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Objective—To determine clinical signs, radiographic and histologic abnormalities, and concurrent diseases in cats with endogenous lipid pneumonia (EnLP) and to determine the pathologic importance of EnLP in cats.

Design—Retrospective study.

Animals—24 cats.

Procedure—Medical records of cats in which EnLP was confirmed by histologic examination of necropsy specimens were reviewed. Information collected from the medical records included signalment, body weight, clinical signs, and results of clinicopathologic tests. Thoracic radiographs were reviewed by a radiologist; histologic specimens were reviewed by a pathologist.

Results—All cats had nonspecific clinical abnormalities, such as lethargy, anorexia, or weight loss; 16 had signs of respiratory tract disease. All cats had concurrent systemic diseases, and clinicopathologic abnormalities were reflective of these conditions. Nonspecific abnormalities were detected on thoracic radiographs from 9 of 11 cats. Most cats had macroscopic, multifocal, subpleural lesions; inflammatory infiltrates, cholesterol clefts, and multinucleated giant cells were common. Ten cats had an underlying obstructive pulmonary disease that was the likely cause of EnLP. Lesions of EnLP were not considered to be severe enough or extensive enough to be the cause of death in any of these cats.

Conclusions and Clinical Relevance—EnLP is an uncommon respiratory tract disorder of cats with no pathognomonic clinical, laboratory, or radiographic findings. Although EnLP was not the cause of death in any of these cats, results of the present study do suggest that EnLP may be a marker for potentially severe underlying obstructive pulmonary disease. (J Am Vet Med Assoc 2000;216:1437–1440)

Pneumonia is defined as inflammation of the pulmonary parenchyma caused by bacterial, viral, fungal, protozoal, rickettsial, or parasitic infection; inhaled or circulating toxins or irritants; or noninfectious inflammatory or immune-mediated disorders. Lipid pneumonia is a type of irritant pneumonia characterized by patchy pneumonic consolidations secondary to accumulation of lipid, usually within macrophages. Lipid pneumonia is further classified as exogenous or endogenous on the basis of the source of lipid. Exogenous lipid pneumonia is uncommon in human beings and only isolated cases involving dogs, cats, cattle, and horses have been reported. In human beings, exogenous lipid pneumonia is most often a result of aspiration of mineral oil preparations administered for treatment of chronic nasal disease or gastrointestinal disturbances. In cats, exogenous lipid pneumonia has been associated with use of petroleum-based products for treatment of hairballs and constipation.

Endogenous lipid pneumonia (EnLP) is more common in human beings than is exogenous lipid pneumonia, and cases of EnLP involving cats, dogs, raccoons, opossums, ferrets, llamas, laboratory rats, and mice have been reported. In human beings, EnLP most commonly results from pneumocyte injury associated with obstructive pulmonary neoplasia or other types of obstructive pulmonary disease. Pneumocyte injury leads to cellular degeneration, causing release of membrane cholesterol and cholesterol esters and proliferation of type II pneumocytes, resulting in overproduction of surfactant with a high cholesterol content. These lipids are phagocytosed by macrophages, leading to the classic histologic pattern of alveoli filled with foamy macrophages. A small subset of human beings with EnLP have underlying disorders of lipid storage or metabolism characterized by high serum lipid concentrations and lipid deposition in multiple organs, including the lung. Endogenous lipid pneumonia may also be idiopathic in human beings.

To our knowledge, no studies of the features of naturally developing EnLP in cats have been published. The purposes of the study reported here were to determine clinical signs, radiographic and histologic abnormalities, and concurrent diseases in cats with EnLP and to determine the pathologic importance of EnLP in cats.

