History

A 2-year-old 29.5-kg (64.9-lb) castrated male mixed-breed dog that had a 4-month history of coughing was referred to the Michigan State University Veterinary Teaching Hospital following an acute onset of dyspnea and anorexia. Diagnostic testing prior to referral included urine antigen tests for *Blastomyces dermatitidis* and *Histoplasma capsulatum* as well as serologic testing for *Cryptococcus* antigen, *Dirofilaria immitis* antigen, anti-*Coccidioides immitis* antibody, and anti-*Aspergillus* antibody; results were negative. The dog had no history of travel outside southeastern Michigan.

Treatment prior to referral included administration of fenbendazole, furosemide, antimicrobials, a bronchodilator, cough suppressants, and Yunnan Baiyao over an extended period; later, immunosuppressive doses of prednisone were administered. Initial improvement was noted following treatment with prednisone.

Clinical Signs and Clinicopathologic Data

On initial evaluation, the dog was pyrexic (39.61°C [103.3°F]), tachycardic (200 beats/min), and unable to rise, and it had muddied mucous membranes and bounding femoral pulses. Lung sounds were diffusely harsh, with focal inspiratory crackles and muffled heart sounds over the right cranioventral portion of the thorax. Thoracic radiography revealed multiple coalescing, soft-tissue-opacity masses throughout the lungs and increased opacity in the cranial mediastinum. Abdominal ultrasonography revealed that the liver was hyperechoic and enlarged, and the pancreas had heterogeneous echotexture. Relevant abnormalities on CBC and serum biochemical analysis included marked neutrophilic and eosinophilic leukocytosis with a regenerative left shift, markedly high alkaline phosphatase activity, moderately high alanine aminotransferase activity, and moderate hyperbilirubinemia and hypercholesterolemia. Ultrasound-guided fine-needle aspirate biopsy of masses in the lungs was performed. Owing to the progressive deterioration of the dog’s clinical condition and poor response to treatment, the dog was euthanized by an IV overdose of barbiturate solution and submitted to the Diagnostic Center for Population and Animal Health for necropsy.

Gross Necropsy Findings

The right cranial lung lobe parenchyma was expanded by coalescing, white, solid masses that were firm and homogenous on cut surfaces (Figure 1). Similar, occasionally coalescing masses measuring 1 mm to 9 cm in diameter had invaded all other lung lobes and the mediastinum and were adhered to the parietal pleura of the left 8th rib, right 6th intercostal space, and right 11th rib. Marked mediastinal and tracheobronchial lymphadenomegaly and 50 to 60 mL of serosanguineous pleural effusion were found. The liver was diffusely enlarged.

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

The lung aspirate specimen (Figure 2) was of low to moderate cellularity, with a moderate amount of blood. The population of cells was mixed and included nondegenerate neutrophils (approx 55% to 65%), large pleomorphic mononuclear cells (approx 15% to 20%), eosinophils (approx 15% to 20%), and macrophages (approx 5% to 10%). The pleomorphic mononuclear cells had moderately abundant, moderately basophilic, frequently lightly vacuolated cytoplasm, with round to slightly oval nuclei containing clumped chromatin and inconspicuous to sometimes prominent round to oval nucleoli. Anisocytosis and anisokaryosis were moderate, and there were rare mitotic figures. Occasional macrophages had phagocytized nucleated cells or erythrocytes.

**Histopathologic Findings**

All examined sections of lung tissue contained a poorly demarcated, nonencapsulated, densely cellular, infiltrative proliferation of neoplastic round cells accompanied by many neutrophils, lymphocytes, and eosinophils (Figure 3). The neoplastic cells were arranged in sheets and anastomosing rows and often had marked angiocentricity. The neoplastic cells were large (10 to 25 µm in diameter) and round to polygonal, with distinct cell borders, small to moderate volumes of amphophilic cytoplasm, and large, oval to indented nuclei containing vesicular chromatin and 1 to 3 variably sized nucleoli. Anisocytosis and anisokaryosis were marked, with common karyomegaly and nucleolar atypia. There were 22 mitotic figures/10 hpfs (400X). The neoplastic cells and accompanying inflammatory cells were within many alveoli and small (respiratory) bronchioles. The neoplastic cells and accompanying inflammatory infiltrate surrounded and invaded numerous arterioles and small veins, with fibrinoid degeneration of the tunica media of affected vessels. There was multifocal, segmental infiltration of the pleura and multifocal necrosis of neoplastic cells and pulmonary parenchyma. Comparable neoplastic cells and intermixed inflammatory cells were seen in a sample of mediastinal lymph node.

