History

A 4-year-old 10-kg castrated male Maine Coon Cat mix was referred to the Midwestern University’s veterinary teaching hospital because of a 3-day history of seizure-like activity, severe anemia, and dyspnea. This cat was kept indoors only.

Clinical and Gross Findings

After being presented to the veterinary teaching hospital, the patient developed severe subcutaneous edema and widespread ecchymoses. Hematologic findings indicated anemia (Hct, 18% [reference range, 29.5 to 48%]; RBC count, \(3.7 \times 10^6\) RBCs/μL [reference range, \(5.92 \times 10^6\) to \(9.93 \times 10^6\) RBCs/μL]; hemoglobin concentration, 5.9 g/dL [reference range, 9.3 to 15.9 g/dL]; mean corpuscular volume, 49 fL [reference range, 37 to 61 fL]; mean corpuscular hemoglobin concentration, 32 g/dL [reference range, 30 to 38 g/dL]; reticulocyte percentage, 1.3% [reference limit, ≤1%]; absolute reticulocyte count, 47,500 cells/μL [reference limit, <45,000 cells/μL]; nucleated RBC (nRBC) count, 20 nRBCs/100 WBCs [reference limit, ≤1 nRBC/20 WBCs]), slight polychromasia, moderate toxic change, few giant platelets, severe thrombocytopenia (36 X 10^3 platelets/μL; reference range, 200 X 10^3 to 500 X 10^3 platelets/μL; automated platelet count validated by blood smear examination), high total bilirubin concentration (1 mg/dL; reference range, 0.1 to 0.4 mg/dL), and high activities of aspartate aminotransferase (347 U/L; reference range, 10 to 100 U/L), alanine aminotransferase (314 U/L; reference range, 10 to 100 U/L), and creatinine kinase (7,799 U/L; reference range, 56 to 526 U/L). Urinalysis (collection method not specified) abnormalities were occult blood (3+) and proteinuria (1+). Results were negative for a Coomb test as well as PCR assays for *Toxoplasma gondii*, Feline coronavirus, FeLV, *Coccidioides*, *Hemoplasma* spp, *Ehrlichia canis*, and 3 species of *Mycoplasma* (*M. hemofelis*, *M. hemominutum*, and *M. turicensis*). Despite supportive care, the patient continued to decline over the course of 2 days, showed progressive increase in respiratory effort including open-mouth breathing, and then ultimately became obtunded. Due to a lack of improvement, the owner elected for euthanasia and postmortem examination of the cat.

At necropsy, there was severe mucous membrane pallor. The subcutis was diffusely expanded by abundant clear, watery fluid. The lungs were diffusely wet and heavy, and airways exuded frothy fluid on cut section. The myocardium was mottled pale pink to tan, and the coronary vasculature was less distinct (Figure 1). The femoral bone marrow was diffusely dark red. The thorax and abdomen each contained approximately 100 mL of serosanguineous fluid. The proximal small intestinal contents were light pink to...
red and gradually became red-brown to dark purple in the jejunum and ileum. Within the jejunum, the mucosa contained multifocal random, flat areas of dark red. The liver was diffusely light tan with multifocal random, pin-point areas of dark red distributed throughout all lobes. The mucosa of the urinary bladder was severely and diffusely expanded by abundant dark red gelatinous material.

Formulate differential diagnoses, then continue reading.

Histopathologic and Immunohistochemical Findings

Representative samples of lung, liver, heart, kidney, pancreas, small and large intestines, urinary bladder, brain, and bone marrow were collected and placed in neutral-buffered 10% formalin. All tissue samples were routinely processed and then stained with H&E stain. Throughout all examined tissues, but most prominently identified in the heart, brain, kidney, liver, and small intestines, there was marked, widespread, variably occlusive, intravascular spindle cell proliferation with occasional fibrin thrombi (Figure 2) and perivascular hemorrhage. As a consequence of vascular occlusion, there was associated coagulative necrosis identified within the liver, heart, small intestine, and brain. In the small intestine, the previously described vascular changes were predominately within the tunica muscularis. The urinary bladder mucosa and submucosa were markedly expanded by hemorrhage and edema; however, the vascular changes were not observed. Lastly, within the bone marrow, vascular proliferation was present but less frequent. Additionally, there was a marked increase in the myeloid-to-erythroid ratio, right shift of erythroid precursors, and severe megakaryocyte hyperplasia. Immunohistochemical staining of brain tissue was performed, and the intravascular spindle cells were variably positive for factor VIII and smooth muscle actin and strongly positive for vimentin (Figure 3); cells were negative for cluster of differentiation (CD) 3 and CD79a.

Morphologic Diagnosis and Case Summary

Morphologic diagnosis: severe widespread multisystemic intraluminal vascular spindle cell proliferation with variable thrombosis and resultant parenchymal coagulative necrosis.

Case summary: feline systemic reactive angioendotheliomatosis (FSRA).

Figure 2—Photomicrographs of sections of affected thalamus (A), kidney (B), heart (C), and bone marrow (D) from the Maine Coon Cat mix described in Figure 1. Within all sections, small to medium caliber arterioles are variably occluded by intravascular proliferations of plump spindle cells (arrows). A thrombus (asterisk) is also present within an arteriole in the thalamus. H&E stain; bar = 75 µm.
Figure 3—Photomicrographs of 2 arterioles within the thalamus of the Maine Coon Cat mix described in Figure 1 showing that the intravascular proliferations of plump spindle cells are variably positive for factor VIII (A) and smooth muscle actin (C) and strongly and diffusely positive for vimentin (B). Immunohistochemical staining for factor VIII (A), vimentin (B), and smooth muscle actin (C); bar = 75 µm.

