



CASE REPORT

Pulmonary Leucocytoclasitic Necrotizing Vasculitis in a Dog with Uncorrected Tetralogy of Fallot and Peritoneopericardial Diaphragmatic Hernia

Hyun-Ah Park¹, Min-Hee Kang¹, Dae-Young Kim² and Hee-Myung Park^{1*}

¹Department of Veterinary Internal Medicine, College of Veterinary Medicine, Konkuk University, Seoul 143-701, South Korea; ²Veterinary Medical Diagnostic Laboratory, College of Veterinary Medicine, University of Missouri, Columbia, MO 65211, USA

*Corresponding author: parkhee@konkuk.ac.kr

ARTICLE HISTORY (14-532)

Received: October 18, 2014

Revised: February 01, 2015

Accepted: February 02, 2015

Key words:

Hypoxia
Leukocytoclastic vasculitis
Pulmonary necrotizing
Vasculitis
Pulmonary vasculitis
Tetralogy of Fallot

ABSTRACT

A 5-year-old, 5.4 kg, intact female mixed-breed dog presented with acute respiratory distress. Echocardiography showed pulmonary valvular stenosis with narrowing valvular annulus, ventricular septal defect, overriding aorta and the right ventricular hypertrophy. Other concurrent abnormality included sternal deformity, peritoneopericardial diaphragmatic hernia. The dog was diagnosed as a Tetralogy of Fallot. Despite treatments, the dog died 4 days after hospitalization due to respiratory arrest. A complete necropsy was performed. Histopathologic examination of the lung revealed lipid granuloma, pulmonary leukocytoclastic necrotizing vasculitis of the medium- and large-sized arteries, pulmonary thrombosis, and fibrinoid depositions. This case report describes pulmonary leukocytoclastic necrotizing vasculitis in a dog with Tetralogy of Fallot and peritoneopericardial diaphragmatic hernia. To our knowledge, this is first report of leukocytoclastic necrotizing vasculitis of the pulmonary arteries in uncorrected Tetralogy of Fallot with peritoneopericardial diaphragmatic hernia.

©2015 PVJ. All rights reserved

To Cite This Article: Park HA, MH Kang, DY Kim and HM Park, 2015. Pulmonary leucocytoclasitic necrotizing vasculitis in a dog with uncorrected tetralogy of Fallot and peritoneopericardial diaphragmatic hernia. Pak Vet J, 35(2): 260-263.

INTRODUCTION

Tetralogy of Fallot (TOF) is a rare and complex congenital structural cardiac defect; its incidence in dogs has been estimated to be 0.0025% (Fukushima *et al.*, 2013; Kittleson, 1998). The four major characteristics of TOF are pulmonic stenosis (PS), ventricular septal defect (VSD), overriding aorta, and secondary right ventricular (RV) hypertrophy (Fukushima *et al.*, 2013; Kittleson, 1998). Occasionally, TOF is accompanied with other cardiac anomalies such as atrial septal defect, patent ductus arteriosus (PDA), patent foramen ovale, and pulmonary atresia (Andriko *et al.*, 1992). In addition, other congenital abnormalities including ventral abdominal wall herniation, peritoneopericardial diaphragmatic herniation (PPDH), sternal deformity, persistent pupillary membrane, retinal dysplasia, and tracheal hypoplasia can co-occur with TOF in animals and humans (Altun *et al.*, 2014; Hicks *et al.*, 2013; Kittleson, 1998). Clinical symptoms can vary in the severity of the PS and the size of the VSD, and the most dogs dying within a year after birth due to hypoxemia and complication of polycythemia (Kittleson, 1998; Laniesse *et al.*, 2014).

To our knowledge, to date pulmonary leukocytoclastic necrotizing vasculitis (PLcNV) with TOF in this case has not been described in veterinary medicine. Thus, this case report herein describes unusual case of PLcNV in a dog with uncorrected TOF and PPDH.

History and clinical examination: A 5-year-old, 5.4 kg, intact female mixed-breed dog presented with acute respiratory distress. Upon physical examination, the dog showed tachypnea with shallow open-mouth breathing, cyanosis of extremities and muffled heart sound. The heart rate (120 beats per minute) and blood pressure (systolic blood pressure, 136 mmHg) were normal.

