Ectopic medullary (C-cell) thyroid carcinoma in a dog with pericardial effusion.

Summary

A 6-year-old, female, neutered crossbreed was presented to the University of Liverpool Small Animal Teaching Hospital for evaluation of pericardial effusion. Diagnostic imaging confirmed pericardial effusion and cardiac tamponade in addition to a mass located at the heart base. Thoracic computed tomography revealed a strongly contrast enhancing soft-tissue mass right lateral to the ascending aorta and ventral to the cranial vena cava with no evidence of metastatic disease. Subsequently, a subtotal pericardectomy was performed and the mass was incompletely excised. Histopathology and immunohistochemistry revealed the mass to be an ectopic thyroid carcinoma of medullary (C-cell) origin. The patient was treated with adjunctive chemotherapy (toceranib phosphate). Repeat staging 2 months later revealed no evidence of macroscopic tumour recurrence or metastatic disease. The patient was subsequently euthanased 2 months later due to complications of concurrent but unrelated hepatic disease.

Background

Primary cardiac tumours are uncommon in dogs with a reported incidence of 0.19% 1. The most common type of cardiac tumour is haemangiosarcoma followed by heart base tumours (e.g. aortic body tumour)1. Cardiac ectopic thyroid carcinomas are uncommon in canine patients with only sporadic reports in the veterinary literature2–9. They are most frequently documented on post mortem examination and can be a diagnostic and therapeutic challenge in the clinical setting. This case report describes the clinical presentation, imaging, histopathological and immunohistochemical findings, treatment and follow-up of a dog with an ectopic medullary (C-cell) carcinoma at the heart base diagnosed during investigations for aetiology of a pericardial effusion.

Case Presentation

A six- year old female neutered, 29.1kg (body condition score 6/9) cross-breed dog was presented as an emergency following a 2 week history of abdominal distension, progressive hyporexia and lethargy. The patient had a concurrent medical history of multiple acquired portosystemic shunts and portal hypertension, diagnosed 3 years previously, which was medically managed with amoxicillin-clavulanate, spironolactone and lactulose. No signs of hepatic encephalopathy had ever been reported.

On presentation the patient was quiet but responsive. Physical examination revealed the mucous membranes to be pink and tacky with capillary refill time of 2 seconds’ duration. The heart rate was 100bpm with a regular rhythm and synchronous peripheral pulses, with pulsus paradoxus. The respiratory rate was 20bpm with normal effort. Thoracic auscultation revealed indistinct cardiac sounds and no evidence of adventitious pulmonary sounds. There was moderate abdominal distension with a positive fluid wave on ballottement.

Investigations

Routine haematology and serum biochemistry revealed a mild segmented neutrophilia (13x109/L ref: 2.9-11.6) but no other significant abnormalities.

Thoracic ultrasound (Figure 1; A and B) revealed a large volume pericardial effusion with evidence of cardiac tamponade and a homogeneous, soft tissue opacity, mass-like structure within the pericardial sac in the region of the heart base. The patient was sedated for pericardiocentesis which was performed under ultrasound guidance and 1.1 litres of serosanguinous fluid was drained without complication. 2D echocardiography (GE Healthcare Vivid E95) following the procedure revealed no evidence of residual effusion and resolution of cardiac tamponade. Cytological analysis of the pericardial effusion revealed a transudate (protein <10g/l, nucleated cell count 0.21x109/L, haematocrit 0.0 L/L). Nucleated cells comprised low numbers of macrophages which often contained granules of haemosiderin; this suggested chronic low-grade haemorrhage but there was no evidence of erythrocytes. There was no evidence of neoplastic cells or infectious agents. Cytological analysis of the peritoneal effusion revealed a protein rich transudate most likely secondary to right sided congestive heart failure. Ascites secondary to portal hypertension was less likely based on the classification of the effusion.

