pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 35(5) : 218-221 (2018)
http://dx.doi.org/10.17555/jvc.2018.10.35.5.218

Journal of Veterinary Clinics
www.ksvc.or.kr

Successful Management of a Life Threatening Canine Multicentric Lymphoma with Pulmonary Thromboembolism

Min-Young Moon, Guk-Hyun Suh, Hyeong-Il Choi, Joonyoung Kim and Ha-Jung Kim[1]

Department of Veterinary Internal Medicine, College of Veterinary Medicine, Chonnam National University, Gwangju 500-757, South Korea

(Received: August 22, 2018 / Accepted: October 13, 2018)

Abstract : A 12-year-old, intact female Jindo was referred to our clinic due to the enlargement of all lymph nodes, as well as severe dyspnea. All palpatible lymph nodes were highly swelling and enlargement. The dog was diagnosed as end stage of multicentric lymphoma with multi-organ metastasis. In addition, the dog was diagnosed as having a pulmonary thromboembolism via computed tomography (CT) and D-dimer concentrations and prothrombin time (PT) results. This case report describes that lymphoma can be associated with pulmonary thromboembolism which is life threatening complication in dogs. The present case was managed successfully with chemotherapy and antithrombotic treatment.

Key words **:** dog, lymphoma, pulmonary thromboembolism.

Introduction

Pulmonary thromboembolism (PTE) is caused by thrombotic material that disseminates from a primary thrombus within the heart or vascular system (5,6,10,11,15,17,20,22, 23,24). Disease states that fulll Virchow's triad (a hypercoagulable state, endothelial damage, and blood stasis) lead to thrombus formation within the blood vessels (5,6,10,11,15, 17,20,22,23,24). Embolization of these thrombi can result in vascular occlusion within the pulmonary vasculature (5,6,10, 11,15,17,20,22,23,24). Clinical signs of PTE typically include respiratory distress and tachypnea. PTE formation in dogs has been associated with immune-mediated hemolytic anemia, neoplasia, cardiac diseases, protein-losing enteropathies and nephropathies, hyperadrenocorticism (HAC), sepsis, disseminated intravascular coagulation (DIC), trauma, vasculitis, and surgery (5,6,10,11,15,17,20,22,23,24).

Lymphoma is one of the most common cancers in dogs, comprising 7% to 24% of all canine neoplasia (13). Boxers, Scottish Terriers, Airedale Terriers, Basset Hounds, German Shepherds, Bulldogs, and Bernese Mountain dogs are most commonly affected. The dog described in this report was administered chemotherapies to treat multi-centric nodal lymphoma with PTE.

Case

A 12-year-old, intact female Jindo was referred for enlargement of systemic lymph nodes. On physical examination, the peripheral lymph nodes showed swelling and enlargement, without any pain in that region. History taking revealed that the enlargement of the lymph nodes started 2 months ago, and that the dog demonstrated exercise intolerance. The clinical signs were anorexia, weakness, and coughs. In addition, mucous membrane pallor was noted. Abdominal palpation revealed organomegaly. The dog demonstrated dyspnea, a life-threatening emergency. Air movement was audible in all lung fields during auscultation.

Cytological examination of the mandibular and inguinal lymph nodes revealed that there were more than 50% blastic cells, which are characterized by predominance of large lymphoblasts and a mitotic activity ranging from low to high in the collected aspirate (Fig 1). Numerous lymphoblasts with anisocytosis and prominent nucleoli in the cells were noted. The complete blood count revealed mild regenerative anemia and mild thrombocytopenia, with no autoagglutination noted on the glass slide agglutination test. Serum biochemical analysis revealed hypoproteinemia and mildly elevated levels of alkaline phosphatase and creatine kinase. Radiographic examination revealed main pulmonary artery dilatation, parenchymal pulmonary artery enlargement, and a peripheral multifocal alveolar pulmonary pattern. Enzyme-linked immunosorbent assay (ELISA) tests performed with a commercial heartworm antigen kit yielded negative results. The elevated D-dimer concentration (1900 ng/mL; reference interval, 0-300 ng/mL) and delayed prothrombin time (PT) results (19 s; reference interval, 11-17 s) indicated the possibility of significant blood clot (thrombus) formation and breakdown in the body, which in turn may cause DIC. The dog demonstrated exercise intolerance, rapid fatigue with exercise, and coughing. Chest and abdominal radiographs showed abnormally enlarged lymph nodes that affected the liver and spleen, in addition to other abnormal radiographic findings including alveolar or interstitial pulmonary infiltrates and thoracic lymphadenomegaly.

