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Sawang Kesdangsakonwut

See next page for additional authors

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Authors

Nawat Sannamwong, Saikaew Sutayatram, Nardtiwa Chaivoravitsakul, Patharakrit Teewasutrakul, Sawang Ksdangsakonwut, and Chollada Buranakarl

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Nawat Sannamwong¹ Saikaew Sutayatram² Nardtiwa Chaivoravitsakul³

Patharakrit Teewasutrakul⁴ Sawang Kesdangsakonwut⁵ Chollada Buranakarl^{2*}

Abstract

A four-year old, intact female Labrador Retriever dog was presented with a history and clinical signs of vomiting, anorexia and mild dyspnea. Further laboratory examination, by specific canine pancreatic lipase (cPL) test kit and abdominal ultrasound, indicated acute pancreatitis. Results from thoracic radiography and computerized tomography scan showed masses in the cranial and middle mediastinal areas. A cytology examination revealed pyogranulomatous inflammation with the presence of fungal hyphae whereas *Aspergillus niger* was isolated and identified. Systemic aspergillosis was diagnosed. Many antifungal drugs were introduced and the clinical outcomes were discussed with careful consideration.

Keywords: antifungal drugs, *Aspergillus niger*, dog, systemic aspergillosis

¹Residency Program in Internal Medicine, Faculty of Veterinary Science, Chulalongkorn University, Henri Dunant Rd., Pathumwan, Bangkok 10330, Thailand

²Department of Physiology, Faculty of Veterinary Science, Chulalongkorn University, Henri Dunant Rd., Pathumwan, Bangkok 10330, Thailand

³Diagnostic Imaging Unit, Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University, Henri Dunant Rd., Pathumwan, Bangkok 10330, Thailand

⁴Oncology Unit, Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University Henri Dunant Rd., Pathumwan, Bangkok 10330, Thailand

⁵Department of Pathology, Faculty of Veterinary Science, Chulalongkorn University, Henri Dunant Rd., Pathumwan, Bangkok 10330, Thailand

*Correspondence: bchollad@chula.ac.th (C. Buranakarl)

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Introduction

Aspergillus spp. are ubiquitous filamentous fungi found in the environment and can infect both humans and animals as opportunistic pathogens (Corrigan *et al.*, 2016; Billen and Peeters, 2017). Transmission commonly occurs via airborne conidia caused by environmental contaminated during construction work (Pilmis *et al.*, 2017). Although the respiratory defense system can eliminate most of the pathogens, the infection may develop especially in cases where a component of the defense system is impaired (Balloy and Chignard, 2009). Aspergillus infection has two forms in dogs which are, sinonasal aspergillosis, in which the infection only involves the nasal cavities and the frontal sinuses, and systemic aspergillosis, in which the infection disseminates to many organs (Day, 2006). Sinonasal aspergillosis is a common disease while systemic aspergillosis has had scanty reports in dogs (Day 2006; Mathews and Sharp, 2006).

In the case of systemic aspergillosis, *Aspergillus* spp. enters the respiratory tract before invading the hematogenous system. The target tissues or organs include the intervertebral disc, bones, lungs, kidneys, eyes, lymph nodes, the central nervous system and gastrointestinal tract. Patients may not have a history of nasal infection (Billen and Peeters, 2017). In dogs with systemic aspergillosis, *Aspergillus terreus* and *Aspergillus defluctus* are the most common pathogens (Schultz *et al.*, 2008; Corrigan *et al.*, 2016). Moreover, the host defense system, including intracellular and extracellular killing pathways, plays a major role in systemic aspergillosis in humans (Hohl, 2017). However, dogs with systemic aspergillosis usually do not have a history of immunosuppressive diseases nor are receiving immunosuppressive drugs (Schultz *et al.*, 2008; Corrigan *et al.*, 2016). The clinical signs for systemic aspergillosis in dogs are non-specific depending on the infected organs and include back pain, pelvic limb ataxia, decreased appetite, weight loss, lethargy, vomiting, diarrhea, lameness, polyuria, polydipsia, anterior uveitis, vestibular signs, skin lesions, lower urinary tract signs and peripheral lymphadenopathy (Corrigan *et al.*, 2016). The gold standard diagnosis for canine systemic aspergillosis is by culture of *Aspergillus* spp. from suspected tissues or body fluids such as the urine and bronchoalveolar lavage (Schultz *et al.*, 2008; Garcia *et al.*, 2012). Treatment with surgical removal of mass and multiple antifungal drugs therapies have previously been demonstrated (Billen and Peeters, 2017; Schultz *et al.*, 2008). The prognosis of systemic aspergillosis is poor in animals even with proper antifungal therapy and supportive treatment (Billen and Peeters, 2017). The purpose of this report is to provide information regarding the clinical presentation, diagnostic tools and treatment options in dogs with systemic aspergillosis.

