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Ectopic Follicular Thyroid Carcinoma in a Dog: A Case Report

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ABSTRACT

A 10-year-old male mixed breed dog was referred for evaluation with ascites, vomiting and progressive weight loss. Following a clinical and cardiological examination, an ultrasound was performed with findings consistent with a mass at the base of the heart. Computed tomography showed that the mass involved cranial aorta, aortic arch, pulmonary artery, cranial vena cava and atrial wall, as well. Multiple pulmonary nodules and lymph node involvement were confirmed. Pericardiectomy and incisional biopsy were performed via left lateral thoracotomy. Histopathology and immunohistochemistry revealed an ectopic follicular thyroid carcinoma. Primary thyroid carcinoma was ruled out. The patient remained stable for 300 days following combined oncology therapy, which included chemotherapy and tyrosine kinase inhibitors, with no significant hemodynamic changes or respiratory failure.

Keywords: Heart, Lung, Computed tomography, Toceranib, Immunohistochemistry

INTRODUCTION

Ectopic thyroid refers to the presence of thyroid tissue in locations other than the normal anterior neck region between the second and fourth tracheal cartilages (Ibrahim and Fadeyibi 2011). The formation of accessory thyroid tissue could occur during thyroid development, so thyroid carcinomas can arise from ectopic thyroid tissue in the tongue, along the trachea distant to the thyroid glands and in the thoracic inlet, cranial mediastinum, and pericardium, and along the descending aorta and heart base (Liptak 2007). During embryological development, such ectopic tissue is formed when small groups of thyroid primordial cells separate from the main mass of developing thyroid as it migrates from the primitive pharynx (pharyngeal gut) along a midline path of descent to its normal ectopic location. Failure of the thyroid primordium (or a portion of it) to fully descend leads to the development of lingual or sublingual ectopic thyroid tissue, whereas additional descent of the thyroid beyond its normal craniocervical location results in ectopic cranial mediastinal, heart base thyroid tissue, or both (Broome et al. 2014).

Ectopic thyroid tissue can be subject to the same pathological processes as normal ectopic thyroid tissue such as inflammation, hyperplasia, and tumorigenesis (Klubo-Gwiaździńska et al. 2011). Cardiac ectopic follicular thyroid carcinomas are uncommon in canine patients with few reports in the veterinary literature (Hamilton-Elliott et al. 2018). This case report and literature review, describes the clinical presentation, diagnosis, treatment and follow up of an ectopic thyroid carcinoma in the base of the heart and medial lobe of the left lung in a mixed-collie breed dog in Medellín, Antioquia, Colombia. Besides it summarizes a literature review with the ectopic thyroid carcinomas reports in dogs made until April 2024.

Case history, clinical examination and findings

A 10-year-old male mixed-collie breed dog was submitted to a veterinary medical hospital in Medellin - Colombia, with ascites, vomiting, lethargy and progressive weight loss. The cardiologist performed an evaluation finding 200bpm, strong and non-concordant pulse, marked tachypnea and a 2/6 systolic heart murmur. No abnormalities in the complete blood count, ionized calcium, troponin, alanine aminotransferase, creatinine, alkaline phosphatase, urea, blood urea nitrogen, cholesterol and thyroid profile (TSH, T4T, T4f) were found. However, a significantly elevated level of PropBNP was detected (1929.9pmoles).

Different diagnostic tests were carried out in this case. The echocardiography revealed a rounded structure

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between large vessels, especially the aorta, pulmonary artery and the vena cava about 60x50mm in diameter (Fig. 1A). Both mitral and tricuspid valves showed thickening, and valve regurgitation consistent with degenerative bi-valvular disease. Auricular fibrillation was shown on the electrocardiogram (ECG). On chest radiographic study, the cardiac silhouette indicates cardiomegaly with a cardio vertebral index of 11.5. A diffuse structured nodular interstitial pattern composed of soft tissue density rounded nodules of defined contours ranging from 4.5 to 10mm in diameter was observed in the lung fields (Fig. 1B). No proliferative lesions were observed in thyroid lobes with clinical examination and ultrasonography.

