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Neuroendocrine carcinoma of the heart base in a dog: A case report

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Abstract: A case of a nine-year-old, intact female, American Bulldog with a heart mass is described. Echocardiography was used to identify this pathological lesion. Part of the mass and pericardial sac were surgically removed for histopathological examination. A final diagnosis of neuroendocrine carcinoma was diagnosed by necropsy and histopathology. To the author's knowledge, there is very limited information in the literature about this pathology.

Keywords: cardiac tumour; echocardiography; heart; histopathology; immunohistochemistry

Cardiac tumours are uncommon in the canine population (Treggiari et al. 2017) with a reported incidence from 0.12% to 4.33% (Prange et al. 1988; Ware and Hopper 1999). The most common heart neoplasms in small animals are haemangiosarcomas (Ware and Hopper 1999), aortic body tumours/chemodectomas (Treggiari et al. 2017), mesothelioma, lymphoma, ectopic thyroid carcinoma, and parathyroid tumours (Ware and Hopper 1999; Rajagopalan et al. 2013). A neuroendocrine carcinoma is a relatively rare tumour in dogs. Only a few case reports document its presence in dogs. The liver, gallbladder, kidneys, gastrointestinal tract, nasal cavities, apocrine glands of the anal sac, mammary glands and skin were reported to be the place of occurrence of neuroendocrine carcinomas in dogs (Sako et al. 2005; Birettoni et al. 2008; Joiner et al. 2010; Ogawa et al. 2011; Nakahira et al. 2015; Morgan et al. 2019; Sozmen et al. 2020). Case reports, which describe the occurrence of neuroendocrine carcinomas of the heart, exist in human literature (Guajardo-Salinas et al. 2013; Wißt et al. 2018). To the best of our knowledge, no studies nor case reports have been published about a neuroendocrine carcinoma of the heart in a dog, unless these tumours originated from paraganglion cells of the aortic body.

Case description

HISTORY, CLINICAL EXAMINATION

A nine-year-old, American Bulldog, intact female was presented to the emergency service of the Small Animal Clinic, University of Veterinary Sciences Brno with a history of respiratory distress and abdominal distension lasting four days. Clinical examination by auscultation revealed the presence of a bronchial type of breathing and absent

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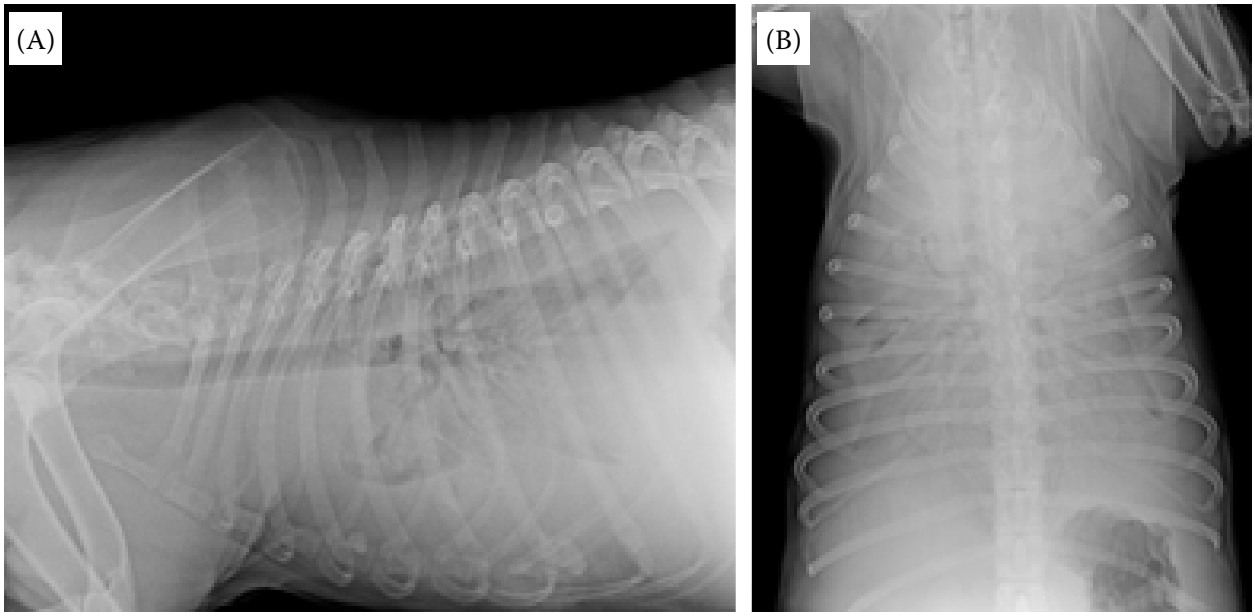

