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<Case Report>

Combination therapy of cyclosporine and prednisolone in a dog with systemic lupus erythematosus

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Abstract : An 11-year-old, spayed female poodle presented with fever and shifting lameness. Physical examination revealed hyperthermia (40.6ºC), and proteinuria was detected upon urinalysis. Increased neutrophils (83%) and decreased viscosity were revealed upon synovial fluid analysis. Serum antinuclear antibody was positive at 1 : 80. Based on these findings, the dog was diagnosed with systemic lupus erythematosus. Immunosuppressive therapy was initiated with prednisolone and cyclosporine, and the condition was markedly improved after the treatments. This case report describes the clinical and laboratory findings, imaging characteristics and successful outcomes after prednisolone plus cyclosporine therapy in a canine systemic lupus erythematosus case.

Keywords : antinuclear antibody, cyclosporine, glomerulonephritis, polyarthritis, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder in which immunity is directed against various tissues or tissue components [1]. The most common clinical features include shifting lameness from polyarthritis, ulceration of extremities caused by vasculitis, icteric and pale mucous membranes resulting from immune-mediated hemolysis, and peripheral edema or pleural effusion due to hypoalbuminemia secondary to glomerulonephritis. Additionally, dermatologic lesions may be present, including crusting, alopecia, erythema, ulceration, and hyperkeratosis [8].

Major signs of SLE are skin lesions, non-erosive polyarthritis, hemolytic anemia, glomerulonephritis, polymyositis, leukopenia, and thrombocytopenia [1]. Minor signs are fever, central nervous system symptoms, oral ulcerations, lymphadenopathy, pericarditis, and pleuritis [2]. The antinuclear antibody (ANA) test and lupus erythematosus (LE) cell preparations are used clinically for the diagnosis of SLE, but until recently, the ANA test is considered the most sensitive [3, 14]. Immunosuppression is vital to treating this abnormal immune response, and patients can be treated with high dose of prednisolone (1–2 mg/kg, per oral [PO], q12h) and cytotoxic drugs, such as azathioprine, cyclosporine, and cyclophosphamide [4, 5]. This case report describes successful treatment using prednisolone and cyclosporine in a dog with SLE.

An 11-year-old, 6.1 kg, spayed female poodle dog presented with fever, lethargy, anorexia, and shifting lameness. The dog had a history of reluctance to stand up and walk, which was intermittent and partially responsive to non-steroidal anti-inflammatory drugs. Physical examination was unremarkable except for hyperthermia (40.6ºC). A complete blood count (CBC) revealed leukocytosis ($27.1 \times 10^3/\mu L$; reference interval, $5.05–16.7 \times 10^3/\mu L$) with degenerative neutrophilia (26,558/μL; reference interval, 3,000–11,000/μL). A serum biochemical profile revealed elevated creatine kinase (270 U/L; reference interval, 100–200 U/L) and C-reactive protein (> 108 μmol/L; reference interval, < 20 μmol/L) (Table 1). A polymerase chain reaction (PCR) testing with a tick-borne disease panel including *Babesia* spp., *Haemobartonella* spp., *Anaplasma* spp., *Ehrlichia* spp. and *Borrelia burgdoferi*, was performed to rule out tick-borne diseases, and the result was negative. Radiographically, there were no evident abnormalities on all four limbs (Fig. 1). Under general anesthesia, synovial fluid was obtained via fine needle aspiration from multiple joints (both stifles, carpi, and elbows). The fluid was transparent and had decreased viscosity. Aerobic and anaerobic bacterial cultures of the synovial fluid were negative, and the fluid cell count showed neutrophil predominance (83%). The results characterized an inflammatory arthropathy (Fig. 2), and the ANA test was positive (1/80). Moderate proteinuria (100 mg/dL) without urinary tract infection was detected on urine dipstick and sediment examination. Urinary specific gravity was 1.025 (Table 2). Both aerobic and anaerobic bacterial cultures from the urine sample were performed, and the results were negative. Therefore, the proteinuria was caused by glomerular damage, not lower urinary tract diseases.

