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# A case of feline systemic reactive angioendotheliomatosis

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## Abstract

A 3-year-old domestic shorthair cat presented with lethargy and anorexia. A blood test showed regenerative anaemia and thrombocytopenia. Thoracic radiographs showed a small amount of pleural effusion. The cat did not respond to treatment and died on the fifth day. Necropsy revealed moderate pericardial effusion, and multifocal coalescing haemorrhages were observed on both atria. Histological analysis revealed that the most severe lesions were located on the heart. Numerous arterioles supplying the heart were partially to completely filled with plump spindle cells that often formed glomerulus-like arrangements within the lumen. Similar vascular proliferative lesions were also found in the liver, pancreas and kidney. Immunohistochemical analysis showed that these intraluminal proliferative spindle cells were positive for anti-von Willebrand factor (vWF). Strongly positive antismooth muscle actin staining was observed at the periphery of these intraluminal proliferations (comprising arteriolar smooth muscle) and certain intraluminal cells (pericytes). The intraluminal thrombi were also positive for vWF. Those thrombi were confirmed as platelet thrombi by phosphotungstic acid haematoxylin and Masson's trichrome staining. These results were consistent with feline systemic reactive angioendotheliomatosis.

## Keywords

FSRA, Blood vessels, Feline diseases, Heart

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Since 1985, the unusual non-neoplastic multisystemic vascular proliferative disease termed feline systemic reactive angioendotheliomatosis (FSRA) has been documented in 12 cats.<sup>1–4</sup> The median age of the cats affected by FSRA, including the cat reported herein, was 4 years. Nine of the 13 cases were intact or castrated males, including nine domestic shorthair and two domestic longhair cats, a Sphynx and a Maine Coon. The cats were predominantly young adults and male, with no breed predilection.<sup>1–4</sup> In all cases, FSRA was diagnosed following post-mortem examination.<sup>1–4</sup> The vascular FSRA lesions were characterised by glomeruloid spindle cell proliferations that partially to completely occluded arteriolar lumens. Further, the proliferating cells were endothelial cells and pericytes without atypia.<sup>2</sup> Consequently, FSRA is believed to represent a reactive proliferation process.<sup>2</sup> The heart is the most severely affected organ, while other organs involved include the brain, spinal marrow, kidney, spleen, gastrointestinal tract, eyes and pancreas.<sup>2</sup> The most common clinical signs include dyspnoea, anorexia and lethargy.<sup>2</sup>

The cat presented herein was a 3-year-old spayed shorthair female that lived indoors. It presented with a 3 day history of lethargy and anorexia. As a kitten, the cat had presented with thrombocytopenia, and later with fungal pneumonia, which was treated by the administration of itraconazole. Despite its prior medical history, the cat underwent an ovariohysterectomy at 1 year of age. Blood tests revealed regenerative anaemia, thrombocytopenia, mildly elevated aspartate aminotransferase, and hyperbilirubinaemia. The results of an enzyme-linked immunosorbent assay (SNAP FIV/FeLV Combo Test; IDEXX Laboratories) were negative for feline immunodeficiency virus and feline leukaemia virus. Polychromatic erythrocytes and anisocytosis were observed; however,

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examination of blood smears did not reveal Heinz bodies or parasitic organisms. The results of the autoagglutination and direct Coombs tests (IDEXX) were likewise negative. A urinalysis revealed positive occult blood test results. A small amount of pleural effusion was detected on thoracic radiographs. The pleural effusion appeared milky, and primarily contained mature lymphocytes. Echocardiography did not reveal any distinct abnormalities, and the thickness of the myocardial wall was apparently normal (left ventricular wall thickness in diastole was 5.2 mm; intraventricular septum thickness in diastole was 4.2 mm).

We suspected the cat was suffering from immune-mediated haemolytic anaemia or feline haemotropic mycoplasmosis, and thus the appropriate treatment regimens were initiated during hospitalisation. On day 1, the cat received 5 mg/kg enrofloxacin (Baytril; Bayer) subcutaneously once daily. On day 2, the cat's anaemia had progressed, and was accompanied by intermittent haematuria. Additional treatments, including the subcutaneous injection of 2 mg/kg prednisolone (Predonine; Kyoritsu Seiyaku), and the oral administration of 100 units/kg of low molecular weight heparin (Dalteparin; Taiyo Pharmaceutical) and 10 mg/kg of ciclosporin (Atopica; Novartis), were delivered q24h. On day 4, the cat presented with laboured breathing, and a subsequent ultrasound examination revealed a large amount of pleural effusion. Despite all therapeutic efforts, the cat died on day 5.

