*Case Report*

# Case Report: Long-Term Management of Imidacloprid-Moxidectin in a Dog with Caval Syndrome

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**Received: 14 July 2021; Revised: 11 September 2021; Accepted: 15 September 2021**

## Abstract

**Caval syndrome is a condition from heavy heartworm infestations, causing intracardiac obstruction, potentiating in multiple fatal complications, and poor prognosis. Early diagnosis is imperative for prompt treatment and echocardiography has the benefit of aiding in exploring the cardiac structure and the worm burden. According to The American Heartworm Society guideline (2020), it has established several treatment regimens both medical and surgical. The purpose of this case report is to determine the clinical efficacy of long-term macrocyclic lactone in the treatment of heartworm in a dog with caval syndrome. An 8-year-old female French bulldog was presented with ascites. Numerous heartworms were detected intracardiac from an echocardiography. A monthly application of 10% imidacloprid and 2.5% moxidectin with 4 weeks of 10 mg/kg doxycycline had shown the efficacy in controlling heartworms of a dog with caval syndrome thus far, along with an exercise restriction to prevent complication from pulmonary thromboembolism. Reassessment of this patient was planned for a monthly health screening and a 3-month echocardiography for worms migration, thrombi, and antigen testing. After 3 months, the worms were unable to detect from echocardiography and the dog was no longer required abdominocentesis. The dog is currently living well and planned on giving a regular heartworm prevention program after 12 months.**

**Keywords:** caval syndrome, canine heartworm, long term macrocyclic lactone

# รายงานสัตว์ป่วย: การรักษาพยาธิหนอนหัวใจระยะที่ 4 (Caval Syndrome) ในสุนัขด้วย อิมิดาโคลพริด ม็อกซี่เด็กติน แบบระยะยาว

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**Received: 14 July 2021; Revised: 11 September 2021; Accepted: 15 September 2021**

## บทคัดย่อ

**การติดพยาธิหนอนหัวใจระยะที่ 4 (Caval syndrome) เกิดจากการติดเชื้อหนอนพยาธิในปริมาณมากจนเกิดการอุดตันในหัวใจ ส่งผลให้เกิดภาวะแทรกซ้อนที่หลากหลายซึ่งเป็นอันตรายต่อชีวิต และการพยากรณ์โรคไม่ดี ความรวดเร็วในการวินิจฉัยเป็นสิ่งจำเป็นเพื่อทำการรักษาได้อย่างทันท่วงที การตรวจหัวใจด้วยคลื่นเสียงความถี่สูงถือเป็นเครื่องมือที่ช่วยให้เห็นโครงสร้างของหัวใจและตัวหนอนพยาธิที่อยู่ในหัวใจ โดยในปี ค.ศ. 2020 American Heartworm Society ได้ออกแนวปฏิบัติในการรักษาทั้งการรักษาทางยาและผ่าตัด รายงานสัตว์ป่วยนี้มีวัตถุประสงค์เพื่ออภิปรายผลการรักษาพยาธิหนอนหัวใจระยะที่ 4 ด้วยอิมิดาโคลพริด ม็อกซี่เด็กติน แบบระยะยาว สุนัขพันธุ์เฟรนช์บูลด็อก เพศเมีย อายุ 8 ปี มาด้วยปัญหามีน้ำคั่งในช่องท้อง เมื่อตรวจด้วยคลื่นเสียงความถี่สูงพบหนอนพยาธิหัวใจจำนวนมากในหัวใจ รักษาโดยให้ยา 10% อิมิดาโคลพริด และ 2.5% ม็อกซี่เด็กติน ร่วมกับด็อกซีไซคลิน 10 มก./กก. เป็นเวลา 4 สัปดาห์ ผลการรักษาพบว่ายาดังกล่าวมีประสิทธิภาพในการควบคุมหนอนพยาธิในสุนัขป่วยด้วยโรคพยาธิหนอนหัวใจระยะที่ 4 มีการจำกัดกิจกรรมของสุนัขร่วมด้วยเพื่อป้องกันภาวะลิ่มเลือดอุดกั้นในปอด ทำการการติดตามผลการรักษาทุกเดือนและตรวจด้วยคลื่นเสียงความถี่สูงเมื่อครบ 3 เดือน เพื่อประเมินการเคลื่อนย้ายของหนอนพยาธิ ลิ่มเลือด และตรวจหาแอนติเจนต่อพยาธิ โดยไม่พบหนอนพยาธิเมื่อผ่านไป 3 เดือน จากการตรวจด้วยคลื่นเสียงความถี่สูง และไม่ต้องเจาะระบายน้ำในช่องท้องสุนัข สุนัขยังคงมีชีวิตและวางแผนป้องกันพยาธิหนอนหัวใจต่อไปหลังรักษาครบ 12 เดือน**

