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Pulmonary artery dissection causing haemothorax in a cat: potential role of *Dirofilaria immitis* infection and literature review.

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Abstract

A 7 year old male castrated Domestic Shorthair cat suddenly died. Gross examination revealed severe right-sided haemothorax with blood clots, four adult filarid nematodes in the blood clots and the caudal vena cava and haemorrhage dissecting into the tunica media of the right pulmonary artery. Histopathological investigation showed fibrosis of the tunica intima and disorganization/fragmentation of the elastic fibers accompanied by fibrous tissue deposition in the tunica media of both branches of pulmonary artery. Degenerative vasculopathy (intimal fibromuscular hyperplasia and medial hypertrophy/hyperplasia) involving pulmonary arteries was also observed. PCR amplification and sequencing confirmed the identification of the parasite as *Dirofilaria immitis*. A diagnosis of pulmonary artery dissection with haemothorax and concomitant heartworm disease was formulated. Degenerative processes of the tunica media have been reported to cause pulmonary artery dissection in both humans and animals. Pulmonary artery remodeling induced by heartworms may be considered the underlying cause in the first case of feline pulmonary artery dissection herein described.

Keywords

Feline;

Heart;

Heartworm disease.

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A 7 year old male castrated Domestic Shorthair cat weighing 4.5 kg was referred for vomiting and lack of appetite at the Department of Veterinary Sciences of the University of Turin. Blood analyses (complete blood count, biochemical analysis, blood gas analysis and coagulation profile) showed no significant alterations. Abdominal ultrasound examination revealed mesenteric lymphadenomegaly and dilated colon with fecal impaction. Fine needle aspiration cytology of mesenteric lymph nodes showed reactive hyperplasia. A diagnosis of colic fecal impaction with lymph nodal reactivity was made. Therapy consisted of carprofen (2mg/kg PO q 24 hr) and lactulose (0.5 ml/kg PO q 24 hr) associated with mono-protein diet and the cat was discharged. The patient's initial clinical signs appeared to have resolved and the cat seemed to be in good health conditions for the following month. However, at the beginning of the second month of the post-discharge period, the animal suddenly died overnight and was found dead by the owners the next morning.

At post mortem examination, upon opening the thoracic cavity, severe right-sided haemothorax with at least 100 mL of blood and blood clots was observed. Four adult filarid nematodes were found in the blood clots (three parasites) and, after the opening of the pericardium, in the caudal vena cava (one parasite) (Fig. 1A). The right pulmonary artery was diffusely red and severely dilated. Large and multifocal to locally extensive peri-adventitial haematomas were also observed. Upon opening the lumen, the wall of the right pulmonary artery was split with haemorrhage dissecting into the tunica media. The dissection extended from the bifurcation of the pulmonary trunk throughout the proximal segment of the right pulmonary artery for a length of 2 cm (Fig. 1B). The endothelial surface of both right and left pulmonary arteries was severely, multifocally and irregularly thickened. The heart was externally examined and opened following the inflow and outflow tracts after transverse sectioning at the level of the middle third of the ventricles in order to

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evaluate all the cardiac structures. Heart weight (18.2 g), heart weight to body ratio (4.04 g/kg) and wall thicknesses (6.5 mm for the left ventricular free wall, 6.1 mm for the interventricular septum and 2.0 mm for the right ventricular free wall) fell within the normal values reported in cats [1,2], thus revealing no signs of cardiac hypertrophy. No enlargement of both atria and ventricles was observed and the atrio-ventricular and semilunar valves morphology was normal. The venae cave did not also show any significant changes. The lungs showed severe and multifocal irregular red areas with parenchymal haemorrhages on cut surface. Serial sections performed perpendicularly to the pulmonary hila also revealed severe and multifocal perivascular haemorrhages involving the right lobar pulmonary arteries. The spleen was severely and diffusely pale. The other organs showed no significant gross abnormalities. Samples of heart, lungs, spleen, liver, kidney, stomach, intestine, thyroids, adrenal glands and pancreas were collected and fixed in 10% buffered formalin solution. Organs samples were successively processed by routine methods, embedded in paraffin wax blocks, sectioned at 5µm thickness and stained with Haematoxylin & Eosin. Selected serial sections of the pulmonary lobes and both right and left pulmonary artery were also stained with Elastic Red Picro Sirius, Phosphotungstic Acid Haematoxylin and von Kossa in order to investigate collagen, elastic fibers, fibrin and calcium deposition. Tissue sections were examined by light microscopy. The tunica media of the right pulmonary artery was dissected by haemorrhage in its proximal segment (Fig. 2A-B). Severe and multifocal disorganization/fragmentation of the elastic fibers accompanied by mild fibrous tissue deposition and large regions of calcifications was observed in the tunica media of both dissected and non dissected segments. Large and multifocal peri-adventitial haematomas with fibrin deposition were also detected. The left pulmonary artery showed severe and multifocal neoangiogenesis with mononuclear and eosinophilic infiltrates and immature

