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CASE REPORT

Glycogen storage disease in a young cat with heart failure

Shigeki Tanaka[1] | Ryohei Suzuki[2] | Hidekazu Koyama[2] | Noboru Machida[3] | Akira Yabuki[4] | Osamu Yamato[4]

[1]Alpha Animal Hospital, Kawanakajima, Nagano, Japan

[2]Nippon Veterinary and Life Science University, Musashino, Tokyo, Japan

[3]Tokyo University of Agriculture and Technology, Fuchu, Tokyo, Japan

[4]University of Kagoshima, Kagoshima, Kagoshima, Japan

Correspondence
Shigeki Tanaka, Alpha Animal Hospital, 1075-1 Imai, Kawanakajima, Nagano 381-2226, Japan.
Email: alphaah@sea.plala.or.jp

Abstract

An 8-month-old domestic short-haired female cat presented with acute tachypnea, poor growth, hypothermia, and lethargy. Thoracic radiography showed cardiomegaly with mild pleural effusion, and transthoracic echocardiography identified dilatation of both atria and left ventricular systolic dysfunction. Although clinical signs improved temporarily with treatment, the cat died of pulmonary edema 135 days after the first visit. At necropsy, the heart was grossly enlarged. Microscopic examination of the heart identified severe vacuolization of cardiac muscle cells in histologic sections stained with hematoxylin and eosin. Examination of periodic acid-Schiff stained preparations of formalin-fixed heart tissue disclosed coarse granules within vacuoles that disappeared on predigestion with diastase, indicating that they were glycogen. On the basis of these findings, a necropsy diagnosis of glycogen storage disease type II (Pompe disease) was made. This report is the first case of a young cat with clinical signs closely resembling infantile Pompe disease of humans.

KEYWORDS
arrhythmia, cardiomyopathy, glycogenosis, Pompe disease

1 | INTRODUCTION

An 8-month-old female domestic short-haired cat weighing 2.4 kg presented for evaluation of tachypnea, loss of appetite, and lethargy. The cat had shown poor growth (body condition score, 2/5) and had developed an unexplained fever 3 months earlier. Laboratory tests performed at that time identified increased liver enzyme activity (alanine transaminase, 284 U/L; aspartate transaminase, 97 U/L; alkaline phosphatase, 243 U/L). At the time of presentation, the cat was mildly hypothermic (37.4°C). Heart rate was 250 beats per minute (bpm), and the possibility of a cardiac murmur could not be evaluated because of loud respiratory sounds. A CBC disclosed no abnormalities. Routine serum biochemistry identified marked increases in liver enzyme activity without an increase in serum bilirubin concentration. Serum l-thyroxine and D-dimer concentrations were normal, and no other abnormalities were observed (Supplemental S1). Cardiac troponin I (cTnI) concentration was 1.15 ng/mL (reference range, 0-0.17 ng/mL; i-STAT; Heska[1]). Tests for feline immunodeficiency virus and feline leukemia virus were negative.

Noninvasive blood pressure measurements were normal (113/96 mm Hg; mean, 102 mm Hg). A 6-lead surface ECG disclosed tachycardia (283 bpm) consisting of slightly wide QRS complexes (approximately 80 ms), but no P waves were observed. The QRS complexes were considered to be consistent with ventricular tachycardia. Thoracic radiographs identified cardiomegaly (vertebral heart score, 8.7) with mild pleural effusion and mild pulmonary edema. Mild hepatomegaly also was observed. Two-dimensional echocardiography identified systolic dysfunction (fractional shortening of 6.9%) and dilatation of both atria (Figure 1A, Videos S1

Abbreviations: cTnI, cardiac troponin I; GSD, glycogen storage disease; LV, left ventricle; PAS, periodic acid-Schiff.

