Diagnostic Exercise

From The Davis-Thompson Foundation*

Case # **277**; Month: **March**; Year:**2026**

Answer sheet

Title: Pulmonary vascular amyloidosis in an aged dog

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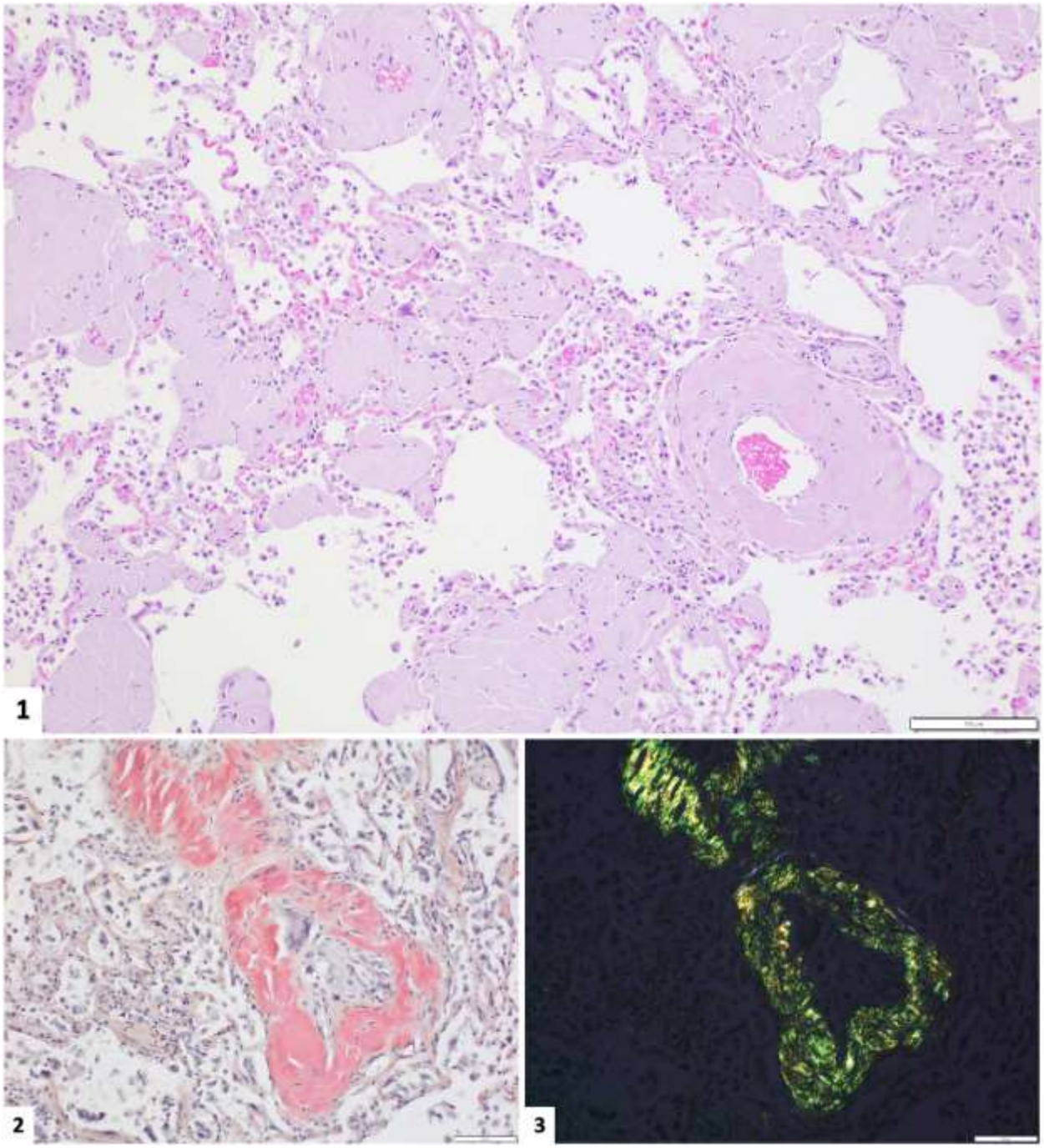
History: The carcass of a 14-year-old, female Boston Terrier was submitted for necropsy. The clinical history for the last year was dominated by recurrent and progressive episodes of dyspnea, stertor, and tachypnea. The patient had a prior history of a grade 3 cutaneous mast cell tumor that was excised years ago. Clinical investigations during the dog's life included thoracic radiographs, which revealed a mild patchy interstitial pattern and tracheal collapse. The owner declined blood analysis and other diagnostics on several occasions due to financial constraints. The final episode was characterized by a severe respiratory crisis with oxygen saturation below 90%. Given the poor prognosis and the animal's deteriorating condition, humane euthanasia was performed.

Necropsy findings: The carcass was received frozen. The dog was in good body condition. The atrioventricular valves had mild, white, nodular thickening (endocardiosis). The liver was subjectively enlarged with rounded margins and contained a single mass approximately 7 cm in diameter. The rest of the hepatic parenchyma showed no significant gross abnormalities. No other gross lesions were observed in the remaining organs. Samples were collected from the lung (Figs. 1-3), liver, kidney, spleen and other internal organs.