Immunohistochemical analysis revealed that most large neoplastic cells had membranous labeling for CD20 (pro-B-cell marker) and most of the small lymphocytes had membranous labeling for CD3 (T-cell marker). The large neoplastic cells were negative for CD3.

**Other Gross Necropsy Findings**

The remainder of the necropsy revealed multifocal, necro supplicative pancreatitis and peripancreatitis, with saponification. Mild interstitial pancreatic and peri pancreatic hemorrhage was associated with foci of inflammation and necrosis. There was diffuse...
hepatocellular glycogen vacuolation, mild intrahepatic cholestasis, and no evidence of neoplastic cells in the examined sections of liver.

**Morphologic Diagnosis and Case Summary**

Morphologic diagnosis and case summary: lymphomatoid granulomatosis of lung tissue and mediastinal lymph node in a dog.

**Comments**

The list of differential diagnoses for primary pulmonary neoplasia in young dogs is small. Combined radiographic, cytologic, and histologic findings in the case described in this report were supportive of a diagnosis of lymphomatoid granulomatosis, a malignant neoplasm of lymphocytes. Lymphomatoid granulomatosis in cats, humans, and dogs has been reported. In 1979, lymphomatoid granulomatosis was identified in three 18-month to 3-year-old dogs with 3- to 7-month histories of respiratory tract disease. Two of those 3 cases were characterized by radiographic opacity of the right caudal lung lobe, whereas the right cranial lung lobe was primarily affected in the third case. In all 3 dogs, firm pale neoplastic tissue obliterated the pulmonary parenchyma in the most radiographically altered lobes, and multifocal to coalescing nodules affected all lung lobes, as evident in the dog of the present report.

Similarly, many of the most commonly reported clinical signs in dogs with lymphomatoid granulomatosis including cough, dyspnea, and anorexia were noted in the case described in this report, although cutaneous lesions, which are also common, were not. In affected dogs, nonspecific clinical signs including anorexia, vomiting, lameness, weakness, weight loss, and nasal discharge also have been reported. Cough can be due to pulmonary parenchymal disease or tracheobronchial compression by lymphadenopathy. Clinicopathologic findings include marked leukocytosis with neutrophilia and eosinophilia. As found for the dog of the present report, results of a serum biochemical profile are frequently unremarkable, but mild hyperglobulinemia and hypoalbuminemia can develop in dogs with lymphomatoid granulomatosis. In the dog of this report, the serum biochemical alterations reflected cholestasis and prednisone-related hepatopathy, which were confirmed histologically, and the cholestatic and hepatocellular changes may also have been exacerbated by pancreatitis.

Clinically, lymphomatoid granulomatosis is less often suspected as the cause of multinodular pulmonary lesions than infections with fungi, protozoa, or parasites; eosinophilic bronchopneumopathy; or other primary or metastatic pulmonary neoplasms. Cytologically, lymphomatoid granulomatosis is characterized by large atypical round cells admixed with inflammatory cells including small lymphocytes, eosinophils, and plasma cells (Figure 2). The large round cells have variable lymphoid, plasmacytoid, or histiocytic morphology and may comprise the majority of the cell population; mitoses and binucleate cells may be common. Owing to the pleomorphic pattern of findings, reported cytologic interpretations have been variable, including lymphoma, large lymphohistiocytic cell infiltrate, eosinophilic granulomatous inflammation, and pyogranulomatous inflammation. Although cytologic evaluation can be highly suggestive, histopathologic findings are required for a definitive diagnosis.

