Shiraz University

IJVR

ISSN: 1728-1997 (Print)
ISSN: 2252-0589 (Online)

Vol. 20 No. 3 Ser. No. 68 2019

IRANIAN JOURNAL OF VETERINARY RESEARCH

Scientific Report

Pericardial effusion in a dog concurrent with carcinoma of unknown primary origin

Kang, M. H.[1]; Sur, J. H.[2] and Park, H. M.[1*]

[1]Department of Veterinary Internal Medicine, College of Veterinary Medicine, Konkuk University, Seoul 05029, South Korea; [2]Department of Veterinary Pathology, Small Animal Tumor Diagnostic Center, College of Veterinary Medicine, Konkuk University, Seoul 05029, South Korea

[*]***Correspondence:*** *H. M. Park, Department of Veterinary Internal Medicine, College of Veterinary Medicine, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, South Korea. E-mail: parkhee@konkuk.ac.kr*

(Received 17 Mar 2018; revised version 18 Mar 2019; accepted 20 Apr 2019)

Abstract

Background: Pericardial effusion (PE) due to secondary metastasis has rarely been reported in dogs. **Case description:** This case describes clinical signs and further diagnostics regarding metastatic carcinoma of unknown primary origin (CUP) in refractory PE of a dog. **Findings/treatment and outcome:** A nine-year-old, castrated male Shih Tzu dog was referred for evaluation of cough and dyspnea. On presentation, tachypnea, intermittent cough, and muffled heart sounds were noted. Thoracic radiography, electrocardiography, and echocardiography confirmed a PE. No mass lesion was detected at the heart base, aorta, or right atrium (RA). Analysis of the PE showed hemorrhagic cytology, and an idiopathic hemorrhagic PE was tentatively diagnosed. The dog responded to conservative treatment with steroid and diuretics, but the clinical sign recurred. Further evaluation with multi-detector computed tomography (MDCT) was non-diagnostic. The dog died 457 days after initial presentation. Necropsy and histopathology revealed metastatic CUP origin. **Conclusion:** This case illustrated a rare cause of recurrent PE in dogs.

Key words: Dog, Dyspnea, Metastatic cancer, Pericardial effusion

Introduction

A biopsy-proven malignancy of epithelial and undifferentiated cancer with unknown anatomic origin is defined as carcinoma of unknown primary origin (CUP) (Varadhachary, 2007; Pavlidis *et al*., 2015). Carcinoma of unknown primary origin is common and well-recognized in humans; and is reported in approximately 2-5% of all cancer cases (Pavlidis and Fizazi, 2009). Complete medical history, a careful physical examination, blood tests including liver and kidney function tests, chest radiography, and further imaging such as computed tomography (CT) is essential for diagnosis of CUP (Pavlidis *et al*., 2003; Varadhachary, 2007). The prognosis of metastatic carcinoma in humans is poor, frequently 6 to 12 months (Pavlidis *et al*., 2003). In veterinary medicine, few studies have focused on CUP (Morrison, 2002; Rossi *et al*., 2015).

Common causes of pericardial effusion (PE) in dogs can be divided into neoplastic and non-neoplastic conditions (Stafford Johnson *et al*., 2004; MacDonald *et al*., 2009; Cagle *et al*., 2014). Neoplastic conditions include hemangiosarcoma of the right atrium (RA), chemodectoma of the heart base, and mesothelioma. Non-neoplastic causes of PE include idiopathic pericarditis, acquired cardiac disease such as right heart failure and left atrial rupture, and a few congenital disorders. Metastatic carcinoma is a common cause of PE in humans, but is seldom reported in dogs (Refaat and Katz, 2011).

This case reports clinical signs and further diagnostics regarding metastatic CUP origin in refractory PE of a dog.