[1]Corresponding author.
E-mail : kimhj614@jnu.ac.kr

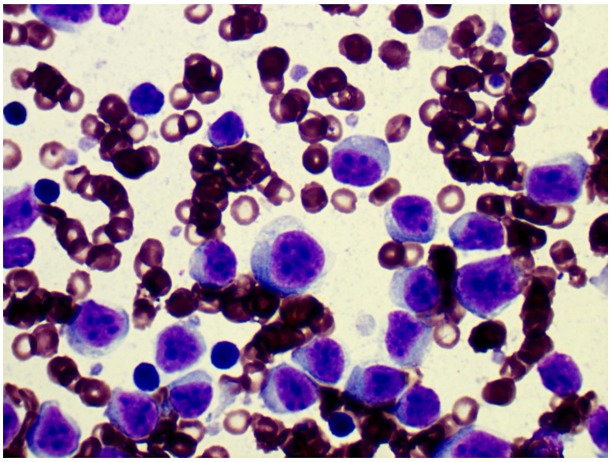

Fig 1. Cytology of the mandibular lymph node. Typical lymphoma cells are characterized by large nucleoli and scanty basophilic cytoplasm (Differential staining, × 1,000).

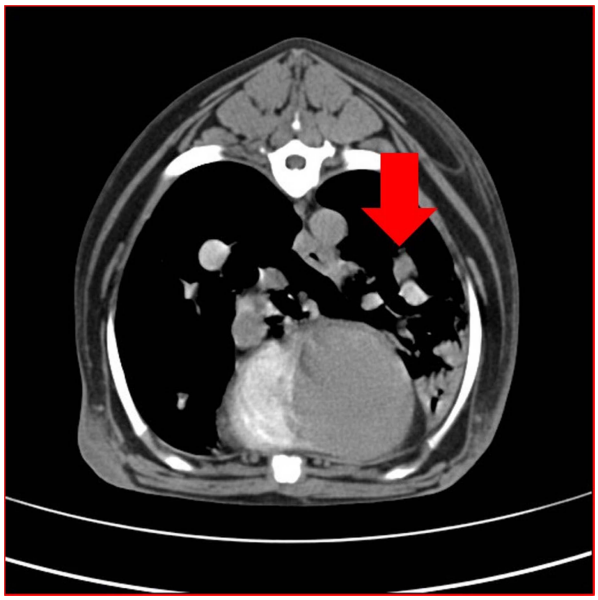

Fig 2. Chest spiral computed tomographic scan with a radio contrast agent showing the filling defect in the pulmonary arteries relating with pulmonary thromboembolism.

On computed tomographic (CT) examination, most of the lymph nodes including the bilateral submandibular, parotid, retropharyngeal, prescapular, axillary, sternal, cranial mediastinal, and tracheobronchial lymph nodes were markedly enlarged. PTE was diagnosed via CT, which facilitated direct visualization of intraluminal clots: partial and complete filling defects in the central pulmonary arteries. Therefore, the dog was definitively diagnosed as having a multicentric lymphoma with metastasis (TNM stage IV) and PTE secondary to the lymphoma.

After establishing the diagnosis of PTE, dalteparin sodium (Fragmin®; 150 IU/kg, SC, bid; Pfizer, New York, U.S.A.) with aspirin (Rhonal®; 1 mg/kg, PO, bid; Alvogen Korea, Seoul, South Korea) and clopidogrel bisulfate (Plavix®; 2 mg/kg, SC, sid; Ilyangbio, Jecheon, South Korea) were administered for anticoagulant and antiplatelet therapy. Additionally, aminophylline (Aminophylline®; 10 mg/kg, IV, tid; Daewonpham, Incheon, South Korea) was administered to make breathing easier and keep air passages. The PTE-related symptoms, i.e., coughing, dyspnea, and exercise intolerance were gradually improved. The D-dimer concentration, PT, and PTT tests yielded the following results: 100 ng/mL, 12 s, and 72 s, which were all in normal range, and were indicative of low risk following application of bronchodilator, anticoagulant, and antiplatelet agents. The UW-19 protocol involves administration of vincristine, cyclophosphamide, doxorubicin, and prednisolone for a 19-week period. Tramadol and a fentanyl patch were used to reduce pain and discomfort. The dog with stage IV lymphoma and PTE was successfully treated with the UW-19 protocol, and was responsive to anticoagulant therapy. These treatments was successfully performed becoming the size of lymph nodes without any respiratory complication.