Case description

A four year old, intact female Labrador Retriever dog was referred to the Small Animal Teaching Hospital, Faculty of Veterinary Science, Chulalongkorn University, due to signs of anorexia and vomiting for 2 weeks. Upon arrival, its body

weight was 24.5 kg with a body condition score of 2/5. The dog lived outdoors in the area around the house with three other dogs that appeared to be normal. The dog had received vaccination annually but the ectoparasite prevention program had not been applied regularly. Physical examination revealed that the dog was mildly depressed. The rectal temperature was 101.8 °F with a pink mucus membrane and a capillary refilling time of one to two seconds. The heart rate was 120 beats per minute with a normal heart sound. The respiratory rate was 60 times per minute with increased lung sound. The breathing pattern was rapid and shallow with mild dyspnea. The abdominal palpation was normal.

The hematology and blood chemistry analysis results during the course of treatment are presented in Table 1. Hematology at first admission (D0) used an automate machine (BC-5000Vet, MINDRAY, Shenzhen, P. R. China) and revealed leukocytosis with neutrophilia, lymphopenia, and monocytosis indicating stress leukogram. Serum chemistry analysis using an automate machine (BC-800, MINDRAY, Shenzhen, P. R. China) showed mild increases in alkaline phosphatase (ALP) and globulin. The quantitative measurement of canine pancreatic lipase by fluorescent immunoassay (Vcheck cPL 2.0, BIONOTE, Hwaseong-si, South Korea) was 1,422 ng/mL, which was considered as pancreatitis (normal < 400 ng/mL). The venous blood gas analysis (RAPIDLab 348EX, SIEMENS, Erlangen, Germany) showed normal pH (7.393). The partial pressures of O₂ and CO₂ were 31.5 and 37.1 mmHg, respectively. The HCO₃⁻ was 22.1 mmol/L while the base excess was -2.8 mmol/L. No blood parasite was found from light microscopic examination.

The urinalysis from cystocentesis revealed a pH of 6 with a urine specific gravity higher than 1.050. The urine strip test (Combur[®] Test, Roche Diagnostics, Mannheim, Germany) showed proteinuria (protein 3+) and bilirubinuria (bilirubin 2+) while urinary sedimentation indicated inactive sediment.

Thoracic radiography (Brivo DR-F, GE Healthcare, USA) revealed a widening of the cranial mediastinum with a large soft tissue opacity mass sized 11.7 x 7.6 cm with dorsal deviation of the intrathoracic trachea and an obscured cranial cardiac silhouette border on the lateral view (Figure 1). There was a large soft tissue opacity mass sized 2.6 x 3.1 cm at the middle mediastinum over the tracheal bifurcation suggesting severe tracheobronchial lymph node enlargement. This mass compressed the tracheal bifurcation and caudal mainstem bronchi. Patchy alveolar pattern of cranial lung lobe ventral to cranial mediastinal mass was found. No foreign body or obstructive signs in the gastrointestinal tract were found by abdominal radiography. Abdominal ultrasound (LOGIQ P6, GE Healthcare, Waukesha, USA) revealed mild enlargement with a decreased echogenicity of the right lobe of the pancreas.

Cytology specimens were collected from the cranial mediastinal mass using the thoracic ultrasound guide fine needle aspiration technique and stained with Diff-Quik[™]. Cytology specimen revealed pyogranulomatous inflammation characterized by the presence of mixed inflammatory cells, predominately

activated macrophages and multinucleated giant cells (Figure 2). In addition, a lot of thin (4-5 μm width), parallel, septate, dichotomous hyphae suspected to be *Aspergillus* spp. were observed.