Repeat echocardiography 48 hours later revealed recurrent pericardial effusion and cardiac tamponade. Pericardiocentesis was repeated and 850ml of serosanguinous fluid was drained. Computed tomography (CT, Toshiba Aquilion 64-slice) (Figure 2; A and B) of the thorax and abdomen at this time confirmed the presence of a strongly contrast enhancing mass to the right and lateral to the ascending aorta and ventral to the cranial vena cava. There was no evidence of local or distant metastatic disease.

Differential Diagnoses

Pericardial effusion with subsequent cardiac tamponade is commonly associated with cardiac tumours in dogs1,10. The most common types of cardiac tumour reported in dogs include haemangiosarcoma, aortic body tumours (e.g. chemodectoma/paraganglioma), lymphoma and ectopic thyroid carcinomas1,11. Heart base tumours, as in this case, are most commonly aortic body tumours and chemodectomas. However haemangiosarcomas and ectopic thyroid carcinomas have also been reported within the heart base region in dogs1,10.

Treatment

Due to the recurrent nature of the pericardial effusion, pericardectomy and attempted excision of the heart base mass was recommended. A right fourth intercostal thoracotomy was performed, and the lung lobes were packed cranially and caudally with moistened sponges to expose the heart and the pericardial sac. A subphrenic subtotal pericardiectomy was performed releasing a large volume of serosanguinous effusion into the thoracic cavity. The cardiac mass could be clearly identified through the pericardial opening. Grossly, the mass was red, spherical, smooth and measured 20x20x30mm in dimension (Figure 3 A-C). It was pedunculated and located ventral to the cranial vena cava, lateral to the ascending aorta and cranial to the right atrial appendage. It also appeared to involve the right atrial wall with indistinct margins. Two tangential Satinsky vascular clamps were placed across the base of the mass, one close to the tumour and the second proximal to the heart leaving ca. 1 cm of tissue between the two clamps. A continuous horizonal mattress 2-0 Prolene suture was applied allowing excision of the mass with ca. 0.5 to 0.8 cm margin of grossly normal tissue distal to the resection site. Following removal of the mass, the cuff of tissue remaining beyond the most proximal Satinsky forceps was oversewn with a simple continuous 4-0 Prolene suture. Once the last Satinsky forceps was removed, an additional simple interrupted 4-0 Prolene suture was placed to control oozing.

The mass was resected without complication.

In order to allow regular thoracocentesis in the long term, in the event of continued significant pericardial effusion production, a pleural port (*Companion Port, Norfolk Vet Products, Illinois, USA*) was placed within the 6th intercostal space, adjacent to the thoracotomy site. The titanium port was sutured to the thoracic wall at level of the third proximal of the 8th intercostal space (Figure 3; C). For post-operative management of the iatrogenic pneumothorax and pleural effusion, a temporary chest drain was also inserted within the 6th rib space below the pleural port insertion site. The thoracotomy site was closed routinely. No significant anaesthetic complications were encountered. Despite the macroscopic clean tissue margins, histopathology did not confirm complete excision.

Histopathological examination of the mass (Figure 4; A) revealed neoplastic tissue, which was moderately well demarcated, unencapsulated, densely cellular and infiltrative. The neoplastic cells were a monomorphic population of polygonal cells with central, round, slightly ovoid nuclei displaying mild to moderate anisokaryosis. The mitotic count was 5 mitosis in 10, tumour representative, microscopic 400× (ocular field number: 22; objective 40x/0.65) high power fields (HPFs). Cells also exhibited moderate amounts of slightly granular eosinophilic cytoplasm. The cells were predominantly arranged in solid areas, small lobules and narrow trabeculae with some arranged around small blood vessels. Infiltration of the neoplastic cells into the surrounding mediastinal adipose tissue confirmed incomplete surgical excision.