Case description

A 9-year-old castrated male Shih Tzu dog was admitted with a 10-day history of cough and progressive dyspnea. The dog also had recently decreased appetite and weight loss. On presentation, the dog was mildly depressed. Tachypnea (62 breaths/min), weak femoral pulses, intermittent cough, and serous nasal discharge were observed. Auscultation revealed muffled heart sounds (heart rate, 168 bpm), with crackles in the left lung fields. Thoracic radiography revealed an increase in the cardiac silhouette and mild left pleural effusion (Figs. 1A-B). Electrocardiography showed low R wave amplitude and a deep S wave with electrical alternans. Clinical examination was consistent with PE. Echocardiography revealed anechoic fluid surrounding the heart and collapse of the RA during diastole (Figs. 2A-B). Hematology and serum chemistry showed elevated alanine aminotransferase (82 U/L; reference interval, 19-70 U/L), alkaline phosphatase (183 U/L; reference interval, 15-127 U/L), and aspartate amino-transferase (157 U/L; reference interval, 17-44 U/L) activities. Coagulation profiles were within normal range (prothrombin 8 s, reference interval 6.2-8.2 s; activated

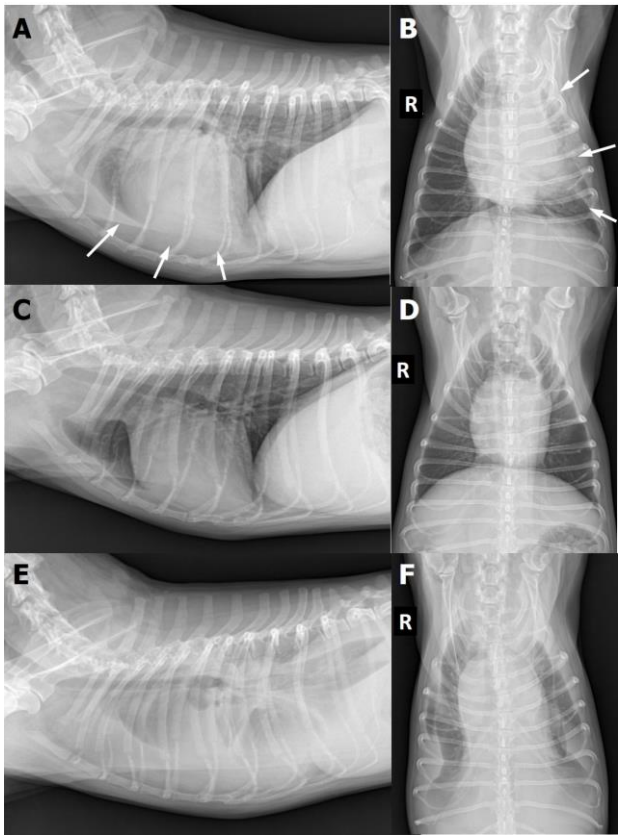

Fig. 1: Thoracic radiography showing recurrent pericardial and pleural effusion in the dog. Lateral (**A**) and dorsoventral thoracic radiography (**B**) at first presentation showed a globoid cardiac silhouette and a left pleural effusion (arrows). Pleural and pericardial effusions disappeared within a month after starting treatment (**C**, **D**), but recurred 4 months later and were uncontrolled before death (**E**, **F**)

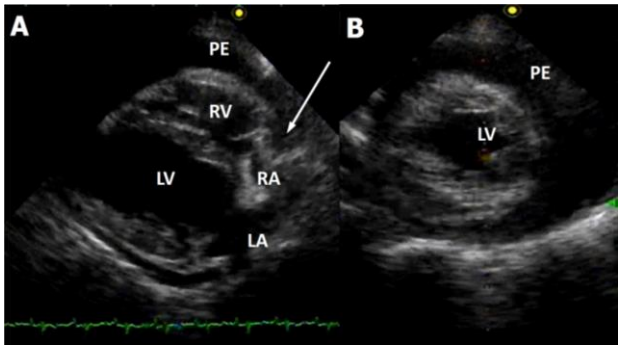

Fig. 2: Echocardiographic examination showing recurrent pericardial effusion in the dog. Anechoic space surrounding the heart and diastolic collapse of the right atrium (RA, arrow) was noted on transthoracic 4-chamber (**A**) and short axis views (**B**). LA: Left atrium, LV: Left ventricle, RA: Right atrium, RV: Right ventricle, and PE: Pericardial effusion

