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Necropsy findings in a cat with diabetes mellitus and heart failure

Melanie J Dobromylskyj[1] and Christopher JL Little[2]

Abstract

Case summary A 7-year-old male neutered domestic shorthair cat, previously diagnosed and treated for diabetes mellitus (DM), subsequently presented in heart failure (HF). Echocardiography revealed biatrial and biventricular dilation with poor myocardial function, and a left atrial-to-aortic ratio of 1.95:1. There was caudal vena cava dilation, hepatomegaly and ascites. The HF was treated with furosemide for 5 weeks, but thereafter the cat presented recumbent and moribund, and was euthanased. Post-mortem findings included dilation of all four cardiac chambers with an increased heart weight. Microscopic examination of the heart revealed mild, predominantly interstitial or perivascular fibrosis throughout most of the myocardium, with small-to-medium-sized foci of replacement fibrosis within the left ventricular free wall and interventricular septum. There was evidence of myocyte degeneration, but myofibre disarray was mild and there was minimal evidence of inflammation.

Relevance and novel information Cardiac disease is common in cats and while HF is less common, it is a frequent cause of clinical signs and death. DM is a relatively common feline endocrinopathy. This case report describes DM and HF presenting as comorbidities, including detailed ante- and post-mortem findings. The case, and the epidemiology of these conditions, raise the question of whether a form of diabetic cardiomyopathy exists in cats, as it appears to do in humans.

Keywords: Diabetes mellitus; cardiomyopathy; heart failure; histopathology

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Introduction

Both diabetes mellitus (DM) and cardiac disease are common conditions in cats.[1,2] For DM, one study demonstrated a prevalence of one in 230 cats within a large insured UK-based cohort,[3] while another showed an increasing prevalence over time.[4] Another authoritative publication cited the incidence of new cases of feline diabetes as 0.2–1%.[5] Cardiac disease and heart failure (HF) are also significant causes of mortality in the feline population. One large-scale UK study screening an apparently healthy feline population residing in rehoming centres found a prevalence of hypertrophic cardiomyopathy (HCM) of 14.7%.[2] A smaller US study reached similar conclusions.[6] Another study looking at >1000 cats undergoing necropsy found that of those presenting as unexpected deaths, 55.1% had no potential cause other than the cardiac disease found, while for expected deaths/euthanasia, 2.8% had congestive HF (CHF) and another 7% had incidental heart disease diagnosed.[7] In a 2020 study of 260 cats treated for CHF in two US University veterinary hospitals, 19 (7.3%) had concurrent DM, making it the third most common comorbidity after chronic kidney disease (CKD) and hyperthyroidism.[8] Furthermore, it should be remembered that there may be under-representation of diabetes in some feline heart disease studies, as exclusion criteria often include diabetes, other endocrinopathies or other systemic diseases.

In humans, the effects of diabetes on the cardiovascular system have long been recognised, in particular diabetic

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angiopathy. However diabetic cardiomyopathy (DMCMP) is also recognised, albeit as a somewhat controversial entity, defined as the existence of left ventricular dysfunction in diabetic patients arising in the absence of coronary artery disease, hypertension, myocardial infarction or other potential causes.[9] DMCMP presents with both morphological and functional alterations.

A few published studies have questioned whether DMCMP arises in cats, although, to date, none of these has included histopathological assessment, and currently there is no consensus that feline DMCMP exists. One retrospective case-control study found that the relative risk of HF in diabetic cats was 10.4 times that of the control cats.[10] In a study of 260 cats treated for CHF, 19 (7.3%) had concurrent DM, making it the third most common comorbidity after CKD and hyperthyroidism.[8] This is a striking observation because the prevalence of DM is higher than that seen in the general feline population. There is convincing evidence that feline hyperthyroidism causes cardiac pathology and that renal failure can predispose to heart disease by inducing hypertension. To date, a pathological mechanism to explain why diabetes might induce HF in cats has not been proposed, but the data suggest that feline DM predisposes to HF.

Another study sought to assess cardiac function in feline patients with newly diagnosed DM and to characterise any development over the course of 6 months.[11] This showed that cats with DM had evidence of diastolic, but not systolic, dysfunction, in the absence of structural heart disease and when compared with healthy controls. This study excluded cats with primary heart disease as far as possible, including those with evidence of HCM on echocardiography; however, there was no histopathological assessment of these cases. The authors did not document any structural cardiac changes in the diabetic cats, although the study had a short duration and the study criteria may have excluded cats with structural heart disease present secondary to diabetes.