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fibrous tissue in the tunica intima and media, sometimes resulting in the formation of villous-like structures that protruded into the lumen. Marked and multifocal fibrosis of the tunica intima and disorganization/fragmentation of the elastic fibers accompanied by mild fibrous tissue deposition in the tunica media were also observed (Fig. 2C). The right lung lobes showed severe and multifocal perivascular haemorrhages associated with segmental coagulative necrosis of the lobar pulmonary arteries. In both lungs marked and diffuse alterations of the tunica intima and media of the medium- and small-size arteries were detected (Fig. 2D). Intimal changes were represented by fibromuscular hyperplasia with loose, fragmentation and/or replication of the internal elastic membrane. The tunica media was characterized by both proliferative (hypertrophy/hyperplasia of the smooth muscle cells) and degenerative (reorientation and vacuolar degeneration of the smooth muscle cells and fibrous tissue deposition) changes. Furthermore, both lungs showed severe and multifocal interstitial, subpleural and bronchoalveolar haemorrhages. Marked and multifocal hyperplasia of the bronchial and bronchiolar glands accompanied by mild lymphoplasmacytic infiltrates within the lumen and hypertrophy of the bronchiolar smooth muscle was observed. Severe and multifocal subpleural atelectasis with mild reactive hypertrophy/hyperplasia of the mesothelial cells was detected. Mild and multifocal alveolar emphysema accompanied by proliferation of smooth muscle cells in the alveolar walls was finally found. Apart from severe and diffuse red pulp depletion observed in the spleen, the other organs showed no significant alterations.

Two filarial nematodes were stored at -20°C for biomolecular identification by means of PCR amplification and sequencing. Total genomic DNA was extracted from ≈ 25mg of tissue of adult worms using PureLink Genomic DNA Kit[a] following manufacturer's instructions. A PCR protocol using primers ITS2F-Di and ITS2R-Di [3] was used to amplify a specific portion of ≈ 540 bp the ITS2 gene of *D. immitis*. To confirm species

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identification, a second PCR protocol using primers DICOI-F1 and DICOI-R1 [4] was used to amplify a portion of 203 bp of the mitochondrial cytochrome oxidase subunit I of *D. immitis*. The PCR amplification and sequencing of specific portions of ITS2 and COI genes confirmed the identification of the parasite as *D. immitis*. The obtained sequences were compared to the ones available in GenBank[b] through BLAST[c] search. The specific portion of the ITS2 gene resulted 100% identical to *D. immitis* (GenBank accession number: AF217800[d]) and the COI fragment amplified resulted 100% identical to *D. immitis* deposited under the GenBank accession number AB192887[e].

Based on gross and histopathological findings, a diagnosis of pulmonary artery dissection with severe right-sided haemothorax and concomitant *Dirofilaria immitis* infection was formulated.

Discussion

Dissection of an elastic artery is generally defined as a tear in the tunica intima and consequent infiltration of blood into the vessel wall, resulting in separation of the tunica intima from the tunica media [5]. Pulmonary artery dissection is a very unusual finding in veterinary medicine, since it has only been reported in dogs [6,7,8,9] and cattle [8]. Pulmonary artery dissection is generally associated with aortic dissection [4,5,8], but single pulmonary artery involvement is also described [8,9]. Sporadic cases of aortic dissection associated with systemic hypertension have been observed in cat [11,12], but to the best of authors' knowledge no reports of pulmonary artery dissection are currently available in feline species. Contrarily to the aortic dissection, which is generally attributed to systemic hypertension [7,11,12,13] or heritable defects in the connective tissue components including elastin [10,14] or collagen fibrils [15], the pathogenesis of pulmonary artery dissection is not well understood. Aneurysmal dilatation of the pulmonary artery associated