partial thromboplastin time 12.4 s, reference interval 12-14 s; activated clotting time 128 s, reference interval <140 s). After stabilization with oxygen treatment, pericardiocentesis was performed. A total of 80 ml of cloudy, dark red fluid (total protein 2.8 g/dL, 1.69×10^3 nucleated cells/µL, packed cell volume 27%) was removed. Cytological evaluation of the fluid showed numerous erythrocytes with a few mesothelial cells. Hemorrhagic PE was confirmed, and culture results were negative. Antinuclear antibody was negative. Serum troponin-I (0.1 ng/ml; reference interval, <0.2 ng/ml) and D-dimer levels (0.1 µg/ml; reference interval, 0.1-0.3 µg/ml) were also normal. Idiopathic hemorrhagic PE was strongly suspected.

The dog was stabilized after pericardiocentesis and discharged 2 days later. Prednisolone (1 mg/kg, twice daily, tapered to 0.5 mg/kg twice daily within 2 weeks) and furosemide (1 mg/kg, twice daily) were initiated. The dog was evaluated 7 and 30 days later. Pleural and PE disappeared, and the general condition of the dog improved (Figs. 1C-D). However, clinical signs recurred 4 months after initial presentation. The dog was partially responsive to steroids, but slowly deteriorated. Periodic pericardiocentesis and thoracentesis were performed. Abundant mesothelial cells with variable size were noted on repeated cytological evaluation of the pericardial fluid. Multi-detector computed tomography (MDCT) (Asteion Super 4 apparatus, Toshiba, Tokyo, Japan) was performed (Ian Animal Diagnostic Center, Seoul, Korea) to evaluate other possible causes of recurrent pericardial and pleural effusion. Computed tomography showed a PE with smooth pericardial thickening and a pleural effusion (Figs. 3A-B). No other abnormalities were noted. However, the severe pleural and PE was not controlled (Figs. 1E-F) and D-dimer level increased to 1.3 µg/ml. The dog died 457 days after initial diagnosis. Necropsy revealed thick, fibrotic pericardial adhesions involving surrounding structures. Sternal lymph nodes were enlarged. Mild ascites and hepatomegaly were found. Histopathologic examination revealed metastatic carcinoma involving epicardium, sternal lymph nodes, and multiple lung lobes (Figs. 4A-F). Thickening of the pericardium was marked with dense fibrous tissue and inflammatory cells (plasma cells and lymphocytes) were infiltrated around vessels. Hepatic histopathology was non-specific. Further immunohistochemistry staining demonstrated highly positive immunoreactivity for pan-cytokeratin antibody (AE1/AE3) and negative immunoreactivity for vimentin. Thus, metastatic carcinoma rather than mesothelioma was suggestive. However, the accurate primary tumor site was not identified.

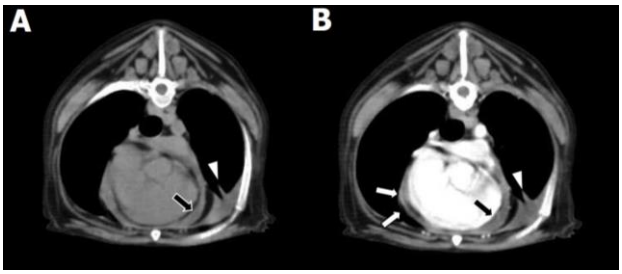

Fig. 3: Computed tomography of the thorax in a dog with recurrent pericardial and pleural effusion. Before (**A**) and after contrast-enhanced (**B**) transverse CT of the thorax at the level of the heart showed pericardial effusion (black arrow) with smooth pericardial thickening (white arrows) and pleural effusion (arrowhead)

