2017 Northeast Veterinary Pathology Conference – Joint Pathology Center April 1-2

Case Submission Form

NEVPC CASE #12

IDENTIFICATION NUMBER ON SOURCE MATERIAL: Cornell University 6190-17

INSTITUTIONS: Cornell University, College of Veterinary Medicine, Department of Biomedical Sciences, Section of Anatomic Pathology, Ithaca, NY

SIGNALMENT: 12 year old, male castrated, Shih-Tzu dog

HISTORY: A 12-year-old, male castrated, Shih Tzu dog presented to his primary care veterinarian for a one day history of inappetence and an increased respiratory rate en route to the veterinarian. Thoracic radiographs demonstrated an increased broncho-interstitial pattern. The dog was then transferred to a referral hospital for further evaluation and treatment. Additional radiographs confirmed heavy broncho-interstitial pattern and demonstrated possible right ventricular enlargement. Bloodwork revealed an inflammatory leukogram, mild hepatic enzymopathy, hyperglycemia, hypoalbuminemia, and hyperphosphatemia. The patient was treated with oxygen therapy, a single dose of furosemide, Baytril, and insulin. He developed progressive hypoglycemia and required dextrose supplementation overnight. During treatment the patient developed abdominal distension and abdominal radiographs showed severe gastric distension with poor abdominal serosal detail.

The patient was referred to the Cornell University Hospital for Animals. Intake blood work demonstrated a mixed acid base disturbance (primary respiratory alkalosis), mild to moderate hypoalbuminemia, mildly elevated ALT, mildly elevated ALP, hyperglycemia, and a mild inflammatory leukogram (leukocytosis with a left shift).

A computed tomography (CT) revealed diffuse bronchial thickening, interstitial changes, probable septal thickening of the pulmonary lobules, and “honeycombing” around the pleural margins. The right cranial lung lobe was the most affected. The pulmonary arteries were also enlarged. The patient arrested under anesthesia following the CT.

Additional prior medical history includes being managed for diabetes mellitus with 6.5 units of insulin-NPH (Humulin-N) for unknown duration, bilateral cataracts, keratoconjunctivitis sicca and atopic dermatitis. The dog was also suspected of having Cushing’s, but the endocrine testing is reported to have been inconclusive as he had a normal low-dose dexamethasone test. In October 2016, the patient had an episode of diabetic ketoacidosis (DKA) with pancreatitis and at that time gastric wall thickening with layering changes was noted on ultrasound.

GROSS FINDINGS:

Diffusely the lungs were grossly abnormal. The right cranial lung lobe was most severely affected and was diffusely pale tan to white and slightly firm and contracted with rounded, nodular margins. The left cranial lung lobe is similarly contracted with a remodeled periphery. The caudal 50% of the right and left caudal lung lobes are mottled tan to white with indistinct coalescing, firm, nodular regions. The remaining lung lobes are mottled tan to red with multifocal firm regions. On section, all lung lobes have multifocal to coalescing, poorly defined, tan to white

regions, predominately along the margins. The tracheobronchial lymph nodes are mildly prominent, the largest of which is 1.2 cm x 0.4 cm x 0.2 cm. The pulmonary arteries are prominent and mildly dilated up to three times normal.

Other significant gross findings included moderate cardiomegaly (1.48% of body weight) with right ventricular dilation (cor pulmonale), mild cranial vena cava dilation, and multifocal acute infarcts in both kidneys.

HISTOPATHOLOGIC FINDINGS:

Lung: All sections representing different lung lobes show similar but variable changes. Predominately subpleural, approximately 10-40% of the lung parenchyma is remodeled by multifocal to locally extensive regions of honeycombed alveolar septa which are mildly to markedly expanded by nodules and sheets of dense eosinophilic fibrillar collagen along with fusiform and plump spindle cells (fibroblasts). The thickened septa are often lined by attenuated or cuboidal epithelial cells occasionally crowded in multiple layers (type II pneumocytes). In some regions, there is loss of alveolar spaces and consolidation of the parenchyma with contraction to the lobe. Multifocally, alveolar spaces contain small to moderate numbers of alveolar macrophages, small amounts of pale, homogenous, eosinophilic material (edema), homogenous to fibrillar, eosinophilic protein material and rare, small, basophilic mineralized foci. In one section, at the lobe periphery, is a locally extensive region where alveoli contain small accumulations of an amorphous, homogeneous, basophilic, hyaline extracellular material (pulmonary hyalinosis) surrounded by small numbers of macrophages and reactive fibroblasts. Approximately 10% of another section has a locally extensive region of alveoli filled with moderate numbers of neutrophils admixed with a few alveolar macrophages and occasional hemorrhage. Small numbers of lymphocytes and plasma cells infrequently infiltrate the interstitium. Throughout the sections, the walls of small, medium, and large pulmonary arteries are thickened vessel walls and correspondingly the lumina are narrowed. Predominately in the large vessels, the media and intima are expanded by mucinous deposits with fragmentation of the elastin fibers and disorganization of the internal elastic lamina. Multifocally, there is mild to moderate intimal proliferation. Diffusely, the pleural is mildly expanded approximately 3x normal by increased connective tissue.