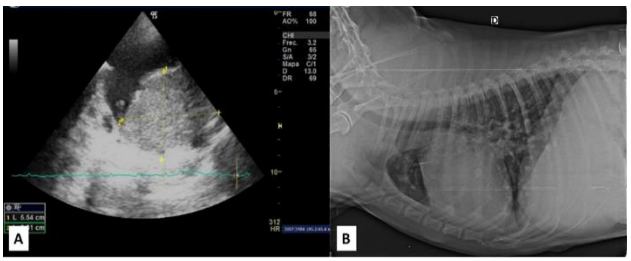

Fig. 1: A) Echocardiography, yellow marks surrounding a tumor at the base of the heart, and B) Right lateral thoracic radiography. Cardiomegaly and pulmonary nodular pattern.

Computed tomography showed a solid mass at the base of the heart, with heterogeneous enhancement with the contrast, without calcifications in intimate contact with the cranial aorta, aortic arch, pulmonary artery, cranial vena cava and atrial wall, without apparent intracardiac or endovascular invasion. It measures approximately 45x40x74mm. Tumoral tissue had CT attenuation values between 30HU and 48HU precontrast and between 99.5HU and 122.3HU postcontrast. Enlargement of multiple mediastinal and sternal lymph nodes were seen. The largest mediastinal lymph node measures 20x14.5mm, while the sternal lymph node measures 32x15mm. Multiple solid pulmonary nodules, hypodense with hyper-capturing halo to the periphery. The smaller is 0.14mm and the largest is 10.6mm, some of them have halo in tarnished glass (Fig. 2A, 2B, 2C). There was bilateral pleural effusion and hepatomegaly as well. No interventricular septum changes were observed.

Lateral thoracotomy was performed for therapeutic and diagnostic purposes. Before the surgery the patient was in Diltiazem 15mg/kg BID, sildenafil 50mg/kg TID, furosemide 80mg/kg BID and amiodarone 200mg/kg SID to treat congestive signs and auricular fibrillation. The surgery was performed with a left lateral thoracotomy technique throughout the fourth intercostal space in the chest medium third. Pale pinkish 2mm nodules were found infiltrating the pulmonary parenchyma in the left side, especially in the medium left lobe. Subphrenic pericardiectomy was performed finding a moderate amount of serosanguineous effusion. After a pericardiectomy at the base of the heart a 4x4cm irregular mass was found attached to the pericardium and cranial mediastinum, it was impossible to remove the totality of the mass because it compromised the pulmonary artery and left epicardium, so an incisional biopsy was made. Additionally, a constriction biopsy was performed in the apical region of the medium pulmonary lobe.