Histologically, the hallmark of the disease referred to as pulmonary lymphomatoid granulomatosis in dogs is multifocal to coalescing, nodular, often angiocentric and angiodestructive infiltrates of large, atypical lymphocytes, accompanied by some combination of eosinophils, neutrophils, lymphocytes, and plasma cells. Most reported cases have primarily affected the caudal lung lobes, and cutaneous metastases have been reported. At the time of death, most dogs with pulmonary lymphomatoid granulomatosis have multiorgan involvement, including metastases to the mediastinal and peripheral lymph nodes, liver, and spleen. Reports suggest that young (mean age, 5.3 years old) large-breed dogs are overrepresented, but specific breed predilections have not been identified.

The prognosis for dogs with this disease is poor. Reported median survival time is 3 months after diagnosis, and the condition of most dogs rapidly deteriorates because of progressive pulmonary disease. A small number of dogs have had long-term responses to prednisone and cyclophosphamide treatment (17, 32, and 37 months without recurrence) and a single case report describes long-term survival of a dog following treatment with a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) protocol and a monthly mitoxantrone rescue protocol after relapse. In the report describing successful treatment with a CHOP-based protocol, clinical improvement correlated well with resolution of radiographic lesions.

The histologic and immunophenotypic profile of lymphomatoid granulomatosis in humans and dogs is a topic of discord, both within and between the 2 species. In addition to the histologically pleomorphic mononuclear cell population identified in humans with lymphomatoid granulomatosis, dogs with lymphomatoid granulomatosis have a marked neutrophilic, eosinophilic, lymphocytic, and plasmacytic infiltrate. In humans, lymphomatoid granulomatosis had previously been designated as atypical, angiocentric, T-cell lymphoma, but it is currently considered a distinct T-cell–rich, B-cell lymphoma, with the B cells containing Epstein-Barr virus DNA. The specific criteria for diagnosis of lymphomatoid granulomatosis in people currently includes the presence of Epstein-Barr virus–positive, neoplastic B cells admixed with T cells and often plasma cells and histiocytes as well. The diagnosis is supported by the presence of necrosis, multiple lung nodules, or additional cutaneous and nervous involvement. Necrosis and multiple nodules in the lungs were detected in the dog of the present report.

Reported immunohistochemical findings for neoplastic lymphocytes in cases of canine pulmonary lymphomatoid granulomatosis have varied from predominantly CD79a positivity with some CD3-positive cells to predominant CD3 positivity with negative findings for CD79a. Additionally, a recent case report described a 10-month-old American Cocker Spaniel that had neoplas-
tic lymphocytes with B-cell (CD20 and CD79) and T-cell markers (CD3) as well as interspersed large CD13-positive, CD30-positive cells. These findings indicated an immunophenotypic characterization that is a hybrid of lymphomatoid granulomatosis and pulmonary Hodgkin disease in humans. With these discrepancies taken into consideration, there are questions as to whether the term lymphomatoid granulomatosis is appropriate for this disease entity in dogs. In the dog of the present report, the large, pleomorphic, neoplastic cells were positive for CD20, and the small lymphocytes were positive for CD3.

Prior to euthanasia, the dog of this report was treated with supplemental oxygen, cyclophosphamide (250 mg/m², IV), dexamethasone (0.2 mg/kg [0.09 mg/lb]), and aminophylline (10 mg/kg [4.55 mg/lb]) to treat pulmonary lymphoma on the basis of the cytologic evaluation findings. However, as the dog’s clinical condition continued to worsen, it became dyspneic and distressed and was euthanized 36 hours after initiation of chemotherapy. The radiographic, necropsy, cytologic, and histopathologic findings in the present case were highly consistent with what is currently termed lymphomatoid granulomatosis in dogs. Although rare, this disease entity should be included among differential diagnoses for young to middle-aged dogs with clinical signs of respiratory tract disease, 1 or more radiographic nodular opacities, and leukocytosis, especially with no strong evidence of an infectious disease. Further studies to immunophenotype and analyze genomic information for clonality and potential viral infection of neoplastic cells are warranted to more accurately characterize, and potentially rename, lymphomatoid granulomatosis in dogs.

References