**คำสำคัญ :** Caval syndrome พยาธิหนอนหัวใจ แม็คโครไซคลิกแลคโตนแบบระยะยาว

## Introduction

Caval syndrome is known as dirofilarial hemoglobinuria (AHS 2020). The condition develops in dogs which severely infested with heartworms. The presence of worms in right atrium, ventricle, pulmonary artery, and often vena cava causes blood flow obstruction (Jones 2016). The dogs constantly present signs of acute anorexia, respiratory distress, weakness, right-sided cardiac murmur, anemia, hemoglobinuria, hepatic and renal dysfunction, signs of forward and backward heart failure, and possibly, disseminated intravascular coagulation (DIC) (Strickland 1998).

*Dirofilaria* spp., a juvenile form called microfilaria, is the main cause of heartworm disease. It could be encountered through a modified Knott or a filtration test (Kamyingkird et al., 2017). Another screening test using antigen detection can be done through a rapid test kit. Nevertheless, it takes up to 6 months post-infection, as well as the detection of microfilariae, to be able to reveal the antigen from the active adult female (Atkins 2003; Taylor et al., 2016). Thus, the acceptable gold standard for heartworm testing is the presence of adult worms in the pulmonary arteries and/or heart on necropsy examination. The visualization of heartworms within the tricuspid orifice and posterior vena cava from echocardiography can be performed (Courteney and Zeng 2001; Atkins 2003). Considering necropsy is the terminal decision and gives no benefit in the individual treatment. Early diagnosis can help to reduce the inevitable dilemma and favoring the treatment plan.

The treatment goal of heartworm disease is to eliminate all stages of this nematode and to improve the quality of life of the patient (AHS 2020). Multimodal treatment and slow-killing of the heartworm have been proposed after fatal complications from mechanical removing or using an adulticide of melarsomine dihydrochloride. The adult worms are less susceptible and taking longer to die. However, within 2 years of treatment, it is expected that 95% of the worms should be killed (Bowman 2012). The anecdotal reports a supplementation of doxycycline has been widely used to eliminate intracellular bacteria and it works against gram negative bacteria called Wolbachia spp. in all stages of the worms (Bazzocchi et al., 2008). Bacteria are living with the worm as symbiosis microorganisms and are essential to the development of larvae into adult worms (McCall et al., 2008). By reducing the bacteria, it is subsequently reducing the number of adult worms as well as microfilaria (Frank and Heald 2010). Several case reports have been attempted to find a safe approach for physical removal of heartworms. In Yoon et al., the study had demonstrated success in using a nitinol basket with catheter-guided to remove the worm (Yoon et al., 2010). When killing heartworm by using any medicine, it should be taken with precautions from wormís debris inducing thrombi. As from Virchowís triad, it has been explained that such case as heartworm is predisposed to thrombi formation, Hypercoagulable state, vascular stasis, and damage to the vascular endothelium, which often encountered in dirofilariasis (Yun et al., 2010). The thrombi prevention was performed with clopidogrel (Sanofi-Aventis, France) 2-4 mg/kg, q24h.

Accordingly, the case report aimed to use a long-term macrocyclic lactone as the alternative method, with adjunctive therapy for heart failure and inflammation from the wormís antigen in dogs with the severe manifestation of heartworms and expressed the signs of caval syndrome.