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Table 1. A complete blood count and serum biochemical results in a dog with systemic lupus erythematosus

Parameters	0 D	15 D	30 D	60 D	Reference interval
WBC (10^3/μL)	27.1	18.34	21.02	20.7	6–17
RBC (10^6/μL)	5.9	6.32	6.1	5.8	5.5–8.5
PCV (%)	40	41	40.6	43.3	37–55
Hb (g/dL)	13.2	14.3	14.1	12.9	12–18
PLT (10^3/μL)	190	399	410	360	148–484
ALT (U/L)	259	487	259	243	17–78
AST (U/L)	110	67	58	36	1–37
ALP (U/L)	921	2645	1961	1351	47–254
BUN (mg/dL)	10	11	9	ND	5–30
Creatinine (mg/dL)	0.8	0.8	0.6	ND	0.5–1.5
Total protein (g/dL)	7.5	7.4	6.9	ND	5.2–8.2
Albumin (g/dL)	3.5	3.4	3.9	ND	2.3–4.0
Creatine kinase (U/L)	270	185	152	ND	100–200
C-reactive protein (μmol/L)	108	24	27	ND	< 20

D, days after first examination; WBC, white blood cells; RBC, red blood cells; PCV, packed cell volume; Hb, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; ND, not determined.

Table 2. Urinalysis in a dog with systemic lupus erythematosus

Parameters	0 D	15 D	30 D	60 D	90 D	Reference interval
USG	1.025	1.028	1.018	1.019	1.023	1.015–1.030
pH	8	7	7	7	7	5.5–7.5
Leukocytes	–	–	–	–	–	–
Glucose	–	–	–	–	–	–
Erythrocytes	1+*	–	–	–	–	–
Protein	2+†	1+‡	1+	Trace	–	–
UPCR	ND	3.42	1.49	ND	ND	< 0.5

USG, urine specific gravity; UPCR, urine protein creatinine ratio. *5–10 cells/μL. †100 mg/dL. ‡30 mg/dL.

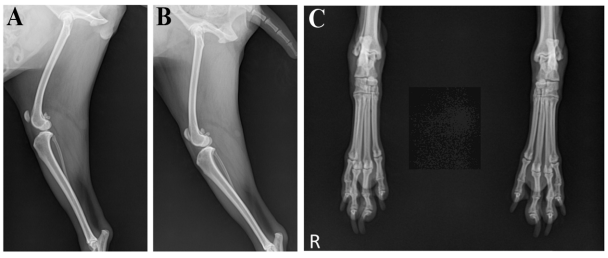

Fig. 1. Radiographs of four limbs in a dog with systemic lupus erythematosus. No evidence of bone density loss was found in the limbs. (A) Left stifle joint. (B) Right stifle joint. (C) Both carpal joints.

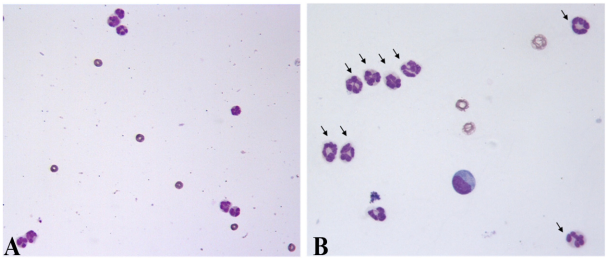

Fig. 2. Synovial fluid from the left stifle of a dog with systemic lupus erythematosus. Nucleated cell counts were increased (A), and non-degenerative neutrophils (B, arrows) showed predominance (83%). Diff-Quik stain. 400× (A) and 630× (B).

This dog satisfied the criteria for a definite SLE condition, with two major signs (polyarthritis and glomerulonephritis) and a positive ANA assay; therefore, a diagnosis of definite SLE was made. Prednisolone (1 mg/kg, PO, q12h; Yuhan, Korea) and cyclosporine (8 mg/kg, PO, q24h; Novatis, Switzerland) were initiated, and the dog's clinical signs including lameness, fever, and anorexia were improved over the next two days. However, markedly increased liver enzymes were detected on the 15th day after treatment began. These changes suggested secondary hepatocellular damage due to prednisolone administration. To prevent further hepatocellular damage, a liver protectant (Zentonil 0.1 T/kg divided; Vétoquinol, France) was additionally prescribed. As the dosage of prednisolone administration was tapered every two weeks, the liver enzymes also decreased.