Representative sections of the lesions were subsequently selected for immunohistochemistry. Scattered positivity within the cytoplasm of neoplastic cells to synaptophysin (MRQ-40, MoAb, Ventana Medical Systems, Tucson, AZ, USA, Figure 4; B) confirmed the neuroendocrine differentiation. Thyroid transcription factor-1 (TTF-1) (8G7G3/1 MoAb, Ventana Medical Systems, Figure 4; C) staining was positive in the nuclei of the majority of neoplastic cells, suggesting the tumour to be of thyroid origin. Subsequently, calcitonin staining was performed (SP17, MoAb, Ventana Medical Systems,) and this was overall mildly but diffusely positive within the cytoplasm of the neoplastic cells, with focal areas of moderate intensity (Figure 4, D). Based on these results, a diagnosis of ectopic medullary (C-cell) carcinoma was made. Histopathological assessment of the resected pericardium revealed mesothelial cell hypertrophy and mild inflammation but no evidence of neoplastic proliferation.

The patient recovered well from surgery and subsequently began adjunctive target therapy with toceranib phosphate (2.5mg/kg three times a week; Palladia®, Zoetis, Tadworth, UK).

Outcome and Follow Up

Within 1 month of beginning therapy the patient experienced multiple adverse effects including Veterinary Co-operative Oncology Group (VCOG) grade 1 neutropenia, anaemia, melaena, elevated hepatic enzymes and muscle pain. At the owner’s request, the toceranib was therefore stopped and a decision was made to actively monitor for disease progression instead. Repeat thoracic CT 2 months following diagnosis revealed no evidence of macroscopic tumour recurrence and/or metastatic disease. The patient was subsequently euthanased 2 months later for suspected gastric perforation secondary to a pyloric ulcer which was attributed to chronic hepatic dysfunction. Repeat staging was not performed at this time. Necropsy was not performed following euthanasia.

Discussion

Pericardial effusion, the excessive accumulation of pericardial fluid within the pericardial sac, is the most common pericardial disease in dogs10. It is most frequently associated with cardiac neoplasia or is idiopathic10,11. Less common aetiologies include infectious diseases (bacterial, parasitic, fungal)12, ruptured left atrium secondary to severe mitral regurgitation13, metabolic disease (e.g. systemic inflammatory disease syndrome)14 and foreign bodies 15,10.

Intrapericardial pressure is normally sub-atmospheric through most of the cardiac cycle, paralleling the intrapleural pressure, however pericardial effusion increases intra-pericardial pressure, transmitting this pressure equally to all the cardiac chambers in diastole and systole. As right ventricular filling pressures are less than that of the left ventricle, the increased intrapericardial pressures rise to equilibrate with or exceed right ventricular filling first, leading to compression of the right ventricle, defined as cardiac tamponade. Right ventricular cardiac tamponade compromises right ventricular filling with subsequent reduction of stroke volume and right sided cardiac output. This results in reduced venous return to the left ventricle, reduced left ventricular preload and therefore reduced left ventricular stroke volume and cardiac output. Therefore, patients with pericardial effusion can present in cardiogenic shock. This clinical presentation is generally observed in patients with acute accumulation of pericardial effusion secondary to rapid increases in intrapericardial pressure10. Chronic accumulation of pericardial effusion tends to stretch the pericardium so that it may accommodate much larger volumes of pericardial effusion without clinically significant increases in intrapericardial pressure. These patients tend to present in right sided congestive heart failure (e.g. with ascites) secondary to chronically elevated right ventricular diastolic pressures10, as demonstrated in this case.

In one case series of 107 dogs with pericardial effusions, 71% were caused by neoplastic disease10. Haemangiosarcomas have a strong predilection for the right atrium and atrial appendage. Whilst they can occasionally affect the heart base (13% of heart base tumours)10,11, most heart base masses, typically associated with the ascending aorta at the aortic root are neuroendocrine tumours (e.g. chemodectoma)1,10,11. Less commonly reported heart base tumours include mesothelioma (although usually not a discreet mass lesion), lymphoma and ectopic thyroid/parathyroid carcinoma1,11. Our knowledge of the clinical presentation of ectopic thyroid carcinomas of the heart in dogs is limited to sporadic case reports2-9. The majority of these reports describe the tumours as involving the interventricular septum or right ventricular outflow tract resulting in mechanical obstruction 2-4,9. Only in one report has an ectopic thyroid carcinoma presented in the context of pericardial effusion where the tumour was localised to the right atrium7. With this case report, the authors hope to contribute to our knowledge of the clinical presentation, diagnostic findings and outcome of this rare cardiac tumour in dogs.