Figure 1. (A) Right lateral view. A severe amount of pleural effusion is present and, in consequence the lung parenchyma, has diminished space. (B) Dorsoventral view. Mediastinum, cardiac silhouette, lung vessels are not visualised due to the border effacement of the pleural effusion [seen also in (A)]

right-sided heart sounds. The temperature, pulse rate and respiratory rate were 37.9 °C, 130/min and 100/min, respectively. Also, the presence of free abdominal fluid was suspected due to the positive fluid wave. The rest of the clinical examination was unremarkable. A complete blood count (CBC) was within the physiological range. The serum biochemical analysis showed mild ALT at 1.8 µkat/l (reference interval 0–1 µkat/l) and AST at 1.6 µkat/l (reference interval 0–1 µkat/l) elevations, hypoproteinaemia at 46.9 g/l (reference interval 55–75 g/l) and hypoalbuminemia at 21.2 g/l (23–34 g/l).

The thoracic radiographs were consistent with the presence of a large amount of pleural effusion. The mediastinum, cardiac silhouette, and lung vessels were not visualised due to the border effacement with the pleural effusion. The lung parenchyma was diminished by the pleural fluid and not evaluable (Figure 1A,B). An abdominal ultrasound confirmed the presence of a moderate amount of ascites and hepatic vein distension.

An echocardiographic examination (Vivid 7; GE Vingmed Ultrasound, Horten, Norway) confirmed the pleural effusion and revealed the presence of a diffusely thickened pericardial sac (5 mm) with a considerable amount of pericardial effusion and a large mass at the base of the heart (Figure 2). The mass was well demarcated, hypoechoic and with a homogenous parenchyma with a size of 4.5 cm × 3.8 cm. The mass was assumed to be located between the right and left atrium.

Ultrasound-guided pericardiocentesis and thoracocentesis were performed under deep sedation with butomidor at 0.2 mg/kg i.v. (Torbugesic; Zoetis Inc., Olot, Spain), diazepam at 0.4 mg/kg i.v. (Apaurin; Krka, Novo Mesto, Slovenia), and propofol at 2 mg/kg slow boluses to effect (Propofol; Fresenius, Bad Homburg, Germany). A total of 60 ml

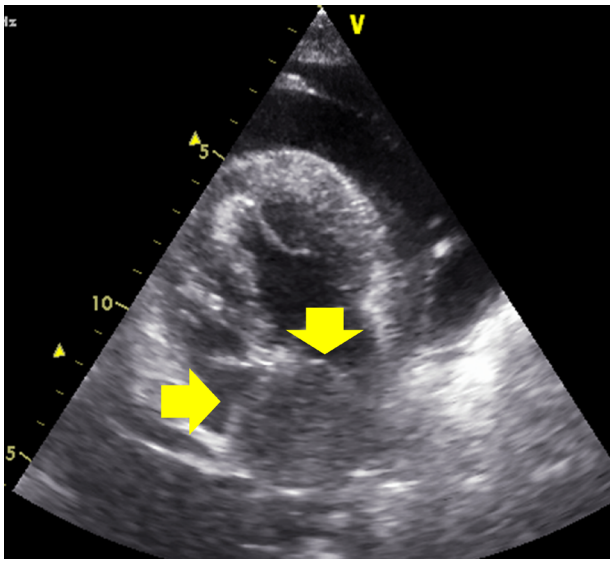

Figure 2. Echocardiographic left apical view displaying a hypoechoic mass between the left and right atrium (arrows)

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of haemorrhagic fluid was obtained from the pericardial sac and 1 000 ml of straw yellow fluid was tapped from the pleural cavity. The cytological and biochemical examination of pericardial and pleural effusion confirmed the presence of transudate (total protein: 20.9 g/l; glucose: 7.1 mmol/l; lactate: 1.62 mmol/l; CK: 1.06 µkat/l; LDH: 0.92 µkat/l) with the presence of moderate cellularity (neutrophils 39%, macrophages 10%, lymphocytes 51%) with a low number of reactive mesothelial cells and erythrocytes.