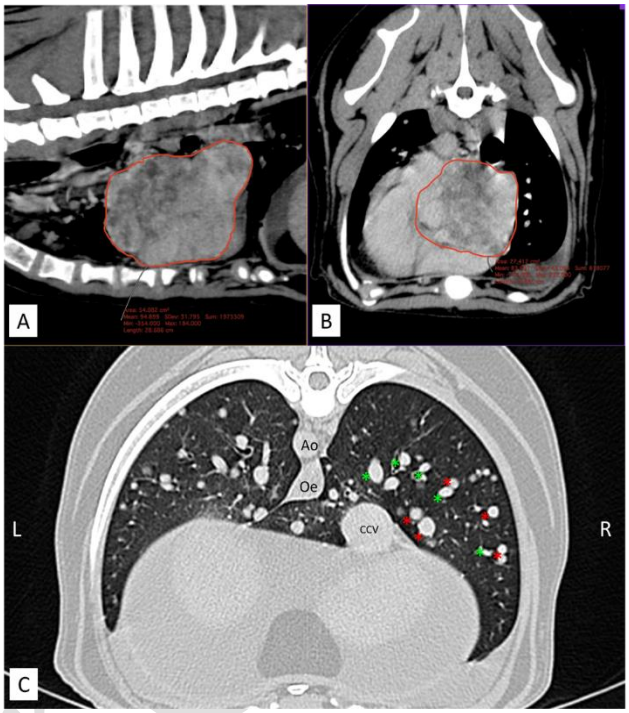

Fig. 2: Computed tomography image showing A) Axial mass cut at the base of the heart, with projection towards the right side and dorsal displacement of the trachea (mass is delimited with red line). Solid, with irregular contours and hypocaptants, B) Cross section of mass at the base of the heart, with projection towards the right side and dorsal displacement of the trachea (the mass is delimited with red line), and C) Computed tomography. Cross-sectional, caudal lobes in the thorax flow region at the height of T8, showing multiple hypodense nodules with peripheral hypercaptative halo (red asterisks show nodules on their right, green asterisks show vascular structures). * (Ao) aorta, (Oe) esophagus, (CCV) caudal vena cava.

Confirmatory diagnosis

The histopathological examination at the heart base sample revealed a non-encapsulated and no lobulated expansive nodular neoplasia. The neoplasm exhibits sheets of densely packed epithelial polygonal cells arranged in a solid pattern with occasional formation of follicular structures and supported by a fine fibrovascular stroma. Neoplastic cells were cuboidal with indistinct cell borders and revealed mild pleomorphism, mild anisokaryosis and mild anisocytosis. The mitotic count was 2 per 2.37mm² (10 hpf). In lung samples a similar neoplasm was observed, however in these samples the formation of follicles filled with pale eosinophilic homogenous material (colloid) was more evident. The mitotic count was 3 per 2.37mm² (10 hpf). The pericardium was moderately and diffusely thickened, characterized by marked fibroplasia and mild perivascular lymphoplasmacytic infiltration (Fig. 3A, 3B). The immunohistochemistry revealed a moderate positive stain for thyroglobulin in the neoplastic cells of both anatomical localizations described above. No positive staining for chromogranin was observed (Fig. 3C, 3D).

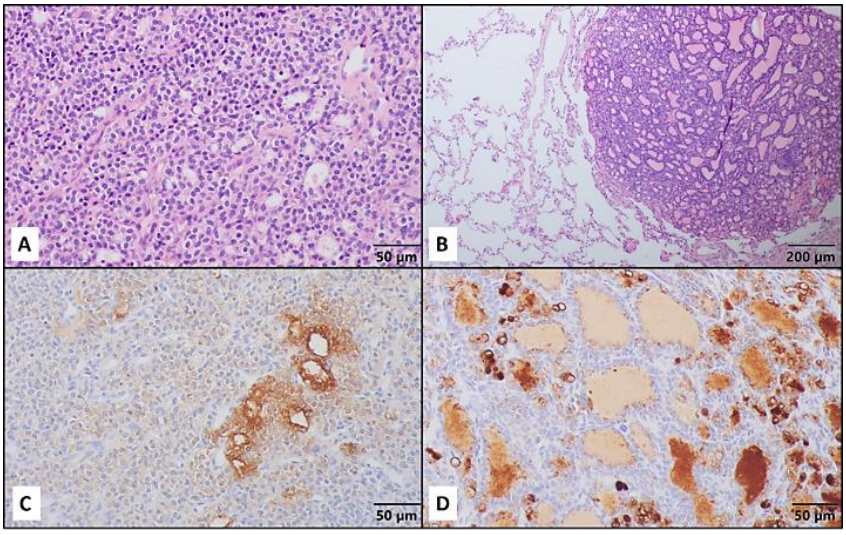

Fig. 3: Microphotography. A) tumor on the base of the heart Note the presence of neoplastic cells arranged in a predominantly solid pattern with few follicular structures, B) One of the neoplastic nodules affecting the pulmonary parenchyma. Note the presence of a well-defined nodule composed of neoplastic cells arranged in a predominantly follicular pattern. The follicles contain colloid material, C) IHC Thyroglobulin of the mass on the base of the heart, and D) IHC Thyroglobulin of the neoplastic nodules in the lung.