Fungal culture using Sabouraud Dextrose Agar (Scharlau, Scharlad S.L., Spain) was employed on the first day of admission and the result was found to be *Aspergillus niger* by its colonial morphology and

microscopic appearance. (Figure 3). The colony was initially white in color, becoming black later on giving a salt and pepper appearance. The reverse had a cream color. The microscopic feature consisted of large fruiting heads looking like small black balls with spherical vesicle bearing large mutilations to which the smaller phialides were attached.

Table 1 Hematology and blood chemistry results of the dog

Parameter	D0	D31	D60	D192	D228	Normal range
Hematology						
RBC $\times 10^6$ (cell/ mm^3)	5.45	5.29	5.22	5.21	4.44	5.2-8.06
Hemoglobin (g/dL)	13.3	11.3	12.6	11.9	10.6	12.4-19.1
Hematocrit (%)	36.7	38.26	35	35.4	31.8	29.8-57.5
Platelet $\times 10^3$ (cell/ mm^3)	234	358	301	407	506	160-525
WBC $\times 10^3$ (cell/ mm^3)	23.76	13.41	8.52	8.87	11.51	5.4-15.3
Neutrophils $\times 10^3$ (cell/ mm^3)	18.39	10.77	6.0	5.67	6.99	3-11.5
Eosinophils $\times 10^3$ (cell/ mm^3)	0.38	0.12	0.66	0.56	0.22	0.1-1.25
Lymphocytes $\times 10^3$ (cell/ mm^3)	0.64	1.8	1.09	1.03	2.49	1-4.8
Monocytes $\times 10^3$ (cell/ mm^3)	4.30	0.66	0.75	1.60	1.82	0.15-1.35
Blood chemistry						
ALT (U/L)	74	60	39	126	55	4-91.0
ALP (U/L)	318	148	98	160	118	3-60.0
BUN (mg/dL)	21.8	42	17.8	28.9	47.9	7-26.0
Creatinine (mg/dL)	0.7	2.5	1.3	1.6	2.1	0.6-1.4
Total protein (g/dL)	8.5		6.5	7.5	7.5	5.8-7.9
Albumin (g/dL)	2.6		2.4	2.3	2.5	2.6-4
Globulin (g/dL)	5.9		4.1	5.2	5	2.6-4.5
Calcium (mg/dL)	9.9		10.3	10.0		9.6-11.6
Phosphorous (mg/dL)	6		3.2	5.4		2.5-6.2
Bilirubin, total (mg/dL)	0.35					0.1-0.7

RBC=red blood cells; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; WBC=white blood cells; ALT=alanine aminotransferase; ALP=alkaline phosphatase; BUN=blood urea nitrogen