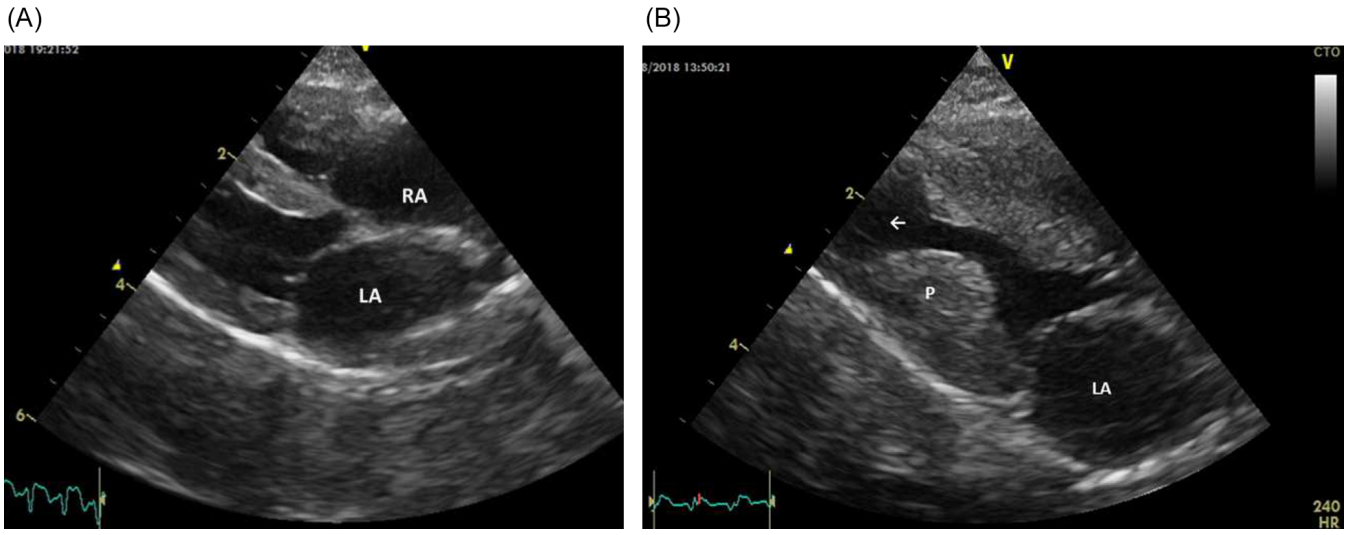

FIGURE 1 Two-dimensional echocardiographic images. (A) Right parasternal long axis, 4-chamber view at the initial presentation. Note the dilatation of both atria. LA: left atria RA: right atria (B) Right parasternal long axis, four-chamber view on day 130 of the illness. Note the left ventricular apical dilatation. arrow, the LV apical aneurysm; LA, left atrial; P, a hypertrophied posterior papillary muscle

and S2). Mild tricuspid regurgitation (2.4 m/s; pressure gradient, 23 mm Hg) and mild mitral regurgitation (velocity could not be measured) also were seen, but there was no evident systolic anterior motion of the mitral valve. The short-axis view at the papillary muscle level indicated no thickening of the left ventricular (LV) wall (end-diastolic interventricular septum thickness, 4.6 mm; LV free-wall thickness, 4.1 mm). The ventricular septum and posterior wall of the left ventricle showed nearly uniform echo levels. The LV papillary muscles were observed to be mildly hyperechoic. We diagnosed congestive heart failure caused by myocarditis or unclassified cardiomyopathy and liver dysfunction. The cat received oxygen in the intensive care unit and was treated with furosemide (1.2 mg/kg PO q12h), pimobendan (0.35 mg/kg PO q12h), carvedilol (0.05 mg/kg PO q12h), and prednisolone (1.0 mg/kg PO q24h). Twenty-four hours after admission, the cat was able to have oxygen treatment discontinued. Respiratory rate decreased to 28 breaths per minute and appetite improved. On day 3 of hospitalization, the cat had a normal level of consciousness but remained inactive. The ECG showed sinus rhythm (heart rate, 159 bpm). The PR interval (0.07 second) was not shortened and the R wave potential was markedly increased (3.2 mV). Echocardiography identified substantial improvement in several parameters (Supplemental S2, Videos S3 and S4). However, atrial fibrillation with premature ventricular contractions was observed on day 6 of the illness. The cat returned to sinus rhythm on day 13 but developed an accelerated idioventricular rhythm with supraventricular contractions on day 59 and returned to atrial fibrillation on day 115. On day 130, apical dilatation of the LV and LV systolic dysfunction were observed (Figure 1B) and cTnI concentration was increased to 28.0 ng/mL (Supplemental S1). Despite increases in the doses of pimobendan (to 0.40 mg/kg PO q12h) and carvedilol (to 0.30 mg/kg PO q12h), the cat died of pulmonary edema and heart failure on day 135 (Videos S5 and S6, day 134). Blood glucose concentrations consistently remained within the normal range (Supplemental S1).