Therapeutic approach and outcome

Therapy was established with six cycles of Carboplatin (240mg/m2) every 21 days and Toceranib (2.75mg/kg) every 48 hours lifelong. The medications and their doses were defined according to Wouda et al. (2018) and Gregory et al. (2022) recommendations. Adverse events such as anemia and neutropenia occurred during treatment; those were graded according to the veterinary Cooperative Oncology Group (VCOG-CTCAE) as grade 2. The patient's survival after diagnosis and the described therapy was 330 days, during which there was an initial expansive growth of the cardiac mass with chronic congestive cardiovascular failure and associated cardiorenal syndrome. Treatment response was assessed through RECIST criteria established by VCOG (Veterinary Cooperative Oncology Group).

DISCUSSION

There are 20 reports in the literature between 1982 and 2024 described in Table 1, that consider ectopic thyroid carcinoma in canines, many of these reports are not exclusive to this type of neoplasia (ETC). The information obtained was limited, the publications that included multiple patients did not specify the age, sex, breed, location of the lesion, diagnostic technique or follow-up performed on animals that had a presumptive diagnosis of ectopic thyroid carcinoma. That's why a correlation of the variables evaluated in this study could not be performed. Only 40% (8/20) mentioned making a definitive diagnosis by immunohistochemistry, since in the remaining 60% (12/20) only histopathology, cytology or imaging tests were performed to diagnose ectopic thyroid carcinoma. C cell follicular carcinoma and Carcinosarcoma are not included in Table 1.

Ectopic thyroid is the presence of thyroid tissue in locations other than normal in the neck region, between the second and fourth tracheal cartilages (Ibrahim and Fadeyibi 2011) and could be frequently observed in thoracic organs (Liptak et al. 2008). Ectopic thyroid tissue has identical physiological and pathological behavior as normal thyroid glands and can be affected by pathological processes including neoplasia (Liptak et al. 2008; Klubo-Gwiaździńska et al. 2011). Although benign thyroid neoplasms affecting the heart have been described (Di Palma et al. 2010), most of the diagnoses correspond to follicular carcinomas as shown in Table 1. The most reported sites affected by ETC are lower neck, tongue, along the trachea distant to the thyroid glands, cranial mediastinum and pericardium, along the descending aorta and heart base (Liptak et al. 2008), so ectopic thyroid carcinomas (ETC) should be always included as a differential diagnosis of tumors at the base of the heart. (Rosol 2016). However, the most common neoplasm arising at this location is the chemodectoma (Gal and Castillo 2017). C cell carcinoma and carcinosarcoma arising ectopic thyroid tissue have been reported in cardiac and extracardiac locations (Grubor and Haynes 2005; Almes et al. 2008; Hamilton-Elliott et al. 2018). Thyroid carcinosarcoma has thyroid neoplastic tissue and sarcomatous components such as endothelium or bone (Almes et al. 2008). Most of these reports describe the tumors as involving the interventricular septum or right ventricular outflow tract resulting in mechanical obstruction (Hamilton-Elliott et al. 2018).

Histologic diagnosis of follicular ectopic thyroid carcinomas should be straightforward in well differentiated tumors but in solid or anaplastic types could be challenging. Histopathology was the most common method for definitive diagnosis used in reports (17/20) as shown in Table 1. Nevertheless, a case reported by Liptak et al. (2008) with a histopathological diagnosis of thyroid carcinoma was reclassified as a non-thyroid neuroendocrine tumor after using IHC. This suggests that heart-base tumors and subclassification of thyroid carcinomas should be confirmed through IHC for definitive diagnosis in some cases, because differentiating ectopic thyroid carcinomas from other heart-base tumors and distinguishing between follicular and c cell thyroid carcinomas based on histological criteria alone may be difficult (Liptak et al. 2008). As mentioned above, in 12 reported cases there was no confirmation by IHC, which could limit the scope of diagnosis. Holscher et al. (1986) was the first to compare histopathological diagnosis with immunohistochemistry using anti-thyroglobulin antibodies followed by Constantino et al. (1996), Almes et al. (2008), Bracha et al. (2009), Kang et al. (2012) and Rossi et al. (2013).