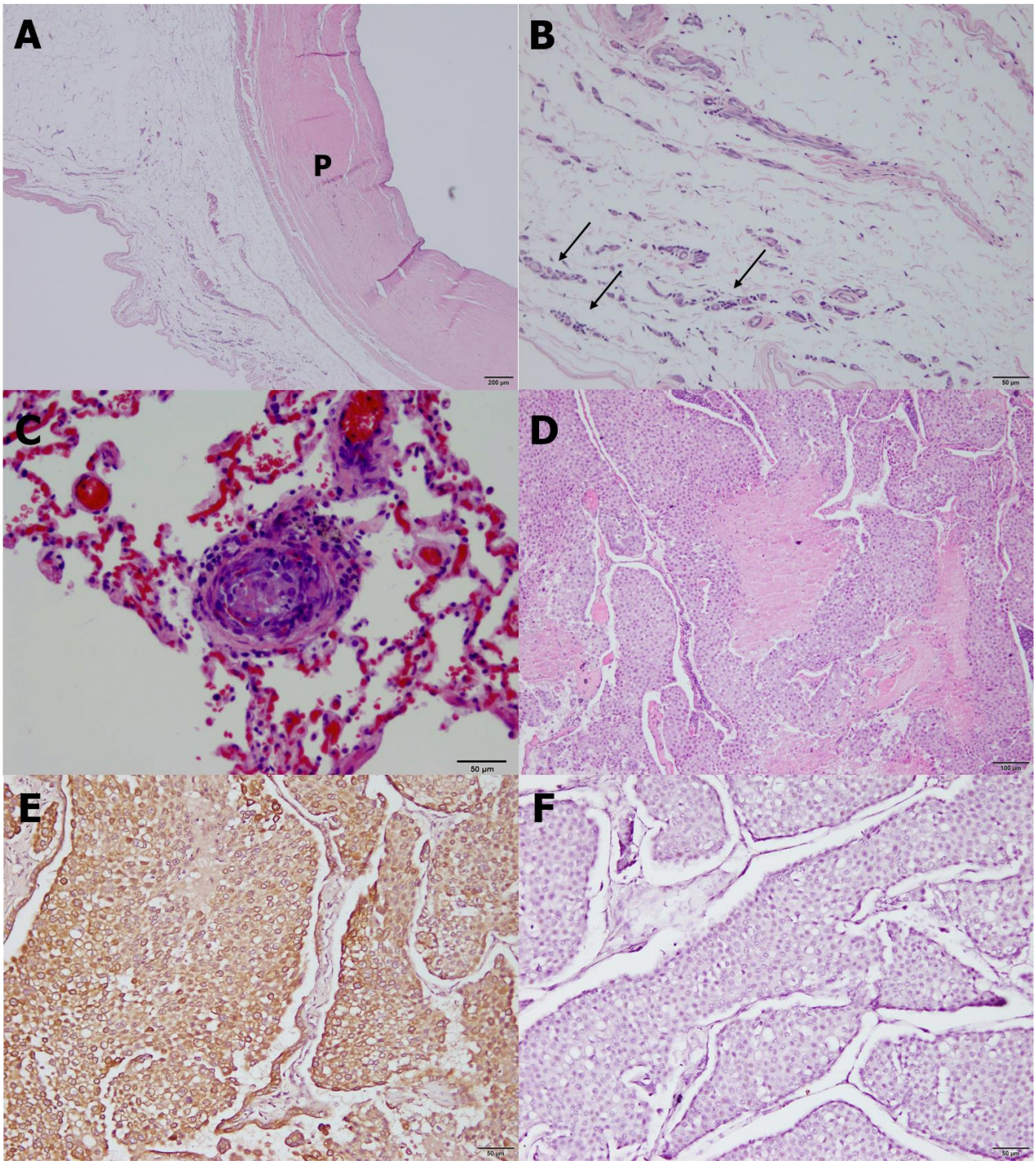

Fig. 4: Histopathological evaluation of a dog with recurrent pericardial and pleural effusion. Marked pericardial thickening and fibrosis (P) (**A**; H&E stain, scale bar, 200 µm) and infiltration of the inflammatory cells around vessels (black arrows) in the adipose tissue (**B**; H&E stain, scale bar, 50 µm) were demonstrated in the pericardium. Metastatic foci were observed in the lung (**C**; H&E stain, scale bar, 50 µm) and sternal lymph nodes (**D**; H&E stain, scale bar, 100 µm). The metastatic polyhedral cells were positive for cytokeratin AE1/AE3 (**E**; Mouse cytokeratin AE1/AE3 immunohistochemistry stain, scale bar, 50 µm) and negative for vimentin (**F**; DAB stain and Gill's hematoxylin counterstain stain, scale bar, 50 µm)

Discussion

Despite a thorough diagnostic workup for malignancy, detailed investigations fail to reveal a primary site in about 3-5% of metastatic tumors (Pavlidis and Pentheroudakis, 2012). Carcinoma of unknown primary is common and well-recognized in humans, only two large studies examined CUP in dogs (Morrison, 2002; Rossi *et al*., 2015). In both studies, most dogs with CUP were older than 7 years of age (100% and 64%). Clinical signs included weakness, cough, and pain in one study (Morrison, 2002), and dyspnea, lameness, depression, and lethargy in the other (Rossi *et al*., 2015). Three of the 21 dogs were asymptomatic (Rossi *et al*., 2015). The

histologic types of CUP were mostly undifferentiated carcinoma (11 of 21 dogs), followed by undifferentiated sarcoma (3 of 21 dogs), fibrosarcoma and hemangiosarcoma (2 of 21 dogs), and others (amelanotic melanoma, mast cell tumor, and squamous cell carcinoma) (Rossi *et al*., 2015). The other study reported carcinoma (15 of 22 dogs) as the most common type of tumor, followed by adenocarcinoma (5 of 22 dogs), undifferentiated sarcoma, and fibrosarcoma. Metastatic sites were only reported in one study (Rossi *et al*., 2015), and frequently included bone, lymph nodes, lung, and spleen. The prognosis was poor in all cases (Morrison, 2002; Rossi *et al*., 2015). The dog in the present case was 9 years old and had cough and dyspnea on admission. The sites of metastasis were intrathoracic lymph nodes, and lungs. The dog lived 457 days with conservative treatment.