Histopathology



Histologic description:

- **Lung (Fig. 1):** Diffusely, the pulmonary interstitium, including the alveolar septa and the walls of small and medium-caliber pulmonary arteries, is markedly expanded by an amorphous, amphophilic, acellular, proteinaceous material. This material is predominantly located in the tunica media of the vessels. Toegether with these deposits, there are hyaline membranes, intra-

alveolar fibrin, type II pneumocyte hyperplasia, and interstitial inflammatory infiltrates composed of lymphocytes, plasma cells, and macrophages.
- To characterize the nature of the proteinaceous material observed, a Congo red stain was performed. Under bright-field microscopy, the amorphous material deposited in the pulmonary interstitium and vascular walls stains an intense **orange-red** color **(Fig.2)**. When the same sections are examined with polarized light, this material exhibits the **apple-green birefringence (Fig.3)**. These findings confirm that the deposited material is amyloid.

Other histopathology findings (not included):

- **Kidney:** A moderate to marked membranoproliferative glomerulonephropathy is identified, characterized by mesangial thickening and proliferation of mesangial/endothelial cells. Additionally, multifocal, segmental to global glomerular lipoidosis is observed. The interstitium has mild lymphoplasmacytic infiltrates and occasional fibrosis.
- **Liver:** In one section, a poorly demarcated, unencapsulated mass composed of cords of well-differentiated hepatocytes is observed, consistent with a hepatocellular adenoma. The remaining parenchyma shows marked lipid-type vacuolar degeneration of hepatocytes.

Morphologic diagnosis:

1. **Lung:** A. Pulmonary amyloidosis, severe, diffuse, with congophilic material deposited in the pulmonary vasculature, and B. interstitial pneumonia, marked, multifocal, with type II pneumocyte hyperplasia, fibrin in alveoli and moderate inflammation.

Other findings (not included):

2. **Kidney:** Membranoproliferative glomerulonephropathy, segmental to global, multifocal, and mild interstitial lymphoplasmacytic inflammation and fibrosis. No amyloid detected.
3. **Liver:** Hepatocellular adenoma, focal.

Etiology (lung): Deposition of an N-terminal fragment of the precursor protein Apolipoprotein A-I (ApoA-I).

Name the disease: Senile (or age-associated) pulmonary vascular amyloidosis.

Comments:

Amyloidosis is a group of diseases characterized by the extracellular deposition of misfolded proteins that form insoluble fibrils with a β-pleated sheet structure (4, 8). This unique conformation confers resistance to proteolysis and is responsible for its characteristic staining properties. A definitive diagnosis relies on demonstrating these structures with Congo red stain, which produces a characteristic apple-green birefringence under polarized light (3, 10). Electron microscopy is a valuable

confirmatory tool, revealing the ultrastructure of the deposit as non-branching fibrils of approximately 8-12 nm in diameter (3).

The classification of amyloidosis is based on the biochemical nature of the precursor protein (4). In animals, several types have been identified. Reactive (AA) Amyloidosis is the most common systemic form in dogs, where the precursor is the acute-phase protein serum amyloid A (SAA), produced in response to chronic inflammation or neoplasia (2, 8). AL Amyloidosis is derived from immunoglobulin light chains secreted by clonal populations of plasma cells and is rare in animals. Islet Amyloid Polypeptide (AIAPP) Amyloidosis is a localized form in the pancreas, mainly seen in cats (4).

The case presented corresponds to a distinct and much less common entity: Age-associated Apolipoprotein A-I (ApoA-I) amyloidosis (4, 5, 6). The pathogenesis of this condition is considered an age-associated ("senile") process. Its precursor, ApoA-I, is an essential component of the body, being the main protein of high-density lipoproteins (HDL). The amyloid is derived from a fragment of normal canine ApoA-I, indicating it is not a hereditary disease caused by a mutation, but likely the result of altered protein metabolism or clearance during aging (5). This distinct entity was first described in an aged dog in 1988 (7), with its specific precursor identified in 1992 (5). It affects dogs older than 10 years, with a reported prevalence of up to 22% in this population, and the deposits are located almost exclusively in the pulmonary vasculature (6). The massive infiltration of the lung parenchyma in this patient was a direct consequence of this process, causing a restrictive pulmonary disease and impaired gas exchange which explains the clinically observed dyspnea.

Currently, there is no treatment that can eliminate existing amyloid deposits. Therefore, in the case of ApoA-I amyloidosis, treatment is based on supportive care. This contrasts with AA amyloidosis, where management focuses on decreasing the levels of the precursor protein, SAA, which is an acute-phase protein (9). In AA amyloidosis, treatment is aimed at controlling the underlying inflammatory disease to halt precursor production. In the case of age-associated ApoA-I amyloidosis, this strategy is not feasible, as its precursor is not an inflammatory-response protein but rather a normal and essential component of the body.

Given the clinical presentation of an aged dog with progressive dyspnea and concurrent renal disease, several important differential diagnoses must be considered before arriving at the final diagnosis:

- **Pulmonary Thromboembolism (PTE):** This is the top differential in a dog with glomerular disease. The associated proteinuria can cause loss of antithrombin, leading to a hypercoagulable state (1, 2). In our case, necropsy and histopathology revealed no thrombi.
- **Metastatic Neoplasia:** Radiographically, pulmonary amyloidosis can mimic pulmonary metastases, often requiring a biopsy for a definitive diagnosis.
- **Systemic AA Amyloidosis:** Given the renal involvement, AA amyloidosis should be considered. However, in AA amyloidosis, renal pathology is typically the most severe and clinically significant finding (8), whereas in our case, the pulmonary pathology was the primary cause of the severe clinical signs.

The other findings (kidney and liver) are considered concurrent age-related changes. It is noteworthy that amyloid deposits were not identified in the kidney or spleen, and the hepatocellular adenoma is interpreted as an incidental finding common in aged dogs. These lesions were not the direct cause of the clinical crisis.

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*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation (DTF). These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the DTF website.

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