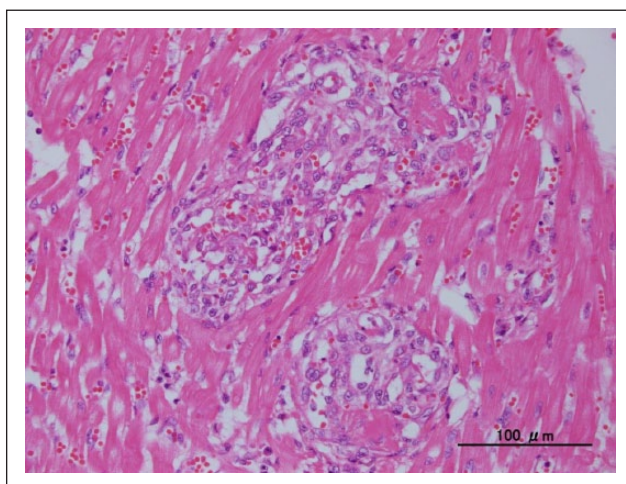
A necropsy was performed, and tissue samples were collected for histopathological analysis. The significant gross pathological findings discovered post mortem were primarily confined to the heart. The moderate level of pericardial effusion present contained a small number of yellow-tinged and slightly viscous fibrinous clots. Multifocal to coalescing haemorrhage was apparent in both atria, but the right atrium was more severely affected. No abnormalities were detected in the shape of the heart (Figure 1), and no significant changes were apparent in the other organs examined. However, a small amount of chylous pleural fluid had accumulated in the thoracic cavity.

Tissue samples were collected from the heart, lung, thymus, spleen, kidney, stomach, duodenum, jejunum, ileum and pancreas, and processed for histological examination. The tissue samples were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 4 µm and stained with haematoxylin and eosin. Phosphotungstic acid haematoxylin (PTAH) and Masson's trichrome staining were likewise performed.

Immunohistochemistry was performed on the sections using a streptavidin–biotin complex method and a Dako autoimmunostainer. The primary antibodies used were monoclonal antismooth muscle actin (high pH retrieval solution pretreatment, 1:500 [Dako]) and polyclonal anti-von Willebrand factor (vWF; proteinase K pretreatment, 1:1000 [Dako]). The antigens detected were



**Figure 1** Right atrium showing severe hemorrhage (formalin-fixed sample)



**Figure 2** Arterioles are partially to completely filled with plump spindle cells that often form glomerulus-like arrangements within the lumens. Haematoxylin and eosin ( $\times 400$ )

visualised with 3, 3'-diaminobenzidine tetrahydrochloride staining with Mayer's haematoxylin counterstain.

Histological analysis revealed that the most severe lesions were localised in the heart. Numerous cardiac arterioles were partially to completely filled with plump spindle cells that often formed glomerulus-like arrangements within the lumens. Within the nests of spindle cells, slit-like, narrow channels were present, occasionally containing erythrocytes and eosinophilic microthrombi (Figure 2). The spindle cells had a plump, round-to-oval nucleus with a single small nucleolus, clumped or stippled chromatin and thin eosinophilic cytoplasm. The nuclei lacked features of atypia and signs of mitosis were rare. Vascular lesions were identified on both atria, both ventricles and septa. Other larger arterial

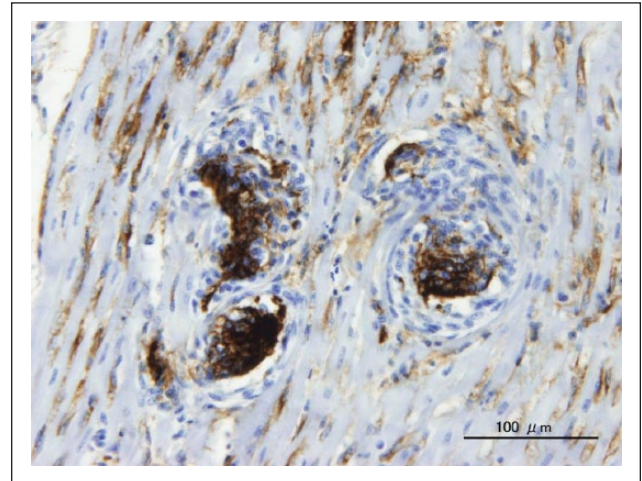
vessels, veins and lymph vessels did not exhibit any changes. The right atrium exhibited extensive haemorrhage accompanied by plasma exudation, split cardiomyocytes, minimal fibrosis, and minor infiltration of macrophages, lymphocytes and plasma cells. A focal myocardial necrosis was concentrated in the right ventricular papillary muscle. Other areas of the myocardium with apparent vascular lesions were accompanied by minimal haemorrhage, scattered cardiomyocyte degeneration and necrosis/loss with mild fibrocyte proliferation. The level of inflammatory infiltrate was marginal.

Similar vascular proliferative lesions were found in the liver, pancreas and kidney. However, these lesions were comparatively minor to those observed in the heart. Other secondary findings included mild emphysema and extramedullary haematopoiesis in the lungs, mild-to-moderate hepatocellular vacuolar degeneration and extramedullary haematopoiesis in the liver, mild lymphoplasmacytic duodenitis and a small area of necrosis in the pancreas.