In the case described here, PE was the major clinical sign. According to a human study, about 20% of symptomatic PEs without an obvious etiology at presentation were later diagnosed as unrecognized cancer (LeWinter and Tischler, 2011). However, PE due to secondary metastasis has rarely been reported in dogs. One case report described PE associated with metastatic disease of unknown primary origin (Kirsch *et al*., 2000). The dog was treated with pericardiectomy, but the follow-up period was only 12 days. Thus, the prognosis could not be evaluated. In this case, the dog lived 457 days with conservative treatment and concurrent pericardiocentesis.

Echocardiography, cytologic analysis, and CT can be used to identify the etiology of PE (MacDonald *et al*., 2009; Cagle *et al*., 2014; Scollan *et al*., 2015). Echocardiography has high sensitivity and specificity for cardiac tumor diagnosis and differentiation of heart base and right atrial masses from other causes of PE (MacDonald *et al*., 2009). The sensitivity and specificity increase with repeat echocardiographic examination. Cytologic analysis of PE showed variable diagnostic ability depending on the underlying etiology (Cagle *et al*., 2014). The overall diagnostic utility was 7.7%, with an increase to 20.3% in dogs with a lower hematocrit (<10%). In human medicine, overall diagnostic utility is also variable (Saab *et al*., 2017). Computed tomography identified extracardiac pulmonary metastases, but was not superior to echocardiography for detection of cardiac masses (Scollan *et al*., 2015). This dog had no cardiac or extracardiac masses on echocardiography and CT evaluation. Furthermore, the PE showed hemorrhagic cytology and was nondiagnostic for underlying disease.