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with patent ductus arteriosus [6,9] or anomalous vessels [8] is considered the main predisposing cause in dogs. Marfan's syndrome [10] and secondary degenerative cystic wall changes [9] are also reported as underlying causes in cattle and dogs, respectively. Pulmonary artery dissection due to chronic pulmonary hypertension has also been observed in one dog [9]. In people, pulmonary artery dissection usually develops in patients with pulmonary hypertension of various causes [16]. However, Marfan's syndrome, cystic medionecrosis and systemic inflammation of unknown cause have also been reported as possible causes in patients without underlying pulmonary hypertension [17]. As opposed to humans, whose pulmonary artery appears more likely to rupture [18] with bleeding into pericardium, lungs, mediastinum or pleural cavity [17], rupture of the dissected pulmonary artery with bleeding into the perivascular tissue has only been observed in an adult dog [6].

Dirofilaria immitis infection was observed in the cat of the present case report. Domestic cats can be infected with heartworms in a similar manner as dogs, even if the frequency of infection is lower and the heartworm's lifespan is shorter [19]. There are two main phases of infection: (1) the arrival of immature worms in the pulmonary arterial vessels and (2) the death of adult heartworms [20]. Generally, most of the immature worms reach the caudal pulmonary arteries, die and induce a strong vascular and parenchymal inflammatory response known as heartworm-associated respiratory disease [19]. Adult heartworms seem to have an anti-inflammatory effect that minimizes clinical signs in infected cats [20] and the animals may be asymptomatic until they show acute respiratory distress or sudden death caused by deterioration, death, and embolization of worms or worm fragments [19]. Gross and histopathological findings have been widely described in both experimentally [21,22] and naturally [23] heartworm-infected cats. As seen in the cat of the present case report, most commonly there are 1 to 4 adult heartworms per cat [23] with villous

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eosinophilic and lymphoplasmacytic endarteritis, intimal proliferation with fibrosis, and frequently observed pulmonary arterial medial hypertrophy and hyperplasia [21,22,23]. Other lung alterations occurring less frequently and also detected in the present case include bronchitis/bronchiolitis, bronchi and bronchiole gland hyperplasia, bronchiolar smooth muscle hypertrophy, disorganization and vacuolization of muscle cells of the tunica media of pulmonary arteries, alveolar emphysema, and proliferation of smooth muscle cells in the pulmonary parenchyma [22].

In this case, *Dirofilaria immitis* is implicated in the pathogenesis of the pulmonary artery dissection. Since heartworm infections in cats usually have a small number of worms and are of relatively short duration, pulmonary hypertension development is less common in cats as compared to dogs [20]. Considering the absence of right ventricular hypertrophy in the cat of the present report, the hypothesis of pulmonary artery dissection consequent to pulmonary hypertension seems unlikely. Severe and chronic endo-mesoarteritis associated with medial degeneration observed in the cat of the present report, which was attributable to the mechanical action of the parasites [22], could be considered as the most reliable predisposing factor for the pulmonary artery dissection development. Indeed, degenerative processes of the tunica media (such as cystic medionecrosis or cystic medial degeneration) have been reported as underlying causes in both human [17] and canine [9] pulmonary artery dissection. Furthermore, inflammatory reactions in the dissecting artery wall have been observed in two human patients with pulmonary artery dissection [17]. The identification of pulmonary rupture without intimal tears is similar to that observed by Le Bret et al. [18], which reported that the thin wall of the pulmonary artery in people appears less likely to dissect with an intimal flap. The segmental necrosis of the lobar pulmonary arteries was probably subsequent to the compression by the dissecting haemorrhage and further contributed to blood loss via parenchymal hemorrhages.

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To the best of authors' knowledge, this is the first report of pulmonary artery dissection causing haemothorax in cat, which hypothesizes a potential role of the concomitant *Dirofilaria immitis* infection in its pathogenesis.

Footnotes

[a]Thermo Fisher Scientific Inc., MA, USA.