Another recent study looking at feline acromegalic cardiomyopathy included a control group of cats with DM but no acromegaly.[12] Assessment via echocardiography demonstrated that the acromegalic cats had a greater maximum left ventricular wall thickness than the diabetic, non-acromegalic cats and controls, and that the diabetic non-acromegalic cats did not appear to have clinically significant myocardial hypertrophy. However, no histopathological assessment was performed for the control cases with DM in the absence of acromegaly.

The current case report describes a cat with previously diagnosed and treated DM, which presented in cardiac failure. This is the first case, to our knowledge, with detailed cardiac investigation both ante and post mortem, including histopathological assessment, of such a case. We raise the question of whether a form of diabetic cardiomyopathy exists in cats.

Case description

A 7-year-old male neutered domestic shorthair cat, weighing 4.3 kg and with an indoor/outdoor lifestyle, was diagnosed with DM based on a clinical history of polydipsia, polyuria (PU/PD) and polyphagia, hyperglycaemia (31.2 mmol/l; reference interval [RI] 3.8–7.6), glycosuria and elevated serum fructosamine levels (559.7 µmol/l [RI 175–400]). Serum total thyroxine (TT4) was slightly below normal (4.4 nmol/l [RI 7.5–55]), ruling out hyperthyroidism. Treatment was initiated with prozinc insulin (2 IU q12h [Boehringer Ingelheim Vetmedica]) and a proprietary diabetic diet (RCW dry and wet; Royal Canin). PU/PD was well controlled and no episodes of frank hypoglycaemia were diagnosed, but serum fructosamine monitoring implied that overall control was imperfect (fructosamine levels ranged from 550 to 660 µmol/l on repeat testing). The cat had concurrent flea allergic dermatitis, managed by vigorous flea control and occasional short courses of systemic corticosteroids (lasting up to 14 days). After 25 months of treatment for DM the cat developed a severe dental abscess with loss of a canine tooth, managed with a 10-day course of amoxicillin/clavulanate (Synulox; Zoetis) and meloxicam (Metacam Cat; Boehringer Ingelheim Vetmedica).

Two weeks after the dental abscess resolved the cat presented with tachypnoea (60 breaths/min), hyperpnoea and abdominal swelling. Clinical examination revealed hypothermia (37.1°C). The heart rate was regular at 164 beats/min (bpm), but pulses were impalpable. A gallop sound was present during cardiac auscultation, but a heart murmur was not. A sinus rhythm was present.

Echocardiography (Figures 1–3) revealed biatrial and biventricular dilation with poor systolic myocardial function (particularly of the interventricular septum [IVS]) and a left atrial (LA) to aortic ratio, measured during diastole, of 1.95:1 (Table 1 and Figure 3). LA_{max} (Table 1 and Figure 1) was markedly elevated at 25 mm (where $>$ 16.5 mm is considered highly suggestive of HF).[14] A small pericardial effusion was present. The caudal vena cava was dilated (diameter 8 mm [no published reference data found for cats]). Hepatomegaly and ascites with a total protein content of 34 g/l were found. A diagnosis of biventricular HF associated with DM was made.

The HF was treated with furosemide (Frusedale; Dechra Veterinary Products), initially at a dosage of 20 mg q12h, reduced to 10 mg q12h once the tachypnoea and ascites had resolved. Additional treatment with benazepril and clopidogrel were advised, but the client declined these owing to difficulties administering tablets to the cat. Insulin treatment continued. The client reported marked improvement in the cat's quality of life. Five weeks after the HF was diagnosed, the cat suffered a nocturnal seizure episode. It was presented recumbent