Minimum data, including a complete blood count (CBC), serum biochemical profiles, and electrolyte levels, were evaluated. All parameters were normal, except for polycythemia. Arterial blood gas analysis revealed decreased saturated oxygen concentration (SaO_2). A serum level of erythropoietin was markedly elevated. To rule out thromboembolic condition due to polycythemia, fibrin degradation product and D-dimer concentration were measured and the results were normal (Table 1).

Table 1: Hematologic and echocardiographic findings in a dog with tetralogy of Fallot

Parameter	Recorded value	Reference values
Hematologic findings		
PCV (%)	64	37–55
SaO ₂ concentration (%)	55–58	95±1.1
Serum erythropoietin (mIU/mL)	50.26	5–22.00
fibrin degradation product ($\mu\text{g}/\text{ml}$)	5	1–10
D-dimer ($\mu\text{g}/\text{ml}$)	0.2	0.0–0.3
Echocardiographic findings		
PA:Ao ratio	0.69	0.85–1.15
Transpulmonary pressure gradient (mmHg)†(peak velocity flow)	47.9 (3.46 m/s)	25
Pulmonary hypertension (mmHg)† (tricuspid regurgitation jet velocity flow)	49.08 (3.32 m/s)	15–20

†Pressure gradient was calculated with using Modified Bernoulli equation, $\Delta P = 4V^2$. Pulmonary hypertension was calculated with adding estimated right atrium pressure, 5mmHg. Ao, aorta; PA, pulmonary artery; PCV, packed cell volume; SaO₂, saturated oxygen.

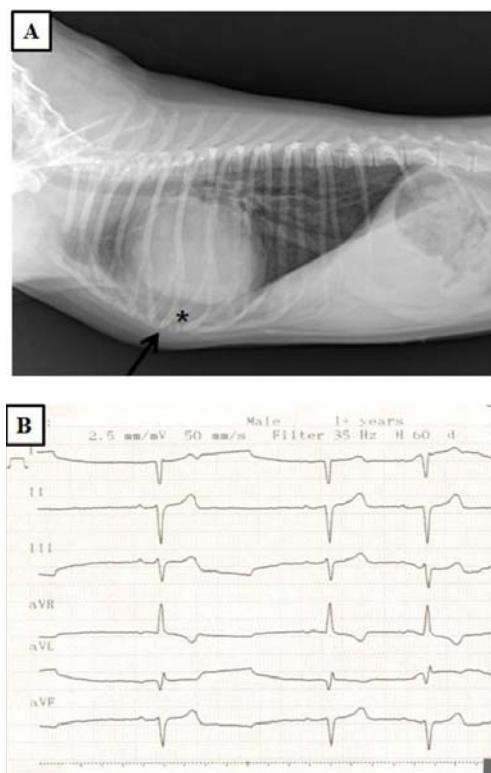


Fig 1: (A) Survey radiography of the thorax showed a globoid-shaped heart with cardiomegaly, fat density within the pericardial sac (asterisk), and sternal deformity (arrow). (B) The electrocardiogram showed a deep S wave in leads I, II, III, and aVF. The QRS axis is shifted to the right (+229 degrees). Paper speed = 50 mm/s, 2.5 mm = 1 mV.

Thoracic radiography showed a globoid-shaped heart with fat density within the pericardial sac, dorsal deviation of caudal vena cava and sternal deformity in the right-lateral view (Fig. 1A). Electrocardiography displayed the right axis deviation, a deep S wave in leads I, II, III, and aVF which is consistent with severe RV concentric hypertrophy in TOF patient (Fig. 1B) (Kittleson, 1998). Echocardiography showed pulmonary valvular stenosis with narrowing valvular annulus, VSD, overriding aorta and the RV hypertrophy (Fig. 2A-C). The ratio of the diameter of the main pulmonary artery (PA) to the ascending aorta was increased (Table 1). Post-stenotic dilation of main PA (1.96 times larger than pulmonary

valve diameter) was also noted (Fig. 2C). To assess PS severity, transpulmonary peak velocity flow was measured. The result was consistent with moderate PS. Furthermore, tricuspid regurgitation jet velocity revealed mild pulmonary hypertension (PH) (Table 1) (Steiner *et al.*, 2010). Shunting of the blood flow from RV to the aorta through the VSD was confirmed by means of an agitated saline injection on the right parasternal long axis view at the level of aortic valve (Fig. 2D).

