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Arrhythmogenic right ventricular cardiomyopathy associated with severe left ventricular involvement in a cat

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Abstract An 8-year-old, 4 kg, intact female, domestic shorthaired cat was referred for tachypnea and pleural effusion. A 24-h Holter recording showed numerous polymorphic ventricular premature complexes with left and right bundle branch block morphology. Echocardiographic examination revealed right atrial and ventricular dilation. The right ventricular free wall was thin and aneurysmal. The cat died 10 days after initiation of antiarrhythmic therapy. Gross and histopathological findings were consistent with arrhythmogenic right ventricular cardiomyopathy (ARVC) associated with severe left ventricular involvement.

An 8-year-old, 4 kg, intact female, domestic shorthaired cat was referred to the Veterinary Teaching Hospital of Naples University ''Federico II'' with a two week history of progressive lethargy, anorexia, and dyspnea. The cat lived indoors, was regularly vaccinated, and was fed commercial canned pet food. Treatment initiated by the referring veterinarian included oral furosemide,[c] 6 mg twice daily and oral enrofloxacin,[d] 20 mg once daily. This resulted in transient relief of dyspnea.

On physical examination the patient was underweight, lethargic and moderately (5%) dehydrated. Mucous membranes appeared pale and dry, and capillary refill time (5 s) was increased. Both femoral pulses were palpable. Pulse rate was

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[d] Baytril, Bayer, Milan, Italy.

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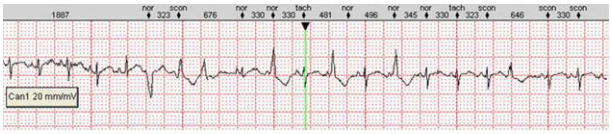

Figure 1 24-h Holter recording. Note the polymorphic ventricular arrhythmias. 25 mm/s.

210 beats/min. Shallow breathing was noted with tachypnea (56 breaths/min) and abdominal effort. Rectal temperature was 38.1 °C (100.6 °F). Thoracic auscultation revealed muffled lung sounds and heart sounds. Heart murmur was not detected. Systolic and diastolic arterial blood pressure measured by an oscillometric method[e] was within normal range (140/100 mmHg). Dilated jugular veins and liver enlargement were detected. Serum biochemistry abnormalities included increased blood urea (17.8 mmol/L; normal, 6.5—10.5 mmol/L), creatinine (201 μmol/L; normal, 133—175 μmol/L), and alanine aminotransferase (79 IU/L; normal, 15—45 IU/L). Serum total proteins were slightly reduced (56 g/L; normal, 60—75 g/L). Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections were ruled out by routine antigen serology assay.[f] Standard 6-lead electrocardiography (ECG) showed sinus rhythm and numerous, polymorphic, ventricular premature complexes. A 24-h Holter recording revealed ventricular premature complexes with left bundle branch block (LBBB) morphology (25,920 complexes) and right bundle branch block (RBBB) morphology (6480 complexes) (Fig. 1). Ventricular couplets (4,320) and R-on-T phenomenon (220 complexes) were also noted. Average heart rate was 213 ± 12 beats/min (median 210, interquartile interval 201—235). No change in heart rate or severity of the arrhythmia was observed during sleep. A right lateral thoracic radiograph revealed pleural effusion. Mild increase in caudal lung lobe opacity was noted and hepatic enlargement was present. No abdominal effusion was evident. Thoracocentesis yielded 120 ml of serous fluid. Cytology was consistent with modified transudate. B-mode echocardiography showed severe right atrial and right ventricular dilation. The right ventricular wall appeared very thin and hypokinetic. Aneurysms were detected in apical and subtricuspid regions. Flattening of interventricular septum at end-diastole and mild dilation of the pulmonary trunk were observed. The left atrium and ventricle appeared to be unremarkable. M-mode echocardiography revealed paradoxic interventricular septal motion which prevented accurate left ventricle measurement. The right ventricular chamber was severely dilated (end-diastole, 15.0 mm). Doppler echocardiography revealed mild tricuspid regurgitation (maximal velocity, 107 cm/s; maximal pressure gradient, 4.54 mmHg) and decreased maximal pulmonary artery velocity (maximal velocity, 39.4 cm/s). Based upon physical examination, ECG and 24-h Holter recordings, and echocardiographic findings, a diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) was made. Initial therapy included administration of furosemide,[c] 10 mg subcutaneously every 12 h, enalapril,[g] 1 mg per os every 12 h, and sotalol,[h] 8 mg per os twice daily. Mild clinical improvement was observed during the following four days and the owner continued to treat the pet at home. The cat died suddenly 10 days after initiation of therapy.