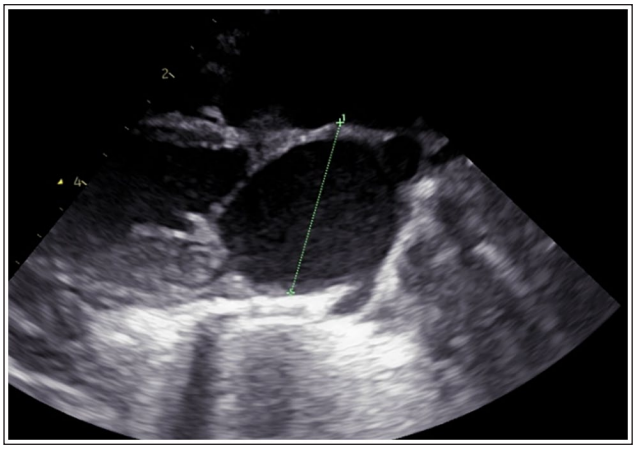

Figure 1 Right parasternal long-axis B-mode ultrasound image of the left heart showing measurement of the dilated left atrium (LA), designated LA_{max} (25 mm, see Table 1)

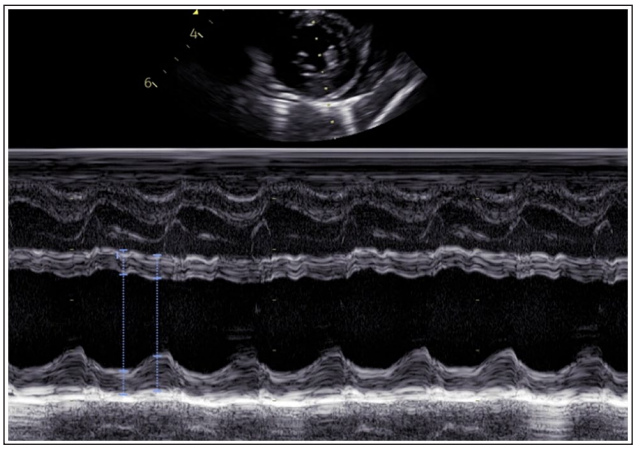

Figure 2 Right parasternal short-axis duplex ultrasound images of the left ventricle. The upper portion shows a B-mode image of the ventricles and the orientation of the M-mode cursor. The lower image is an M-mode study showing right and left ventricular dilation, as well as diminished systolic function, especially of the interventricular septum

and moribund with hypothermia (36.4°C), tachypnoea, hyperpnoea and regular bradycardia (132 bpm). The client requested euthanasia. A limited post-mortem examination was permitted.

At post-mortem examination, the cat weighed 3.8 kg, with a body condition score of 3/9. Free fluid was absent from the abdominal and thoracic cavities. The heart, and samples from the left and right lung lobes, and from the liver and pancreas were submitted for histopathological assessment. On gross examination, the samples of fixed liver tissue had an enhanced lobular pattern throughout. Samples from the lung floated in formalin (ie, contained air). The pancreas contained numerous, variably sized

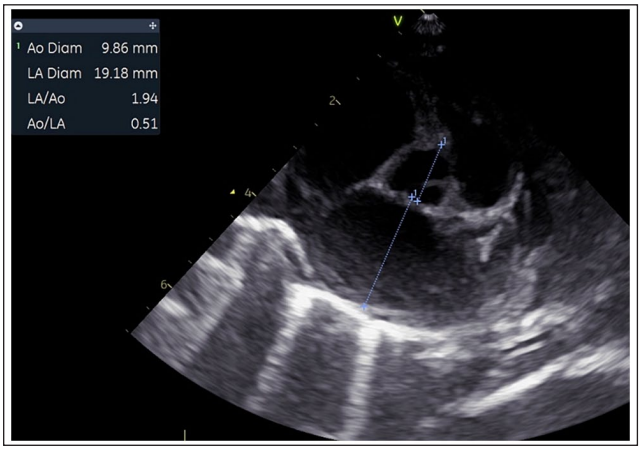

Figure 3 Right parasternal short-axis B-mode image of the heart base showing measurement of the aortic root (Ao) and left atrium (LA) performed towards the end of diastole. This method of measurement is used to give the LA:Ao ratio (see Table 1)

Table 1 Echocardiographic findings

	Case	Outside the reference interval?[13]
IVSd (mm)	3.7	No
LVDd (mm)	18.3	Yes
LVFWd (mm)	6.5	Yes
IVSs (mm)	5.0	No
LVDs (mm)	14.3	Yes
LVFWs (mm)	9.4	Yes
FS%	22	Yes
LA (mm)	19.2	Yes
Ao (mm)	9.9	No
LA:Ao	1.95	Yes
LA_{max} (mm)	25	Yes[14]