To assess respiratory distress, screening tests for common infectious diseases were performed. The results of heartworm antigen test kit and microfilaria test were negative. Polymerase chain reaction analysis for respiratory viral agents such as the canine distemper virus, influenza virus, and herpes virus yielded negative results.

Diagnosis and postmortem findings: The dog was diagnosed as a typical right to left shunt TOF with mild PH. Emergency treatments including oxygen supplement and phlebotomy were initiated immediately. Despite treatments, the dog died 4 days after hospitalization due to respiratory arrest.

A complete necropsy was performed. The greater omentum herniated through the perforated diaphragm, and was located between the sternum and heart, inside the pericardial sac (Fig. 3A). Fat density within the pericardial sac on the radiography revealed as a PPDH of great omentum.

The lung showed multifocal yellowish spots (Fig. 3B). Histopathologic examination of the lung showed lipid granuloma and PLcNV of the medium- and large-sized arteries, pulmonary thrombosis, and fibrinoid deposition (Fig. 4). Upon heart dissection, all the structural defects indicative of TOF and thickened hypoplastic pulmonic valve leaflets were observed (Fig. 3C and 3D). To identify other causes, which can trigger leukocytoclastic reaction to the lung, additional tests for fungal and protozoal infection, including aspergillosis, histoplasmosis, coccidioidomycosis, blastomycosis, cryptococcosis, *Toxoplasma gondii* and *Neospora caninum*, were conducted and the results were negative.

DISCUSSION

A few reports of pulmonary necrotizing vasculitis related to PDA and PH have been published in veterinary medicine (Russell *et al.*, 2008). Leucocytoclastic vasculitis (LcV) is an inflammation of small vessel wall, mainly affects skin and the postcapillary venules, rarely affects medium- and large-size vessels or internal organs including lung (Brown, 2010; Sunderkötter, 2008). The main cause of LcV is deposition of immune complexes at the vessel walls by various drugs, infection, tumor or hypersensitivity reaction (Brown, 2010; Sunderkötter, 2008). When it affects medium-sized vessels, the intramural and perivascular infiltration in the vessels occurs. Later stage, impairment of the anti-thrombogenic activity of the endothelial surface leads thrombosis and necrosis of the tissue are developed (Sunderkötter, 2008). As described earlier (Brown, 2006), primary, idiopathic, small-vessel vasculitis is most commonly seen with the lung involvement. Rarely, primary immune complex-mediated vasculitis and primary idiopathic medium- and

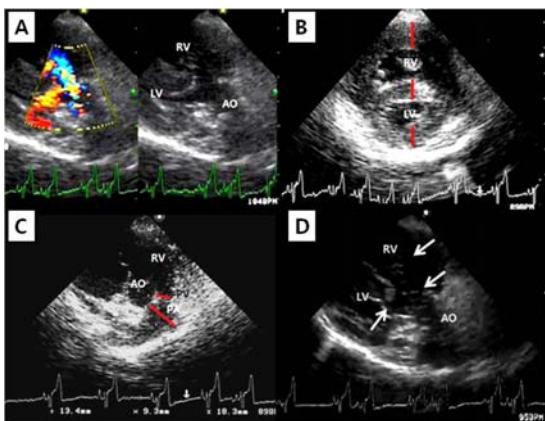


Fig 2: (A) Color flow Doppler echocardiogram from the right-parasternal long axis 5 chamber view showed a ventricular septal defect and an overriding aorta. (B) Right ventricular hypertrophy at the level of right-parasternal papillary muscle view and (C) pulmonic valvular stenosis and post-stenotic dilation of the main pulmonary artery at the level of the pulmonic valve view was observed. (Ao, 13.4 mm; PV, 9.3 mm; main PA, 18.3 mm). (D) Saline bubble (arrows) flow from the right ventricle to the left ventricle and the aorta. Ao, aorta; LV, left ventricle; PA, pulmonary artery; PV, pulmonic valve; RV, Right ventricle.

