Case Report

Use of PCSO-524® and Cyclosporin for Treatment of Immune-Mediated Polyarthritis in Dogs

Irin Kwananocha, DVM
Small Animal Hospital, Chulalongkorn University

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Case Study Contest 2020

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Abstract

An 8 years old Chihuahua dog was admitted to the Small Animal Hospital at Chulalongkorn University due to signs of depression, lethargy, lameness and joint effusion. Hematological examination and test of synovial fluid indicated Immune-Mediated Polyarthritis (IMPA).

Prednisolone, Gabapentin and Amoxillin-clavulanic acid were prescribed for the treatment.

Abnormally increase of ALT, ALK and AST enzyme was observed 1 week later, therefore, the treatment was changed to Cyclosporin, Gabapetin, and PCSO-524®.

The clinical signs continued to improve after the adjustment of prescription and Cyclosporin and Gabapetin were terminated after 3 and 4 months, respectively.

A follow-up examination at 4 months later showed no signs of lameness and joint effusion and no adverse effects caused by the long-term use of PCSO-524®.

The success of **IMPA treatment** is a result of rapid diagnosis and appropriate treatment protocol. Follow-up for treatment evaluation is necessary during the treatment course in order to reduce the impact on health and minimize the medication dosage without risk of causing adverse effects or recurrence of the disease.

Keywords: Cyclosporin, dog, Immune Mediated Polyarthritis, PCSO-524

Introduction

Immune-Mediated Polyarthritis (IMPA) is a common disease in dogs. Clinical signs are various and include walking reluctance, abnormal walk gesture, lameness, joint effusion, and joint pain that usually occurs at multiple sites. Stilted gait is common and sometimes fever, lethargy, loss of appetite, vomiting, and diarrhea can be found. Incidence of IMPA occurs in dogs regardless of their breed, age, gender and size.

IMPA is caused by accumulation of immune complex in the articular membrane which results in inflammation and increased migration of neutrophils into the joints[1]. IMPA is categorized as primary and secondary IMPA.

Primary IMPA is an idiopathic disease and secondary IMPA is caused by external stimulant, for example, immunological response to vaccine or medication, blood parasitic infestation, diseases of gastrointestinal tract, and tumors.

Preliminary diagnosis of IMPA is based on case history, physical examination, hematological test, and examination of synovial fluid. Dogs with IMPA usually have synovial fluid that contains protein higher than 2.5 g/dl, white blood cells greater than 3,000 cells/µl of which more than 10% are neutrophils, and shows negative result on bacterial culture (2).

Recommendation for treatment of IMPA includes **steroid use for immune suppressant**, for example, prednisolone, or immunosuppressant drugs such as cyclosporin and azathioprine. Complications that are side effects of the medication must be monitored closely. When the clinical signs are improved, the medication dosage should be tapering down. For treatment of secondary IMPA, **elimination of the stimulating factors** is crucial for treatment success. Medication for pain relief is essential in dogs that show signs of painful joints. Pain control drugs that can be used with immunosuppressant steroid are, for example, opioids, gabapentin and amantadine [2].

PCSO-524® is extracted from New Zealand Green Lipped Mussel that is an enriched source of **polyunsaturated omega-3 fatty acids (n-3 PUFAs)** which consisting of eicosatetranoic acid (ETA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The fatty acids have anti-inflammatory effects as a result of ability to **block lipoxygenase (LOX) and cyclooxygenase (COX) pathway** by decreasing leukotriene and prostaglandin production [3, 4].

Effect of n-3 PUFAs is to reduce concentration of omega-6 fatty acid, as a result, the inflammatory action is prohibited. The effect is caused by reduction of eicosanoids, such as Prostaglandin E2, leukotriene B4, leukotriene C4 and thromboxane A2, which are derived from omega-6 and act as proinflammatory mediator in arachidonic pathway. Eicosanoids that are derived from omega-3 fatty acid has **anti-inflammatory effect** since they can replace eicosanoids derived from omega-6 and thus reduces the mechanism of inflammation. Supplementation of omega-3 therefore has anti-inflammatory action [5].

The objectives of this study were to determine the effect of PCSO-524® when used with immunosuppressant drug for treatment of joint pain and arthritis caused by IMPA and the potential for PCSO-524® to shorten the duration of pain relief and immunosuppressant drug use.

Case History

An 8 years old Chihuahua dog with body weight 4.2 kilograms was referred to the Surgery unit of Small Animal Hospital at Chulalongkorn University for treatment of patella luxation.