Echocardiography revealed biatrial and biventricular dilation with poor systolic myocardial function and a left atrial to aortic ratio (LA:Ao), measured in diastole, of 1.95:1 from a right parasternal short-axis view of the heart base

IVSd = interventricular septal thickness in diastole; LVDd = left ventricular diameter in diastole; LVFWd = left ventricular free wall thickness in diastole; IVSs = interventricular septal thickness in systole; LVDs = left ventricular diameter in systole; LVFWs = left ventricular free wall thickness in systole; FS% = percentage fractional shortening; LA = left atrial diameter; Ao = aortic root diameter; LA_{max} = measurement of the dilated left atrium using a right parasternal long-axis B-mode ultrasound image of the left heart

firm nodular areas throughout. The fixed heart weighed 27.7 g. Measurements of the right ventricular free wall, IVS and left ventricular free wall (LVFW) were 2 mm, 4 mm and 8 mm, respectively, giving a ratio of 1:2:4 (a normal ratio is typically considered to be 1:3:3). All cardiac chambers were dilated (Figure 4).

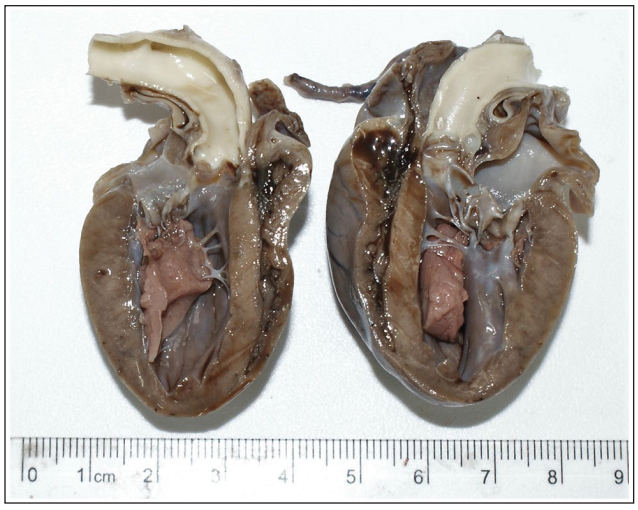

Figure 4 Gross appearance of the heart, fixed and opened to show dilation of the left ventricle and atrium, as well as the right ventricle and atrium

Sections through the heart, both transverse and longitudinal, were sampled and 4 µm-thick sections stained either with haematoxylin and eosin (HE) or Masson's trichrome (stain for connective tissues) were examined microscopically. Mild interstitial and perivascular fibrosis was observed throughout most of the myocardium; however, there were several small-to-medium-sized foci of replacement fibrosis (scarring) present within parts of the LVFW and the IVS. The abnormal ratio of the IVS to the LVFW and the presence of replacement fibrosis within parts of the IVS would be supportive of a previous septal infarct, and this would also correlate with the septum appearing thin on echocardiography and the myocardial systolic function being poor. There was evidence of myocyte degeneration; some myocytes demonstrated loss of striations, with a granular or vacuolated appearance to their cytoplasm, while occasional individual cells appeared shrunken with more brightly eosinophilic cytoplasm. There was a degree of nuclear pleomorphism and nuclear enlargement. Myofibre disarray was present but mild. Inflammation appeared largely absent (Figure 5).

Representative sections through the pancreas stained either with haematoxylin and eosin or Congo red (stain for amyloid) were also examined microscopically. The nodules noted macroscopically corresponded to areas of nodular hyperplasia of the exocrine pancreatic parenchyma, or to foci of acinar atrophy. There was mild, interstitial and predominantly periductular fibrosis with low numbers of lymphocytes and plasma cells. Islets were not readily apparent; where present the islet cells often appeared vacuolated or to have been effaced by brightly eosinophilic amorphous extracellular material,