Discussion

At initial presentation, the dog demonstrated life-threatening emergency because of dyspnea and abdominal respiration. Immediately, oxygen therapy was administered to relieve the aforementioned symptoms. The elevated D-dimer and delayed PT results indicate that there may be significant blood clot (thrombus) formation. History taking revealed that the dog demonstrated reluctance to exercise, rapid fatigue with exercise, and coughing recently.

The D-dimer concentration was elevated at 1900 ng/mL, and the PT was 19 s. The sensitivity and specificity of D-dimer for TE diagnosis have been demonstrated in a previous report, which have shown that evaluating D-dimer concentration > 300 ng/mL for TE was 100%, and the specificity of D-dimer for TE at that concentration was 70% (8). An elevated D-dimer concentration indicates the presence of a clot. A pulmonary embolism is associated with the possibility of occurrence of those conditions. In the present case, PTE was diagnosed via CT, which facilitated the direct visualization of intraluminal clots: partial and complete filling defects in the central pulmonary arteries. CT revealed that the PTE caused partial obstruction of the PA and its branches by thrombi (Fig 2).

The relation between cancer and thrombosis is well recognized (13,14,21) and the occurrence of thrombotic complications in patients with cancer has important implications, including need for chronic anticoagulation with the associated risk for bleeding, possible delays in delivering chemotherapy, a high risk for recurrence of thrombosis, and a decreased quality of life. Approximately 10-15% of patients with cancer demonstrate clinical features indicative of thromboembolism, with greater numbers of patients with certain tumor types identified at the time of autopsy (7). The risk for thrombus formation in individuals with neoplasia increases 4-fold compared with the general population and is even higher for those receiving chemotherapy (16). As the second leading cause of death in those with malignant conditions, hypercoagulability and thrombosis associated with neoplasia are extensively studied and anticoagulation protocols have been established for this patient population (12).

In a previous study, Kristensen *et al.* found hemostatic dysfunction in 57% of dogs with neoplasia (20). Hemostatic dysfunction and hypercoagulability in patients with cancer are complex conditions with a multifactorial etiology that includes expression of procoagulant molecules such as tissue factor on the surface of malignant cells, release of fibrinolytic peptides, inhibition of endogenous anticoagulation, release of cytokines by cancer cells, and interaction with host cells including endothelial cells and blood leukocytes (9,25). Increased number of activated platelets and release of platelet micro vesicles have also been related to hypercoagulability in cancer (1,18,19). All these mechanisms additionally support cancer cell growth and metastasis (1,18,19). Therefore, anticoagulant therapy in combination with chemotherapy should be administered to relieve the pulmonary thromboembolism.

Mechanisms by which hypercoagulability develops in response to neoplasia are multifactorial, which affect all 3 aspects of Virchow's triad, and are still not completely understood (4). Tumor cells themselves may be prothrombotic, inducing thrombin generation through tissue factor expression or fibrinogen production, or by downregulation of the endogenous anticoagulant proteins antithrombin (AT), protein C, and protein S (4).

Downregulation of fibrinolysis through altered tissue plasminogen activator expression will also promote a procoagulant state (4). Platelet hyper-reactivity in cancer has been also documented in multiple tumor types, and it has been suggested that inappropriate platelet activity may promote metastasis (4). Increased platelet micro-particles, which provide additional phospholipid surfaces for tissue factor expression, have been documented in several forms of cancer and may be linked to the risk for thrombosis and development of metastasis (3). Cytokine-induced endothelial injury, as evidenced by changes in von Willebrand factor antigen levels, further contributes to thrombotic tendency and may increase platelet adhesion (11).

Changes in thrombomodulin expression on the endothelial surface, typically anticoagulant by virtue of protein C binding, is another finding indicative of a hypercoagulable state in patients with cancer.

