CHARACTERIZATION OF BRONCHOINTERSTITIAL DISEASE IN CATS: SPONTANEOUS DISEASE & EXP MODELS

A. Ray Dillon, DVM, MS, MBA; DACVIM (IM)
Auburn University, AL

INTRODUCTION

A clear understanding of the nature of feline lower respiratory disease has been lacking. Based on response to therapy, the general approach to a chronic coughing cat with or without intermittent dyspnea has been to rule out obvious infectious agents and treat with a combination of corticosteroids via different routes with bronchial dilating agents. Thoracic radiographs demonstrating a "bronchial pattern" and a response to therapy resulted in a tentative diagnosis of feline asthma. On examination of bronchial alveolar lavage fluid, an increase in percent eosinophils tended to reinforce the tentative diagnosis. The gradual increase in severity or frequency of clinical signs resulted in a confirmation of the need for long term management and often maintenance medications.

SPONTANEOUS DISEASE

A prospective study of first time coughing/dyspneic client owned cats over 6 months of age was conducted in 14 practices in 212 cats over a 2 year time. At presentation, 45 days and 60-90 days after initial presentation thoracic radiographs, CBC, heartworm antigen and antibody were collected. Practitioners treated clients as per their normal approach with most all receiving corticosteroid medications resulting in abatement of signs. All data analysis and radiographs interpretations were blinded. The original intent to identify the incidence of feline *D. immitis* infection was supported by the finding that approximately 40% were antibody positive at one of the 3 observation point. However, a pattern emerged of cats which were presented for coughing but the antibody titer often became negative even as lung lesions persisted for 90 days. Likewise, of 41% of cats with normal lungs on initial presentation, 43% demonstrated bronchointerstitial changes at later examinations even though asymptomatic. Of cats with lung bronchial scores > 1 (0-3 scale) on presentation, at 45 or 60-90 days later the disease was unchanged (54%), improved (16%), or became more severe (30%). Clinical outcomes were unrelated to radiographs, CBC, or heartworm antibody/antigen test results. Thus, these results lead to the consideration of a transient immature heartworm infection with lung disease (later defined as HARD) which does not develop into an adult heartworm.

This consideration was further bolstered by histopathologic necropsy studies from shelter cats where a high incidence of bronchial disease and pulmonary arterial changes were noted without adult heartworms at necropsy and a negative antibody titer. The high incidence of pulmonary arterial disease was assumed to be associated with prior heartworm infections.

To investigate this further, 120 clinically normal shelter cats were studied using thoracic radiographs, HW serology, fecal examination, and necropsy and lung histopathology at fixed infusion pressure. Included in the radiographic data was the finding that 40 % of the cats had bronchial grades of > 2 (scale 0-3) and 95% had grades of > 1. Prominent caudal pulmonary arteries (>2, scale 0-3) were noted in 50%. Adult heartworms were recovered in 3 cats, 8 were antigen positive, and 29 antibody positive. Greater than 20 % of the pulmonary arteries were abnormal (histologic thickened wall/lumen ratios) in 47% of cats. The correlation of radiographic bronchial scores of > 2 was most consistently associated with alveolar and interstitial proliferation with or without airway lesions (bronchioles or bronchi). The high incidence of abnormal radiographic lung patterns and interstitial lesions with mixed bronchial and pulmonary arterial changes was not consistent with *D. immitis* being the only etiology.

Thus many clinically normal cats had radiographically abnormal "bronchial patterns" which were not directly related to histologic evident of airway disease but instead more closely correlated with interstitial disease. The interstitial densities added to the radiographic peribronchial contrast around unaffected air filled bronchioles. The result was "railroad tracks" and "donuts". This concept was later reinforced by CT studies in experimental models.

Confusion of these and other studies and the lack of correlation of spontaneous disease with radiographic patterns, histologic lesions, and other diagnostic modalities opened the consideration of different causes of feline lung disease. The use of only radiographs, BALF, and serology to accurately diagnosis and treat active lung disease is improbable.

EXPERIMENTAL MODELS

For the purpose of this presentation, the extensive evidence and modeling of induced feline bronchial reactivity via hypersensitization will not be discussed. However, the recent studies of parasitic induced lung disease provide direct clinical relevance. Evaluated in total, a different picture is emerging relative to feline lung disease. Consideration of these studies indicate that an eosinophilic BALF has multiple clinically relevant causes associated with common parasites.