**Figure 1.** The dog had abdominal distention and was difficult to stand on the first visit. General body condition was poor and given 2/9 on her body condition score

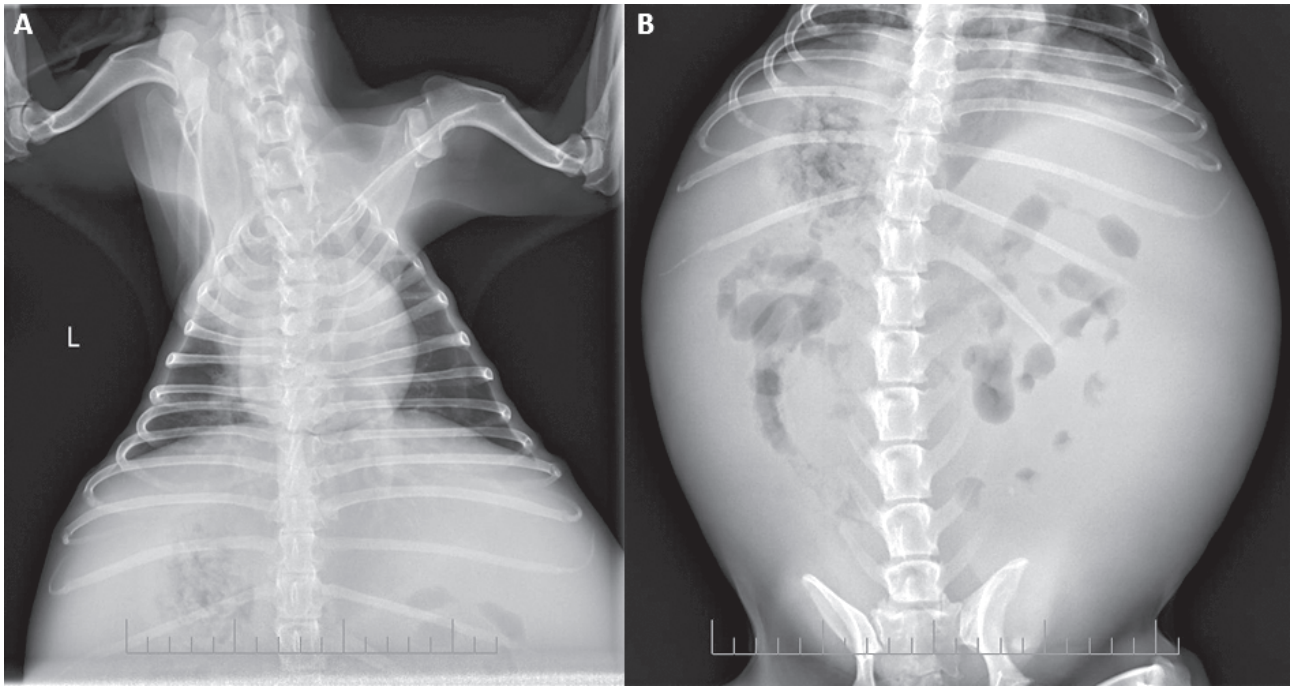


**Figure 2.** Radiography of thoracic and abdominal cavity ventrodorsal view. Inverted D-shape heart with pulmonary knob was seen with tortuous pulmonary artery and pulmonary artery enlargement (A). Ground-glass soft tissue opacity in the abdominal cavity was marked (B).

