Pulmonary Lymphomatoid Granulomatosis in a Dog

A Case Report and Literature Review

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Introduction

Canine pulmonary lymphomatoid granulomatosis (PLG) is a rare lymphoproliferative disorder of the pulmonary parenchyma, which is characterized by the infiltration of angioinvasive and angiodestructive neoplastic lymphoid cells. PLG was initally described in humans in 1972, but was not reported in dogs until 1979.[1] Although common in human medicine, PLG is rarely diagnosed in dogs. In fact, less than 50 cases have been reported in the veterinary literature.[1-10] This disorder typically affects young to middle age dogs; the age of onset ranging from 9 weeks to 14 years.[1-4] PLG causes fibrinoid necrosis of the lung parenchyma and associated vasculature of one or more lung lobes.[2,5] The caudal lung lobes are most commonly affected.[5] Characteristic histopathologic features of PLG include angiocentric, neoplastic lymphoid proliferation and signs of vascular destruction and necrosis.[5-6]

Although classically described as a disease of unknown etiology, recent histochemical marker studies suggest that PLG starts as a polyclonal lymphoreticular proliferation during which patients may remain asymptomatic.[5-6] However, as the disease progresses, patients commonly develop lethargy, anorexia, and respiratory disease characterized by a progressive, non-productive cough.[1-2] Other clinical signs reported include lameness, fever, enlarged peripheral lymph nodes, and skin lesions.[1-3] These clinical signs are rare and associated with extrathoracic metastasis of advanced disease.[1] Transformation of PLG to pulmonary lymphoma has been documented, which appears similar to Hodgkin's lymphoma histologically.[2]

History and Presentation

A 5-year-old spayed female mixed-breed dog (24.0kg [52.8lb]) presented to Mississippi State University Animal Health Center (MSU-AHC) for evaluation of a dry non-productive cough of 1-day duration. Upon physical examination, the dog's body temperature was 38.4°C

(101.1°F) and heartrate was 120 beats per minute. The dog was panting and coughing intermittently throughout the exam. Thoracic auscultation revealed harsh lung sounds ventrally, and a cough was elicited upon palpation of the trachea. No additional abnormalities were found. The dog was presumptively diagnosed with kennel cough and prescribed minocycline hydrochloride (8 mg/kg [3.6 mg/lb], PO, q 12 h, for 14 days), trimeprazine (0.6 mg/kg [0.3 mg/lb], PO, q 12 h, for 3 days), and prednisolone (0.2 mg/kg [0.1 mg/lb], PO, q 12 h, for 3 days). The clinical signs improved with treatment, but returned after discontinuing trimeprazine and prednisolone.

Six days after initial presentation, the dog returned to MSU-AHC for an acute onset of lethargy, anorexia, and vomiting. Physical examination revealed no abnormal findings. A mild respiratory alkalosis with metabolic compensation was detected on blood gas analysis. Complete blood count (CBC) and serum biochemistry were within normal limits with the exception of a moderate lymphopenia (762/ul; reference range: 1200-6500/ul), mild hyperphosphatemia (5.2 mg/dl; reference range: 2.5-5.0 mg/dl), mildly increased alkaline phosphatase (143 U/L; reference range: 11-140 U/L), and mildly increased blood urea nitrogen (26 mg/dl; reference range: 8-24 mg/dl). The dog was treated with maropitant citrate (1 mg/kg [0.5 mg/lb], PO, q 24 h, for 5 days), omeprazole (1 mg/kg [0.5 mg/lb], PO, q 24 h, for 2 days), sucralfate (1 g/dog, PO, q 12 h, for 2 days), tramadol (2 mg/kg [0.9 mg/lb], PO, q 8 h, for 5 days), famotidine (1 mg/kg [0.5 mg/lb], PO, q 24 h, for 2 days), and lactated Ringer's electrolyte solution (200 mls, SC, q 24 h, for 5 days).

Nine days after initial presentation, the dog presented to MSU-AHC for a persistent cough and anorexia. Upon physical examination, the dog was depressed, dyspneic, and exhibited marked stertor and abdominal effort on expiration. Thoracic auscultation revealed increased

bronchovesicular sounds in the cranioventral lung fields and crackles in the area of the right middle lung lobe. The abdomen was tense upon palpation. The dog was presumptively diagnosed with pneumonia subsequent to kennel cough and treated with amoxicillin and clavulanic acid (15 mg/kg [6.8 mg/lb], PO, q 12 h, for 9 days) and prednisone (0.5 mg/kg [0.2 mg/lb], PO, q 12 h for 3 days, then q 24 h for 3 days). Initially, the dog's clinical signs improved slightly with treatment, but worsened after discontinuing the prednisone.