[b]GenBank® (http://www.ncbi.nlm.nih.gov/genbank/)

[c]BLAST® (Basic Local Alignment Search Tool - http://blast.ncbi.nlm.nih.gov/Blast.cgi)

[d]GenBank: AF217800.2 (Dirofilaria immitis 18S ribosomal RNA gene, partial sequence; internal transcribed spacer 1, 5.8S ribosomal RNA gene and internal transcribed spacer 2, complete sequence; and 28S ribosomal RNA gene, partial sequence)

[e]GenBank: AB192887.1 (Dirofilaria immitis mitochondrial coi gene for cytochrome oxidase subunit I, partial cds, isolate: dog).

Conflict of interest

The authors declare no conflict of interest.

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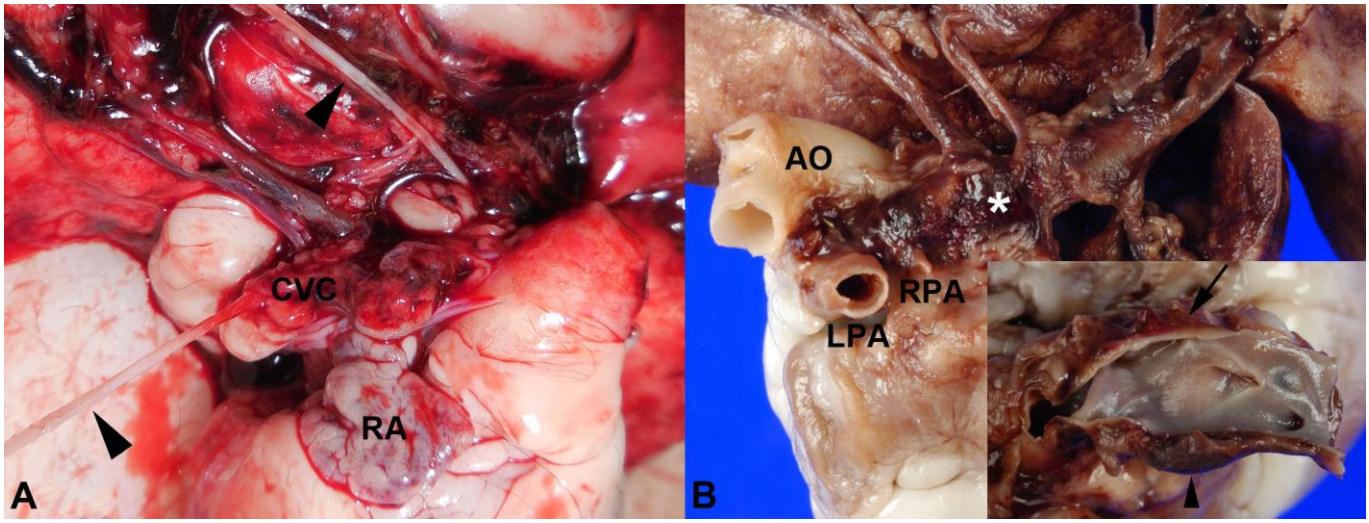