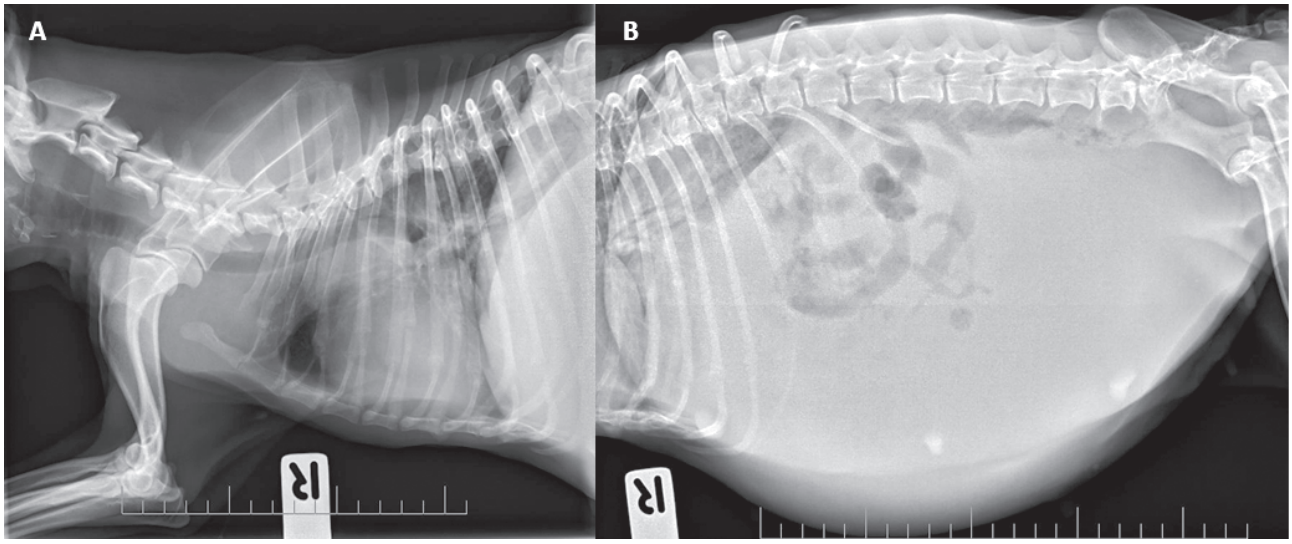


**Figure 3.** Radiography of thoracic and abdominal cavity lateral view. Sternal contact of the heart, elevated trachea, thickening vena cava (comparing to the 9th rib), vascular pattern of lung and unstructured interstitial pattern at perivascular region, especially at large pulmonary artery of caudodorsal lobe in thoracic cavity(A). Liver enlargement and ground glass soft tissue opacity in the abdominal cavity (B).

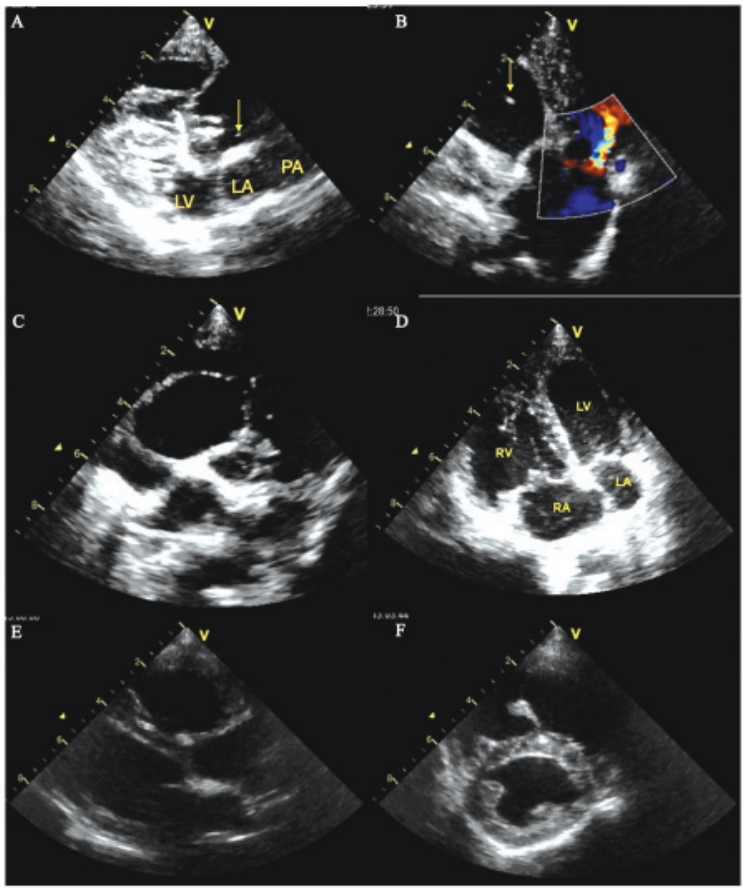


**Figure 4.** Echocardiogram images of the heart from right parasternal long-axis and short-axis with intracardiac heartworm, appearing as parallel hyperechoic line (A and B). Severe right atrial enlargement can be observed from right parasternal short axis (B and C). Marked thickening of tricuspid valve can be seen from left apical four chamber view (D and F). No worm detected after 3-6 months of treatment (E and F).