Eighteen days after initial presentation, the dog presented to MSU-AHC for progressive respiratory distress in addition to a persistent cough and anorexia. Upon physical examination, the dog was tachypneic and dyspneic with a respiratory rate of 50 breaths per minute. The dog was also tachycardic with a heartrate of 160 beats per minute. Crackles were heard bilaterally in all lung fields. Bronchovesicular sounds were increased dorsally and muffled ventrally. Peripheral oxygen saturation was decreased (90-93%). CBC revealed moderate rubricytosis (11 nRBC/ 100 WBC), mild thrombocytopenia (117 K/ul; reference range: 160-650 K/ul), and a moderate leukocytosis (45.2 K/ul; reference range: 7.0-22.0 K/ul) characterized by a marked mature neutrophilia (39324/ul; reference range: 3500-14200/ul), moderate monocytosis (2712/ul; reference range: 174-1700/ul), and moderate eosinophilia (1808/ul; reference range: 120-1300/ul). Serum biochemistry was also performed and revealed moderate hyponatremia (124.5 mmol/L; reference range: 143.0-53.0 mmol/L), moderate hypochloremia (98.6 mmol/L; reference range: 106.0-122.0 mmol/L), mild hypoproteinemia (4.7 g/dl; reference range: 5.5-8.0 g/dl), mild hypoalbuminemia (2.2 g/dl; reference range: 2.5-3.9 g/dl), mild hypocalcemia (8.4 mg/dl; reference range: 8.8-11.2 mg/dl), mild hyperphosphatemia (6.3 mg/dl; reference range: 2.5-5.0 mg/dl), mild hypocholesterolemia (127 mg/dl; reference range: 140-360 mg/dl), moderate hypoosmolality (244 mOsm/kg; reference range: 280-305 mOsm/kg), and decreased

ALT (<4 U/L; reference range: 10-90 U/L). Two-view thoracic radiographs were performed and revealed a loss of detail due to the presence of a large, gravity dependent, fluid opaque material. The dog was immediately sedated with butorphanol (0.2 mg/kg [0.1 mg/lb], IV) and administered lactated Ringer's solution (2.5 ml/kg/hr [1.1 ml/lb/hr], IV). A thoracocentesis was performed, and 590 milliliters of cloudy serosanguinous fluid were obtained. Upon aspiration of the fluid, oxygenation immediately improved, but rapidly declined over the next hour. The thoracic effusion was submitted for cytological evaluation which revealed a high protein concentration (4.1 g/dL) and high cellularity (36,700 nucleated cells/uL) composed of neutrophils, macrophages, and large, neoplastic, round cells. A moderate amount of red blood cells (70,000 RBC/uL) was also present. No etiologic agents were identified.

Pathophysiology

Due to the rarity and complexity of this disease, the exact etiology of PLG remains unknown. However, recent histochemical marker studies suggest that PLG starts as a benign polyclonal lymphoreticular proliferation in response to chronic inflammation. This proliferation of polyclonal B-cells is regulated by cytotoxic T-cells. However, a functional deficiency of immune regulation facilitates the progression of this polyclonal proliferation to an angiocentric neoplasm of monoclonal B-cells.[2,5] The combination of chronic inflammation and an immunodeficient state has been suggested as a potential etiology for canine PLG, and has been confirmed as the etiology for PLG in humans and mice.

In humans, PLG is an Epstein-Barr virus-associated, angiocentric, T-cell-rich, B-cell lymphoma.[2,11-12] Polymerase chain reaction (PCR) and in situ hybridization of affected tissues have demonstrated the presence of Epstein-Barr virus (EBV) RNA within malignant B-cells.[11-16] Initially, EBV, a human herpes virus, binds to the complement receptor CD21 on B-cells,

resulting in polyclonal, B-cell proliferation.[13-14] This proliferation is usually controlled by immune regulation involving cytotoxic T-cells, helper T-cells, and natural killer cells. However, in immunodeficient states, the host's defenses may be unable to control EBV-induced B-cell proliferation, resulting in malignant transformation.[13-16]

The presence of a herpes viral infection in combination with pre-existing immunodeficiency has not been identified as the initiating cause of PLG in dogs.[7] However, a chronic inflammatory cause is strongly suspected due to the initial proliferation of polyclonal B-cells, the presence of closely associated mixed inflammation, and malignant transformation to pulmonary lymphoma.[2-3,7]

Diagnostic approach/considerations

A CBC and chemistry panel are both important aspects of the initial workup for any respiratory case. However, the results of these diagnostics are generally unremarkable and non-specific for cases of PLG. CBC most commonly reveals a mild to moderate leukocytosis characterized by neutrophilia and lymphopenia.[2] No consistent changes in chemistry panels or urinary analyses have been identified.

