Case Reports

Budd-Chiari-Like Syndrome Associated with a Pheochromocytoma Invading the Right Atrium in a Dog

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ABSTRACT

An 8 year-old spayed female Jack Russell Terrier dog was presented with severe abdominal distension due to ascites and discomfort of five days duration. Abdominal ultrasound revealed ascites and a mass invading the caudal vena cava pointing to Budd-Chiari-like syndrome (BCLS). The peritoneal fluid was a modified transudate. The BCLS was a result of a left adrenal mass that invaded the caudal vena cava to a length of 14 cm, up to the right atrium. A phaeochromocytoma was highly suspected and due to its aggressiveness and poor prognosis the dog was euthanized. The diagnosis was confirmed by histopathology after post mortem. This is a rare case of a 14 cm-long phaeochromocytoma associated with BCLS illustrating the *in vivo* diagnostic approach. A phaeochromocytoma should be considered in cases presenting with BCLS.

Key words: Budd-Chiari-like syndrome, abdominal effusion, abdominal distension.

INTRODUCTION

Budd-Chiari-like syndrome (BCLS) refers to hepatic venous outflow obstruction, resulting in post-sinusoidal portal hypertension and peritoneal effusion. The obstruction may occur anywhere along the post-hepatic veins, caudal vena cava (CVC), up to the right atrium (1, 2). Causes of BCLS include CVC intra-luminal obstruction (e.g., thrombosis and neoplasia) (2, 3, 4), extra-luminal compression (e.g., mass or neoplasia) (1) and kink (5), as well as, cardiac diseases (e.g., right heart failure, pericardial tamponate, constrictive pericarditis, (6) cor triatriatum dexter (7) and heartworm disease) (1, 6, 7) and miscellaneous causes including diaphragmatic hernia (8, 9).

In general, post-hepatic portal hypertension most commonly originates in the hepatic veins, CVC or right atrium and is frequently caused by right heart failure, pericardial disease, liver disease, pulmonary hypertension and BCLS (1, 10, 11). The localisation of the portal hypertension site has clinical relevance, because the location of obstruction often dictates the clinical presentation (e.g., ascites, hepatic encephalopathy and multiple acquired portosystemic shunts), diagnostic evaluation (e.g., liver function tests, peritoneal fluid analysis and imaging technique) and treatment (1, 2).

The peritoneal fluid in BCLS is a modified transudate (2, 11-14, 15, 16-18) with moderate cellularity (1000-7000 cells/μl) and protein concentration (2.5-7.5 g/dl) (10). It accumulates secondary to post-sinusoidal portal hypertension. The obstruction of the CVC leads to an imbalance in Starling´s law (1), where fluid is driven into the interstitial space due to the portal hypertension, and when the capacity of the regional lymphatics is overwhelmed, ascites develops (1, 10). From a diagnostic point of view, presence of a modified transudate is non-specific. The main differential diagnoses include right heart failure, liver diseases, neoplasia and BCLS (1, 10, 11).

Phaeochromocytoma is a rare cause of BCLS, and only five confirmed cases have been described previously (2, 4, 13). Only one of these has been described as extending from the adrenal gland through the CVC up to the right atrium (2). This current report describes a case of phaechromocytoma

that has invaded the CVC intraluminaly and extended along the entire vessel up to the right atrium.

CASE HISTORY

An 8 year-old spayed female Jack Russell Terrier weighing 7.6 kg was presented with a 5-day history of abdominal distention and intermittent abdominal pain. Upon physical examination, the dog was bright, alert and responsive. The body temperature was 39 ºC, heart rate was 156 beats/minute and respiratory rate 28 breaths/minute. The mucous membranes were pink and the capillary refill time was 1.5 sec. Thoracic auscultation was normal. Severe abdominal distention with a palpable fluid wave was present.

Abdominocentesis was performed and fluid analysis revealed a modified transudate, with high protein content (4.1 g/dL) and low cellularity (940 cells/μl). The main differential diagnoses were right-sided heart failure, abdominal neoplasia, portal hypertension or CVC obstruction (BCLS).