The dog showed signs of depression, lethargy, fever, anorexia, and intermittent lameness of the left leg for 2 weeks. The lameness was gradually deteriorated to the point that the dog was reluctant to walk. The dog was previously treated with non-steroidal anti-inflammatory drug (NSAIDs) but the signs were not improved. Abnormality of gastrointestinal tract was not detected. There was no history of vaccine or medication prior to the incidence.

Physical examination

The dog was depressed but responded to environmental stimuli.
The examination found normal color of mucous membrane and 103.6 oF body temperature.
All 4 legs were able to bear weight, but the walking was unsteadily with **lameness score 3/5** (Table 1).

Plantigrade stance was detected from both forelimbs. Palpation identified joint effusion at carpal, tarsal and stifle joint on both sides. **Medial patella luxation** (MPL) scored 2/4 with positive drawer sign was detected on both sides and the pain score was 2/4 (Table 2).

Cervical and lumbar stiff with 2/4 pain score was found and there was no neurological disorder. Radiographic images showed MPL on both sides (Figure 1) but did not find any disorder of cervical and thoracic vertebrae (Figure 2).

Table 1. Lameness score 0-5 (6)

Lameness score	Signs
0	Normal walk
1	Slightly lame
2	Apparent lameness but weight bearing is maintained
3	Severe lameness but weight bearing is maintained
4	Occasionally avoid weight bearing on affected leg
5	Always avoid weight bearing on affected leg

Table 2. Pain score 0-4 (6)

Pain score	Signs
0	No sign of pain during palpation
1	Slight pain during palpation
2	Moderate pain during palpation
3	Severe pain during palpation
4	Unwilling to allow palpation

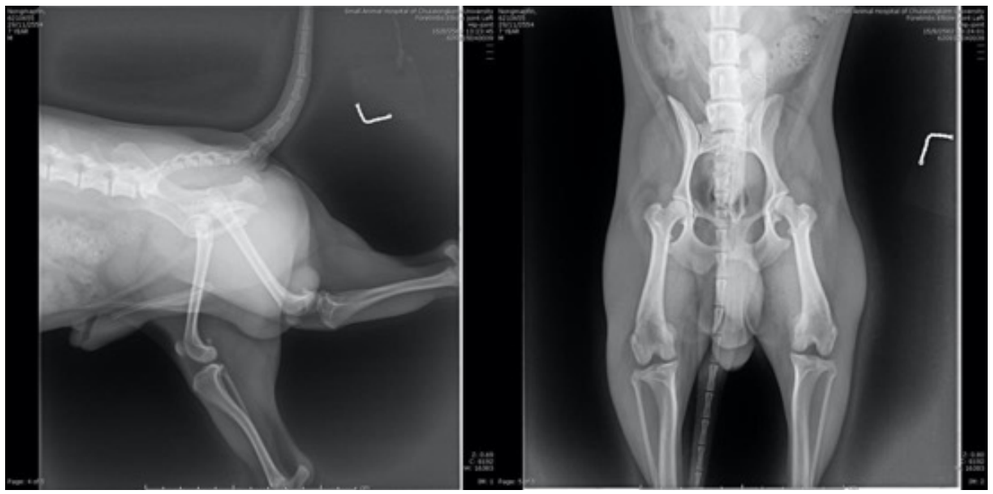

Figure 1. Radiographic images from ventrodorsal view
showing patella luxation towards medial trochlear groove (medial patella luxation) on both sides

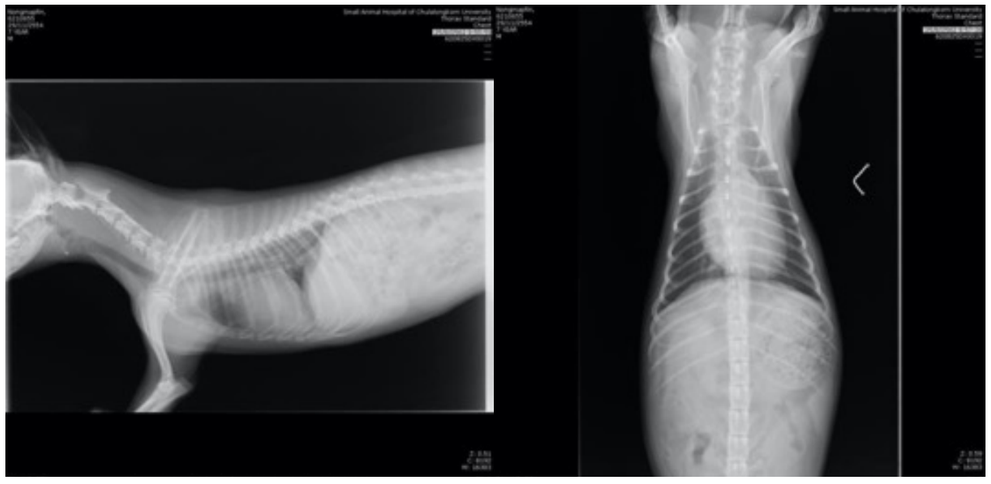

Figure 2. Radiographic images from lateral ventrodorsal view found no disorder of cervical and thoracic vertebrae