Table 1: Literature available data on follicular ectopic thyroid carcinoma in dogs

References	Patients #	Sex	Age (Y)	Breed	Location	Associated clinical signs	Diagnostic methods performed	Follow up
Stephens et al. (1982)	1	♀	10	Beagle	Lungs, pancreas, and kidney	NR	Necropsy Histopathology	NR
Holscher et al. (1986)	1	♂	8	Mixed breed	Mediastinum (aorta and pulmonary artery)	NR	Necropsy Histopathology IHC	NR
Bright et al. (1990)	1	♀	8	Basset Hound cross	Base of the pulmonary valve and the right ventricle adjacent to the valve	Anasarca and dyspnea	Histopathology	NR
Constantino et al. (1996)	1	♂	7	Old English sheepdog	Base of heart	Vomiting, polyuria, polydipsia	Necropsy Histopathology IHC	NR
Girard et al. (1999)	1	UI for ETC	UI for ETC	NR	Intrapericardial	NR	NR	NR
Reichle and Wisner (2000)	1	♂	12	Yorkshire terrier	Cranial mediastinum	NR	Histopathology	NR
Liptak et al. (2008)	4	UI for ETC	UI for ETC	UI for ETC	Cranial mediastinum	UI for ETC	Histopathology IHC	1, 5, 301, 512 days after diagnosis.
Bracha et al. (2009)	1	♀	9	Bouvier de flandes	Right ventricular outflow tract	Coughing and lethargy	RX'S, echocardiogram Histopathology, IHC	11 months after the diagnosis the dog was euthanized because of the non-resolving chylothorax.
Kang et al, (2012)	1	♀	12	Shih tzu	Right atrium	Coughing, exercise intolerance and abdominal distention	Echocardiography, CT, histopathology IHC	The patient lived 428 days beyond diagnosis with only medical management
Rossi et al. (2013)	8	4♀ 4♂	Mean 7,6 Range 5-11	3 mixed breed 1 Dachshund 1 Boxer 1 Great Dane 1 Staffordshire Bull Terrier 1 German Shepherd	Ventral to the larynx	All dogs were asymptomatic except the presence of a firm swelling in the ventral laryngeal region	Cytology (2 cases) Histopathology (6 cases) CT guided biopsy (4 cases) Tissue from surgical debulking (2 cases) IHC (1 case)	Two dogs were euthanized after 1 and 6 years, respectively, the first had no treatment and the second underwent surgery and chemotherapy. Three dogs, treated with radiotherapy alone (1 case), radiotherapy and chemotherapy (1 case), and surgery and radiotherapy (1 case), are still healthy respectively 9, 12, and 16 months after presentation. Three dogs were lost to follow up.
Broome et al. (2014)	41	23♀ 18♂	Mean 9.1 years Range 4–15 years	14 mixed breed 13 Labrador or Golden Retriever 14 NR	Sublingual	NR	Histopathology (23 cases) Cytology (18 cases)	The median survival was 562 days. 9 dogs (24.3%) died of causes related to their thyroid neoplasia, 3 died of unrelated malignancy, 9 died or were euthanized, 20 were alive at