Criteria for Selection of Cases

Medical records of all cats necropsied at the University of California-Davis Veterinary Medical Teaching Hospital between January 1985 and September 1998 in which a diagnosis of lipid pneumonia was made were reviewed. Cats were included in the study only if medical records were complete and the diagnosis of EnLP was confirmed by means of histologic examination of necropsy specimens by a single pathologist. Endogenous lipid pneumonia was diagnosed histologically if aggregates of lipid-laden macrophages were seen within the airways and did not appear to be responding to a primary insult. Twenty cats, 18 of which met the criteria for inclusion in the study, were identified with this initial search. An additional search of medical records for the same period was performed to identify all cats for which...
a diagnosis of pneumonia was made, because necropsy records for cats with histologic evidence of lipid pneumonia may have lacked the key word “lipid pneumonia” used for the initial search. Pathology reports for 155 cats were reviewed, and 6 were confirmed to have EnLP and met the criteria for inclusion in the study.

Procedures

Information collected from the medical records included signalment, body weight, clinical signs, and results of clinicopathologic tests. Lateral and dorsoventral radiographic projections of the thorax were reviewed by a board-certified radiologist (VFS). When serial thoracic radiography was performed, radiographs obtained closest to the date of necropsy were reviewed. Concurrent systemic diseases were identified from clinical data and results of postmortem examination.

All histologic specimens were reviewed, and lesions were classified according to distribution (multifocal, focal, or diffuse), size (microscopic or macroscopic), location (subpleural, parenchymal, or perivascular), and special features (cellular infiltrates, cholesterol clefts, multinucleated giant cells, necrosis, fibrosis, or mineralization). The underlying cause of EnLP was identified, if apparent.

Results

Of the 24 cats that met the criteria for inclusion in the study, all were found to have endogenous, rather than exogenous, lipid pneumonia. Mean ± SD age of the cats was 8.9 ± 3.7 years (range, 1 to 15 years). Twelve cats were castrated males, 11 were spayed females, and 1 was a sexually intact female. There were 8 domestic shorthairs, 7 domestic longhairs, 3 American Shorthairs, 2 Manx, 1 Persian, 1 Himalayan, 1 Siamese, and 1 Russian Blue. Mean ± SD weight of the cats was 4.1 ± 1.4 kg (9.0 ± 3.1 lb; range, 2.0 to 7.0 kg [4.4 to 15.4 lb]).

The most common clinical abnormalities were lethargy (22 cats), anorexia (22), and weight loss (16). Sixteen cats had clinical signs referable to respiratory tract disease, including tachypnea or dyspnea (11 cats) and coughing (8). Results of clinicopathologic tests were nonspecific and likely reflected concurrent disease. There was no evidence of gross lipemia in any blood sample, and serum cholesterol concentration was within reference limits in the 12 cats in which it was measured. Two of 7 cats tested were positive for FeLV antigen; both cats tested were negative for feline immunodeficiency virus antibody. Arterial blood gas partial pressures were measured in 4 cats; $P_{\text{aO}_2}$ were 31, 60, 70, and 70 mm Hg, and $P_{\text{aCO}_2}$ were 45, 40, 51, and 70 mm Hg. Pleural fluid from 6 cats was analyzed and was characterized as a modified transudate (4 cats) or chyloous effusion (2). One cat underwent bronchoscopy and bronchoalveolar lavage; results of cytologic examination of lavage samples were unremarkable, but bacterial culture yielded small numbers of mycoplasma. Cytologic evaluation of a percutaneous fine needle aspirate of the pulmonary parenchyma revealed cryptococcal pneumonia in 1 cat. An ante-mortem diagnosis of EnLP was not made in any cat.

Thoracic radiographs from 11 cats were available for review. The most common radiographic abnormalities were pleural effusion (5 cats), diffuse pulmonary interstitial or bronchointerstitial pattern (4), multifocal pulmonary infiltrates with or without confluence near the pulmonary hilus (3), discrete pulmonary nodules (2), and pulmonary hyperinflation (1). For 2 cats, thoracic radiographs were interpreted as normal.

Most cats (18) had a multifocal distribution of histologic lesions; 3 had focal lesions and 3 had diffuse lesions. In 13 of 24 cats, lesions were macroscopic. Macroscopic lesions were ≤ 1 cm in diameter in 9 cats and > 1 cm in diameter in 4 cats. Lesions of EnLP were subpleural in 19 cats (Fig 1), parenchymal in 9, and perivascular in 3; 6 cats had lesions in more than 1 location. Cellular infiltrates other than lipid-laden macrophages were common (16 cats), with most cats having a mixed pattern of inflammation consisting of lymphocytes (11), neutrophils (11), and plasma cells (6). Special features that were identified included cholesterol clefts (12 cats; Fig 2), multinucleated giant cells (12), necrosis (6), fibrosis (3), and mineralization (2).