The dog, after the pericardiocentesis, improved clinically and was discharged the same day in the evening and was scheduled for thoracoscopic pericardiectomy. The dog was premedicated with sufentanil at 1 µg/kg (Sufentanil Torrex; Chiesi Pharmaceuticals, Vienna, Austria), and anaesthesia, used in an oxygen/air mixture, was induced with propofol at 2 mg/kg (Propofol; Fresenius, Bad Homburg, Germany), and atropine at 0.04 mg/kg (Atropin Biotika; BB Pharma, Prague, Czech Republic) and maintained with isoflurane (Isofuran; Torrex Chiesi, Prague, Czech Republic).

A subtotal pericardiectomy was performed using a paraxiphoidal approach. A 30° rigid telescope was inserted through the right paraxiphoid transdiaphragmatic portal and two working portals were placed in the middle 3rd of the right and left hemithorax in the 7th intercostal space. After puncturing the pleural cavity with a Veress needle, approximately one litre of diluted pinkish fluid was aspirated. A pericardiocentesis was performed under thoracoscopic control. A subtotal pericardiectomy was performed by using Harmonic scissors (Harmonic Ace®; Ethicon, Johnson & Johnson, Neenah, USA). The resected tissues were submitted for a histopathology. After revision of the pleural cavity, no other findings were noted. A thoracic drain was placed through the paraxiphoidal port and left in the chest cavity for 24 h postoperatively. The dog was medicated after surgery with morphine at 0.3 mg/kg i.m., q.i.d. (Morphin Biotika; BB Pharma, Prague, Czech Republic) and amoxicillin clavulanate at 20 mg/kg (Amoksiklav 600 mg; Lek Pharmaceuticals d.d., Ljubljana, Slovenia) i.m., s.i.d. The dog recovered well from the surgery and hospitalisation lasted three days. According to the owners, the dog was clinically stable without any signs of dyspnoea or abdominal distension for eleven days. On the 12th day after the surgery, the dog was presented at the clinic with clinical signs of restrictive dyspnoea and abdominal distension. The presence of a large volume of pleural effusion was again confirmed by radiographs and a repeated thoracentesis was performed. Four litres of macroscopically diluted pinkish fluid were obtained. The owners declined further diagnostic and therapeutic procedures due to the poor prognosis and requested euthanasia to give informed consent to a necropsy.

NECROPSY, HISTOPATHOLOGY

A necropsy examination was performed at the Department of Pathological Morphology and Parasitology, Faculty of Veterinary Medicine, University of Veterinary Sciences in Brno. A neoplastic mass was located in the area of the base of the heart, approximately in the apex of the aortic arch, without any evident involvement or connection to the aortic wall. The mass had an irregular nodular shape and measured 4 × 5 cm. On the cut section, the mass had a white to grey colour and showed a solid structure, with the presence of smaller foci of haemorrhages in some areas of the tumour (Figure 3).

Collected tissue specimens of the mass were prepared for a histopathological examination, fixed in 10% buffered neutral formalin, dehydrated, and embedded in paraffin wax for cutting. Tissue sections, each prepared on a microtome at a thickness of 4 µm, were stained with haematoxylin and eosin (H&E). In addition, an immunohistochemistry was conducted on the samples to confirm the neuroendocrine origin of the neoplastic cells. Immunohistochemical

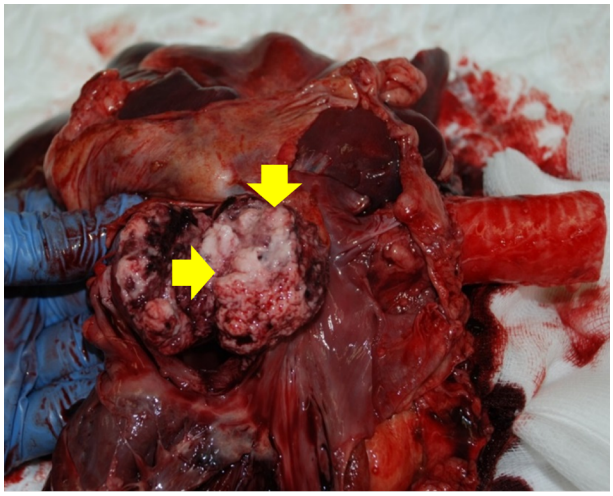

Figure 3. Necropsy – Heart base tumour (arrows) in the position of the aortic arch