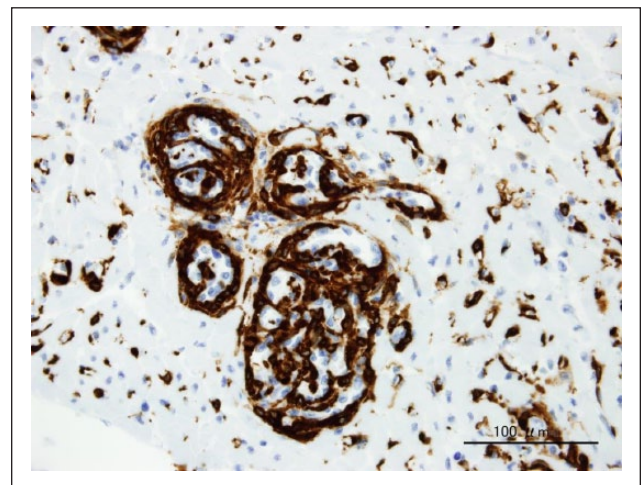
Immunohistochemical analysis revealed that many intraluminal proliferative spindle cells were positive for vWF (Figure 3). Intense smooth muscle actin (SMA) staining was observed on the periphery of the intraluminal proliferations (arteriolar smooth muscles), and on some intraluminal cells (pericytes; Figure 4). The intraluminal thrombi were also positive for vWF, and stained pink with PTAH and blue with Masson's trichrome stain (data not shown).

The histological and immunohistochemical results were consistent with previously documented cases of FSRA.<sup>2</sup> In the current case, the heart exhibited the most severe lesions, which was in accord with most prior reports. Accordingly, the cause of death was likely cardiac failure due to the observed pathological changes in the heart. Although FSRA did not cause any notable morphological abnormalities in the heart and myocardial degeneration/necrosis was relatively mild, vascular proliferation may have impeded the conducting system of the heart, and induced cardiac failure.

The pleural effusion noted may have been associated with heart failure. Further, Masson's trichrome and PTAH stains revealed that the microthrombi present in cardiac intravascular proliferative lesions were platelet thrombi rather than fibrin. The consumption of platelets within the cardiac intravascular proliferative lesions may have exacerbated the apparent thrombocytopenia. We concluded that the regenerative anaemia and hyperbilirubinaemia observed were caused by haemolysis due to occluded vascular lumens. Our positive finding of occult blood in the urine was associated with myoglobinuria resulting from myocardial degeneration/necrosis, in addition to globulinuria due to haemolysis. Although the vascular lesions in the heart were histologically distinct, the shape of the organ was not affected, which could potentially explain why an ante-mortem diagnosis was difficult.



**Figure 3** Many intraluminal spindle cells stained positive for von Willebrand factor (vWF) antigen, which indicates endothelial cell histogenesis. Microthrombi also stain positive for vWF. Immunohistochemistry ( $\times 400$ )



**Figure 4** Arteriolar smooth muscle and some intraluminal cells (pericytes) stain positive for smooth muscle actin(SMA). Immunohistochemistry ( $\times 400$ )

Occlusive intra-arteriolar endothelial and pericytic proliferations have been described in human cases of thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC).<sup>6</sup> Glomeruloid structures within arterioles have been associated with TTP.<sup>5,6</sup> The five most common symptoms for TTP are destructive thrombocytopenia, microangiopathic haemolytic anaemia, intracapillary platelet thrombi, fever and labile neuropsychiatric disorders.<sup>7</sup> Histologically, TTP is characterised by platelet thrombi within the small vessels of multiple organs, primarily the brain and the kidneys.<sup>8</sup> Although the present case involved haemolytic anaemia and thrombocytopenia, there was no sign of renal dysfunction or a neuropsychiatric disorder. Further, histological results indicated that microthrombi were only present in cardiac arterioles.

Consequently, this case did not meet the criteria for TPP. Similarly, the cat did not exhibit any clinical signs that strongly suggested DIC, which is a multisystemic coagulative abnormality. Likewise, none of the histological changes that are consistent with DIC, including fibrinous microthrombi within capillaries, multifocal haemorrhage and tissue degeneration/necrosis in various organs, were observed. Thus, we concluded that the observed thrombocytopenia was not associated with TTP or DIC.

Proliferative endothelial cell lesions have also been reported in association with infectious disease in humans.<sup>9–11</sup> *Bartonella* species have been detected in vasoproliferative haemangiopericytomas in dogs, horses and red wolves, and in systemic reactive angioendotheliomatosis lesions in cats and steers using molecular assays.<sup>12</sup> In a previous study, *Bartonella* species DNA was amplified and sequenced from paraffin-embedded tissues from four cats with FSRA.<sup>12</sup> However, *Bartonella* species DNA could not be amplified and sequenced from the heart tissue obtained from our case (real-time PCR; IDEXX).

## Conclusions

To date, only a limited number of cases of FSRA have been reported. Accordingly, further clinical and pathological studies are required to elucidate the pathogenesis of FSRA.

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**Conflict of interest** The authors declare no conflicts of interest.

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