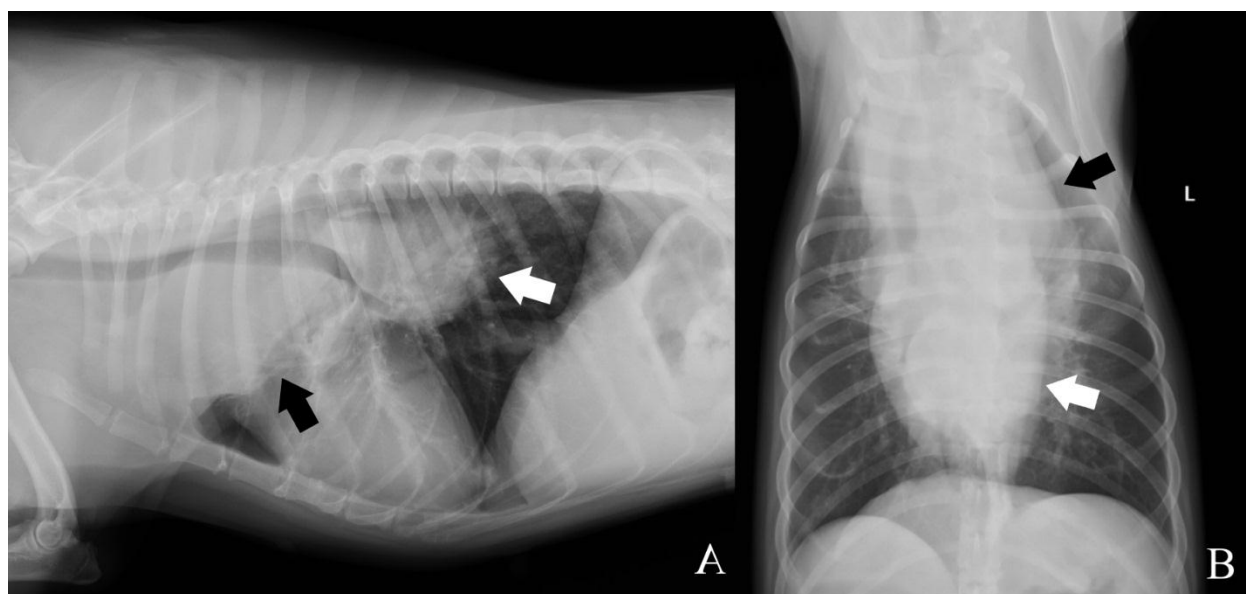


Figure 1 The right lateral view (A) and ventrodorsal view (B) of the thoracic radiograph revealed a large soft tissue opacity mass of the cranial mediastinum (black arrow) and a soft tissue opacity mass (white arrow) at the middle mediastinum.

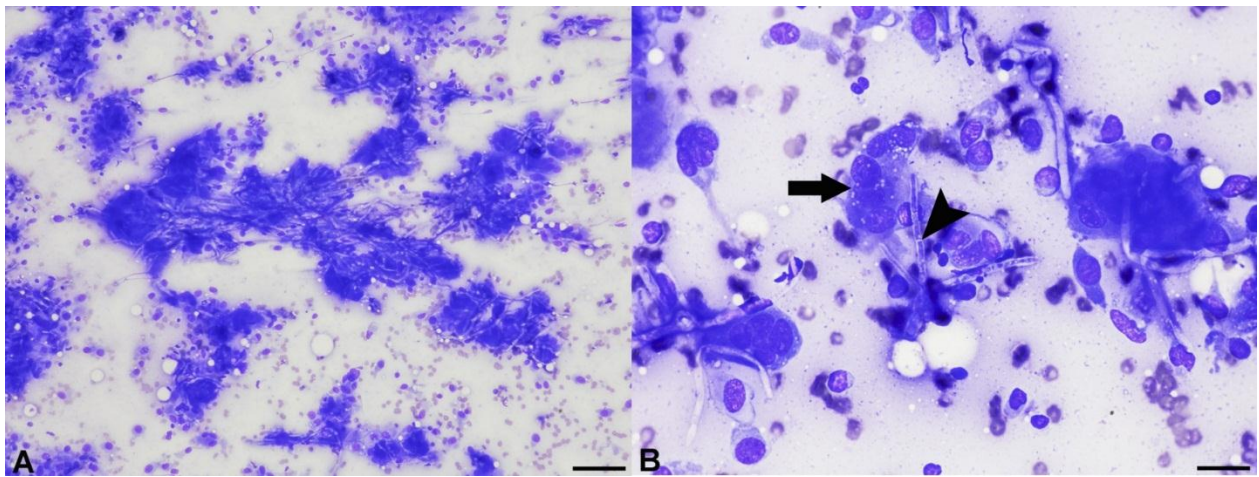


Figure 2 Pyogranulomatous inflammation with numerous fungal hyphae were noted. Diff-Quik™, bar 100 um (A). Mixed inflammatory cells predominately activate macrophages and multinucleated giant cells (arrow) accompanied with thin, parallel, septate, dichotomous hyphae (arrowhead) were seen. Diff-Quik™, bar 25 um (B).



Figure 3 The fungal culture using Sabouraud Dextrose Agar plate revealed *Aspergillus niger*.

While waiting for fungal culture results, the dog had periodic fever with increased white blood cell count up to 36,030 cell/mm³ on day 3 after admission. Repeated thoracic radiograph on day 5 revealed worsening alveolar pattern of both cranial lung lobes and more interstitial pattern of other lung lobes than previous radiograph.