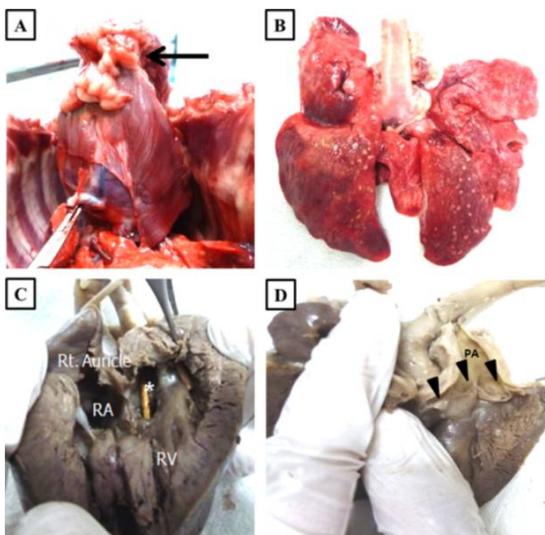


Fig 3: (A) Gross lesions after necropsy showed that the greater omentum was located between the sternum and the pericardial sac (a black arrow). (B) Multiple spots were noted on the lung. (C) Upon heart dissection, ventricular septal defect (asterisk) and a thickening of the right ventricle wall were noted. (D) A degenerated and stretched pulmonic valve was also observed (arrowheads). RA, right atrium; RV, right ventricle; Rt. Auricle, right auricle.

large-vessel vasculitis may also present, which is consistent with that of the case.

In this case, the dog had been under the chronic systemic hypoxic state and SaO_2 concentration was lower than a dog with TOF previously described (SaO_2 concentration < 65%) (Kittleson, 1998). Several studies demonstrated that the pulmonary vascular remodeling is closely associated with chronic hypoxia leading to PH. Decreasing nitrogen oxide secretion, increasing secretion of endothelin-1, a potent endogenous vasoconstrictor and growth factor, and hypoxia-inducible factors-1 α play a major role in pulmonary vascular remodeling. Those vascular remodeling includes vasculitis in response to

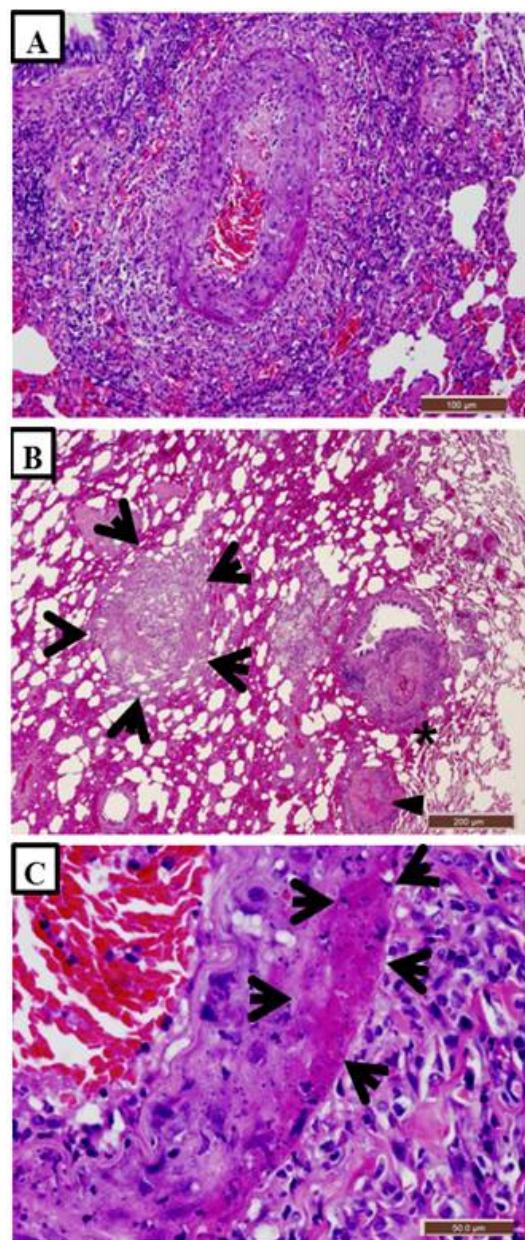


Fig 4: (A) Photomicrographs of the lung. Histopathology of the lung showed marked leukocytoclastic necrotizing vasculitis of the medium- and large-sized arteries (Bar=100 μm). (B) Pulmonary thrombosis (arrowhead), lipid granuloma (arrows), and vasculitis (asterisk) were observed. (Bar=200 μm). (C) Fibrinoid depositions (arrows) were observed. (Bar=50 μm). Hematoxylin and Eosin (H&E) staining.

hypoxia, PH and pulmonary thromboembolic conditions (Ball *et al.*, 2014; Kim *et al.*, 2000).