**Figure 5.** A serosanguineous fluid acquired from an abdominocentesis

**Table 1.** Hematology report (absolute) from the first visit.

| Parameters | First visit | Normal value |
|---|---|---|
| WBC (/ul) | 12,510 | 6,000 - 17,000 |
| Monocyte | 500.4 | 150 - 1,350 |
| Neutrophil | 10,633.5 | 3,000 - 11,500 |
| Band | 0 | 0 - 300 |
| Lymphocyte | 1251 | 1,000 - 4,800 |
| Eosinophil | 125.1 | 100 - 1,250 |
| Basophil | 0 | < 100 |
| RBC ($10^6$/ul) | 5.41 | 5.0 - 9.0 |
| Hb (g/dl) | 12.2 | 10.0 - 18.0 |
| Hct (%) | 35.4 | 35 - 55 |
| MCV (fL) | 65.5 | 60 - 77 |
| MCH (pg) | 22.6 | 20 - 25 |
| MCHC (g/dl) | 34.4 | 32.0 - 36.0 |
| PLT ($10^3$/ul) | 317 | 200 - 500 |
| Platelet smear | Adequate | |
| Plasma Protein | 6.0 | 6.0-7.5 |
| ALT (U/L) | 42 | 10 - 100 |
| ALP (U/L) | 38 | 23 - 212 |
| BUN (mg/dL) | 25 | 7 - 27 |
| Creatinine (mg/dL) | 1.76 | 0.50 - 1.80 |
| Albumin | 2.8 | 2.7-3.8 |

**Table 2.** Echocardiogram variables from the first and recent visit.

| Variables | First visit | At 6 months |
|---|---|---|
| HR (BPM) | 132.37 | 130 |
| LVIDd (mm) | 15.23 | 28.0 |
| LVIDs (mm) | 8.88 | 16.0 |
| LA diameter (mm) | 15.77 | 21.0 |
| Ao diameter (mm) | 11.55 | 14.0 |
| LA:Ao short axis | 1.37 | 1.53 |
| TR Max PG (mmHg) | 75.83 | 55.40 |
| PR Max PG (mmHg) | 72.52 | 38.83 |
| RA Max PG (mmHg) | 65.5 | - |
| PV Max PG (mmHg) | 14.27 | 17.58 |
| AV Max PG (mmHg) | 1.82 | 2.69 |
| MV Max PG (mmHg) | 34.4 | - |
| MR Max PG (mmHg) | 88.68 | 57.29 |
| MV E:A ratio | 0.948 | 0.83 |

**Case description**

An 8-year-old intact female French bulldog was presented with 3-month abdominal distension. The dog has never undergone any vaccination program or heartworm prevention and had no previous medical history. She was kept outdoor with 3 other dogs in the house. Cough, fatigue, and difficulty breathing were occasionally observed.

During the first visit, the dog was moderately depressed and weak. She was emaciated with a body condition score of 2/9. From the physical examination, murmur heart sound was graded 5/6 and prominent at the pulmonic region. The mucous membrane was pale pink with prolonging capillary refill time (CRT). Jugular pulsation was markedly seen. The dog had mild tachypnea with mild increase lung sound at the right caudal lobe with an enlarged abdomen. Abdominal ballottement was presented without cramp (Figure 1).