Ectopic thyroid tissue is common in many species, being identified in approximately 50% of adult dogs on necropsy examination16-17. The ectopic tissue can be located anywhere from the tongue to the diaphragm and, in dogs, is detected within the thorax in 23-80% of cases 4,18. During embryogenesis, the thyroid glands develop from the primordial pharyngeal portion of the foregut. The caudal end of the thyroid primordium extends ventrally and caudally into the underlying mesoderm and eventually occupies a portion of the ventral aspect of the developing trachea where it forms two distinct lobes 17, 19.

Ectopic thyroid tissue is formed when small groups of the primordial thyroid cells separate from the developing thyroid gland as it makes its descent from the primitive pharynx. If the primordial thyroid fails to fully descend to the normal cranial cervical location, development of lingual or sublingual ectopic thyroid tissue can occur. However, if further descent beyond the normal eutopic location occurs, ectopic thyroid tissue may develop in the cranial mediastinum, heart base or both16,19.

Although most canine thyroid tumours arise from the follicular epithelium of the thyroid tissue (follicular thyroid carcinoma), up to one third arise from the medullary C-cells or parafollicular cells (medullary thyroid carcinoma)18,21,22. It can be challenging to differentiate medullary thyroid tumours from follicular tumours on routine histopathology and it has been argued that, perhaps, medullary (C-cell) thyroid carcinomas are underdiagnosed in veterinary patients18,21. C-cells can occasionally form follicle-like structures, similar to thyroid follicular tissue, especially in neoplasms. Additionally, and especially pertinent to this case, the neuroendocrine appearance of medullary (C-cell) tumours can result in misdiagnosis as other neuroendocrine tumours e.g. chemodectoma19.

Immunohistochemistry can be helpful in the classification of medullary (C-cell) carcinoma. Almost all follicular tumours will stain positive for thyroglobulin and TTF-120. Medullary tumours also stain positively for thyroglobulin and TTF-120 however they can be differentiated from follicular tumours due to their variably positivity for calcitonin19,22-24. Calcitonin staining can range from weak to strongly positive in these tumours, thought to be due to either variable production or secretion from the tumour cells19. Additionally, medullary (C-cell) tumours typically stain less positively for calcitonin compared to normal or hyperplastic medullary C-cells19. In dogs, scattered calcitonin-positive cells may be found in follicular thyroid carcinomas implying entrapment of normal medullary C-cells and this can confuse interpretation25. However, it is also reported that medullary (C-cell) tumours can contain normal entrapped thyroid follicles whilst thyroid follicular tumours generally contain few entrapped medullary C cells19. Additionally, mixed follicular/medullary tumours are reported in humans19. In this case, whilst positive TTF-1 staining confirmed a tumour of thyroid origin, the histopathological features in correlation with the positive synaptophysin staining supported a neuroendocrine tumour. These findings in conjunction with the positive calcitonin staining were considered to be highly suggestive of a medullary (C-cell) tumour. To the authors’ knowledge, an ectopic thyroid medullary (C-cell) carcinoma of the heart has not been reported in the veterinary literature.

Differentiation of follicular thyroid carcinomas from medullary (C-cell) thyroid carcinomas may be of clinical significance due to potential differences in their invasiveness and metastatic potential. Thyroid carcinomas in dogs are locally aggressive and often metastasize to local lymph nodes and, distantly, to the lungs26. Although less is known about the behaviour of medullary (C-cell) thyroid carcinomas, there is some evidence to support that they tend to be less invasive with a lower metastatic rate than follicular thyroid carcinomas21. In this case, there was no evidence of local or distant metastatic disease on presentation, however, the incomplete excision of the mass implied a risk of local tumour recurrence.