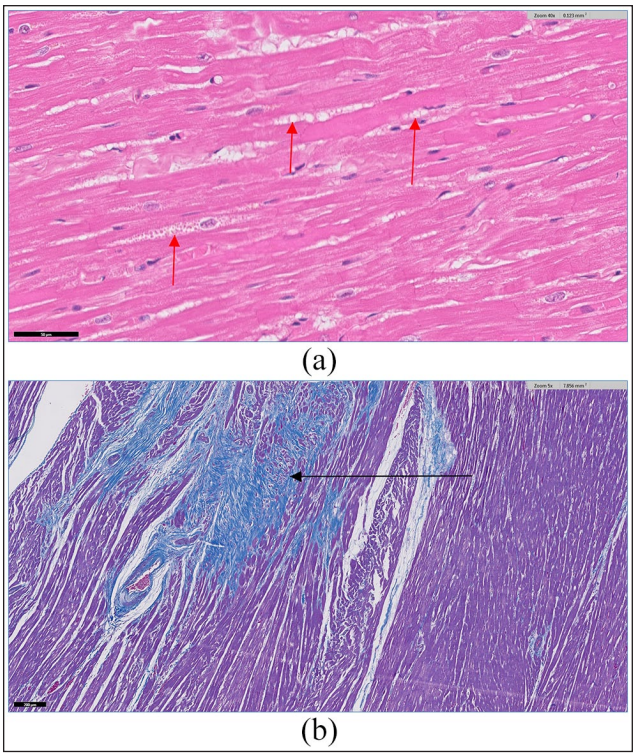

Figure 5 Microscopic appearance of the heart. (a) Left ventricular free wall. Red arrows indicate myocyte degeneration, with loss of striations, and a granular or vacuolated appearance to their cytoplasm. Haematoxylin and eosin stain, × 400. (b) Left ventricular free wall. Black arrow indicates a focally extensive area of replacement fibrosis, stained blue. Masson's trichrome stain, × 50

which stained for amyloid (Figure 6). Microscopic examination of the liver revealed diffuse congestion of blood vessels and sinusoids, while the histological changes within the lungs were consistent with the presence of pulmonary oedema, with some congestion and haemorrhage.

Discussion

Heart disease is very common in cats,[2,6] and while HF is less common, it is a frequent cause of clinical signs and death.[15] Diabetes is also common in the feline population.[1,3,4] Evidence suggests that cats with heart disease that also have or later develop DM may be more likely to subsequently develop HF than those that do not.[8,10] This case report describes DM and HF presenting as comorbidities, including ante- and post-mortem findings. We would like to raise the question of whether feline diabetic cardiomyopathy exists as a phenomenon.

Cardiovascular diseases represent the primary cause of death in the human diabetic population,[16] including deaths due to coronary artery disease, associated hypertension or because of a direct negative effect of

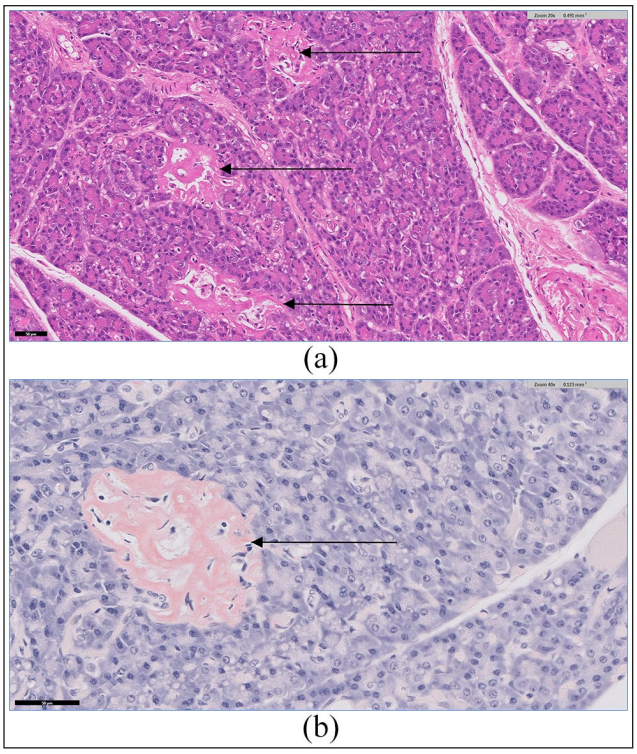

Figure 6 Microscopic appearance of the pancreas. (a) Where present (arrowed), islet cells often appear vacuolated or to have been effaced by brightly eosinophilic amorphous extracellular material. Haematoxylin and eosin stain, × 200. (b) The amorphous extracellular material demonstrates positive staining for amyloid (arrow). Congo red stain, × 400