Thoracic and abdominal radiographs were taken in ventrodorsal and lateral views. Liver enlargement and ground-glass soft tissue opacity were seen in the abdominal cavity. The internal organs were difficult to distinguish from both views (Figure 2 and 3). The thoracic radiography showed an elevated trachea, thickening vena cava, vascular pattern of the lungs and an unstructured interstitial pattern at the perivascular region, especially at the large pulmonary artery of the caudodorsal lobes from lateral view (Figure 3). From the ventrodorsal view, an inverted D-shape heart with pulmonary knob was seen with tortuous pulmonary arteries, and pulmonary artery enlargement (Figure 2A and B).

Hematology values were within the reference interval. No parasite was found from the blood smear

during the first visit (Table 1). An echocardiography revealed parallel hyperechoic lines of numerous heartworms in the right atrium (RA), right ventricle (RV), and pulmonary artery (PA) causing severe tricuspid regurgitation (TR) and marked pulmonary regurgitation. Severe right cardiomegaly and pulmonary hypertension with right-side heart failure signs were also presented (Figure 4). Echocardiography and clinical signs suggested a caval syndrome.

The initial plan was mainly targeting on improving the quality of life for this patient as the prognosis was poor to grave if pulmonary thromboembolism occurred. Thus, abdominocentesis was performed and the 2,000 milliliters of serosanguineous fluid (Figure 5) were obtained for the first time and gradually decrease with diuretic drug (furosemide 1 mg/kg). The fluid was identified as modified transudate. Medical treatment was prescribed, using a long-term macrocyclic lactone with right side heart failure management. A monthly spot on imidacloprid 250 mg and moxidectin 62.5mg (Advocate® spot-on, Bayer Animal Health GmbH, Leverkusen, Germany) was used to kill microfilaria and a 10 mg/kg doxycycline to cut off heartworm life cycle by reducing *Wolbachia* spp. in the adult worms. Prednisolone 0.25 mg/kg was started and planned to taper down each week. Ramipril 0.125 mg/kg and spironolactone 1.25 mg/kg were used for heart failure treatment. The owner was instructed to give the dog an absolute exercise restriction, adequate food and water intake, as well as a recommendation of heart worm prevention for other dogs in the house.

The dog was scheduled for a follow-up and initial reassessment weekly. Her general condition was improved. A reaccumulation of ascites was less and took longer to return. After 3 and 6 months, the patient was reevaluated with an echocardiography and no heartworm was detected in the right atrium, pulmonary artery, and ventricles. Moreover, the parameters from echocardiographic findings and clinical signs are improved (Table 2). Abdominal ultrasound aided in determines the current ascites. A rapid test for heartworm antigen (The SNAP® 4DX® Plus Test, IDEXX Laboratories, Inc., Westbrook, ME) was used at 6 months after treatment and no heartworm antigen was detected. During the 4$^{th}$ month visit, small fluid was found in cystocolic site and difficult to obtain from abdominocentesis. By adjusting diuretic drugs, furosemide 0.5 mg/kg q12h was prescribed along with an adjunctive of spironolactone 1.25 mg/kg q12h. Despite the owner had missed the 3$^{rd}$ and the 5$^{th}$ visit, the dog had a well respond. By the 7$^{th}$ month, abdominocentesis was no longer required. The dog had been living well and was planned on a monthly reassessment with a regular heartworm prevention program (AHS 2020).

## Discussion

Caval syndrome is the final stage of a heartworm disease. The major characteristic signs are intracardiac worms obstruction of blood flow, interference of tricuspid valve closure, causing tricuspid valve regurgitation, heart murmur, and jugular pulsations as a consequence from liver congestion. Other than these clinical signs, caval syndrome is often diagnosed and confirmed by the present of the intracardiac worms from an echocardiography or necropsy. Screening test such as a rapid test kit is useful in early diagnosis and for following up the treatment. However, it requires the antigen from a female heartworm to develop at least 6 months after the dog has exposed to the worm (AHS 2020; TroCCAP 2017). The SNAP 4Dx Plus? Test has a 99.0% sensitivity and a 99.3% specificity, comparing to the gold standard, necropsy (Barr et al. 2011;