A complete blood count, serum biochemistry, urinalysis and fecal analysis were performed. The abnormal findings included mild hypoproteinemia [4.94 g/dL, reference interval (RI) 5.3-7.5], hypoglobulinemia (1.82 g/dL, RI 2.0-3.7), increased albumin-globulin ratio (1.72, RI 0.6-1.2) and thrombocytosis (625 x 10^9/L, RI 200-500 x 10^9/L). The hypoalbuminemia and hypoproteinemia were compatible with loss in the abdominal effusion. The thrombocytosis could be transient, secondary to splenic contraction due to excitement or most likely a reactive thrombocytosis secondary to a neoplasia or hyperadrenocorticism. Chronic gastrointes-
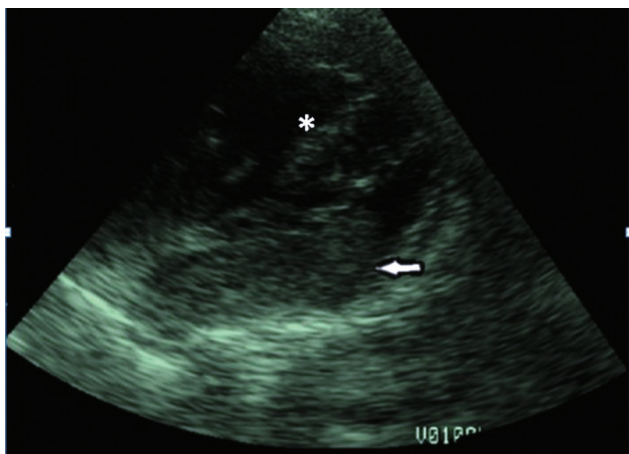
tinal bleeding can also not be ruled out. Other causes were unlikely in this case.

Doppler-measured systolic arterial blood pressure showed hypertension (180 mm Hg, RI 90-140 mm Hg). Ophthalmoscopic examination was performed in order to evaluate possible complications of hypertension, such as retinal detachment or hemorrhage and it was unremarkable.

An abdominal ultrasound revealed an intra-luminal mass obstructing the CVC and extending intraluminally cranially at the level of the liver. The differential diagnoses included thrombosis, fibrous web and neoplasia. Echocardiography demonstrated an extension of the mass into the right atrium, which appeared as an elongated homogenous hypoechoic free intra-atrial structure running along the intra-atrial free wall, making a fibrous web an unlikely cause (Figure 1). The adrenal glands could not be visualized on ultrasound, due to the high volume of ascites. Therefore thoracic and abdominal computed tomography angiogram (angio-CT) was performed in order to define the origin and size of the mass and screen for metastasis. The dog was pre-medicated with 0.2 mg/kg morphine (Morphine PF 10 mg/ml, Fresenius, Port Elizabeth, South Africa) given intramuscularly (IM) and 0.2 mg/kg diazepam (A-Lennon Diazepam 5 mg/ml, Aspen Pharmacare, Durban, South Africa) given intravascular (IV), induced with 2 mg/kg alphaxalone (Alfaxan-CD

Figure 1: Echocardiography demonstrating a right atrial mass (large white arrow), compatible with a thrombus or a neoplasia and mild tricuspid valve endocardiosis (asterisk).
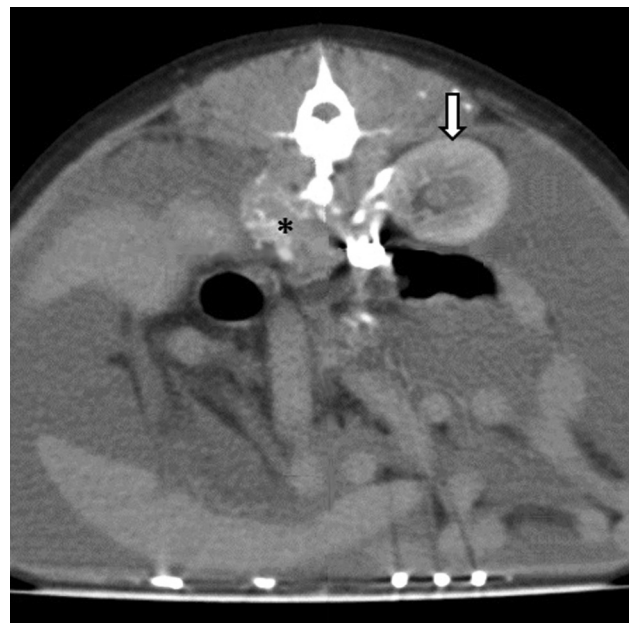