Additionally, a previous study (Stenmark *et al.*, 2006) also demonstrated that when chronic hypoxic state maintained in the systemic circulation, microcirculation of the adventitial vasa vasorum undergoes marked neovascularization. This process serves as a means for the continuous delivery of inflammatory and progenitor cells to the vessel wall and causing vasculitis.

Based on those findings described above, it is possible that the PLcNV and thrombus formation combined with TOF possibly leads to secondary PH in this case. These processes might be accelerate more

formation of vasculitis and thrombus due to PH, decreasing more SaO_2 concentration, aggravating respiratory distress, eventually leads to death (Steiner *et al.*, 2010). Unfortunately, there were no evidences that can trigger leukocytoclastic reaction and it remains as an idiopathic. However, a study on pulmonary vasculitis in TOF with pulmonary atresia has been reported in human medical literature (Andriko, 1992).

Conclusion: This case demonstrates that uncorrected TOF could be one of congenital heart disease that might trigger pulmonary vascular remodeling which results in, pulmonary necrotizing vasculitis, thrombosis and PH.

REFERENCES

- Altun A, SA Kurna, E Bozkurt, G Erdogan, G Altun, OO Olcaysu and SF Aki, 2014. Bilateral persistent pupillary membrane with tetralogy of fallot: a case report and review of the literature. Case Rep Ophthalmol Med, 2014: 581273.
- Andriko JA, M Robinowitz, J Moore, and R Virmani, 1992. Necrotizing arteritis in uncorrected tetralogy of fallot with pulmonary atresia. Pediatr Cardiol, 13: 233-236.
- Ball MK, GB Waypa, PT Mungai, JM Nielsen, L Czech, VJ Dudley, L Beussink, RW Dettman, SK Berkelhamer, RH Steinhorn, SJ Shah and PT Schumacker, 2014. Regulation of hypoxia-induced pulmonary hypertension by vascular smooth muscle hypoxia-inducible factor-1 α . Am J Respir Crit Care Med, 189: 314-324.
- Brown K, J Martin and S Zito, 2010. Severe leukocytoclastic vasculitis secondary to the use of a naproxen and requiring amputation: a case report. J Med Case Rep, 4: 204.
- Brown KK, 2006. Pulmonary Vasculitis. Proc Am Thorac Soc, 3: 48-57.
- Fukushima R, R Yoshiyuki, N Machida, H Matsumoto, S Kim, L Hamabe, H Huai-Che, T Fukayama, S Suzuki, D Aytemiz, R Tanaka and Y Yamane, 2013. Extreme tetralogy of Fallot in a dog. J Vet Med Sci, 75: 1111-1114.
- Hicks KA and AP Britton, 2013. A fatal case of complicated congenital peritoneopericardial diaphragmatic hernia in a Holstein calf. Can Vet J, 54: 687-689.
- Kittleson MD, 1998. Tetralogy of Fallot. In: Small animal cardiovascular Medicine, Mosby, St. Louis, USA, pp: 240-247.
- Laniesse D, J Hébert, S Larrat, P Hélie, B Pouleur-Larrat and MC Belanger, 2014. Tetralogy of Fallot in a 6-year-old albino ferret (*Mustela putorius furo*). Can Vet J, 55: 456-461.
- Russell NJ, PJ Irwin, BJ Hopper, T Olivry and PK Nicholls, 2008. Acute necrotising pulmonary vasculitis and pulmonary hypertension in a juvenile dog. J Small Anim Pract, 49: 349-355.
- Steiner I, V Bolosová and S Fejtova, 2010. Pulmonary hypertensive necrotizing arteritis: an unusual case of unilateral involvement in an infant with congenital heart disease. Pathol Res Pract, 206: 472-475.
- Stenmark KR, KA Fagan and MG Frid, 2006. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circ Res, 99: 675-691.
- Sunderkötter C, 2008. Leukocytoclastic Vasculitis. CME dermatol, 3: 32-50.