Two weeks after admission, a thoracic computerized tomography scan (Optima CT660 64

Slice, GE Healthcare, Waukesha, USA) was performed. There were two large soft tissue granulomatous masses in the cranial mediastinum size 9.4 x 5.8 cm and the hilar region of the lung size 7.3 x 4.9 cm corresponding to cranial mediastinal and tracheobronchial lymph nodes, respectively (Figure 4). These masses caused the dorsal displacement of intrathoracic trachea and esophagus. The underlying lung and the adjacent cardiovascular structures were also displaced ventrally

by masses. There were multiple small ovoid shaped soft tissue nodular-like lesions (1.4 x 0.8 cm, 1.3 x 0.9 cm and size 1.1 x 0.9 cm) arising from the ventral wall of the mid thoracic esophagus (Figure 5A and 5B). However, no mass or lymph node enlargement was found from skull and abdominal views. Thus, from history taking, physical examination and further diagnostic results, the dog was diagnosed with systemic aspergillus and pancreatitis.

The timeline of the treatment protocol is presented in Figure 6. The dog was first treated with supportive intravenous fluid therapy while the diet was changed

to a low-fat diet. Since respiratory infection was suspected from thoracic radiograph and leukocytosis, the antibiotics, amoxicillin-clavulanic acid (Cavumox, Siam Bheasach, Bangkok, Thailand) was started and continued for 7 days. Repeated blood test and radiograph showed more leukocytosis and worsening of lung pattern on day 5. Therefore, marbofloxacin (Marbocyl, Vetoquinol, Lure, France) was added for 14 days. The sign of dyspnea, fever and leukocytosis were improved within a week after marbofloxacin treatment.