Fig. 1

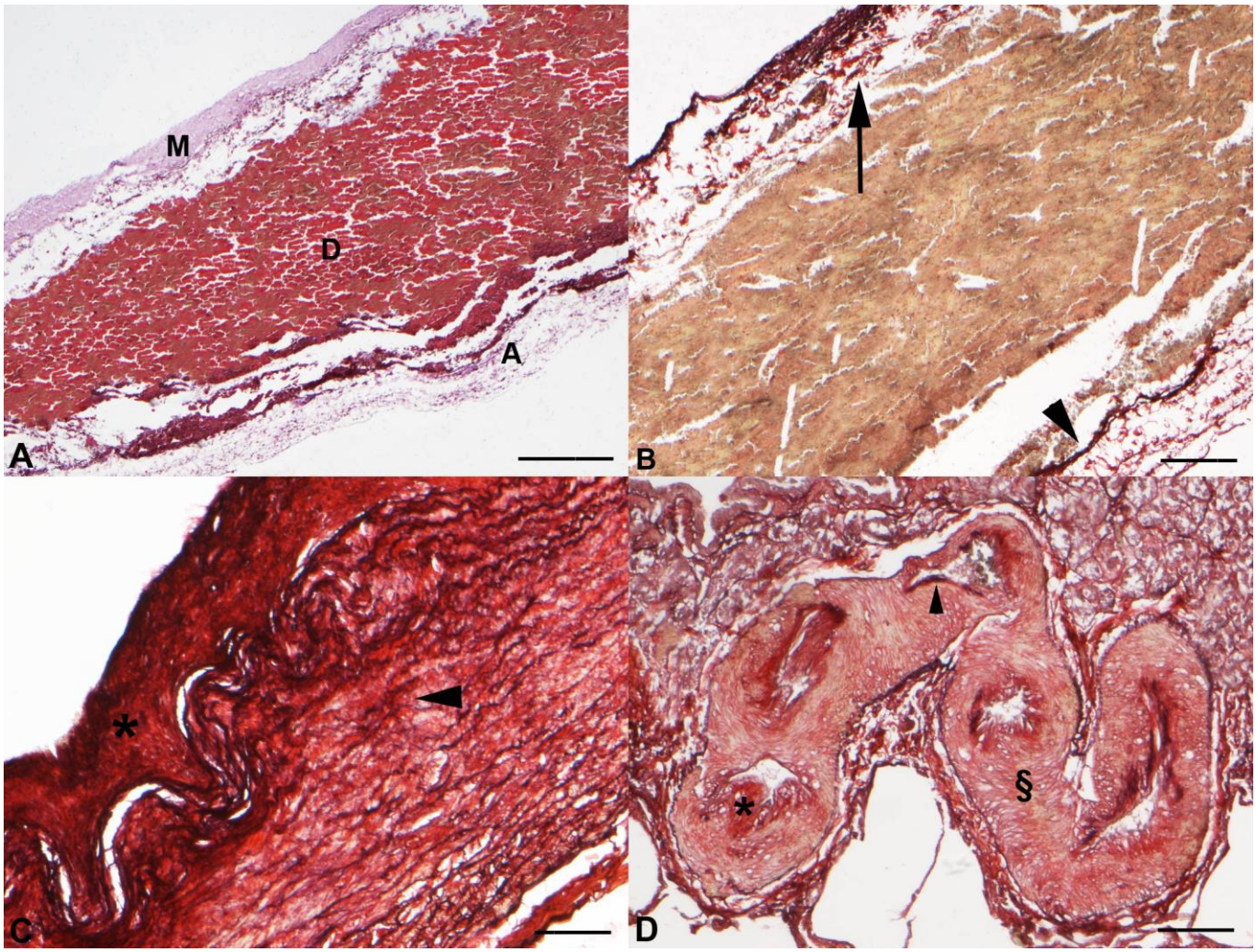

Fig. 2

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Figure captions

Figure 1. Gross examination of the heart. A) View of the right side of the heart. After removal of the pericardial sac, two adult filarial nematodes (arrowhead) are found. One of them is detected in the caudal vena cava (CVC). RA = right auricle. B) Dorsolateral view of the pulmonary artery. Right pulmonary artery (RPA) is diffusely red and tan and severely dilated (*). Upon opening (picture in the lower right), the wall of the right pulmonary artery is split with haemorrhage (arrowhead) dissecting into the tunica media. Large and multifocal peri-adventitial haematomas (arrow) are also observed. AO = aorta; LPA = left pulmonary artery.

Figure 2. Histopathological examination of pulmonary artery and lung. A) The tunica media (TM) of the right pulmonary artery is dissected (*) by haemorrhage (Haematoxylin & Eosin stain, 2.5x magnification, bar = 1000 µm). TA = tunica adventitia. B) In the dissected portion of the right pulmonary artery, residual collagen fibers (arrow) are observed. The external elastic lamina (arrowhead) confirms that the dissection involves the media (Elastic Red Picro Sirius stain, 5x magnification, bar = 1000 µm). C) Marked and multifocal fibrosis (*) of the tunica intima with disorganization/fragmentation of the elastic fibers and fibrous tissue deposition (arrowhead) is observed in the right pulmonary artery (Elastic Red Picro Sirius stain, 10x magnification, bar = 100 µm). D) Right lung lobes. Medium- and small-size arteries were characterized by intimal fibromuscular hyperplasia (*) with loose, fragmentation and/or replication of the internal elastic membrane (arrowhead) and by medial hypertrophy/hyperplasia (§) (Elastic Red Picro Sirius stain, 10x magnification, bar = 100 µm).

Elastic Red Picro Sirius stain = collagen and elastic fibers stain red and black, respectively.

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