Eosinophilic BALF cytology of > 16% of nucleated cells was consistently observed:

1. Adult *D. immitis*
2. Immature *D. immitis* w/ no adult development (HARD)
3. D. *immitis* when preventative (selamectin) initiated 1 mo post L3 infection

4. *D. immitis* even when preventative (selamectin) initiated 1 mo prior to L3 infection (transient)
5. *T cati* infection per os which developed intestinal worms (both kittens & adults)
6. *T cati* infection per os which never developed intestinal worms (both kittens & adults)
7. *T ca*ti infection per os even when moxidectin initiated 2 month prior to infection
8. *Aeolurostrongylus* infection

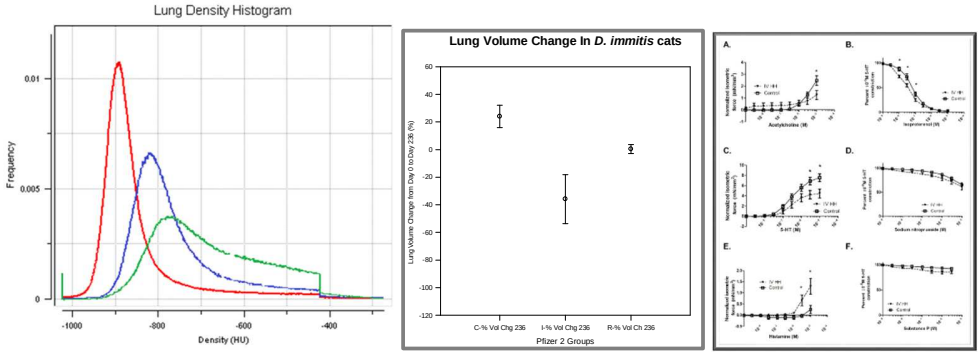
It should be noted that all in the above list (except 3 & 4) are associated with a typical bronchial-interstitial lung pattern on thoracic radiographs, with the notable exception of *D. immitis* on preventative medications. Cats placed on preventative medications one month after infection may become antibody positive, but cats placed on prevention at least one month before infection will remain feline HW antibody negative.

***D. immitis* infection L3**

Various studies have long described significant lung parenchymal and bronchial changes associated with feline heartworm disease. The concept that it is only a pulmonary arterial disease is misguided. The evidence suggested in the field study of 212 cats suggested a transient heartworm infection which differs from the traditional thinking of feline heartworm disease being like canine heartworm disease where the adult is the primary clinical concern. The subsequent series of studies demonstrated that immature adults, which die and never develop, induce pulmonary parenchymal and interstitial disease (HARD) and a transient positive antibody titer. The high mortality of immature adults (2 ½- 4 months post infection) also accounts for lung disease in cats even if a couple of the immature adults survive to fully mature adults and live 3-4 years. Further, interstitial and pulmonary lesions were induced with only ultra-filtered heartworm homogenate over 14 days in the absence of significant bronchial lesions. The character of the parenchymal reaction was myofibrocyte proliferation in the alveolar struts and interstitial parenchyma. Consideration for the role of pulmonary intravascular macrophages (PIMs) to potentially capture and initiate this myofibrocyte proliferation has not been investigated. The interaction of the parasite and host is complex as it has been demonstrated that live adult *D. immitis* infections result in the down regulation of PIM. Cats with adult *D. immitis* and bronchial disease had blunting of the *in vitro* bronchial reactivity response of cats; and moreover blunting was also noted in cats administered only the filtered homogenate, in the absence of bronchial disease.

The bronchial and interstitial disease of HARDs and adult heartworm infection is histologically often unrelated to the location of pulmonary arteries. Homogenate induced interstitial disease enforces the concept that the interstitial and bronchial disease is not an extension of the pulmonary arterial lesion, may be related to soluble products of heartworms, and may or may not be related to PIM activation. The result of *D. immitis* infection is not only a transient eosinophilic dominated airway reaction, limited ability to bronchodilate or constrict. The interstitial, peribronchial, and pulmonary arterial myocyte proliferation was noted even in lobes not associated with the physical presence of an adult worm. The significant pulmonary myocyte proliferation is not associated with cor pulmonale in cats.

