An 8.5-year-old spayed female domestic short-hair cat weighing 3.39 kg (7.46 lb) was submitted to the Athens Veterinary Diagnostic Laboratory at the University of Georgia for postmortem examination following euthanasia by means of an IV overdose of pentobarbital sodium. This outdoor cat had a 1-week history of lethargy with an acute onset of severe icterus and a PCV of 16% (reference range, 24% to 45%). The cat’s vaccination status was reportedly up to date (specific vaccines administered were not reported), and the cat was receiving topical heartworm and parasite treatment.

In cooperation with

**Gross Findings**

On external examination, the cat had a body condition score of 7/9. The mucous membranes and visible skin, such as the pinnae and footpads, were markedly bright yellow (icterus [Figure 1]). The lungs were wet and heavy, with a moderate amount of fluid (edema) in the trachea. The liver had multifocal, tan to white umbilicated (≤ 3-cm-diameter) lesions with dark red margins sharply demarcated from the adjacent parenchyma. The lesions occupied approximately 10% of the liver mass. The kidneys were bilaterally nodular; the right kidney was smaller than normal, and the left kidney was enlarged. On cut surface, the renal nodules were solid tan to white and replaced normal renal parenchyma. The urinary bladder wall contained 3 small (< 0.5-cm-diameter) masses. The spleen was enlarged, firm, and meaty. The perirenal and mesenteric lymph nodes were enlarged. There were no other notable findings.

*Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page*
Histopathologic Findings

Samples of the spleen, kidneys, liver, lymph nodes, lungs, intestines, heart, pancreas, urinary bladder, bone marrow, and brain were fixed in neutral-buffered 10% formalin and processed for histologic examination. Microscopically, there was an infiltration of highly pleomorphic round cells expanding the splenic red pulp (Figure 2). The cells had marked anisocytosis, anisokaryosis, and bizarre nuclei with indentation, lobulation, and some multinucleation. The mitotic rate was 48 mitoses/10 hpf (400X). Some neoplastic cells contained phagocytized RBCs and others contained brown pigment that was confirmed to be hemosiderin by results of Perls iron staining. Foci of necrosis filled with fibrin and numerous fibrin thrombi were also present in the spleen. The renal and hepatic nodules were comprised of neoplastic cells with similar characteristics. Nodules in the liver had extensive necrosis (Figure 3). The liver also had acute coagulative necrosis of centrilobular hepatocytes, likely the result of hypoxia associated with anemia, and many of the remaining hepatocytes had small vacuoles with sharp margins consistent with lipid. Bile plugs were present in many canaliculi, likely a result of hemolysis associated with erythrophagocytosis by the tumor cells coupled with hepatocyte injury associated with the neoplastic infiltration and hypoxia. In addition, the small nodules in the urinary bladder wall were composed of neoplastic cells, and neoplastic cells had effaced lymph nodes. The lungs contained a few fibrin thrombi. Without additional clinicopathologic data, the cause of the thrombosis was speculative, but neoplasia-associated thrombotic microangiopathy was a possibility. Such thrombosis could also lead to microangiopathic hemolysis, thereby worsening the anemia and contributing further to the canalicular plugging. The bone marrow was normocellular (approx 50% fat and 50% cells) with a low ratio of myeloid to erythroid precursors and increased numbers of immature and mature cells of the erythroid series (erythroid hyperplasia), which suggested that the anemia was regenerative.

Immunohistochemical Findings

Immunohistochemical analyses were performed on spleen and kidney sections. Neoplastic cells were strongly positive for CD18 and Iba1 (Figure 4) but lacked immunoreactivity for MAC 387. Tumor cells were negative for CD79 (B-cell marker) and CD3 (T-cell marker).
Of the forms of proliferative histiocytic disorders known in dogs and cats, some affect both species and others are exclusive to 1 or the other species. Cats may develop pulmonary Langerhans histiocytosis, a reactive condition of Langerhans dendritic cell hyperplasia that results in respiratory failure, or feline progressive histiocytosis, a condition that begins as an indolent proliferation of interstitial dendritic cells and insidiously progresses to a more malignant neoplasm resembling HS. Although other histiocytic diseases, such as histiocytoma and cutaneous histiocytosis, are believed to be exclusive to dogs, the malignant neoplasm HS affects both species. Histiocytic sarcoma itself typically originates from interstitial dendritic cells and may develop as a single nodule or in a disseminated form. Characteristics of HS include marked cellular pleomorphism of large mononuclear and multinucleated cells, which may have bizarre nuclei, frequent mitoses, anisokaryosis, and anisocytosis.

Although HS typically originates from interstitial dendritic cells, a unique form of HS—hemophagocytic HS—was evident in the cat of the present report. Hemophagocytic HS appears to be the only form of HS known to originate from macrophages, and it typically originates in the red pulp of the spleen. In contrast with more typical HS, which often develops as a discrete mass or disseminated disease, the hemophagocytic variety of HS is typically associated with uniform, diffuse splenomegaly. However, masses may appear more discrete as the disease progresses. Animals with hemophagocytic HS usually have clinical signs related to regenerative anemia and thrombocytopenia because the hallmark of this disease is marked erythrocyte ingestion by the neoplastic macrophages. Affected animals may also have hypoalbuminemia and hypocholesterolemia. Hyperbilirubinemia and icterus are not typically detected in early-onset disease but may become apparent as the disease progresses.