Conclusions

In conclusion, the present case indicated the association between lymphoma and hypercoagulability in dogs. In the present case, a canine multicentric lymphoma accompanied by PTE was successfully managed over the course of 270 days.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D1A3B04934798).

Conflict of interests

The authors declare no conflicts of interest with respect to the publication of this report.

References

1. Almirall L, Az-Ricart M, Bastida E, Ordinas A. The role of platelets in Cancer metastasis. Blood Coagul Fibrinolysis 1990; 1: 707-711.
2. Andreasen E, Jensen AL, Jessen LR, Kristensen AT, Wiinberg B. Evaluation of human recombinant tissue factor-activated thromboelastography in 49 dogs with neoplasia. J Vet Intern Med 2008; 22: 140-147.
3. Andrew DB, Simon D. Arterial and venous thrombosis in cancer patients. Card Res Pract 2011: 394-740.
4. Armelle DL. Diseases Associated with Thrombosis. Topics in Companion Animal Medicine 2012; 27: 59-64.
5. Baines EA, Stidworthy MF. Watson PJ. Gross pulmonary thrombosis in a greyhound. J Small Anim Pract 2001; 42: 448-452.
6. Baker DC, Johnson LR, Lappin MR. Pulmonary thromboembolism in 29 dogs (1985-1995). J Vet Intern Med 1999; 13: 338-345.
7. Bell WR, Levin J, Sack GH Jr, Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore) 1977; 56: 1-37.
8. Brooks MB, McCullough SM, Stokol-Moncrieff JC, Treadwell NG. Hemostatic abnormalities in dogs with primary immune-mediated hemolytic anemia. JAAHA 2001; 61: 393-398.
9. Caine GJ, Kehoe ST, Lip GY, Stonelake PS. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia 2002; 4: 465-473.
10. Calzolari D, Morini S, Venco L. Pulmonary thromboembolism in a dog with renal amyloidosis. Vet Radiol Ultrasound 1998; 39: 564-565.
11. Carr AP, Kidd L, Panciera DL. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. J Vet Intern Med 2002; 16: 504-509.
12. Donati MB, Cancer and thrombosis: from Phlegmasia alba dolens to transgenic mice. Thromb Haemost 1998; 74: 278-281.
13. Donati MB, Falanga A. Pathogenesis of thrombosis in patients with malignancy. Int J Hematol 2001; 73: 137-144.
14. Donati MB. Thrombosis and cancer: a personal view. Thromb Haemost Pub Med 2007; 98: 126-128.
15. Dow SW, Klein MK, Rosychuk RA. Pulmonary thromboembolism associated with immune-mediated hemolytic anemia in dogs: ten cases (1982-1987). J Am Vet Med Assoc 1989; 195: 246-250.
16. Edwards RL, Levine M, Rickles FR. Hemostatic alterations in cancer patients. Cancer Metastasis Rev 1992; 11: 237-248.
17. Hylands R. Pulmonary thromboembolism. Can Vet J 2006; 47: 385-388.
18. Janowska-Wieczorek A, Kijowski J, Machalinski B, Marquez-Curtis L, Ratajczak J, Ratajczak MZ, Wysoczynski M. Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer 2005; 113: 752-760.
19. Kakkar AK, Nash GF, Scully MF, Turner LF. Platelets and cancer. Lancet Oncol 2002; 3: 425-430.
20. Kornreich B, Pembleton-Corbett JR, Schermerhorn T. Pulmonary thromboembolism in cats. J Vet Intern Med 2004; 18: 533-535.
21. Korte W. Cancer and thrombosis: an increasingly important

association. Support Care Cancer 2008; 16: 223-228.
22. LaRue MJ, Murtaugh RJ. Pulmonary thromboembolism in dogs: 47 cases (1986-1987). J Am Vet Med Assoc 1990; 197: 1368-1372.
23. Liska WD, Poteet BA. Pulmonary embolism associated with canine total hip replacement. Vet Surg 2003; 32: 178-186.
24. Ritt MG, Rogers KS, Thomas JS. Nephrotic syndrome resulting in thromboembolic disease and disseminated intravascular coagulation in a dog. J Am Anim Hosp Assoc 1997; 33: 385-391.
25. Winter PC. The pathogenesis of venous thromboembolism in cancer: emerging links with tumour biology. Hematol Oncol 2006; 24: 126-133.