Based on the location of the cardiac tumour on initial investigations the primary differential was an aortic body tumour especially as they are significantly more common in dog with heart base tumours in comparison to ectopic thyroid tumours1. Aortic body tumours are generally considered to be slowly progressive26. Although development of regional and distant metastatic disease is reasonably common26-28, dogs rarely appear to be negatively affected by their metastatic burden. Although aortic body tumours are associated with development of pericardial effusion10, in many dogs, they are clinically silent and are often found incidentally during investigations of other disease26,27. The prognosis for some cardiac tumours e.g. haemangiosarcomas is poor26 and therefore there is not an incentive to definitively diagnose with surgical biopsy when they are strongly clinically suspected. However, given that the prognosis of aortic body tumours is significantly better 27, when they are suspected, a surgical biopsy is often pursued. Additionally, pericardiectomy at the time of biopsy is associated with prolonged survival in dogs with aortic body tumours27. Given this evidence, pericardiectomy was recommended in this case both with a palliative intent but also to attempt to surgically excise and histopathologically characterise the tumour. It has been shown that the accuracy of echocardiography in the presumptive diagnosis of common cardiac tumours is only moderately accurate (65%) in antemortem29 and therefore, more invasive diagnostics may be warranted to definitively diagnose the tumour, especially in those cases when the tumour is amenable to fine needle aspiration or surgical excision. In this case, this approach was fortuitous in that a more unusual tumour with a potentially different molecular biology was subsequently diagnosed.

Where thyroid tumours are amenable to surgical excision, thyroidectomy can provide a good outcome (median survival time of 3 years if the tumours is freely movable and 6-12 months if it is more invasive26,30). It is unknown if surgical excision is associated with a similar outcome in dogs with ectopic thyroid carcinoma. Given the aforementioned risk of microscopic residual disease and tumour recurrence, adjunctive chemotherapy was recommended. The evidence base for adjuvant chemotherapy for canine thyroid carcinomas is limited and less is known about chemotherapy of ectopic thyroid carcinomas with many diagnosed post mortem. Dogs treated with doxorubicin or cisplastin demonstrated partial response in 30-50% of cases respectively26. Toceranib phosphate, a tyrosine kinase inhibitor (TKI), has been shown to be successful in achieving a partial response in 26.7% of dogs with thyroid carcinoma and stable disease in 53.3%31. A positive response to TKIs for the treatment of thyroid carcinomas has also been reported in humans32. Given the above evidence, toceranib phosphate was prescribed in this case. Reported side effects of toceranib phosphate (*Palladia®*) in dogs include diarrhoea, reduced appetite, lameness (secondary to muscle cramping/pain), weight loss and haematochezia31. Other potential adverse effects include neutropenia, hypoalbuminemia, thromboembolic disease, vasculitis, pancreatitis, nasal depigmentation, epistaxis, seizures, systemic hypertension and pruritus31. Unfortunately, this patient experienced several of these adverse side effects which resulted in discontinuation of treatment 1 month later. Although restaging 2 months following diagnosis revealed no evidence of macroscopic disease recurrence, it cannot be stated that this was related to toceranib and long term follow up was not achieved. Overall, this patient survived 94 days from the point of diagnosis and died as a result of disease unrelated to the cardiac tumour.

This case report describes the unusual presentation of a pericardial effusion in a dog with ectopic thyroid carcinoma of the heart base. Additionally, the histopathological diagnosis, supportive of a medullary (C-cell) thyroid carcinoma of the heart is a novel finding in canine patients.

Learning Points

* Haemangiosarcomas are a common cause of pericardial effusion and many patients are euthanased based on clinical suspicion rather than pursuing further diagnostics. More unusual tumours with a potentially more favourable prognosis may also present in similar locations with similar clinical signs e.g. pericardial effusion. Therefore, further diagnostics may be encouraged, as pursued in this case, in an attempt to more accurately classify cardiac tumours.
* Ectopic thyroid carcinoma is an uncommon cause of pericardial effusion in dogs but may be under-reported with most diagnosed on post mortem.
* Medullary (C-cell) thyroid carcinomas are challenging to diagnose and require a more complex immunohistochemistry panel; differentiation of these tumours from follicular thyroid carcinomas is clinically relevant due to the potential for a lower metastatic rate in medullary (C-cell) carcinomas

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