Figure 2: Computed tomography angiography demonstrating an enlarged homogenous left adrenal gland of 30 mm x 17 mm diameter (large white arrow) invading the caudal vena cava (asterisk).
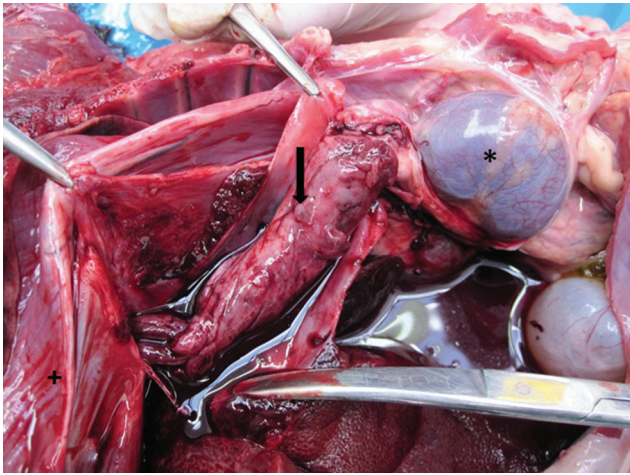
Figure 3: A 14-cm length mass (black arrow), confirmed on post-mortem, originating in the left adrenal, invading the caudal vena cava up to the right atrium (plus, diaphragm; asterisk, left kidney).
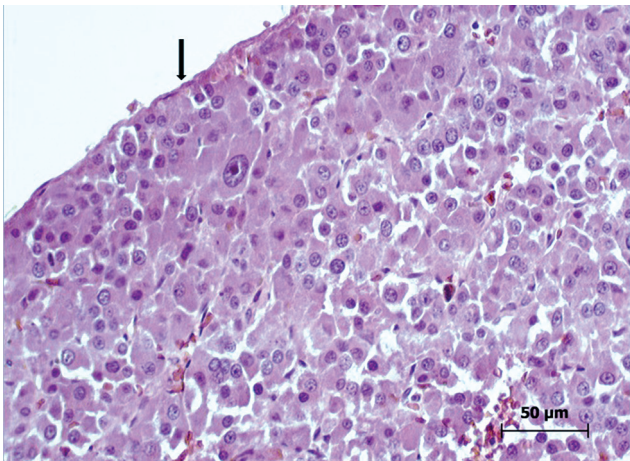

Figure 4: Histopathology of a section of the left adrenal gland showing an abnormal neoplastic proliferation of cells in the adrenal medulla (M) resulting in local invasion (asterisk) of the adrenal cortex (c), capsule and peri-adrenal connective tissues. This adrenal hyperplasia is causing cortical compression and atrophy (Hematoxylin and eosin, original magnification X20).

Figure 5: Histopathology of a section of the caudal vena cava. Invasion of the *tunicas adventitia*, *media* and *interna* by the neoplastic adrenal tissue, but remaining delimitated by the subendothelial layer (marked by the black arrow) of the caudal vena cava. The tumor cells have a well delineated large cuboidal to polyhedral pattern with large amounts of finely granular pale eosinophilic cytoplasm, moderate nuclear pleomorphism round to oval and some large bizarre shaped nucleus. The mitotic index was less than 1 per high field (Hematoxylin and eosin, original magnification X200).

Figure 6: Histopathology of a section of the left adrenal gland showing dense and coarsely stippled chromatin with the presence of one nucleolus. [immunohistochemical staining for endocrine cells with chromogranin A (heat induced epitope retrieval in 0.01 M sodium citrate buffer, pH 6.0), original magnification X 200]

10mg/ml, Kyron Laboratories (Pty) Ltd., Johannesburg, South Africa) IV and maintained on 2% isoflurane (Isofor, Safeline Pharmaceuticals (Pty) Lda, Roodepoort, South Africa) and 100% oxygen.

