturation, as well as supporting B cell–expressed autoimmune antibody class-switching [9]. Regulatory T (T_{reg}) cells are a subset of CD4+ cells that suppress and inhibit autoreactive lymphocytes. T_{reg} cells increase the spectrum of B cells and helper T cells and may thus underlie SLE pathogenesis and related organ damage [10,11]. These cells may serve as a potential principal therapeutic target for T_{reg} cell action *in vivo* with levamisole [12].

Levamisole, a known treatment for parasite infections, was first found to have immunomodulatory functions in the 1970s [3]. The immune suppressing activity of T_{reg} cells in the treatment of SLE is also restored by levamisole [5]. To modulate T_{reg} cell activity, levamisole was used during immunosuppressant tapering in the present case. Following a 4-month course of levamisole, the patient's immunologic and clinical features underwent a marked improvement. This facilitated a rapid reduction in immunosuppressant use and ultimately complete remission of clinical signs. Theoretical considerations for the use of levamisole dovetailed with the observed response to this drug.

Levamisole, the levo-isomer of tetramisole, is an anthelmint-

ic drug used in various animals with immunomodulatory effects [3]. In humans, levamisole has been used to treat many diseases in which a homeostatic immune imbalance is suspected, such as rheumatoid arthritis and SLE [5]. In cattle and sheep, levamisole has relatively good activity against abomasal nematodes, small intestinal nematodes, and lung worm [13]. In horses with equine protozoal myeloencephalitis, levamisole may be effective for the management of clinical signs secondary to inflammation after therapy with antiprotozoal therapy [14]. Furthermore, levamisole has been used in dogs as a microfilaricide to treat *Dirofilaria immitis* infection in the past but is rarely used today [15]. Most patients improve clinically with levamisole therapy and show apparent reductions in disease severity. For instance, in one study of 27 dogs, 55.6% of SLE patients treated with levamisole exhibited long–term remission [1]. However, the present case is the first case report of long-term management of canine SLE with levamisole in the South Korea. Levamisole can also restore normal cell-mediated immune response functions, including T cell proliferation and suppressor activity [5].

The present case has 3 possible limitations as follows. First, previous SLE treatment period might be insufficient. Second, unknown etiology of inflammation was responded to levamisole. Third, because of the use of previous medication, it is not certain that it was treated with the sole effect of levamisole, although finally levamisole was administered solely after discontinuation of previous medications. Nevertheless, since SLE is a difficult disease for complete remission like as in the present case, the levamisole could be considered as an alternative treatment option for SLE, especially in canine patients with financial concern or steroid induced side effects.

Levamisole was originally designed for anthelmintic drug, so clinically used examples of immunomodulatory drugs were sporadically present, but there was no large-scale clinical trial study. For such reasons, it seems that general clinicians have not been able to apply it. However, there were no serious side effects in the results of sporadic studies, and this study showed good results [1,4]. Further large-scale clinical studies are expected to proceed in the future.

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