Necropsy was performed with the consent of the owner. The lungs were diffusely congested and edematous and the liver was swollen and yellow. No clinically relevant abnormalities were noted macroscopically in any of the other organs examined, except for the heart. The heart was grossly enlarged and the epicardial surface was pale and mottled grayish brown. The heart weighed 19.3 g and relative heart weight (ie, heart weight in g/body weight in kg) was 8.0 g/kg (reference ranges, 4.5 ± 0.2 g/kg,[2] 4.8 ± 1.2 g/kg[3]). A longitudinal section through the entire heart (formalin-fixed) showed that the walls of both ventricles and atria were thickened, especially the left ventricular free wall and papillary muscles. The myocardium of both ventricles was rubbery in consistency and focally or uniformly mottled, the involved areas ranging from pale pink to gray-brown in color. In addition, thinning of the wall of the left ventricle and ventricular septum, with dark discoloration, was prominent at the apex, forming an aneurysmal bulge (Figure 2). With the owner's consent, histopathology was performed on heart, liver, and lung. Microscopic examination of the heart identified severe vacuolization of cardiac muscle cells in histologic sections stained with hematoxylin and eosin. Myofibrils were displaced to the periphery of the cells, imparting a lace-like appearance (Figure 3). Periodic acid-Schiff (PAS) staining was used for detection of glycogen in the vacuolated myocytes. In PAS preparations of the formalin-fixed heart, coarse granules were often evident in the vacuoles identified by hematoxylin and eosin staining. These granules disappeared on predigestion with diastase, confirming that they were glycogen (Figure 4). Similar vacuolar changes also were observed in fibers of the atrioventricular conduction system and smooth muscle cells of the intramural coronary arteries. On the other hand, the myocardial lesion with dark discoloration located in the cardiac apex showed extensive cardiomyocyte necrosis. Relatively large, partially organized thrombi were found occluding the intramural coronary arteries within and adjacent to the lesion at the apex of the heart.

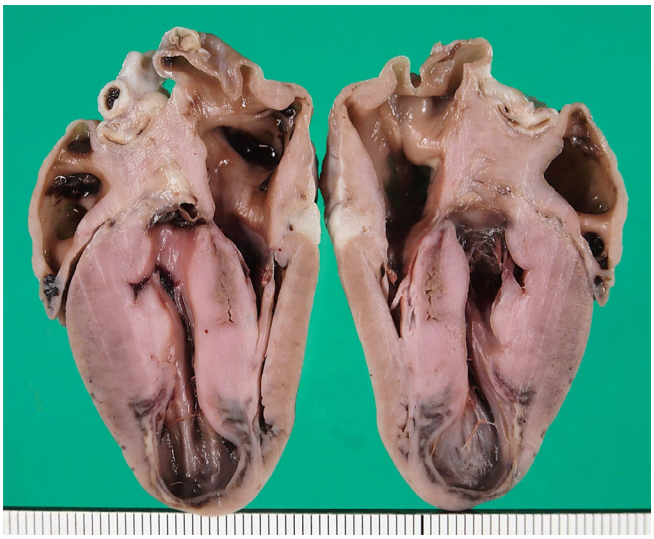

FIGURE 2 Formalin-fixed heart transected along the long axis, showing thickening of the walls of both ventricles and atria, especially the left ventricular free wall and papillary muscles. The wall thinning of the left ventricle and ventricular septum, with dark discoloration, is seen at the apex, forming an aneurysmal bulge. Scale, 1 mm

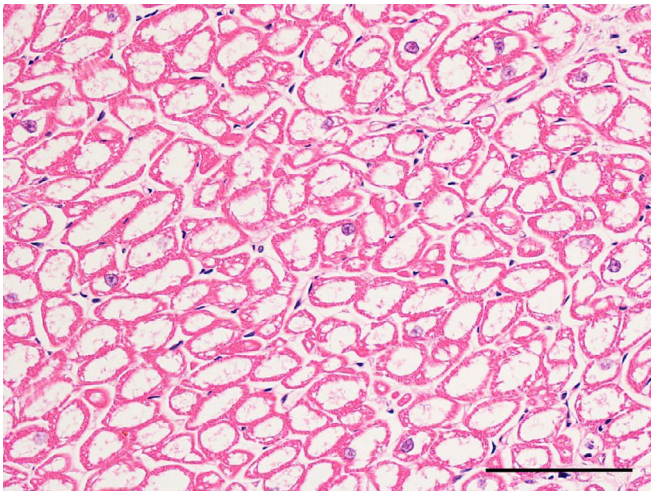

FIGURE 3 Microscopic section taken from the left ventricular wall, showing severe vacuolization of the cardiac muscle cells. Myofibrils are displaced to the periphery of the cells, imparting a lace-like appearance. Hematoxylin and eosin. Bar, 50 μm