Ten cats had an underlying obstructive pulmonary disease that was the likely cause of EnLP, including...
noninfectious inflammatory disease in 4 cats (bronchitis and bronchiectasis, chronic bronchitis, necrotizing bronchiolitis, and uremic pneumonia), pulmonary arterial thrombosis in 3 cats, neoplasia in 2 cats (pulmonary carcinoma and metastatic ileal carcinoma), and cryptococcal pneumonia in 1 cat. Other pulmonary diseases that were identified that did not appear to be the cause or a result of EnLP included pulmonary edema (3 cats), atelectasis (2), pleuritis (2), pulmonary emphysema (1), pulmonary thromboembolism (1), interstitial pneumonia (1), and interstitial fibrosis (1).

The most common concurrent systemic diseases identified included neoplasia (12 cats), renal disease (9), hepatic disease (8), pancreatitis (4), and cardiac disease (4). Diabetes mellitus, hyperthyroidism, enteritis, trauma, neurologic disease, and FeLV-related bone marrow dysplasia were also identified. In all cats, EnLP was considered to be an incidental finding at the time of necropsy, as lesions were not considered to be severe enough or extensive enough to be the cause of death.

Discussion
Histologically, exogenous lipid pneumonia is characterized by large extracellular fat globules surrounded by phagocytic lipid-laden macrophages and multinucleated giant cells; whereas with EnLP, all lipid is confined intracellularly in foamy lipid-laden macrophages that fill the alveoli. Although exogenous lipid pneumonia can develop in cats secondary to aspiration of mineral oil administered for treatment of hairballs or constipation, a search of the records of all cats necropsied during a 13-year period at the veterinary medical teaching hospital failed to reveal any cats with exogenous lipid pneumonia. One possible explanation is that aspiration of mineral oil led to focal exogenous lipid pneumonia in lung lobes (presumably the dependent lung lobes) that were not examined histologically at the time of necropsy. It is also possible that exogenous lipid pneumonia is not fatal in cats and that over time, the extracellular fat globules dissipate.

The pathogenesis of EnLP is multifactorial, but ultimately, lesions develop secondary to injury to pneumocytes. Reported causes of EnLP in humans and animals include inhalation of noxious substances, deranged lipid metabolism, lipid storage diseases, fat emboli, hypophosphatemia, and feeding of diets deficient in pantothenic acid. Endogenous lipid pneumonia may also be idiopathic in humans. The most commonly identified cause of EnLP in human beings is airway obstruction secondary to neoplasia, although infectious and inflammatory obstructive diseases have also been reported to cause EnLP. Obstructive damage to pneumocytes results in degeneration of the cells and release of membrane cholesterol and cholesterol esters. Injury to type II pneumocytes also leads to overproduction of surfactant with a high cholesterol content. Subsequent phagocytosis of this lipid leads to accumulation of foamy macrophages in the alveoli, which incites an inflammatory response. Endogenous lipid pneumonia has been reported to develop in cats secondary to diseases causing airway obstruction, including bronchogenic carcinoma and bronchial dysgenesis. Ten of 24 (42%) cats in the present study had evidence of an obstructive pulmonary disease. In the remaining 14, however, a definitive cause of EnLP was not found. All cats had concurrent systemic illnesses; however, the role these diseases may have played in development of EnLP is unknown.

Most cats in this study were middle-aged to older cats, but cats of a particular breed or sex were not obviously over-represented. Lethargy, anorexia, and weight loss were the most common clinical abnormalities, and as is common in affected human beings, 16 cats had clinical signs suggestive of respiratory tract disease. Clinicopathologic abnormalities in these cats were nonspecific and likely reflected their concurrent diseases. In human beings, EnLP can be caused by disorders of lipid storage or metabolism, but such conditions were not recognized in cats in the present study. Hepatic lipidosis was identified in 4 cats; however, lipid derangements leading to fat deposition in cats with hepatic lipidosis are confined to hepatocytes.