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staining was performed on the 4 µm sections of the formalin-fixed, paraffin embedded tissue samples. Synaptophysin (Novocastra™ liquid mouse monoclonal antibody, dilution 1 : 25; Leica Biosystems Newcastle Ltd., Newcastle upon Tyne, UK), chromogranin A (Novocastra™ mouse anti chromogranin A monoclonal prediluted antibody, clone 5H7; Leica Biosystems Newcastle Ltd., Newcastle upon Tyne, UK) and neuron specific enolase (NSE) (monoclonal mouse anti-human NSE, dilution 1 : 50, clone BBS/NC/VI-H14; DAKO, Glostrup, Denmark) antibodies were used as the neuroendocrine markers. Cytokeratin AE1/AE3 (monoclonal mouse anti-human, prediluted antibody, clone AE1/AE3; Merck, Darmstadt, Germany), anti-vimentin (monoclonal mouse anti-vimentin antibody, dilution 1 : 50, clone V9; DAKO, Glostrup, Denmark) and Melan A (monoclonal mouse anti-human antibody, dilution 1 : 50, clone A103; DAKO, Glostrup, Denmark) antibodies were used as the epithelial, mesenchymal and neuroectodermal markers. The antigens were unmasked at pH 6 and 98 °C for 20 min (vimentin, NSE and Melan A), at pH 6 and 121 °C for 4 min (chromogranin A) and with use of proteinase K for 10 minutes (cytokeratin). The visualisation of the conjunction of the primary antibodies was undertaken by using EnVision+ System-HRP (DAKO, Glostrup, Denmark) for 1 h at room temperature, and DAB (3,3'-diaminobenzidine) stain was used subsequently for 5 min at 37 °C. In the end, the sections were stained with haematoxylin for one minute.

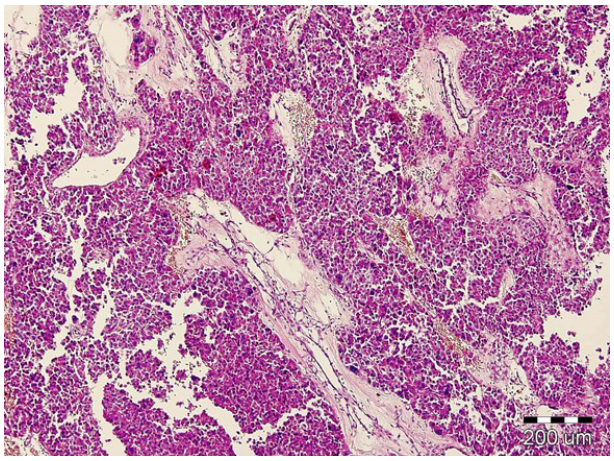

Figure 4. Solid tumorous mass with areas of interstitial loose connective tissue and vessels; H&E stain, × 100

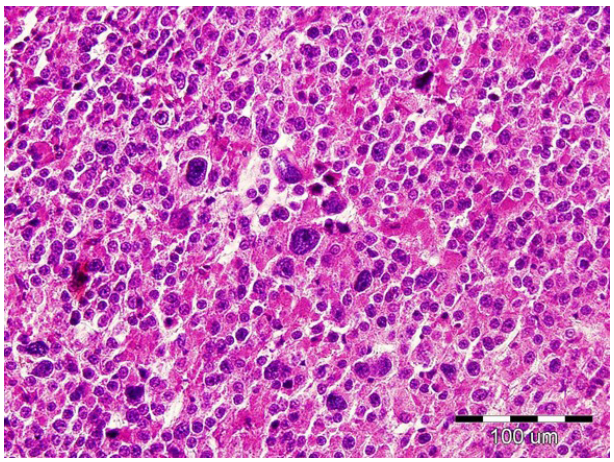

Figure 5. Marked cellular atypia of neoplastic cells (anisocytosis, megalokaryosis); H&E stain, × 400

The histopathological examination of the tumorous tissue showed a solid mass compound of predominantly oval, focally polygonal cells with oval nuclei and granulated chromatin (Figure 4). Neoplastic cells exhibited in most areas marked atypia (anisocytosis, anisokaryosis, megalokaryosis, prominent nucleoli and mitotic activity) (Figure 5). The mitotic count in the examined sections was 15 mitoses per 10 hpf. The pericardial wall was thickened due to the fibrovascular proliferation, reactive fibroplasia and focally haemosiderosis with invasion into the pericardial vessels. The immunohistochemistry showed neoplastic cell positivity for synaptophysin (Figure 6), chromogranin A and NSE. The immunohistochemical evaluation remained negative for cytokeratin AE1/AE3, anti-vimentin and Melan A. Based on the results of the immunohistochemistry, the diagnosis of a neuroendocrine carcinoma of the base of the heart was made.