Fibrin thrombi also were noted in the small arteries of other portions of the heart. Other histological findings included mild to moderate congestive edema of the lungs and microvesicular and macrovesicular hepatocytes. Periodic acid-Schiff staining of hepatocytes was performed, and the vacuoles of hepatocytes were also positive for glycogen. Although we performed electron microscopy of the heart, we were not able to visualize glycogen granules encased in the lysosomal membrane because sections were prepared from formalin-fixed material. However, an accumulation of granules that appeared to be glycogen was observed in the cytoplasm, and these granules seemed to exist as a group, and thus it is highly likely that they were localized in the lysosome (Figure 5).

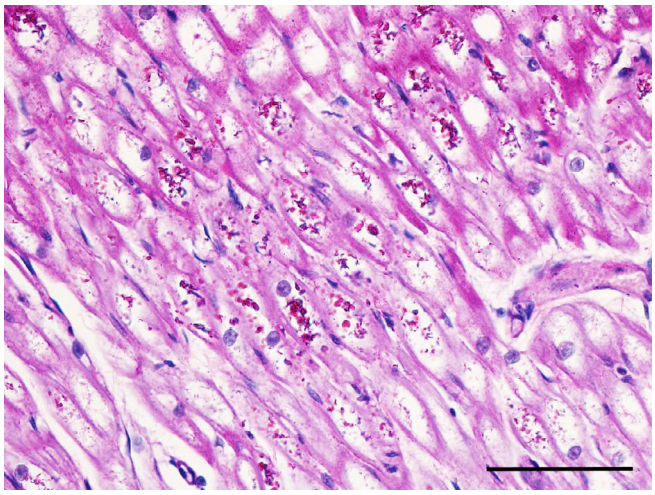

FIGURE 4 Periodic acid-Schiff preparation of the formalin-fixed heart, showing course granules of stored glycogen in the vacuoles demonstrated by hematoxylin and eosin staining. Bar, 50 μm

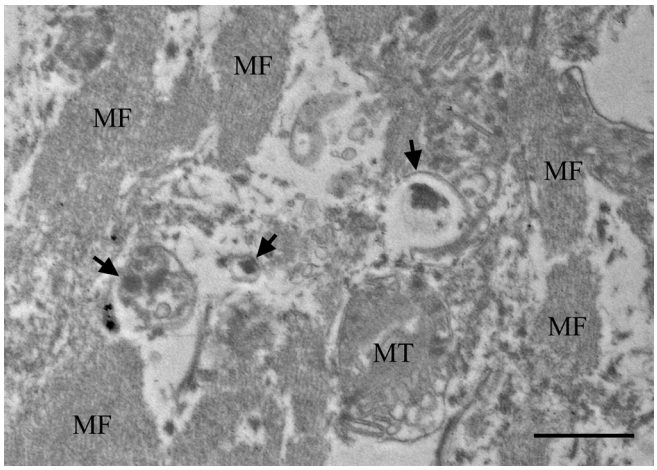

FIGURE 5 Transmission electron microscopy of the storage bodies in the heart. There is an accumulation of dense granules (arrows) that appear to be glycogen in the cytoplasm, and they seem to exist inside membranes, so that it is likely they are localized in lysosomes. Bar, 0.5 μm. MF, myocardial fiber; MT, mitochondria

2 | DISCUSSION

With regard to glycogen storage disease (GSD) in cats, only type IV, characterized by central nervous system abnormalities and hypoglycemia, has been reported in the Norwegian Forest Cat.[4] In the present case, no clinical evidence of central nervous system signs, pain on exercise, myoglobinuria, or hypoglycemia was found. On the other hand, the clinical signs observed were very similar to those of infantile type II GSD, also known as Pompe disease.[5] Furthermore, GSD types

II, III, and IV have been reported to cause myocardial damage in humans.[6] Taking these facts into consideration, the cat of the present report was diagnosed as having GSD type II (Pompe disease), based on clinical signs and histopathological and histochemical findings. Unfortunately, an enzyme reaction test (measurement of lysosomal enzyme activity or acid alpha-glucosidase activity) could not be performed because all biomaterials had been lost before the time of diagnosis.