At post-mortem, gross examination of the heart revealed severe right ventricular chamber dilation with infundibular, apical and inferior aneurysms (triangle of dysplasia). At cross section, the right ventricle (RV) free wall was extremely and diffusely thinned (1 mm) and the wall had a ''parchment-like'' appearance. In the left ventricle (LV) free wall there were whitish scars in the sub-epicardial layer (Fig. 2). The heart was fixed in 10% phosphate-buffered formalin. Tissue sections were cut 5 μm thick and stained with haematoxylin and eosin and Heidenhain (azan) trichrome stains. They revealed massive fibrous tissue replacement associated with mild fatty tissue infiltration in the right ventricular free wall. Similar features were observed on the right side of the interventricular septum. A circumferential band of replacement-type fibrosis was also present, confined to the sub-epicardial, outer third of the LV free wall (Fig. 3). This band was detected in multiple, serial, cross sections sampled from the cardiac base to the mid-portion of the LV chamber. In right ventricular sections patchy, lymphocytic inflammatory infiltrates were present with myocyte abnormalities that included dysmetric and dysmorphic nuclei and perinuclear halo (Fig. 4). Focal myocyte apoptotic nuclei were also observed. Collectively, these pathological lesions were consistent with a diagnosis of ARVC associated with severe left ventricular involvement.

Discussion

Arrhythmogenic right ventricular cardiomyopathy is an uncommon, spontaneous, cardiomyopathy which has been described in cats, dogs and

[e] MEMOPRINT®, S + B medVET, Babenhausen, Germany.
[f] Feline SNAP® Combo Plus, IDEXX Laboratories, Milan, Italy.
[g] Enacard, Merial, Milan, Italy.
[h] Sotalex, Brystol Myers, Rome, Italy.

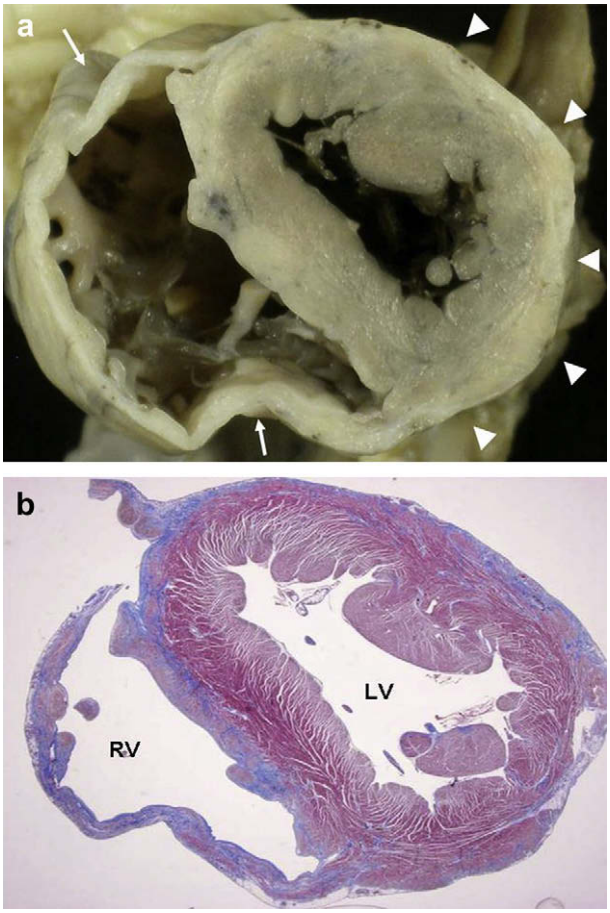

Figure 2 (a) Post-mortem transverse cardiac section made at the mid-ventricular level. The right ventricle is greatly dilated. Note the diffuse thinning of the right ventricular free wall. There are antero-infundibular and inferior aneurysms (arrows). Along the entire circumference of the left ventricular free wall is evident a whitish, sub-epicardial band (arrowheads); (b) Corresponding histologic section showing transmural fibro-fatty replacement of the right ventricular free wall. A circumferential band of replacement-type fibrosis is also present and is confined to the outer layer of the left ventricle and the right-side of the interventricular septum. LV = left ventricle; RV = right ventricle.

humans.[1–3] It is an unique heart muscle disease, clinically characterized by marked right ventricular cavity enlargement with ventricular arrhythmias, congestive heart failure and/or sudden cardiac death. The remarkable interest in this cardiomyopathy is associated with difficulty in early clinical diagnosis, and its propensity to cause sudden death in apparently healthy patients. Regarding feline ARVC, the disease was described for the first time by Fox et al. in 2000.[2] This report consisted of a retrospective series of 12 cases of feline ARVC from the USA. In Europe, the incidence of feline ARVC is unknown and only two cases have been reported from the United Kingdom.[4]