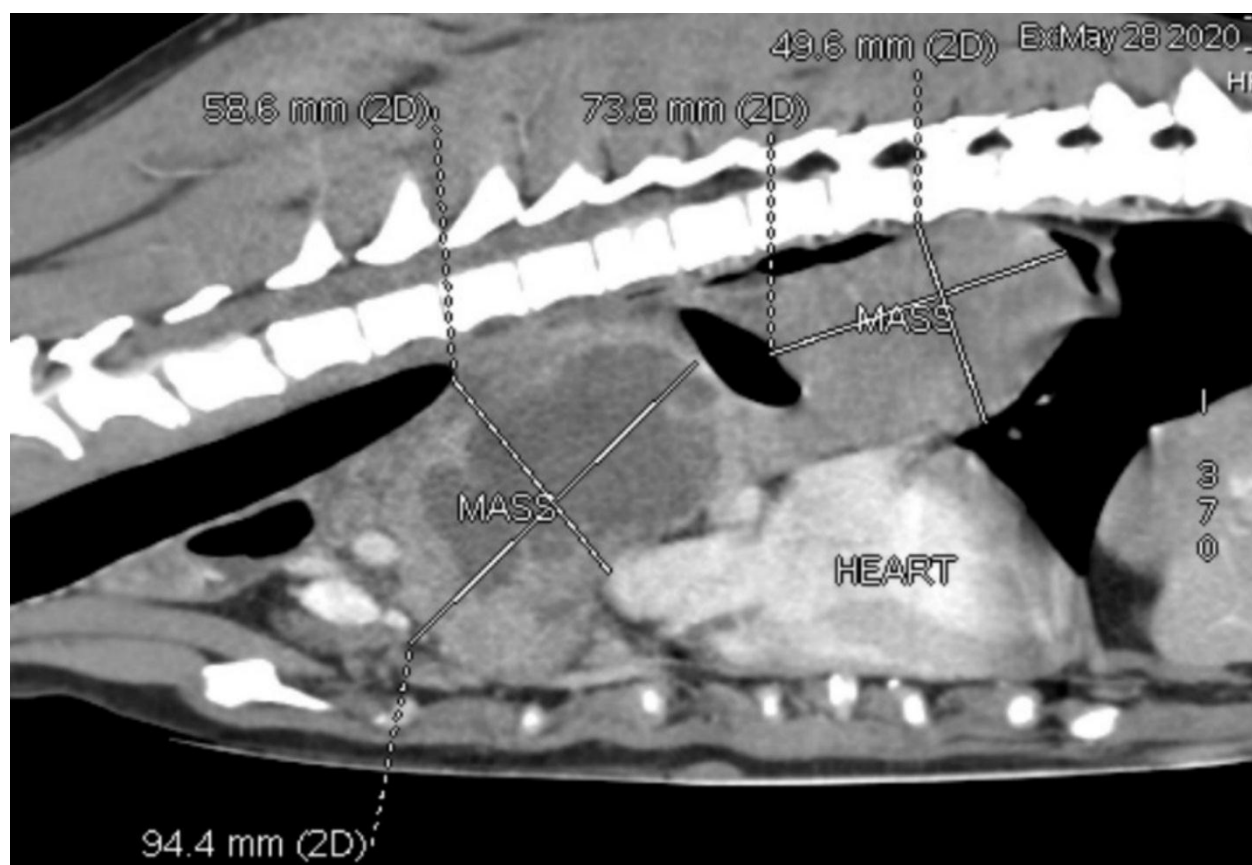


Figure 4 The sagittal plane of thoracic computerized tomography scan revealed large heterogeneous mycotic granulomatous masses of the cranial and middle mediastinum which displaced the intrathoracic trachea dorsally and compressed the cardiovascular structure ventrally.



Figure 5 The computerized tomography scan at the level of the midpart of thoracic esophagus revealed small ovoid shaped soft tissue nodular-like lesions (white arrow) at the ventral wall of cervical esophagus on a transverse view (A) and a sagittal view (B)

Timeline

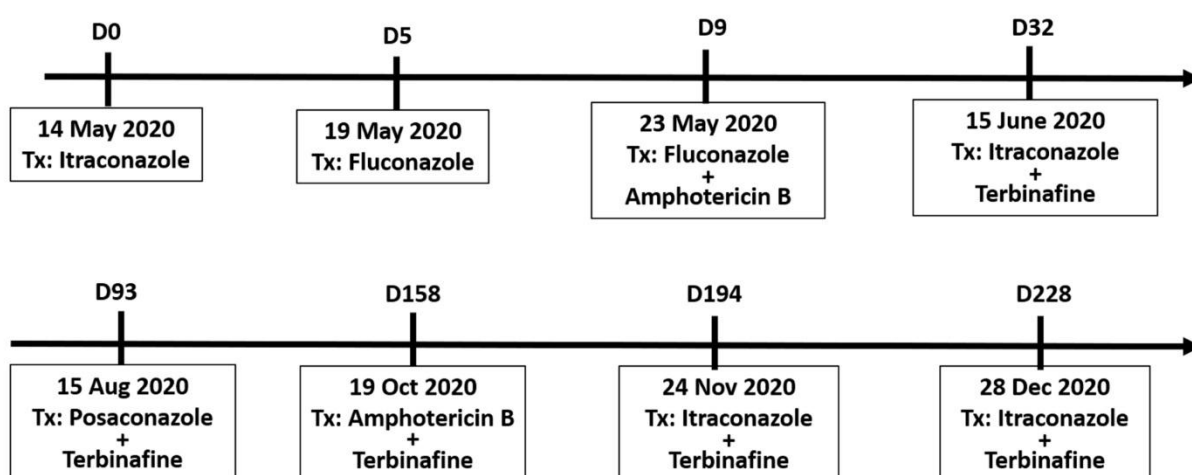


Figure 6 Timeline of the dog during the treatment period.

Antiemetic therapy was used with a combination of ondansetron (Onsia, Siam Bheasach, Bangkok, Thailand) and maropitant citrate (Cerenia, Zoetis). Omeprazole (Amnopra, AMN life Science, Gujarat, India) was given twice a day to reduce gastric acid secretions and the risk of vomiting induced esophagitis.

Itraconazole (Spornar, Charoen Bhaesaj Lab, Bangkok, Thailand) 10 mg/kg was given orally once a day starting at D0 following the cytologic results while waiting for the fungal culture. Due to persistent vomiting and regurgitation, itraconazole was replaced by fluconazole (Flucozole, Siam Bheasach, Bangkok, Thailand) at a dose of 5.9 mg/kg twice a day starting at day 5 after admission (D5). After receiving the fungal culture results on day 9 (D9), an adjunct antifungal treatment using amphotericin B (Fungso-B, Siam Bheasach, Bangkok, Thailand) dissolved in 5% dextrose solution was performed at a dose of 0.5 mg/kg intravenously, three times a week for a total of 10 doses. The clinical signs of vomiting and regurgitation subsided. The canine pancreatic lipase level on day 12 was also reduced to 483 ng/mL and the dog was discharged from hospital at day 20 (D20). A combination of amphotericin B and fluconazole was continued at the same dose and the dog was monitored at a private clinic where azotemia was first detected eighteen days thereafter (day 27) (creatinine 4.1 mg/dL and BUN 94.1 mg/dL) along with signs of depression and vomiting. Supportive fluid therapy was started and blood results at day 31 showed improvement (creatinine 2.5 mg/dL and BUN 42 mg/dL) (Table 1).