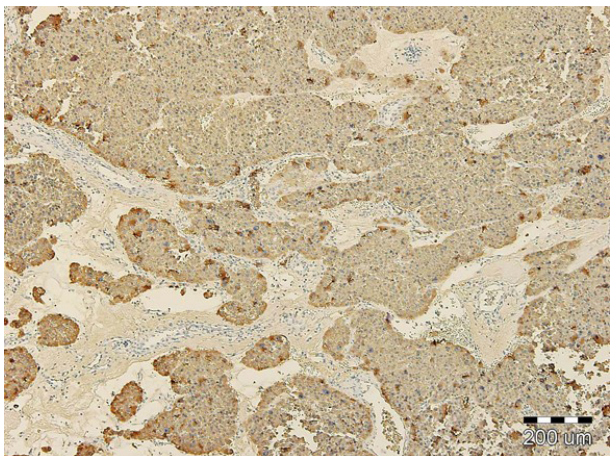

Figure 6. Positivity of neoplastic cells for synaptophysin. Immunohistochemistry, synaptophysin stain, × 100 [staining kit EnVision+ System-HRP (DAKO, Glostrup, Denmark)]

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DISCUSSION

To the best of our knowledge, this is the first report describing the presence of a neuroendocrine carcinoma in the area of the base of the heart in a dog and, at the same time, without any evident involvement or connection of the tumour to the aortic wall. Chemoreceptor organs in the aorta and carotid arteries can give rise to chemodectomas, which are neuroendocrine tumours. Aortic body tumours are more common in dogs but, although a connection with the artery should be expected, this finding was not confirmed in our case during the necropsy. Neuroendocrine tumours of the heart are reported to be very rare in humans and most of them are metastatic lesions. Only sporadic case reports of solitary and primary neuroendocrine carcinomas have been described (Wißt et al. 2018).

The clinical presentation in dogs with cardiac tumours depends on the anatomic localisation, size, and effects on the hemodynamic properties (Johnson et al. 2004). The clinical signs are independent of the histological type of tumour (Treggiari et al. 2017). Dogs may show the presence of respiratory signs, lethargy, abdominal distension, collapse, or could be without any clinical problems. Most commonly, cardiac tumours cause the presence of a pericardial effusion, ascites, exercise intolerance, and syncope, but they also can cause arrhythmias, pulmonary congestion, and sudden death (Rajagopalan et al. 2013; De Nijs et al. 2016; Treggiari et al. 2017). In the presented case, the respiratory distress and distension of the abdominal cavity were the most significant clinical problems.

Echocardiography is the most useful non-invasive diagnostic tool to detect a cardiac mass and the presence of a pericardial effusion, however, its sensitivity is variable and depends on the size, echogenicity and location (Johnson et al. 2004). A presumptive diagnosis is commonly made based on the echocardiographic localisation, echo texture, and invasiveness and is only moderately accurate (Rajagopalan et al. 2013). Pericardial fluid analysis, for the most part, has not been found to be useful in differentiating types of tumours (Sisson et al. 1984). A final diagnosis of a cardiac mass is undertaken only by histopathology (Treggiari et al. 2017). Moreover, non-neoplastic pathologies should be added to the list of differential diagnoses, such as abscess, granuloma or atypical cases of canine coccidioidomycosis (MacDonald et al. 2009; Ajithdoss et al. 2011).

Heart base tumours are neuroendocrine in origin if expressing neuroendocrine markers including synaptophysin, chromogranin A and NSE, which can be detected by using immunohistochemical staining (Kimura et al. 1988; Brown et al. 2003). These tumours grow slowly. Dogs are presented relatively late in the course of the disease with associated signs including pericardial effusion, arrhythmias, caval syndrome, and/or congestive heart failure (Yates et al. 1980; Obradovich et al. 1992).

Multiple treatments exist for cardiac tumours including surgery, chemotherapy and radiotherapy (Treggiari et al. 2017). Pericardiectomy for dogs with a cardiac tumour associated pericardial disease conveyed a median survival time of 52 days in 9 dogs compared to pericardiectomy for non-neoplastic pericardial disease (Kerstetter et al. 1997). In contrast to the findings in this report, our patient died 11 days after surgery. No information is available about the drug treatment of neuroendocrine carcinoma of the base of the heart in veterinary literature. On the other hand, the palliative resection of a large neuroendocrine tumour and heart transplantation due to tumour complexity are documented in human literature (Wißt et al. 2018).

Conflict of interest

The authors declare no conflict of interest.

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