Identification of underlying etiology of a PE is important for determining prognosis. Dogs with a PE and neoplastic involvement had shorter survival times (26 to 56 days), compared with dogs with non-neoplastic causes (790 to 1,068 days) (Stafford Johnson *et al*., 2004; Cagle *et al*., 2014). Mesothelioma-induced PE reportedly showed better prognosis (MacDonald *et al*., 2009).

In conclusion, identification of the etiology of recurrent PE is challenging, especially with a neoplastic origin. This case described clinical characteristics and treatment outcome in a dog with recurrent PE caused by CUP. Metastatic CUP as a cause of recurrent PE is rarely reported in dogs, but should be included in the differential diagnosis.

Acknowledgement

This research was supported by the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (2016M3A9 B6903437).

References

Cagle, LA; Epstein, SE; Owens, SD; Mellema, MS; Hopper, K and Burton, AG (2014). Diagnostic yield of cytologic analysis of pericardial effusion in dogs. J. Vet. Intern. Med., 28: 66-71.

Kirsch, JA; Dhupa, S and Cornell, KK (2000). Pericardial effusion associated with metastatic disease from an unknown primary tumor in a dog. J. Am. Anim. Hosp. Assoc., 36: 121-124.

LeWinter, MM and Tischler, MD (2011). *Braunwald's heart disease*. 9th Edn., Philadelphia (PA), Saunders. PP: 1651-1670.

MacDonald, KA; Cagney, O and Magne, ML (2009). Echocardiographic and clinicopatholgic characterization of pericardial effusion in dogs: 107 cases (1985-2006). J. Am. Vet. Med. Assoc., 235: 1456-1461.

Morrison, WB (2002). *Cancer in dogs and cats: medical and surgical management*. 2nd Edn., Baltimore (MD), Williams & Wilkins. PP: 727-730.

Pavlidis, N; Briasoulis, E; Hainsworth, J and Greco, FA (2003). Diagnostic and therapeutic management of cancer of an unknown primary. Eur. J. Cancer., 39: 1990-2005.

Pavlidis, N and Fizazi, K (2009). Cancer of unknown primary (CUP). Crit. Rev. Oncol. Hematol., 69: 271-280.

Pavlidis, N; Khaled, H and Gaafar, R (2015). A mini review on cancer of unknown primary site: a clinical puzzle for the oncologists. J. Adv. Res., 6: 375-382.

Pavlidis, N and Pentheroudakis, G (2012). Cancer of unknown primary site. Lancet. 379: 1428-1435.

Refaat, MM and Katz, WE (2011). Neoplastic pericardial effusion. Clin. Cardiol., 34: 593-598.

Rossi, F; Aresu, L; Vignoli, M; Buracco, P; Bettini, G; Ferro, S; Gattino, F; Ghiani, F; Costantino, R; Ressel, L; Bellei, E and Marconato, L (2015). Metastatic cancer of unknown primary in 21 dogs. Vet. Comp. Oncol., 13: 11-19.

Saab, J; Hoda, RS; Narula, N; Hoda, SA; Geraghty, BE; Nasar, A; Alperstein, SA; Port, JL and Giorgadze, T (2017). Diagnostic yield of cytopathology in evaluating pericardial effusions: clinicopathologic analysis of 419 specimens. Cancer Cytopathol., 125: 128-137.

Scollan, KF; Bottorff, B; Stieger-Vanegas, S; Nemanic, S and Sisson, D (2015). Use of multidetector computed tomography in the assessment of dogs with pericardial effusion. J. Vet. Intern. Med., 29: 79-87.

Stafford Johnson, M; Martin, M; Binns, S and Day, MJ (2004). A retrospective study of clinical findings, treatment and outcome in 143 dogs with pericardial effusion. J. Small. Anim. Pract., 45: 546-552.

Varadhachary, GR (2007). Carcinoma of unknown primary origin. Gastrointest. Cancer Res., 1: 229-235.