Because hemophagocytic HS is aggressive in nature with rapid metastasis and the development of hemolytic syndrome, this neoplasm has perhaps the worst prognosis of all histiocytic diseases, with a median survival time of 7 weeks after diagnosis in dogs. Histiocytic sarcoma, and in particular hemophagocytic HS, is very rare in cats. Friedrichs and Young identified hemophagocytic HS in a cat that was being evaluated for use as a blood donor, and Ide et al. reported hemophagocytic HS in a cat that was being evaluated because of chronic lethargy, regenerative anemia, and thrombocytopenia. In both of those cases, results of further diagnostic testing, including histologic examination of splenic aspirates and tissue sections, revealed lesions similar to those in the cat of the present report.

**Morphologic Diagnosis and Case Summary**

Morphologic diagnosis and case summary: hemophagocytic histiocytic sarcoma (HS) of the spleen, liver, kidneys, urinary bladder, and lymph nodes with secondary anemia and icterus in a cat.

**Comments**

The findings of acute anemia and icterus with effacement of the splenic red pulp by neoplastic histiocytes that were positive for CD18 and Iba1, engulfment of erythrocytes by neoplastic cells, and metastasis to other organs are characteristic of hemophagocytic HS, a rare condition identified primarily in dogs. However, this disease has been detected in cats, and there is at least 1 report of an affected cow. Hemophagocytic HS is an entity in a diverse complex of histiocytic proliferative diseases encountered in veterinary medicine. This disease complex originates from tissue histiocytes, a heterogeneous population of mononuclear cells of the immune system that reside in tissues throughout the body and are derived from CD34+ precursor cells in the bone marrow. Differentiated histiocytes include macrophages and Langerhans, epithelial, interstitial, and lymphoid dendritic cells. Macrophages are present in a number of tissues, wherein they act as phagocytes of the innate immune system and may function as antigen-presenting cells during infection. The various dendritic cells, such as Langerhans cells found in epithelium, particularly skin, and interstitial dendritic cells found in many visceral tissues are primarily involved in antigen surveillance and presentation.

**Figure 4**—Photomicrograph of a section of a kidney of the cat in Figure 1 following immunohistochemical staining for microglia/macrophage-specific protein Iba1. Notice the dark brown membrane staining of tumor cells. Iba1-specific stain and 3,3'-diaminobenzidine chromogen with hematoxylin counterstain; bar = 100 μm.
For cats with anemia, thrombocytopenia, icterus, or nodular lesions, differential diagnoses should include FeLV or FIV infection, which can be detected with ELISA testing. A Coombs test would help rule out immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, or their concurrent presence (Evans syndrome) because hemophagocytic HS does not induce agglutination or autoantibodies. Icterus can be associated with cytauxzoonosis, a tick-borne infection caused by *Cytauxzoon felis*. Diagnosis of this infection should be based on the presence of a high fever and visualization of organisms (schizonts) in mononuclear cells on microscopic examination. *Mycoplasma hemofelis* infection is also associated with hemolytic disease in cats; PCR analysis is the method of choice for diagnosis of this infection. Cats with feline infectious peritonitis may develop icterus; at necropsy, they may have nodules in various tissues but those nodules represent pyogranulomatous inflammation, and vasculitis may be present. Lastly, hemophagocytic syndrome, a non-neoplastic disease wherein phagocytosis of erythrocytes by macrophages occurs in various tissues, needs to be considered in the differential diagnosis list. However, although cats with hemophagocytic syndrome have anemia, they do not have nodular lesions and their macrophages do not have neoplastic morphologic characteristics.

Histopathologic lesions such as those seen in the case described in the present report are highly characteristic of hemophagocytic HS, and include large, pleomorphic round cells with bizarre or multiple nuclei, high mitotic rate, and engulfment of erythrocytes in multiple tissues, primarily the spleen, with effacement and expansion of the splenic red pulp. Immunohistochemical analysis is a potential tool for phenotyping various forms of HS. Tumor cells that are immunoreactive for CD11d likely have a splenic red pulp histiocytic origin. CD11b staining has also been used to identify HS, although some evidence suggests other cells, such as dendritic cells, may express CD11b. Assessments for CD18 and MAC387 are used to identify HS, but caution must be taken when evaluating immunohistochemical findings, especially those for sections of the spleen, because all leukocytic cells may express CD18, and some anaplastic lymphomas have been associated with MAC 387 positivity.

CD1 is specific for dendritic cells; therefore, a negative test result for CD1 may support a macrophage origin of those cells. An important finding in the case described in the present report was the macrophage lineage of the neoplastic cells; hemophagocytic HS is known to arise only from macrophages and not from dendritic cells or other leukocytes. Iba1 is a calcium-binding adapter molecule frequently used to identify microglia and has recently been demonstrated as a useful marker for histiocytic proliferative disorders because it is expressed in all cells of monocyte lineage. For the icteric and markedly anemic cat of the present report, a diagnosis of a hemophagocytic variant of HS was made. The reactions to immunohistochemical markers indicated that the neoplastic cells were of monocyte lineage; however, we were not able to conclusively determine a macrophage-specific origin. Although reported as a very rare condition, hemophagocytic HS should be on the differential diagnosis list for cats with unexplained regenerative anemia and icterus.

### Footnotes


### References