Thoracic radiographs may reveal a wide range of changes including the presence of pleural effusion, caudal lung lobe consolidation, distinct pulmonary nodules, and hilar lymphadenopathy.[1-2,6] However, these findings are commonly associated with advanced disease, and the usefulness of thoracic radiographs during early stages of the disease may be limited. Thoracocentesis of patients with pleural effusion generally results in a large amount of serosanguinous effusion that may or may not contain neoplastic cellular infiltrates.[1-2,6] Cytological analysis of pleural effusion or fine needle aspiration of affected lung lobes often reveals findings similar to that of pulmonary lymphoma.[6]

Definitive diagnosis of PLG is based on histological evaluation of affected lung parenchyma and the presence of neoplastic lymphoid cells in an angiocentric location.[1-3,11] The angiocentric location of neoplastic lymphoid cells is essential in differentiating PLG from pulmonary lymphoma.[3] Histopathology results are similar to that of human PLG characterized by large, discrete, anaplastic, mononuclear cells with angiocentric location and closely associated mixed inflammation.[5-6] Reed-Sternberg-like cells may also be present, similar to histopathological findings in human Hodgkin's lymphoma.[5]

Immunohistochemistry of reported cases of canine PLG revealed cellular infiltrates positive for variable amounts of B-cell (CD20 and CD79a) and T-cell (CD3) antigens as wells as occasional presence of Reed-Sternberg-like cells (CD15) and lymphocyte activation antigen (CD30).[5-6] The neoplastic cell population appears to be primarily B-cell in origin and is closely associated with large numbers of reactive T-cells and various other inflammatory cells, resembling a T-cell rich B-cell lymphoma.[5-6] The presence of reactive T-cells and subsequent mixed inflammation may be due to a cytotoxic response to the presence of neoplastic B-cells or an inflammatory response to an unidentified etiologic agent.[5] Further evaluation of future cases is necessary to determine the exact etiology of this disease.

Treatment and management

An antemortem diagnosis of PLG is difficult to accomplish and rarely achieved. For this reason, treatment has only been attempted in very few confirmed cases. Multiple studies recommend treatment with a Madison Wisconsin chemotherapy protocol similar to that used to treat canine lymphoma.[2,6,8] This protocol, also known as CHOP, includes a structured administration protocol of vincristine, cyclophosphamide, doxorubicin, and prednisone. CHOP chemotherapy and combination chemotherapy was attempted in 12 reported cases.[2,6] No

consistent improvement in clinical condition was achieved with treatment. Incomplete remission was obtained in three dogs and long-term remission was achieved in one dog. Unfortunately, recurrence of pulmonary involvement or development of lymphoma in other organ systems occurred months to years after apparently successful treatment. Each reported case that received treatment ultimately died or was euthanized due to the progression of the disease or because of side effects of chemotherapy. Chemotherapy was not initiated in the currently described case.

Prognosis

PLG is a progressive and fatal disease. Prognosis is grave since a consistently effective chemotherapy protocol for PLG has not been established. Recent studies report a survival time of 6 days to 4 months without treatment.[1] Clinical course with treatment is variable, with rare reports of prolonged remission and survival times ranging from 4 weeks to 4 years.[2,8]

In human medicine, mortality ranges from 38-85% with a mean survival time of 14 months. Approximately 50% of human PLG cases eventually progress to pulmonary lymphoma.[6] The survival time of canine PLG is much shorter which rarely allows sufficient time for this disease to progress to lymphoma. However, rare case reports suggest that canine PLG has a similar disease course.[2] Pulmonary lymphoma also carries a guarded to grave prognosis due to the progressive nature of this disease and limited treatment options.

Case outcome

Due to the cytological findings and rapidly declining clinical condition of the patient, the dog was humanely euthanized. A necropsy was performed which revealed an enlarged, rough, firm, and mottled accessory lung lobe and right caudal lung lobe with an accompanying serosanguinous pleural effusion. The tracheobronchial lymph nodes were enlarged and multiple small, firm, tan, raised nodules were present on the mediastinal pleura and pericardial adipose

tissue. Histopathology of the affected lung lobes revealed the presence of an angiocentric round cell neoplasm and fibrinoid vascular necrosis with hypereosinophillic deposits in the tunica media with accompanying media necrosis. The neoplastic cells were large, discrete, anaplastic, and mononuclear to binuclear with 4 to 5 mitotic figures per high power field. These cells were surrounded by a mixed inflammatory population composed of eosinophils, neutrophils, reactive macrophages, small lymphocytes, plasma cells, and mast cells. A similar cell population was identified in tissue samples of the mediastinal pleura, pericardial adipose tissue, and necrotic tracheobronchial lymph nodes. Mineralized nematode segments were present within the pulmonary vasculature. This incidental finding was attributed to patient's history of heartworm disease.

Immunohistochemistry was attempted on several tissue samples and revealed an unusual staining pattern of the neoplastic round cells with CD20, a B-cell antigen marker. Pax5, the gene segment encoding B-cell-specific activator protein, is used to identify the prescence of B-cells and was not detected in any sample. These unusual results were likely due to sample autolysis or damage. For this reason, additional immunophenotyping was not pursued.

Conclusion

PLG is a rare pulmonary lymphoproliferative disease that is angiocentric and angioinvasive. Affected dogs present with clinical signs similar to that of pulmonary lymphoma. Definitive diagnosis of PLG requires histopathology which reveals angiocentric large, discrete, anaplastic, mononuclear cells with signs of angiodestruction and closely associated mixed inflammation. CHOP chemotherapy is a proposed treatment protocol, but has not been proven to be consistently effective. The prognosis for PLG is grave, and additional research is necessary to further understand the etiology and most appropriate treatment of this disease.

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