Glycogen storage disease II is an autosomal recessive metabolic disorder caused by mutation of a gene encoding acid alpha-glucosidase, which is a lysosomal enzyme. Glycogen, a substrate of acid alpha-glucosidase, accumulates in the lysosomes of skeletal muscle, liver, and heart muscle.[5] To date, only a few reports of GSD II in a cat and dogs have been published.[7,8] Unfortunately, because the case of GSD II in a cat was identified incidentally during pathological examination of the brain at necropsy, no description of the clinical course or findings of pathological examination of the heart, liver, and skeletal muscle were available.[7] Pompe disease in humans is classified as the infantile (classical) type or late onset (child or adult) type according to the age of onset. The infantile type is characterized by complete enzyme deficiency (<0.1% of the normal amount) and mainly affects the myocardium, skeletal muscle, and liver.[5] Affected individuals have a marked decrease in muscle tone throughout the body, poor growth, hypertrophic cardiomyopathy and subsequent dilated cardiomyopathy, and hepatomegaly.[9] Many individuals with the disease succumb to respiratory disease or heart failure before the age of 1 year. Individuals with the late onset type have residual enzyme activity (<40% of normal) with a slowly progressive myopathy that mainly affects the proximal muscles but the myocardium usually is spared. The cat described here had a young onset clinical presentation (cardiomyopathy and heart failure, hepatomegaly, increased liver enzyme activities, poor growth, and decreased activity) with findings that closely resembled human infantile type Pompe disease. Thoracic radiographs at the first visit identified cardiomegaly, slight pleural effusion, and increased opacity of the lungs, whereas echocardiography disclosed impaired contraction with dilatation of both atria. These findings suggested heart failure as a result of decreased cardiac contractility and were thought to be associated with cardiogenic pulmonary edema and pleural effusion. Furthermore, the ventricular septum and posterior wall of the left ventricle showed nearly uniform echogenicity, and the myocardium had a fine granular appearance. These echocardiographic findings may have been the result of glycogen accumulation. In the infantile type of Pompe disease in humans, myocardial hypertrophy caused by glycogen accumulation is likely to progress to hypertrophic cardiomyopathy and subsequent dilated cardiomyopathy.[9] Also, echocardiography in the cat of this report disclosed hypertrophy of the LV free wall and ventricular septum. Electrocardiography identified persistent ventricular tachycardia at the first examination. Although standard treatment for heart failure brought about a temporary return to sinus rhythm, sinus rhythm could not be maintained in the longer term. In addition, ectopia and conduction abnormalities (atrial fibrillation with premature ventricular contractions, an accelerated idioventricular rhythm with premature supraventricular contractions, atrial fibrillation, persistent ventricular tachycardia) were noted. These complex arrhythmias likely were associated with clinically relevant electrophysiological abnormalities caused by myocardial alterations associated with Pompe disease. In addition, extensive myocardial necrosis in the cardiac apex and abnormalities of cardiac conduction tissue might have induced the various arrhythmias described above.

In the present case, the increase in cTnI concentration reflected severe myocardial necrosis, which was consistent with necropsy findings. Cardiac troponin I is the most sensitive and specific marker of cardiomyocyte necrosis in humans, and increased concentrations are associated with severe myocardial damage.[10] Inclusion of cTnI in the laboratory investigation was useful for detecting myocardial damage in this cat. The cTnI concentration measured when apical dilatation was detected by echocardiography was approximately 165 times higher than the upper limit of normal, accurately reflecting severe damage to the myocardium. The causes of myocardial damage in Pompe disease in humans have been attributed to the abnormal deposition of glycogen in lysosomes, disruption of the normal processes of macroautophagy needed for recycling and degradation in the cell, and mitochondrial damage.[6] The cause of myocardial damage in the cat of this report may have been myocardial hypertrophy caused by glycogen accumulation, similar to Pompe disease in humans, along with acute or chronic ischemia.[11,12] In addition, we cannot rule out the possibility that myocardial necrosis or infarction also was related to degeneration of the coronary arteries associated with glycogen accumulation and thrombosis. Myocardial necrosis and apical dilatation may be the result of severe myocardial damage. Furthermore, possible causes of heart failure in the cat of this report include decreased systolic or diastolic function or both of the myocardium itself, which represents the resultant (or consequential) myocardial hypertrophy and myocardial damage caused by glycogen accumulation similar to what occurs in Pompe disease of humans, and myocardial damage and necrosis caused by ischemia. In terms of myocardial function, systolic and diastolic function would have been decreased, as reflected by tissue doppler imaging on day 6 of the illness, which showed a decrease in both systolic and diastolic indices (S', 3.2 cm/s; E', 3.3 cm/s; reference range: S', 7 ± 1.8 cm/s; E', 6.42 ± 1.83 cm/s[13]; Supplemental S2).