								the time of follow-up, 6 dogs had metastatic disease
Campos et al. (2014)	4	UI for ETC	UI for ETC	NR	Ventral larynx	UI for ETC	Histopathology	NR
McGuire et al. (2017)	1	♂	8	Labrador Retriever	Base of the tongue and base of the heart	NR	Cytology (FNA) and nuclear scintigraphic	5 months after no adverse effects had been observed and the tumor had decreased in size.
Berg et al. (2020)	12	UI for ETC	UI for ETC	NR	8 dogs (sublingual region) 1 dog (mediastinum) 1 dog (heart base)	UI for ETC	Histopathology Cytology Abnormal radionuclide accumulation	NR
Skinner et al. (2020)	1	UI for ETC	UI for ETC	UI for ETC	Hyoid	UI for ETC	Histopathology	NR
Pugh et al. (2022)	1**	♂	11	Border terrier	Cranial aspect of the pericardium	Tri cavitary effusion, dyspnea and lethargy	CT, Histopathology	The owner decided euthanasia
Gouveia (2022)	1	♀	15	Mixed labrador retriever	Base of the heart and aorta	Compatible with heart failure, mucoid diarrhea and hematochezia	Echocardiographycytology, necropsy histopathology	NR
Gregory et al.(2022)	1**	♂	8	Labrador retriever	Heart base and right atrioventricular junction	Cough and tachypnoea	Chest radiographs, Echocardiography, cytology	4 weeks later there was a clinically significant reduction in the size of the mass. Due to right-sided congestive heart failure, the patient was euthanized 10 months after
Yu et al. (2022)	1 2**	UI for ETC	UI for ETC	UI for ETC	2 dogs (cranial mediastinum), 1 dog (base of the heart)	UI for ETC	Necropsy, Histopathology, CT	NR
Greco et al. (2023)	1	♀	13	Mixed beagle	From aortic body to the right auricular appendage	Dyspnoea, tachycardia, tachypnoea, weak femoral pulses, left systolic murmur grade II/VI	Chest radiographs, echocardiogram, Histopathology, IHC	The patient is still alive without evidence of metastasis of the ectopic thyroid carcinoma upon 35 months after initial presentation
Ruiz de Alejos Blanco et al. (2024)	2	UI for ETC	Range 9-13	1 Beagle and 1 Jack Russel Terrier	Mediastinum (between the aortic arch and cranial vena cava)	Dyspnoea, abdominal distension, tachypnoea, vomiting, diarrhea, Polyuria/Polydipsia and weight loss	Postcontrast CT , Cytology and histopathology	NR

NR: Non-reported data; UI: Unspecified information; ETC: Ectopic thyroid carcinoma; IHC: Immunohistochemistry; CT: Computed tomography. ** Non-confirmed but suspected ETC.

In all the immunohistochemistry reports a cytoplasmic brownish immunoreactivity was seen in the neoplastic cells. According to the literature, the recommended IHC panel for carcinomas at the base of the heart should be: thyroglobulin, calcitonin, thyroid transcription factor-1 (TTF-1), synaptophysin and chromogranin. A positive thyroglobulin staining should be sufficient to confirm CTE (Liptak et al. 2008). Although metastatic behavior to the lung has been reported (Stephens et al. 1982), in most of the studies listed in Table 1, this was not a defining clinical feature. Rosol (2016) describes that metastases to regional lymph nodes (retropharyngeal, mandibular and deep cervical) and distant sites are infrequent and should be differentiated from primary ectopic thyroid tissue hyperplasia or neoplasia. According to Bertolini et al. (2017) 60% of patients with thyroid masses have normal function of the gland. Rajagopalan et al. (2013) proposes to include T4 serum concentrations in the diagnostic evaluation. Three cases reported in Table 1. had a T4 measure, two of those with normal levels (Almes et al. 2008). Liptak et al. (2008) reported a case with an increased serum thyroxine level followed by a scintigraphy with evidence of a functional mass in the cranial mediastinum. Broome et al. (2014) found 12 patients with ectopic thyroid neoplasia and an abnormal radionuclide uptake. This validates the importance of complementing the diagnosis with thyroid hormone measurements. Scintigraphy using radiolabeled iodine could also be a useful method to identify functional thyroid tissue in cases of neoplastic ectopic tissue and can also provide information on the response to radioactive iodine treatment or external-beam radiotherapy (Liptak et al. 2008). As thyroid hormones levels were normal and there was absence of morphological alterations of the thyroid gland, non-functional behavior and ectopic origin were considered.