The left adrenal gland was abnormally increased in size upon the pre-contrast scan. When the contrast medium was administered, systolic blood pressure increased significant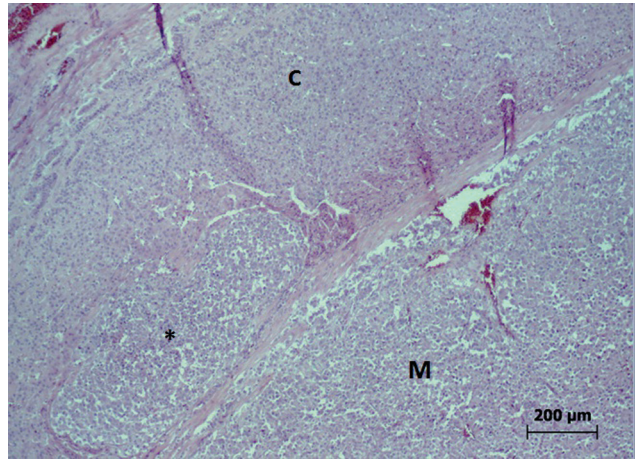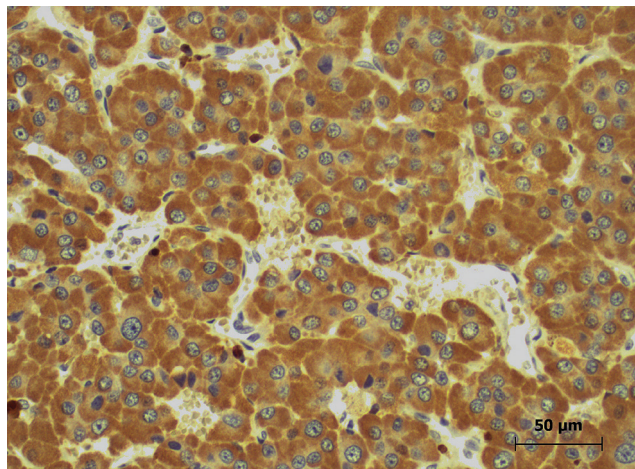ly to 200 mm Hg. On the post-contrast (perfusion phase) the left adrenal appeared as a 30 mm x 17 mm homogenously, mildly enhanced mass, invading the CVC and extending into the right atrium, causing a filling-defect of 16 mm x 7 mm in the right atrium. All the CVC showed poor contrast filling (Figure 2). No metastatic lesions were detected and the right adrenal gland had normal architecture and was within normal limits. The findings were compatible with a left adrenal gland tumor such as pheochromocytoma or adeno-

carcinoma, invading the CVC intraluminally and extending into the right atrium, with a secondary BCLS. The main differential diagnoses for this structure included pheochromocytoma, adrenal adenocarcinoma, haemangiosarcoma and paraglioma.

The owner elected for euthanasia and a post mortem examination was conducted. The gross pathology demonstrated a 14-cm adrenal mass originating from the left adrenal, invading the wall of the CVC and forming a free space occupying "thrombus-like" structure in this vessel and extending into the right atrium (Figure 3). Other post-mortem findings included a severe amount of a serous ascites and mild hepatic fibrosis. There were no evidences of distant metasteses.

Histopathology of the abnormal adrenal gland mass revealed a well demarcated neoplastic proliferation of cells in the adrenal medulla resulting in local invasion of the adrenal cortex, capsule and peri-adrenal connective tissues. This adrenal hyperplasia was causing cortical compression and atrophy (Figure 4). The tumor cells were imbedded in a fine fibrovascular stroma forming tight pockets of cells and on closer examination they appeared as a well delineated pattern of large cuboidal to polyhedral neoplastic cells with large amounts of finely granular pale eosinophilic cytoplasm, moderate nuclear pleomorphism round to oval with some large bizarre shaped nucleus and with a mitotic index of less than 1 per high field. The CVC showed an invasion of the *tunicas adventitia*, *media* and *interna* by the neoplastic adrenal tissue, but still remaining subendothelial and having the same above described characteristics (Figure 5). Immunohistochemical staining for endocrine cells with chromogranin A (heat induced epitope retrieval in 0.01 M sodium citrate buffer, pH 6.0) was performed and a positive result was obtained. The chromatin was fairly dense and coarsely stippled in the presence of one nucleolus (Figure 6). These microscopical features were consistent with neoplastic adrenal medullary cells and supported by the positive immunohistochemical staining. The liver histopathology revealed a widespread central venous duplication and mild centrilobular fibrosis.