The dog was brought back to the hospital on day 32 (D32) and both amphotericin B and fluconazole were stopped. The oral antifungal medication was then changed to a combination of itraconazole at a dose of 5 mg/kg twice a day and terbinafine (Lamisil, Novartis Pharmaceuticals UK, Ltd., London, UK) at a dose of 15 mg/kg twice a day. The dog showed more appetite within a week. At the one-month follow-up appointment (Day 60; D60), the dog appeared to be normal with no clinical signs of vomiting and regurgitation. The blood results were also at the

normal limit (Table 1). The drugs were continued for another month but thoracic radiography on Day 93 revealed no remarkable change in the size of either cranial or middle mediastinal masses.

Due to unchanged mass size, posaconazole (Noxafil, Merck Sharp & Dohme Ltd., Hertfordshire, UK), a delayed release tablet was used to replace itraconazole at a dose of 4.12 mg/kg every other day. However, after approximately two months of posaconazole and terbinafine administration (Day 158), the dog developed sign of regurgitation while thoracic radiography revealed dorsal displacement of the thoracic tracheal and the esophagus due to a thoracic mass which increased in size. The posaconazole was then replaced by amphotericin B (0.5 mg/kg, 3 times a week) for sixteen doses. Unfortunately, a second episode of azotemia developed which could be detected on day 186 (28 days after start amphotericin B) (creatinine 1.8 mg/dL and BUN 22.8 mg/dL) and day 192 (Table 1).

The amphotericin B was then replaced by itraconazole on day 194 at a dose of 5 mg/kg, twice a day along with terbinafine. Until the present time (7 months after the first treatment), the dog was still alive and the mass was growing slowly while the dog had mild azotemia (Day 228) (Table 1).

Discussion

This dog was diagnosed with systemic aspergillosis by the location of lesions that presented somewhere else rather than at the nasal cavity and frontal sinus (Day, 2006). The clinical presentations were related to respiratory and gastrointestinal disturbance. The respiratory distress was due to compression by the cranial and middle mediastinal lymph nodes as shown in the thoracic radiograph and CT scan. Vomiting in this case may have been due to pancreatitis since the cPL value was high, consistent with the results from abdominal ultrasonography. Moreover, the nodular-like lesion at the esophagus may also have caused vomiting. However, pancreatic or gastrointestinal involvement by aspergillus infection was not proved

due to lack of histopathology results. The antibiotics were used for short term duration during first admission period in order to control periodic fever, higher white blood cells count and worsening of lung pattern with possible respiratory infection. Severe vomiting in this case subsided when using a combination of ondansetron (serotonin-3 receptor antagonist) and maropitant citrate (neurokinin-1 receptor antagonist). Maropitant acts on the central nervous system by inhibiting substance P which is the key neurotransmitter involved in vomiting (Plumb, 2015). It suppresses both peripheral and centrally mediated emesis. Additionally, Omeprazole, a proton pump inhibitor in the stomach was used to prevent gastroduodenal ulcer (Plumb, 2015). It had been reported previously that thoracic lymphadenomegaly had been found in 5 dogs out of 26 dogs while pancreatic tissue obtained from necropsy showed the infiltration of fungal hyphae and granulomatous inflammatory cells in 4 out of 18 dogs (Schultz *et al.*, 2008).

The gold standard for diagnosis of aspergillosis infection is the presenting of hyphae combined with typical colonial color and morphology in which the initial growth is white and becomes black later on giving salt and pepper appearance. The reverse remains a cream color. A typical characteristic of fruiting head was examined and used to identify *Aspergillus niger* under microscopic examination (Markey *et al.*, 2013).