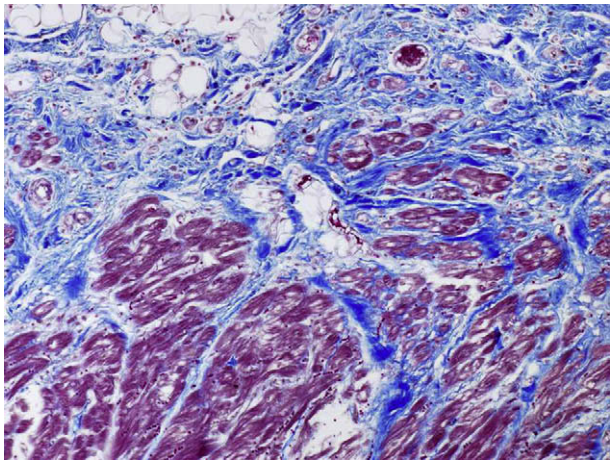

Figure 3 Histology of the right ventricular myocardium, antero-lateral free wall. Note the myocardial replacement by fibrous tissue (blue color) and the presence of some adipocytes. Trichrome Heidenhain stain; ×100.

Diagnosis of feline ARVC can be challenging. No age or breed predisposition has been identified. Clinical signs are not distinctive but include dyspnea/tachypnea, jugular vein distention, abdominal and/or pleural effusion, soft heart murmurs, and arrhythmias. Differential diagnoses include other myocardial disorders as well as acquired or congenital diseases affecting the right heart (such as tricuspid dysplasia and Uhl's anomaly). Currently, the diagnosis of ARVC is based on the combination of a family history, the presence of marked right ventricular cavity enlargement, ventricular and/or supraventricular arrhythmias, and post-mortem

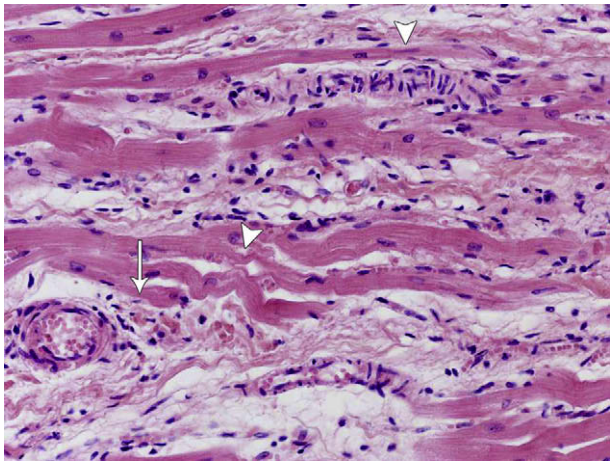

Figure 4 Histology of the right ventricular myocardium, antero-lateral free wall. There is waviness and lengthening of myocytes which is suggestive of focal necrosis (arrowheads). A few round inflammatory cells are also visible (arrow). Haematoxylin–eosin stain; ×200.

pathologic findings that include right ventricular dilation and fibro-fatty replacement.

In the present case the clinical signs were related to right sided congestive heart failure, similar to the other clinical reports.[2,4] No episodes of syncope were observed. The diagnosis was based upon findings from the history, echocardiography and radiography suggesting right ventricular involvement, and from ECG and 24-h Holter recordings that revealed extensive ventricular ectopy.

Arrhythmias are a common finding in feline ARVC. In the largest series of reported cases,[2] recorded arrhythmias included ventricular tachycardia in four cats, atrial fibrillation in four cats, supraventricular tachycardia in one cat, and ventricular premature complexes in eight cats. First and third degree atrioventricular block were also recorded.[2,4] In the present case the ECG and 24-h Holter recording documented a large number of ventricular arrhythmias. In feline ARVC the frequency and severity of left ventricular arrhythmia are not well documented. Six of the eight cases reported by Fox et al.[2] also included ventricular premature complexes with RBBB morphology. In the present case the finding of ventricular extrasystoles with RBBB morphology might be associated with the extensive, sub-epicardial, left ventricular free wall fibrosis detected in this cat.

Arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement has been described to involve sub-epicardial layers — particularly the postero-lateral free wall in people.[1,5] This has been reported in up to 76% of human patients,[6] in 48% of boxer dogs,[3] and in the majority of cats reported by Fox et al.[2] More recently, both clinico-pathologic and magnetic resonance investigations showed a similar pattern of left ventricular involvement in ARVC patients, particularly those linked to desmoplakin gene mutations.[7,8] These findings tend to challenge the traditional view that left ventricular involvement occurs only in late stages of ARVC, and supports the notion of a broader, more inclusive condition that has been termed, ''arrhythmogenic cardiomyopathy.''[9]

Clinical diagnosis of ARVC with left ventricular involvement is difficult to ascertain. Left ventriculography, echocardiography and radionuclide ventriculography cannot directly detect the presence of fibrous and adipose LV tissue. Magnetic resonance imaging and multidetector-row computed tomography methods are considered to be the gold standard for diagnosing left ventricular involvement in human ARVC.[10,11] These methods are not routinely employed in veterinary cardiology.

The echocardiographic findings in this report are consistent with those reported in other cases of feline ARVC.[2,4] Characteristic findings include right atrial and ventricular dilation, and thin, hypokinetic right ventricular wall segments with aneurysms, particularly those localized in the apical and subtricuspid regions. The tricuspid regurgitant jet detected in this cat was mild. This finding is consistent with the observation of Harvey et al.[4]

In our case, gross and histopathologic lesions were similar to the hallmark findings described for ARVC in humans and animals. Histological examination of the right ventricle showed severe atrophy of the myocardium, which was replaced by fibro-fatty tissue (presumed to represent a reparative process), and myocyte death. Myocyte death was associated with inflammatory infiltrates (''myocarditis''). This finding was reported in 75% and 83% of human and feline ARVC cases respectively.[6,2] Inflammation may be a reactive process following cell death, or alternatively, could represent immune or infectious mechanisms.[12] Finally, the mild clinical improvement observed in the present case did not seem to be associated with a change in arrhythmia severity. In humans with ARVC, different antiarrhythmic drugs have been employed. The use of sotalol has been reported to be associated with complete or partial efficacy in 68% of ARVC patients.[13]

ARVC is a recently recognized disorder of uncertain origin in feline patients, and is characterized by fibro-fatty replacement of right ventricular myocardium. Although it more typically involves segmental regions of the right ventricle, the present case illustrates that it can also involve substantial regions of the left ventricle as well. In the cat reported here, 24-h Holter recording revealed extensive ventricular arrhythmias, which may have contributed to sudden, unexpected death of this patient.

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References

1. Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Orphanet J Rare Dis 2007;2:45—60.

2. Fox PR, Maron BJ, Basso C, Liu S, Thiene G. Spontaneously occurring arrhythmogenic right ventricular cardiomyopathy in the domestic cat. A new animal model similar to the human disease. Circulation 2000;102:1863—1870.
3. Basso C, Fox PR, Meurs KM, Towbin JA, Spier AW, Calabrese F, Maron BJ, Thiene G. Arrhythmogenic right ventricular cardiomyopathy causing sudden cardiac death in boxer dogs: a new animal model of human disease. Circulation 2004;109:1180—1185.
4. Harvey AM, Battersby IA, Faena M, Fews PG, Darke G, Ferasin L. Arrhythmogenic right ventricular cardiomyopathy in two cats. J Small Anim Pract 2005;46:151—156.
5. Thiene G, Basso C. Arrhythmogenic right ventricular cardiomyopathy: an update. Cardiovasc Pathol 2001;10:109—117.
6. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom-Lundqvist C, Wlodarska EK, Fontaine G, Camerini F. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 1997;30:1512—1520.
7. Bauce B, Basso C, Rampazzo A, Beffagna G, Daliento L, Frigo G, Malacrida S, Settimo L, Danieli G, Thiene G, Nava A. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. Eur Heart J 2005;26:1666—1675.
8. Norman M, Simpson M, Mogensen J, Shaw A, Hughes S, Syrris P, Sen-Chowdhry S, Rowland E, Crosby A, McKenna WJ. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. Circulation 2005;112:636—642.
9. Basso C, Corrado D, Marcus F, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009;373:1289—1300.
10. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/-cardiomyopathy provides novel insights into patterns of disease expression. Circulation 2007;115:1710—1720.
11. Matsuo S, Sato Y, Nakae I, Masuda D, Yomota M, Ashihara T, Horie M. Left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy demonstrated by multidetector-row computed tomography. Int J Cardiol 2007;115:129—131.
12. Calabrese F, Basso C, Carturan E, Valente M, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: is there a role for viruses? Cardiovasc Pathol 2006;15:11—17.
13. Wichter T, Paul M, Eckardt L, Gerdes P, Kirchhof P, Bocker D, Breithardt G. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? Herz 2005;30:91—101.