DISCUSSION

This is the second descreet canine case report in the literature of a BCLS secondary to a pheochromocytoma. The previous case of a large pheochromocytoma invading the CVC up to the right atrium presented with ascites and a history of two episodes of collapse and a pheochromocytoma was later confirmed by histopathology on post-mortem (2). In the present case, the ante-mortem investigation included an abdominal angio-CT that allowed characterization of the abnormal adrenal mass, which was impossible using ultrasound. This diagnostic imaging modality was not used in the previous case reported. Another suspected case of a BCLS pheochromocytoma has been reported, however, confirmation by histopathology of the adrenal mass was not performed (17).

To the best of the authors' knowledge this is the first case of a 14-cm phaeochromocytoma associated to BCLS demonstrated by CT angiography in a Jack Russell Terrier. Although previous pheochromocytomas cases have been studied using this imaging modality (16, 31), none had presented with such an extensive invasion of the CVC and secondary BCLS.

Pheochromocytoma is an endocrine tumor, of chromaffin cells (phaeochromocytes) of the sympatho-adrenal system, with an occurrence of 0.17–0.76% of all canine tumours (14). These mostly originate in the adrenal medulla, but can also occur in extra-adrenal sites (paragangliomas), including the heart, carotid body, adjacent tissues to the aorta and urinary bladder (13, 15, 19, 20) and are classified as nonfunctional or functional. The latter produce and secrete catecholamines and their prevalence is 40 to 50% of such tumors (12, 15, 21, 22).

Increased plasma and 24-hour urine concentrations of catecholamine metabolites strongly support a diagnosis of phaeochromocytoma and their measurement is particularly useful in cases of small, adrenal masses which are hard to detect, and in hypertension of unknown origin (23, 24). In this case, with the obvious imaging evidence the measurement of catecholamine metabolites was deemed unnecessary.

Catecholamines are responsible for the hypertension and related signs and it occurs in up to 50% of the cases (11, 21, 25-28), but often it is paroxysmal, and therefore repeated blood pressure measurements and fundic examinations are recommended (11-14, 20-21, 27, 29-30). In this case, the hypertension was persistent, supporting the diagnosis of a functional pheochromocytoma.

In canine pheochromocytoma, 30-50% of the cases have invasion of the adjacent vasculature, 20-30% of the dogs develop metastatic disease, mostly hepatic, splenic and pulmonary and up to 5% present bilateral adrenal gland involvement (12). In the present case, the CVC and local vasculature were extensively invaded by the tumor, but no bilateral ad-

renal gland involvement or metastatic disease were seen on the angio-CT or in the post-mortem.

In humans and dogs, CT and magnetic resonance imaging (MRI) are the imaging modalities of choice to diagnose this challenging disorder, with 95% sensitivity to detect and delineate adrenal masses and venous thrombosis (16, 19, 28, 31, 32). In this case the large amount of abdominal fluid hampered the ultrasonographic visualization of the adrenal gland, whilst CT proved superior to detect both the adrenal tumor and its aggressive nature. The increase of the systolic blood pressure, post-administration of the contrast medium, during the angio-CT procedure, is typical of a pheochromocytoma (16, 17), which further increased the index of suspicion of this disorder during the clinical workup investigation.

The definitive diagnosis of phaeochromocytoma can only be made on histopathology. An immunohistochemical staining for chromogranin A and synaptophysin should be used to distinguish phaeochromocytomas from adrenocortical tumours, where positive stains have high sensitivity and specificity for pheochromocytomas (2, 15, 22, 27). In this case, the microscopic features were consistent with neoplastic adrenal medullary cells and supported by positive immunohistochemical staining for endocrine cells with chromogranin A. The mild hepatic fibrosis seen by histopathology could be explained by the portal hypertension secondary to the CVC luminal obstruction.

Taking into account the extensiveness and invasiveness of the tumor it would be expected to have distant metastases, but this was not the case. This could be possibly explained by the fact that the neoplasia invaded the wall of the CVC but remained within the wall delimited by the subendothelial layer and never truly contacting with the blood stream.

We describe a case of an extensive pheochromocytoma arising from the left adrenal gland, invading the CVC intramural and intraluminally up to the right atrium, associated with a BCLS in a dog. This case also shows the value of a CT angiography in order to better define the origin and invasiveness of the tumour and the presence or absence of metastatic lesions.

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