Diagnosis and Results

Hematological test found high number of white blood cells (35,120 cells/µl) and high level of alkaline phosphatase (ALK; 440 IU/Ls) (Table 3)
Examination of synovial fluid detected high number of neutrophils, lymphocytes, and macrophages, 6.2 g/dl protein, and 1.033 specific gravity (Table 3).

Bacterial culture and **minimal inhibitory concentration test (MIC)** did not find bacterial growth which indicated that the fluid was non-septic exudate. From history, physical examination, hematological test, examination of synovial fluid, and radiographic images, the dog was diagnosed with **primary non-erosive immune mediated polyarthritis.**

Table 3. Hematological test results during the treatment course

Date dd/mm/yy	**23/08/19**	**06/09/19**	**20/09/19**	**04/10/19**	**18/10/19**	**01/11/19**	**29/11/19**
RBC (106/µL)	5.43	6.25	6.71	6.86	7.41	7.73	7.67
Hb (g/dl)	12.9	14.9	15.4	15.4	16.9	18.5	17.8
Hct (%)	34.5	41	41.9	44.6	49.9	52.7	49.9
MCV		66.1	62.2	65.1	67.3	68.2	65
MCH		24	22.8	22.5	22.9	23.9	23.2
MCHC		36.2	36.7	34.5	33.9	35.1	35.8
Platelet (103/µL)	260	478	802	712	675	734	484
WBC (103/µL)	35.12 *	18.36 *	12.15	11.79	11.52	10.02	9.16
AST (Units)		101 *					
ALT (Units)	42	519 *	219 *	71	53	31	33
ALK (IU/Ls)	440 *	2538 *	1021 *	269 *	118 *	86	84
BUN (mg%)	13	30.2	23.9	23.3	23.6	19.4	18.6
Creatinine (mg%)	0.8	0.6	0.4	0.5	0.5	0.6	0.6
Total protein (g%)	6.6			7.2	6.8	7.9	6.8
Albumin (g%)				4.1	3.8	4	3.6
SNAP 4Dx	Negative						
Fluid analysis 29/08/19							
TNCC			Undifferentiated cells/µl				
Protein			6.2 g/dl				
Specific Gravity			1.033				
Microscopic examination			Numerous neutrophils, lymphocytes, and macrophages				
Fluid analysis			Exudate				

Note: * Indicates abnormal values

Treatment and Follow up

Prescription during the first week of treatment was

Prednisolone	0.6 mg/kg bid pc
gabapentin	10 mg/kg sid pc
samylin	1 tablet sid ac
amoxicillin-clavulanic acid	20 mg/kg sid ac

Later it was found that enzyme levels were higher than normal ranges; (Table 3) 101 units of aspartate aminotransferase (AST), 519 units of aspartate aminotransferase (ALT), and 2,538 IU/Ls of Alkaline Phosphatase (ALK), therefore **prednisolone was terminated**.

The new prescription then included

cyclosporine	6 mg/kg bid ac
gabapentin	10 mg/kg bid pc
same 90 mg	1 tablet sid ac
PCSO-524®	1 capsule bid pc for 1 month

The clinical signs were improved as decrease of lameness score, pain score and joint effusion was observed.

The following prescription maintained the level of gabapentin but cyclosporine was 25-50% reduced every 2-4 weeks and PCSO-524® was reduced to 1 capsule per day.

Cyclosporin and gabapentin was terminated in the third and fourth month of the treatment, respectively. **Only PCSO-524® was continued for the following 4 months** and no recurrence of lameness or joint effusion was observed.