Although a report that surgical removal of fungal granulomas could lengthen survival time in 2 dogs (Whitley *et al.*, 2010), it was inapplicable due to a possible involvement of the granuloma to the nearby esophagus. In general, the successful rate of treatment was low in dogs (Bruchim *et al.*, 2006; Burrough *et al.*, 2012; Walker *et al.*, 2012; Corrigan *et al.*, 2016). The long term outcome of itraconazole treatment could lead to clinical remission in dogs with aspergillus diskospondylitis (Van Wie *et al.*, 2013). Standard antifungal therapy using itraconazole was started. However, a low efficacy of the drug could be found when combined with gastric acid suppression. The interaction of itraconazole and gastric acid suppression drug had been reviewed earlier (Lahner *et al.*, 2009). Since the dog had concurrent vomiting for a period of 5 days, itraconazole was changed to fluconazole as shown previously in human patients with hematological malignancies for reduced side effects including nausea and vomiting (Morgenstern *et al.*, 1999).

Since the result from fungal culture revealed *Aspergillus* spp., an amphotericin B was administered according to drug recommendation in cases of systemic fungal infection in small animals (Taboada and Grooters, 2008). However, due to the nephrotoxic effect of this drug (Hamill, 2013), azotemia developed as detected 18 days after usage. Amphotericin B can bind to the cell membrane of renal tissue and some are excreted into the urine. It has a biphasic half-life, first of 24-48 hours and, later, more than 15 days (Taboada and Grooters, 2008). It can cause renal vasoconstriction with a reduced glomerular filtration rate and can act as a toxin to renal epithelial cells (Plumb, 2015). In this case, the dose was a recommended dose (Plumb, 2015)

but azotemia could be seen in many cases and close monitoring of renal function was required. Thus, the drug was discontinued and was replaced by itraconazole plus terbinafine. Nowadays, a liposomal encapsulation form known as amphotericin B lipid complex has been introduced with lower nephrotoxicity while retaining the antifungal effect of the active agent. The higher plasma concentration and longer half-life compared with conventional amphotericin B was studied in dogs (Bingöl and Bakirel, 2018).

Terbinafine, a nonazole antifungal drug, was used to treat pulmonary aspergillosis in human patients with a more successful outcome compared with itraconazole (Schiraldi *et al.*, 2016). Nevertheless, the efficacy of terbinafine for treatment of systemic aspergillosis in dogs and cats showed controversial results (Papich, 2017). The synergistic effects of itraconazole or other azoles and terbinafine in *In vitro* study was reviewed earlier (Mukherjee *et al.*, 2005). This synergistic effect is the result of the different mechanism on inhibition of fungal cell membrane biosynthesis (Taboada and Grooters, 2008). However, reports of one canine patient with *Aspergillus niger* infection associated with hilar and mesenteric lymphadenomegaly treated with combination of itraconazole and terbinafine showed no clinical improvement (Schultz *et al.*, 2008).

Posaconazole, a triazole antifungal drug, was reviewed for potent and broad-spectrum efficacy against *Aspergillus* spp. in rabbit and mice models (Groll and Walsh, 2006). In humans, posaconazole was approved for the prevention of invasive *Aspergillus* spp. infection by the Food and Drug Administration (U.S. Food & Drug Administration, 2020). In ten dogs, reports of using posaconazole for systemic aspergillosis infection showed that the drug is safe and well-tolerated with survival times of patients ranging from 44 days to more than 5 years (Corrigan *et al.*, 2016). Among nine dogs which received only posaconazole, eight relapsed while another one was lost in follow up. Only one dog which received a combination of posaconazole and terbinafine had a successful clinical remission. However, in this dog, due to a progression of thoracic mass size within 65 days after administration as well as high cost, posaconazole was discontinued and replaced by amphotericin B at the dose of 0.5 mg/kg IV 3 times a week for 5 weeks. The reason for the repeat administration of amphotericin B was because the dog was not azotemia and it was recommended to be used in the systemic mycoses with a poor response to azole therapy (Taboada and Grooters, 2008). Unfortunately, a second episode of azotemia was detected 27 days after amphotericin B administration. The drug was discontinued and replaced by itraconazole given in conjunction with terbinafine and was prescribed until the present which was 7 months after the first diagnosis.

In this case, many protocols of antifungal therapy were introduced based upon the therapeutic responses and complication of drugs. The protocol using a combination of itraconazole and terbinafine could slow the granuloma growth rate. Other medications, such as posaconazol, were ineffective e with high cost.

Amphotericin B, although it might be justified for systemic mycosis, could not be used for long term treatment due to nephrotoxicity. In systemic aspergillosis, the prognosis was poor due to the progressive lesions of fungal granuloma which may be related to inadequate concentrations of antifungal drug in the lesion area.

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