Special histochemical Stains:

The following histochemical stain was applied to the lung:

Masson's Trichrome (for collagen): The additional stain highlights the increased collagen within septa, predominately subpleural and diffusely along the serosal surface. Also, this stain demonstrates the expansion the media and intima of large vessels with fragmentation of elastin, and highlights the occasional smaller vessels occluded by intimal proliferation.

Immunohistochemical Stains:

The following immunohistochemical stain was applied to the lung:

Smooth muscle actin (for muscle): Multifocally within the regions of fibrosis and small, nodular aggregates expanding alveolar septa are cells with positive cytoplasmic immunoreactivity. Positive and negative controls are appropriate.

MORPHOLOGIC/ETIOLOGIC DIAGNOSES:

Lung:

1) Moderate, multifocal to locally extensive, interstitial and subpleural fibrosis with type II pneumocyte hyperplasia, alveolar proteinosis and locally extensive pulmonary hyalinosis

2) Moderate, multifocal, chronic, arterial medial and intimal hypertrophy and fibrosis (arteriosclerosis)

3) Mild, locally extensive, acute, neutrophilic alveolitis

DISCUSSION:

Histologic examination of the lungs revealed patchy, often subpleural regions of interstitial fibrosis with “honeycombing”, type II pneumocyte hyperplasia, occasional fibroblastic foci, mild smooth muscle hyperplasia, and frequent distortion of the alveolar architecture with contraction of some lung lobes. Multifocally, there is also evidence of protein rich fluid accumulation in alveolar spaces and a locally extensive region of pulmonary hyalinosis. In one section, there is accumulation of neutrophils within alveolar spaces, which likely developed secondary to the interstitial lung changes. Ultimately, the gross and histologic findings in conjunction with the clinical picture are consistent with interstitial lung disease or idiopathic pulmonary fibrosis.

In dogs, idiopathic pulmonary fibrosis (IPF), which is one form of canine chronic interstitial lung disease, is most commonly reported in West Highland White terriers and thus the described histopathologic features in dogs are predominately in this breed. However, IPF has been reported in other breeds including Staffordshire bull terriers, Schipperke and a bull terrier (Heikkila-Laurila HP et al, 2014; Lobetti RG et al, 2001), as well as cats (Cohn L et al, 2004). The Shih Tzu may also be breed predisposed to IPF.

In humans, IPF can be separated into two main forms, usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). UIP is characterized by patchy subpleural or paraseptal regions of interstitial fibrosis with “honeycombing”, fibroblastic foci, minimal inflammation, smooth muscle hyperplasia, type II pneumocyte hyperplasia and occasional bronchial metaplasia of alveolar epithelium. NSIP is characterized by relatively diffuse interstitial fibrosis with mild to moderate inflammation (Cavazza A et al, 2010; Myers JL et al, 2009). West Highland White terriers have been reported to have features of both usual interstitial pneumonia and non-specific interstitial pneumonia (Syrja P et al, 2013). The patchy, often subpleural pattern of fibrosis in our case is more consistent with the UIP variety of IPF.

In humans, idiopathic pulmonary fibrosis is suspected to arise secondary to chronic insult to alveolar epithelium, with a subsequent dysregulated wound healing and the excessive accumulation of extracellular matrix (Barratt S et al, 2014; Heikkila-Laurila HP, 2014). While the exact etiopathogenesis of idiopathic pulmonary fibrosis in humans and dogs is unknown, it is likely multifactorial with genetics, environmental factors, infectious processes, drug reactions, toxin exposure, and connective tissue disorders proposed as causes or risk factors (Cavazza A et al, 2010; Heikkila-Laurila HP, 2014). Because idiopathic pulmonary fibrosis is a chronic, often progressive disease, determining and underlying inciting process, such as infections and irritants, can be difficult or impossible.

In the lungs of this dog and also within the major vessels of the heart, there is thickening of vessel walls with variable disruption of the elastin fibers. These changes are considered secondary/ related to the etiology of pulmonary fibrosis; most likely, these changes are secondary to altered blood flow and elevated pulmonary vascular resistance. Interestingly, the dysregulated wound healing often suggested as part of the pathogenesis of idiopathic pulmonary fibrosis, could also result in aberrant microvascular and macrovascular remodeling (Barrat S et al, 2014). However, the sequence of pulmonary damage and vascular changes in idiopathic pulmonary fibrosis is unknown and an area of active research.

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