Table 4. Medication and dosage during the treatment and follow up

Date dd/mm/yy	Medication and dosage	Clinical signs
29/08/19 (VDO 1, 2)	- Prednisolone 0.6 mg/kg bid - Gabapentin 10 mg/kg bid - Amoxicillin-clavulanic acid 20 mg/kg bid - Samylin 1 capsule sid	- depress, anorexia, fever 103.6 °F - lameness score 3/5, pain score 2/4 - joint effusion at both carpal, hock and stifle joint
06/09/19	- Cyclosporin 6 mg/kg bid * - PCSO-524® 1 capsule bid * - Gabapentin 10 mg/kg bid - Same (90) 1 tablet sid *	- responsive, loss of appetite, no fever - lameness score 3/5, pain score 1/4 - joint effusion at both carpal, hock and stifle joint
20/09/19 (VDO 3)	- Cyclosporin 6 mg/kg bid - PCSO-524® 1 capsule bid - Gabapentin 10 mg/kg bid - Same (90 mg) 1 tablet sid	- alert, good appetite - lameness score 2/5, pain score 0/4 - joint effusion at both carpal, hock and stifle joint
04/10/19	- Cyclosporin 4 mg/kg bid * - PCSO-524® 1 capsule sid * - Gabapentin 10 mg/kg bid - Same (90) 1 tablet sid	- alert, good appetite - lameness score 2/5, pain score 0/4 - joint effusion at both carpal and stifle joint
18/10/19	- Cyclosporin 6 mg/kg sid * - PCSO-524® 1 capsule sid - Gabapentin 10 mg/kg bid - Same (90) 1 tablet sid - Metronidazole 15 mg/kg bid for 7 days *	- alert, good appetite, diarrhea - lameness score 2/5, pain score 0/4 - joint effusion at both carpal and stifle joint
01/11/19 (VDO 4)	- Cyclosporin 6 mg/kg q 48 hr * - PCSO-524® 1 capsule sid - Gabapentin 10 mg/kg bid	- alert, good appetite, no diarrhea - lameness score 1/5, pain score 0/4 - joint effusion at both carpal and stifle joint
29/11/19	- Cyclosporin 2.4 mg/kg q 48 hr * - PCSO-524® 1 capsule sid - Gabapentin 10 mg/kg bid	- alert, good appetite - lameness score 1/5, pain score 0/4 - joint effusion at both stifle joint
13/12/19	- Cyclosporin 2.4 mg/kg q48hr * - PCSO-524® 1 capsule sid - Gabapentin 10 mg/kg sid *	- alert, good appetite - lameness score 0/5, pain score 0/4 - joint effusion at left stifle joint
27/12/19 (VDO 5)	- PCSO-524® 1 capsule sid - Gabapentin 10 mg/kg sid	- alert, good appetite - lameness score 0/5, pain score 0/4 - minimal joint effusion at left stifle joint
29/1/20 (VDO 6)	- PCSO-524® 1 capsule sid	- alert, good appetite - lameness score 0/5, pain score 0/4 - minimal effusion at left stifle joint
26/2/20 (VDO 7)	- PCSO-524® 1 capsule sid	- alert, good appetite - lameness score 0/5, pain score 0/4 - No joint effusion
5/5/20 (VDO 8)	- PCSO-524® 1 capsule sid	- alert, good appetite - lameness score 0/5, pain score 0/4 - No joint effusion

Note: * indicates adjustment from the previous prescription

Discussion

Immune mediated polyarthritis is commonly found in small and large breeds of dogs at all ages. The symptoms are various that the diagnosis usually takes some time and thus delays the treatment [2]. In this case at the early stage of the disease, only intermittent lameness of the left hind limb was observed and patella luxation was identified as the cause of lameness. When the dog did not respond to treatment with NSAIDs and joint effusion was additionally shown, further diagnosis was then performed.

The examination of synovial fluid was able to identified **IMPA** as the true cause of the symptoms. Treatment of IMPA usually begins with steroid to suppress the immune for at least 30 days or until the symptoms are improved then gradually taper the dosage of steroid.

Immunosuppresive drugs such as cyclosporine and azathioprine can be used in conjunction with steroid to control the symptoms and to shorten the duration of steroid administration [2]. However, long-term use of steroid and immunosuppressive drugs can cause adverse effects such as **kidney failure, liver failure, gastrointestinal tract ulcer, vomiting, and diarrhea** [7]. We found that ALT, ALK, and AST had increased to abnormal level in this dog after only 7 days of prednisolone 0.6 mg/kg bid administration. So prednisolone was immediately terminated and replaced with cyclosporine, which also raised concern on the long-term use effect.

PCSO-524® was then prescribed in conjunction with cyclosporine and gabapentin to reduce inflammation and pain and to minimize the duration of cyclosporine use and prevent recurrence of the disease.

The dog showed sign of diarrhea after 6 weeks of cyclosporine treatment, so the dosage was 50% reduced and metronidazole was additionally introduced when gabapentin and PCSO-524® dosage remained constant. The diarrhea stopped within 7 days and the joint effusion was gradually improved that we were able to terminate cyclosporine and gabapentin in the third and fourth month after the treatment, respectively. The recurrence of IMPA was not observed at the follow-up 4 months later.