The patient was monitored every 15 days, including physical examination, CBC, serum biochemical profile, urinalysis, and urine protein creatinine ratio (UPCR). The clinical signs improved rapidly with this treatment, whereas the C-reactive protein levels and UPCR gradually improved over a period of months (Tables 1 and 2). Plasma cyclosporine concentration reached the therapeutic level (310 ng/mL; therapeutic range, 100–500 ng/mL) two weeks after treatment. The initial dosage of prednisolone was 1 mg/kg, PO, q12h for 15 days, which was then reduced by half every 15 days. Finally, the prednisolone medication was discontinued 60 days after the first treatment. Plasma cyclosporine concentration was monitored on days 30 and 60, and reached therapeutic levels each time. The dosage of cyclosporine (8 mg/kg, PO, q24h) was maintained depending on the dog's response and her plasma cyclosporine concentration. No recurrence of the condition was observed during three months of follow-up.

SLE is characterized by a broad spectrum of clinical symptoms and a multitude of laboratory abnormalities [3, 5]. The diagnosis of SLE can be described as 'definite SLE' or 'probable SLE', depending on specific criteria [2]. A diagnosis of definite SLE can be made either if a positive ANA titer or LE cell preparation is identified in conjunction with two major signs, or if two minor signs and one major sign are identified along with a positive ANA assay or LE cell preparation [1, 8, 14]. A probable SLE diagnosis can be made either if a positive ANA titer or LE test is identified in conjunction with one major sign, or if two major signs and a negative ANA titer or LE test are identified [5]. In our country, several patients were diagnosed with SLE. There were two cases of definite SLE [9, 11] and one case of probable SLE [11]. One patient with definite SLE presented with thrombocytopenia, polyarthritis, and a positive LE cell preparation [11]. The other definite SLE patient showed skin lesions, polyarthritis, proteinuria, a positive ANA test, and a positive LE cell preparation [9].

For the treatment of SLE, prednisolone is preferred for immune suppression, while cyclophosphamide, cyclosporine, and levamisole are considered as alternatives [5, 10]. Cyclosporine is primarily an immunosuppressive drug that selectively and reversibly inhibits only the T cell-mediated response [6]. In the human literature, the effects and safety of cyclosporine in SLE have been reported [13]. In the veterinary literature, cyclosporine has been shown to effectively control proteinuria that is refractory to steroids [3, 12]. Cyclosporine can also help in treating proteinuria in nephropathy [7].

The two above-mentioned definite SLE patients were treated with prednisolone and azathioprine [11] or prednisolone monotherapy [9]. In the first patient, the clinical signs recurred with prednisolone (5 mg/dog, PO, q12h) alone and appeared iatrogenic hyperadrenocorticism due to administration of prednisolone. Azathioprine (11.4 mg/dog, PO, q12h) was added, but the clinical signs were not completely controlled [11]. The skin lesions and clinical symptoms of arthritis in the second patient recovered with prednisolone (2 mg/kg, PO, q12h), but proteinuria was not controlled [9].

The patient in the current case received treatment with cyclosporine and prednisolone for definite SLE. Cyclosporine was considered first in this case since the main side effect of azathioprine is myelosuppression. Because combination therapy of cyclosporine and prednisolone was applied in the case, the dose of prednisolone used was much lower than was reported in previous case studies. The clinical signs improved, and recurrence of the condition was not observed.

This case showed a diagnosis of definite SLE in a dog that satisfied the criteria of two major signs with a positive ANA test result. Unlike in previous treatment results, improvement of proteinuria was marked with the administration of prednisolone with cyclosporine in this dog. Thus, the use of prednisolone and cyclosporine is worthwhile to try in SLE patients with proteinuria.

In conclusion, definite SLE with proteinuria was well-controlled by using prednisolone and cyclosporine in this dog.

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