A genetic disease seemed likely in our cat because of the young age at onset and poor growth. Until now, however, no reports of hereditary diseases in cats exhibiting a clinical course of heart failure such as that in the present case have been published. Unfortunately, the diagnosis was made on the basis of pathological findings at necropsy, by which time it was no longer possible to investigate enzyme defects or genetic mutations because of the absence of biomaterials. Furthermore, because the cat had been adopted after removal from its littermates, it was not possible to investigate its pedigree. However, it may be possible in the future to confirm the diagnosis by sequencing the causative GAA gene extracted from the paraffin embedded tissue. The cat was diagnosed with GSD II based on clinical signs and findings of histopathology and histochemistry. Our experience with this case emphasizes the need to consider a congenital metabolic disorder such as GSD in a cat that shows poor growth, heart failure of unknown cause, and increased liver enzyme activities at a young age.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Informed consent (verbal) was obtained from the owner of an animal described in this work for all procedures undertaken.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study work for all procedure undertaken.

ORCID

Shigeki Tanaka https://orcid.org/0000-0001-7919-858X
Osamu Yamato https://orcid.org/0000-0002-4430-5645

REFERENCES

1. Côté E. Cardiac biomarkers. In: Côté E, MacDonald KA, Meurs KM, Sleeper MM, eds. *Feline Cardiology*. Ames, IA: John Wiley & Sons; 2011:69-75.
2. Kaneshige T, Machida N, Itoh H, Yamane Y. The anatomical basis of complete atrioventricular block in cats with hypertrophic cardiomyopathy. *J Comp Pathol*. 2006;135(1):25-31.
3. Fox PR, Liu SK, Maron BJ. Echocardiographic assessment of spontaneously occurring feline hypertrophic cardiomyopathy. An animal model of human disease. *Circulation*. 1995;92(9):2645-2651.
4. Fyfe JC, Giger U, Van Winkle TJ, et al. Glycogen storage disease type IV: inherited deficiency of branching enzyme activity in cats. *Pediatr Res*. 1992;32(6):719-725.
5. Tarnopolsky M, Katzberg H, Petrof BJ, et al. Pompe disease: diagnosis and management. Evidence-based guidelines from a Canadian expert panel. *Can J Neurol Sci*. 2016;43(4):472-485.
6. Ruiz-Guerrero L, Barriales-Villa R. Storage diseases with hypertrophic cardiomyopathy phenotype. *Glob Cardiol Sci Pract*. 2018;2018(3):28.
7. Sandström B, Westman J, Ockerman PA. Glycogenosis of the central nervous system in the cat. *Acta Neuropathol*. 1969;14(3):194-200.
8. Walvoort HC, Dormans JA, van den Ingh TS. Comparative pathology of the canine model of glycogen storage disease type II (Pompe's disease). *J Inherit Metab Dis*. 1985;8(1):38-46.
9. Pascual-Pascual SI, Nascimento A, Fernandez-Llamazares CM, et al. Clinical guidelines for infantile—onset Pompe disease. *Rev Neurol*. 2016;63(6):269-279. Article in Spanish.
10. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. *Circulation*. 1997;95(1):163-168.
11. Gao X, Yang J, Zhang X, Wang P, Li H. A case report of apical aneurysms and myocardial perfusion deficit with myocardial necrosis due to hypertrophic cardiomyopathy. *Medicine (Baltimore)*. 2018;97(21):e10829.
12. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. *Hum Pathol*. 2000;31(8):988-998.
13. Koffas H, Dukes-MacEwan J, Cororan BM, et al. Pulsed tissue Doppler imaging in normal cats and cats with hypertrophic cardiomyopathy. *J Vet Intern Med*. 2006;20(1):65-77.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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