Conclusion

The study had shown that PCSO-524® can be used in conjunction with cyclosporine and gabapentin for treatment of non-erosive IMPA. **It is effective against joint pain, arthritis and muscle inflammation.**

The clinical signs continued to improve even when dosage of cyclosporine and gabapentin was reduced and eventually terminated.
The follow-up at 4 months later showed no recurrence of lameness and joint pain from IMPA and lack of adverse effects for the long-term use of PCSO-524®.

Acknowledgement

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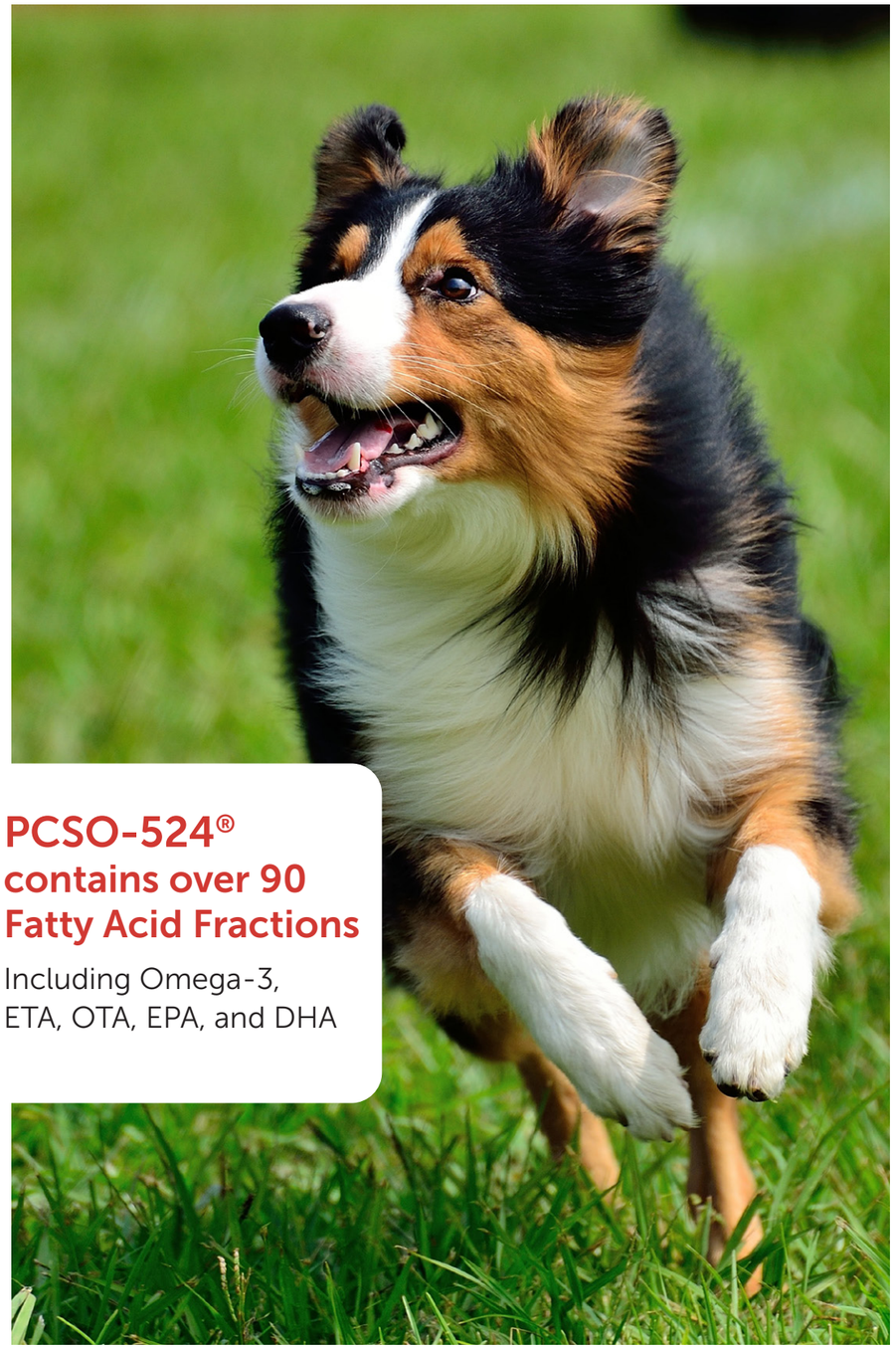

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