Feline heartworm disease ultimately results in lung parenchymal myofibrocyte proliferation, unresponsive diseased airways, but also a restrictive lung disease. CT of the thorax of cats and 3D reconstructions have demonstrated not only a decrease in total air capacity but also a shift in the densities towards more dense tissues. The analysis of the density of Hounsfield Units can only be calculated with a fixed controlled inflation positive pressure, as the use of estimated tidal volumes based on body weight create nonphysiologic tissue pressures in restrictive lung disease.



The graph (left above) is total lung CT 3D reconstructed histogram of a *D. immitis* infected cat at baseline (red), 4 month pi (blue), and 8 months pi (green). Demonstrates the shift in percent of lung from the air density (-900 HU) towards more of the interstitial densities (-600 to -700 range). The middle graph demonstrated the mean of the cats in each group where baseline lung volume is compared to 8 months post infection. Control cats (C= first bar) had over 20% increase in total lung over time, *D. immitis* infected cats (I=middle) had about 30% decrease in lung volume, and selamectin pretreated cats (R=right) were unchanged. The *in*

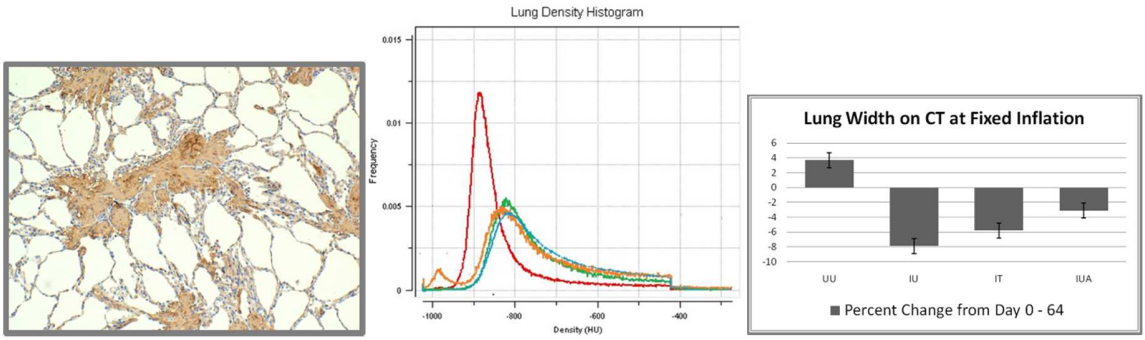
vitro response (right figure) of isolated bronchial rings demonstrated blunted relaxation and constriction even in cats only administered homogenate.

***T. cati* infection per os**

Lung disease and pulmonary artery hypertrophy in cats has been induced by *T. cati* but without careful clinical examination. Recent studies are reason for serious concern to practicing veterinarians. Approximately 25% of shelter cats from all regions of U.S. are shedding *T. cati* eggs in the National Parasite Survey. *T. cati* eggs are viable for years and are found in high concentration in the soil in most of the world. The orally ingested eggs from soil or grooming develop quickly and the L3 penetrate the GI, migrate through the liver, then the lungs, coughed up and swallowed to become adult worms. This migration does not occur when infections is via paratenic hosts.

In a series of *T. cati* infected kitten and adult cats, lung lesions were demonstrated at the first CT time point of 10 days after a single oral dose. The lung injury became more severe over time and repeat infections and was independent of whether GI adults ever developed or not. Thus a fecal was not a valid test for ruling in or out *T cati* induced lung injury. Cats with *T cati* lung injury can be negative on repeated fecal examinations. Adult cats and kittens developed the same severity of lung injury and of more concern was the finding that even pretreatment with moxidectin/imidacloprid for 2 months before infections did not prevent the same degree of lung injury. Thus cats (adults and kittens) infected with oral *T. cati* eggs will develop lung injury, even if on preventative medications. Preventative medications are labeled to prevent the adult stages of the roundworm infection, not the migratory stages. The rapid transient of the L3 from the stomach through the liver and lung would appear to be completed by 7 days in cats. The ability of medications to abbreviate this migration prior to reaching the lungs is being investigated but offers no current practical solution. Thus, outdoor cats can be expected to develop some degree of pulmonary parenchymal disease over the course of their routine exposure.