Complementary diagnostic tests like echocardiography and computed tomography are very relevant tools. Echocardiography was used in this case report, as well as in 5/20 cases from the literature review allowing to identify masses and their location at the cardiac level, as well as pericardial effusions with 100% specificity and 82% sensitivity (Greco et al. 2023). Computed tomography is used for the identification of the anatomic location, metastasis, local invasion and to characterize the magnitude of the intrathoracic tumoral lesions (Kang et al. 2012). Taeymans et al. (2012) and Pugh et al. (2022) recommends CT for preoperative diagnosis and staging purposes. In this study CT scan allows to find multiple pulmonary masses and lymph nodes involvement that haven't been detected by any other technique. Kang et al. (2012) explored this method as well due to its ability to provide the exact anatomic location of the intra- and extracardiac mass and detailed images of pulmonary parenchyma and blood vessels.

CT attenuation values of 56 HU precontrast and 132HU postcontrast were reported for thyroid carcinoma (Taeymans et al. 2012), these values were similar to those presented in this report. Both values are considered lower than those found in normal thyroid tissue, which are approximately 107.5HU precontrast and 123HU postcontrast (Bertolini et al. 2017). Low levels of CT attenuation are thought to be related to decreased metabolism and storage of iodine in neoplastic vr thyroid normal tissue (Taeymans et al. 2012). However, these studies were not made on ectopic thyroid tissue. Mineralization, irregular shape, intratumoral vascularity, elevated size and distant metastases have been associated with malignancy (Bertolini et al. 2017). In this report, all these features were observed on CT evaluation except calcification.

Survival times in the reports presented in Table 1, goes from 1 to 2190 days after diagnosis or surgical intervention. Notwithstanding, follicular ETC with an intracardiac involvement had reported survival times of 300 days (Bracha et al. 2009) and 428 days (Kang et al. 2012), all of them in females. Surgical resection was conducted in the case presented by Bracha. Chemotherapy was declined by owners in all of these cases. Follicular ETC affecting the base of the heart without intracardiac involvement reported survival times in treated dogs from 5 to 2190 days (Liptak et al. 2008; Rossi et al. 2013). A dog with follicular ETC diagnosis that underwent surgery and chemotherapy was euthanized 6 years after diagnosis because of local progressive disease and thoracic metastases (Rossi et al. 2013). However, some cases have been reported with a survival time of one day after diagnosis without surgical or pharmacological intervention.

Carcinosarcomas and interventricular septum tumors are believed to have a poor long-term prognosis, which is supported by other studies (Grubor and Haynes 2005). However, according to the data presented for follicular ETC survival times could be broad even in patients without surgical intervention (Bracha et al. 2009; Kang et al. 2012).

Retrospective studies have described the benefits of pericardiectomy in patients with unresectable masses and severe pericardial effusions (Vicari et al. 2001; Ehrhart et al. 2002). In this patient, hemodynamic parameters associated with right ventricular afterload and central venous pressure, as well as atrial fibrillation, improved with surgical and medical treatment. However, it is not possible to determine in this case the independent role of pericardiectomy because toceranib medication was administered. Current case reports have demonstrated a beneficial effect of toceranib phosphate on signs of right congestion in patients with masses at heart base (Gregory et al. 2022). Even a retrospective study by Coto in patients with chemodectomas showed that survival with toceranib alone was similar to that of patients with toceranib and other ancillary therapies such as pericardiectomy, among others (Coto et al. 2021).

The present study provides a comprehensive and definitive diagnosis of a case of ectopic follicular thyroid carcinoma and describes a therapeutic management experience that is considered successful. Although literature on ectopic carcinoma is available, approaches are directed towards different diagnostic techniques, therapeutics or follow-up. Integration between these elements should be included in management protocols for similar oncological diseases.

Author's Contribution: MA, HS, DA, AM, OR and JM performed the concept and design, data analysis and interpretation, article writing, critical review and discussion. OR was in charge of the imaging techniques and interpretation. DA and AM provided clinical and therapeutic information. MA, HS and JM performed the

laboratory analysis and pathological interpretation.

Conflict of interest: The authors declare no potential conflict of interest.

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