Comments

The described microscopic and immunohistochemical findings of this case were consistent with FSRA, which is an idiopathic, rare, multisystemic intravascular proliferative disorder. Based on immunohistochemical staining, the proliferating spindle cells were thought to have been both endothelial and pericyte origin.\textsuperscript{1–5} The dual origin of the proliferating spindle cells suggested that this was a reactive rather than neoplastic process. To our knowledge, published reports of FSRA are limited to 1 case series of 8 cats and a few other case reports.\textsuperscript{1–4} Collectively within these published reports,\textsuperscript{1–4} and also consistent with the signalment and clinical history of this case, affected individuals are often young males (median age of approximately 5 y) with varied and overall nonspecific clinical histories. Additionally, all patients either died or were euthanized as a direct consequence of this condition.\textsuperscript{1–5}

As with the cat of the present report, the most severely and commonly affected organ in FSRA is the heart.\textsuperscript{1–5} In this cat, myocardial dysfunction likely contributed to the development of pulmonary edema and resultant dyspnea; vascular lesions were not identified in examined sections of lung. Microthrombi were frequently identified within affected vessels, and there was severe megakaryocyte hyperplasia, suggesting that the observed thrombocytopenia in this cat was primarily a result of consumption. Based on the minimally high reticulocyte count and the myeloid-to-erythroid ratio in the bone marrow, this patient’s anemia was considered to be either nonregenerative or minimally regenerative. Additionally, the high nRBC count was suspected to have been secondary to direct bone marrow injury because it was disproportionate to the number of reticulocytes.

The underlying cause of FSRA is unknown; however, given the rarity of the condition, it has not been extensively investigated. Infectious or genetic causes have been suggested, but, to date, genetic causes have not been explored. Of the published cases, viral serology (specifically FIV, FeLV, and mutated enteritis coronavirus) was performed in 2 cases, and both animals tested negative. Modified Steiner staining was performed on heart tissue from 2 cats, and bacteria were not identified. However, in a more recent report,\textsuperscript{6} 5 cases of FSRA were retrospectively tested for Bartonella spp via PCR assay, and all 5 animals tested positive for B. benselae, B. vinsonii subspecies berkboffii, or both. For the cat of the present report, extensive antemortem work up for infectious diseases was performed, and all test results were negative. DNA extraction and Bartonella PCR assay were attempted on formalin-fixed paraffin-embedded tissues (liver, heart, and lung), but sufficient quantities of DNA were not able to be obtained. The identification of Bartonella within FSRA lesions may be important and deserves further study given that angioproliferation has been associated with this gram-negative bacteria in humans and animals.\textsuperscript{6–9} In veterinary species, the lesions observed in FSRA are considered relatively unique to domestic cats. There is 1 report\textsuperscript{10} that describes similar systemic angioproliferation in a 2-year-old steer. Similar to FSRA, the steer had systemic intravascular proliferation of spindle cells, most prominent in the heart, that were immunohistochemically positive for von Willebrand factor-related antigen (vWF) and smooth muscle actin and therefore considered to be of both endothelial and pericyte origin.\textsuperscript{10} It was presumed that the cause of the vascular proliferation in the steer was underlining persistent bovine viral diarrhea virus (BVDV) infection, as BVDV viral antigen was identified immunohistochemically in the epidermis, hair follicular epithelium, and adnexa; BVDV antigen was only occasionally observed within the intravascular spindle cells.\textsuperscript{10} For the steer, the proposed pathogenesis for the BVDV-induced vascular proliferation is similar to that of thrombotic thrombocytopenic purpura (TTP), which has been reported in humans and animals.\textsuperscript{10–14} The underlying cause of TTP is either a congenital or acquired deficiency in a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), a vWF-cleaving metalloprotease.\textsuperscript{11–14} Deficiency in this metalloprotease predisposes to widespread intravascular thrombi formation, and thrombosis ultimately become incorporated into arterioles and surrounded by proliferating endothelial cells and pericytes.\textsuperscript{11–14}
Although angioproliferative disorders have been described in humans, the disorders are largely localized or cutaneous, not systemic. The condition most similar to FSRA is human reactive angioendotheliomatosis (RAE) in which the vascular proliferation is confined to the skin; however, patients frequently have concurrent systemic disease. In comparison to FSRA, human RAE is characterized by intravascular proliferation of reactive spindle cells that are CD31, CD34, and vWF positive, indicating endothelial origin. In the veterinary medical literature, there are conflicting conclusions as to whether the proliferating cells are endothelial cells or lymphocytes; however, support for lymphocytes predominates. In the veterinary medical literature, the terms neoplastic or malignant angioendotheliomatosis (also known as neoplastic or malignant angioendotheliosis). This is a rare disease that can be localized or systemic and is characterized by a proliferation of anaplastic neoplastic cells within the lumen of small vessels. In contrast to FSRA, the proliferating cells in neoplastic angioendotheliomatosis have features of malignancy, including a high nuclear-to-cytoplasmic ratio and increased mitotic rate.

In conclusion, this report highlighted the clinical, gross, microscopic, and immunohistochemical features of a case of FSRA, which is a rare, idiopathic, multisystemic, and ultimately fatal intravascular proliferative disorder.

References