The nature of the lung injury from *T. cati* is difficult to distinguish from *D. immitis* infection. On radiographs, both develop the typical "bronchial" pattern which, based on CT and histopathologic correlation is the involvement of the interstitial tissue. On radiographs, the enlargement of the caudal pulmonary artery is just as prominent in *T. cati* infections as it is in *D. immitis* infections. Histologically, the myocyte proliferation was marked in the alveolar interstitial and the pulmonary arterial, but the airway proliferation is less severe than in *D. immitis* infected cats. It should be noted that *Aelurostrongylus* infection in cats creates similar radiograph patterns but pulmonary arterial enlargement is not prominent and lymph nodes may be enlarged. The *in vitro* bronchial ring reactivity was normal in all infected cats even with bronchial disease, as compared to the blunted response in *D. immitis* cats with adults or even just the homogenate.



The nature of parenchymal myofibrocyte (SMA staining fibrocytes, left figure) proliferation can be severe and be "honey combed" on CT. Sequential (over time) 3D CT lung density histogram (middle figure) demonstrates a shift away from air (-845 to -900 at baseline, red) towards tissue densities (gold, blue, green). The result is a restrictive lung disease and decrease in the total lung volume (right figure) where endpoint volume is compared to baseline. All infected groups (IT=treated kittens, IU=untreated kittens, IUA=adults) compared to normal controls (UU=uninfected kittens). All infected groups demonstrated abnormal CT, bronchial pattern on radiographs, and eosinophilic BALF. The preventative provided no significant protection against the lung injury.

CLINICAL IMPLICATIONS

Based on these data, transient unsuccessful infections from *D. immitis* can result in HARDs and oral *T. cati* infection in adult or kittens, even on appropriately prescribed and administered preventatives, will result in radiographic evident bronchial patterns and eosinophilic BALF. *Aeolurostrongylus* infection can also mimic this presentation. Common to these infections is the myofibrocyte interstitial proliferation resulting in restrictive lung disease. More confusing is the finding that both *D. immitis* and *T cati* can induce radiographically evident enlarged pulmonary arteries. Although after evaluating many CTs of these experimentally

infected cats and clinical experience, there is a subtle different pattern of increased interstitial densities between the *D. immitis, T. cati, and A abstrusus*, but this is not a consistent nor uniformly distributed through all lung and the patterns vary with the stage of the infection. The heartworm antibody and fecal examination offer no absolutes on ruling in or ruling out prior disease. Although the lung disease from *D. immitis* can be prevented by initiating heartworm preventatives before possible exposure to infective mosquitoes, there is currently no practical preventive medication which is believed to abbreviate the lung migration of *T cati* larvae. Adult cats and kittens on or off preventatives would be expected to give additive insults to the lung with repeated exposure. Although there are limited long term studies, it would appear that the myofibrocyte proliferation of interstitium and pulmonary arteries is long term and may not be reversible.

Given the wide distribution of *D. immitis* dogs and mosquito vectors and ubiquitous presence of *T. cati* eggs in the environment, the clinician can assume that many client cats have been infected, subclinically, with these parasites and have subsequent radiographic "bronchial" patterns which become the background on which compounding disease or infection induces clinical signs. When presented for clinical disease, a clinician must consider that the thoracic radiographs may represent disease which has been present for months or years and may or may not be related to present clinical signs.

References: McCall JW et al, AmHWSocProc 1992:71. Dillon AR, VetClinNA 1984;(14):1185. Holmes RA et al, AmHWSym 1992;81. Brawner, B et al Vet Therap: Res Applied Vet 2000;(1,2):81. Robertson, C et al Vet Therap: Res Applied Vet Med 2000;(1,2):88. Dillon, AR et al Vet Therap: Res Applied Vet Med 2000;(1,3):176. Browne LE AmJVetRes; 2005;(66);1544. Dillon AR et al, Vet Par 2008;(158):171. Blagburn BL et al, Vet Med; 2007; (102);7. Wooldridge A, AmJVetRes; 2012;(73,3):439. Dillon AR et al. VetPar 2014;(206,1);14. Venco L et al, VetPar 2008;(158,3);232. Dillon AR et al, VetPar 2013(193:4);413. Dillon AR et al, Vet Par 2014; (206,1):24. Dennler M et al VetRadUlta 2013;(54,5):459.