IDEXX 2016; Liu et al. 2018; Lee et al. 2011). Atkins and Genchi et al. had demonstrated up to 100% sensitivity (95% confidence limit) with 3 worms infestation (Atkins 2003; Genchi et al., 2018). Echocardiography aids in visualizing the structures of the heart with parameters measurement (Romano et al., 2020) and worms migration (Courteney and Zeng 2001; Atkins 2003) despite a lower sensitivity, comparing to antigen detection (DeFrancesco 2001; Esser 2020). Several studies advised a blood collection with N-glycosylation as a biomarker testing (Behrens et al., 2018) for early detection as of 3 weeks post infection and a multiplex qPCR to identify occult form of multiple heartworms species (Laidoudi 2020). Microfilaria was not observed from a blood smear in this case. Nonetheless, explicit clinical presentations, echocardiography, and the rapid test kit were sufficient to make a diagnosis in this case report.

A long-term macrocyclic lactone is another acceptable alternative apart from the gold standard, surgical removal of heartworm and melarsormine adulticide (Jones 2016; AHS 2020). The latters can potentially cause lethal adverse effect from either post operation complications (Bov? et al., 2010) or arsenic poisoning symptoms and was abstained in this patient. Alberigi et al. (2020) had demonstrated the use of semi-annual therapy of 0.5 mg/kg moxidectin injection with oral 10 mg/kg doxycycline were effective against dogs with dirofilaremia and improved the pulmonary conditions with noticeable change within 30 days by dirofilaria counts (Alberigi et al., 2020). Hence, the application of a monthly 10% imidacloprid and 2.5% moxidectin (Advocate®) with 4 weeks of 10 mg/kg doxycycline were proved to be as effective in terms of clinical conditions in this case report.

Notwithstanding the fact that the owner had missed 2 visits and 2 inconsecutive Advocate® administrations, the dog was in an improvement. She expressed a more comfortable being. Due to the severity of worm infestation and the occurrence of right-side heart failure signs, it was not expected to fully recover. Even though the dog survived from a pulmonary thromboembolism and the clinical presentation has improved, it did not show a remarkable change in a cardiac remodeling. Considering a poor prognosis for this disease, the mortality rate of dogs with caval syndrome is expected to be 30-40% (Kittleson 1998) even with the worm extraction (Hoch and Strictland 2008). Nevertheless, improving the quality of life for this patient had been the primary goal. The dog was planned to continue using a longterm macrocyclic lactone for heartworm management protocol and then reassess the worm and possible thrombi through echocardiography and antigen testing after 6 months from the first treatment. Since microfilariae can live up to 2 years (AHS 2018), it could be considered as the point when the treatment outcome should be fully followed, otherwise after antigen test was negeative. Ames et al. (2020) had designed a treatment of topical imidacloprid-moxidectin and doxycycline in dog with heartworm infection, stage 1 and 2 (Ames et al., 2020). The study result that treated with the same protocol was promising with 96% no antigen detection cases and supporting this case report at stage 4 or caval syndrome.

## Conclusions

A prescription of long-term macrocyclic lactone with adjunctive therapy in this case report had demonstrated a satisfying outcome. The dog exhibited an improvement in clinical signs each time of visit at the animal hospital. A monthly application of 10% imidacloprid and 2.5%

moxidectin had shown the efficacy in controlling heartworms of a dog with caval syndrome thus far, along with 4 weeks of 10 mg/kg doxycycline and exercise restriction to prevent complication from pulmonary thromboembolism. Reassessment of this patient was planned for a monthly health screening and a 3-month echocardiography for worms migration, thrombi, and antigen testing. The limitation was to make a substantial regime and an efficient client communication in very poor prognosis patients. Dedication from the owners is strongly supporting the treatment plan. It is important to control the infection of the patient as well as the other dogs in the same house to reduce a local transmission, by vector control and semi-annual heartworm protection regimen.

## Acknowledgements

The authors would like to express their sincere gratitude to all staffs at Prasu-arthorn animal hospital, Assist. Prof. Dr. Somkiat Huaijantug, Dr. Phuttiphan Channgam, with the owner permission and this patient whose support and collaboration made this case report possible.

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