Diagnostic tests specific for respiratory tract disease were performed in only a few cats in this study, making it difficult to draw conclusions about ante-mortem diagnosis of EnLP in cats. Diagnosis of lipid pneumonia in human beings relies heavily on radiography, evaluation of sputum and bronchoalveolar lavage samples, and advanced diagnostic imaging procedures, such as computed tomography and magnetic resonance. Cytologic evaluation of bronchoalveolar lavage fluid may reveal macrophages containing vacuoles that stain positive for lipid, using Sudan black, Sudan red, or oil red O stains. In a retrospective study of 44 human patients with EnLP, the diagnosis was confirmed by use of bronchoalveolar lavage alone in 77% and by bronchoalveolar lavage in combination with transbronchial biopsy in 97%. Endogenous lipid pneumonia was not diagnosed prior to death in any of the cats in the present study, possibly because bronchoalveolar lavage was performed infrequently and because of the low index of suspicion for this disease.

Results of thoracic radiography were abnormal in 9 of 11 cats in the present study. This was consistent with results for human beings, in which thoracic radiographs were abnormal in > 28 of 33 (85%) patients. Patients for which results of thoracic radiography were normal typically had only mild or microscopic disease. However, although radiographic abnormalities are common, findings were not pathognomonic in human beings with EnLP or in the cats described in the present report. The most common radiographic pulmonary abnormalities reported for affected human beings are generalized diffuse interstitial to fine nodular opacities, frequently with an alveolar pattern, with or without a mass effect. These radiographic patterns develop as a result of initial alveolar filling, followed by movement of lipid-laden macrophages into the interstitium and the resultant fibrotic reaction. The radiographic appearance of nodules or masses has been documented to be a result of chronic fibrosis.

To the authors’ knowledge, this is the first study to characterize histologic features of naturally developing EnLP in cats. Most cats had macroscopic, multifocal, subpleural lesions. Obstructive pulmonary disease leads to defects in clearance from the lungs, with sub-
sequent stasis of macrophages in a subpleural location.\textsuperscript{7} Damage to pneumocytes allows for release of lipid from degenerating cells, which acts as a direct irritant to the lung, triggering an inflammatory response.\textsuperscript{8,9} Inflammatory infiltrates consisting of neutrophils, lymphocytes, and plasma cells were found in 16 (67%) cats in the present study. Injury to type II pneumocytes leads to excessive production of surfactant with a high cholesterol content, which, following phagocytosis of surfactant by macrophages, results in intracellular cholesterol crystals or clefts.\textsuperscript{10-12} Twelve (50%) cats in the present study had evidence of intracellular cholesterol clefts. Cholesterol crystals are irritating and stimulate development of multinucleated giant cells,\textsuperscript{13} which were also detected in 12 (50%) cats.

Ten (42%) cats in the present study had an underlying pulmonary disease that was the likely cause of EnLP. In human beings, obstructive neoplasia is the most common cause of EnLP, whereas in these cats, noninfectious inflammatory disease and pulmonary arterial thrombosis were most commonly identified. This is consistent with isolated reports of EnLP in cats\textsuperscript{18,19} in which obstructive or inflammatory pulmonary lesions were implicated in the development of EnLP. It is unknown if treatment or removal of a focal obstructive lesion would have caused eventual resolution of EnLP in these cats. In human beings, focal areas of EnLP are usually removed surgically, along with the inciting obstructive lesion, because carcinomas can develop in areas of chronic EnLP.\textsuperscript{15} Idiopathic EnLP may resolve with steroid treatment in humans.\textsuperscript{16}

Although cats included in this study were selected on the basis of a diagnosis obtained at necropsy, EnLP was not the cause of death in any of these cats. In addition, EnLP was not diagnosed prior to death in any of these cats. Results of the present study do suggest, however, that EnLP may be a marker for potentially severe underlying obstructive pulmonary disease in cats.

References