DM on the myocardium (DMCMP). Two studies[17,18] from the 1970s described post-mortem findings in diabetic patients with HF but without coronary heart disease or other aetiological conditions such as hypertension or obesity, observing left ventricular hypertrophy associated with myocardial fibrosis, although the concept of a cardiomyopathy associated with DM was first proposed before this.[19] Further supportive evidence comes from experimental, mostly rodent-based models and also from multiple large-scale epidemiological studies.[20–22]

One study from the USA estimated that, in 1995, the rate of hospital discharge for human patients with 'idiopathic' cardiomyopathy among individuals diagnosed with diabetes was 7.6 per 1000, substantially higher compared with control subjects and corresponding to a relative odds ratio of 1.75. After adjusting for age, sex, race, hypertension and median income using multiple logistic regression, diabetes remained significantly associated with idiopathic cardiomyopathy.[23]

The pathological changes seen in the hearts of human patients with proposed diabetic cardiomyopathy are still somewhat poorly understood, and there is no clear consensus with regard to the different phenotypic changes seen, and the underlying pathogenesis, or whether there is any correlation or differences between phenotypic changes and type I vs type II DM. Some groups describe two different and distinct phenotypes of the disease; the first presents as a restrictive phenotype, wherein there is normal left ventricular systolic function, concentric left ventricular remodelling and diastolic left ventricular dysfunction.[24] Patients with the restrictive form typically present with a left ventricle of normal size, hypertrophied and stiff, together with hypertrophied cardiomyocytes displaying increased collagen in between, that is interstitial fibrosis. The second proposed phenotype is a dilated form, with eccentric left ventricular remodelling and systolic left ventricular dysfunction.[24] This phenotype typically presents with an enlarged left ventricle and evidence of damage to cardiomyocytes, with increased collagen between and replacing the cardiomyocytes, that is both interstitial and replacement fibrosis. Other groups[9] do not recognise the dilated phenotype associated with diastolic dysfunction; indeed, it is unclear whether these represent different underlying pathophysiological mechanisms or are actually different stages of the same process. The proposed pathogenesis is related to metabolic derangement, specifically hyperglycaemia, lipotoxicity, insulin resistance and hyperinsulinaemia, which induce cardiac insulin resistance and metabolic disorders. In turn, this increases mitochondrial dysfunction, inflammation and oxidative stress, as well as advanced glycation end products, activation of the renin–angiotensin–aldosterone system and autonomic neuropathy, among other factors. These result in cardiac stiffness, hypertrophy and fibrosis, ultimately ending in diastolic and systolic dysfunction and HF.[25,26]

Based on the ante- and post-mortem findings in our case, this cat seemed to show a dilated phenotype, perhaps representative of end-stage/progression of DMCMP. Potential limitations in this report include not being able to entirely exclude underlying diseases that may have contributed to the heart disease, aside from DM, such as acromegaly; however, the clinical signs of DM were controlled on relatively low doses of insulin, which would not be typical for an acromegalic cat. Hyperthyroidism was not noted at the time the DM was diagnosed, when the TT4 was slightly subnormal. The history and clinical signs at the time HF developed months later and were not suggestive of hyperthyroidism, but TT4 measurement was not repeated then. It remains possible that the observed changes correspond to an underlying, previously subclinical HCM progressing to a more end-stage phenotype, although in this case the myofibre disarray present was only very mild, and changes such as lymphohistiocytic infiltrates were not evident.

Conclusions

The proposed DMCMP in humans has both morphological and functional alterations and can present with differing phenotypes, which may reflect differences in the underlying pathogenesis or progression. The current case report describes ante- and post-mortem findings in a previously diagnosed diabetic cat that subsequently developed HF, including histopathological evaluation of the heart. The authors would like to raise the question of whether feline diabetic cardiomyopathy exists as a syndrome, and to suggest that further investigations into any association between the two conditions are warranted. Such further investigation would ideally require a prospective observational study, with sequential monitoring of both DM and cardiac function, ultimately with post-mortem examination and histopathological analysis at the end stage – although, as with humans, progression is obviously difficult to study histologically as samples tend to be predominantly from end-stage disease, thereby missing early or intermediate stages of the disease.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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