History

An 8-year-old 20.3-kg male castrated feral crossbreed dog, rescued by a local animal shelter, was presented to Ross University Veterinary Clinic for panting. All vitals and hematologic and serum chemical analysis results were within the reference range. Two weeks later, the dog was presented again for evaluation of difficulty breathing, nonproductive cough, and inappetence.

Clinical and Gross Findings

In the past 4 months before the last consultation, serial hematologic and serum chemistry analysis during routine checkups showed a combination of mild mature neutrophilia (13.44 X 10^3 neutrophils/μL; reference interval, 3.00 X 10^3 to 12.00 X 10^3 neutrophils/μL), mild nonregenerative anemia, and mild hyperglobulinemia (5.6 g/dL; reference interval, 2.3 to 5.2 g/dL). On a serologic qualitative test (Snap 4Dx Plus; Idexx Laboratories Inc), the sample was negative for all 4 targets: *Dirofilaria*, *Borrelia*, *Ehrlichia*, and *Anaplasma*. On physical examination of the most recent consultation, the dog was depressed with a lowered head carriage and showed signs of dyspnea and abdominal breathing. Auscultation revealed muffled heart sounds. Thoracic radiographs showed loss of silhouette sign, and nodular interstitial pattern of the lungs. After thoracocentesis, which drained out approximately 1.15 L of serosanguineous fluid from each side, a persistent opacity was noted in the left caudal lung field on radiographs. Additionally, irregular periosteal new bone formation on the humerus as well as on the metacarpal and metatarsal bones was seen on radiographs (Figure 1). Abdominal ultrasonography revealed splenomegaly with abnormal echogenicity.

Keywords: lung, dyspnea, pulmonary neoplasia, immunohistochemistry, paraneoplastic syndrome

Figure 1—Eight-year-old mixed-breed dog. A—Radiographic examination of the pelvic limb metatarsal bones revealed diffuse and irregular periosteal bone proliferation (arrows). B—Photograph showing that the left caudal lung lobe is infiltrated by a firm, poorly demarcated, multinodular, irregular mass (10 cm in largest diameter; arrowheads). Multifocal to coalescing, random, raised nodules (arrows) throughout surface of right caudal lung lobe are also noted. Inset shows the cross section of the large mass, which is white-tan and has a central area of necrosis. C—Imprint cytology of the left caudal lung lobe mass demonstrates pleomorphic epithelial cells with high nuclear-to-cytoplasmatic ratios and cytoplasmic vacuolation. Wright stain; 500X.
No additional testing and imaging were performed at the time. The veterinarian discussed the possibility of a late-stage tumor and suggested euthanasia if the condition deteriorated due to quality-of-life concerns. The patient presented again 5 days later with worsened respiratory distress and recurrence of pleural effusion. Euthanasia was elected.

On postmortem examination, the dog was in good body condition (6/10) with pale mucous membranes. Additional radiographs were taken postmortem on the manus and pes, where thickening and periosteal reaction were again noted on radius, carpus, metatarsal, and metacarpal bones. These changes were observed grossly on bones of both front and hind limbs, including the humerus, radius, carpus, tibia, ulna, metatarsal, and metacarpal bones. On gross examination of the affected bones, the surface appeared irregular, and on cross section, the cortices of the bones were markedly thickened. Gross examination of the thoracic cavity revealed that approximately 90% of the left caudal lung lobe was infiltrated by a raised, moderately firm, irregularly shaped tan-white mass, 10 cm in largest diameter, with areas of hemorrhage, necrosis, and mucus on cross sections (Figure 1). The rest of the lung lobes contained multifocal white raised nodules up to 1 cm in diameter. The costal, mediastinal, and diaphragmatic pleura contained foci of white fibrotic plaques and adhesions to the pericardium. The pericardium was diffusely thickened with multiple coalescing white raised nodules. The distal esophagus near the cardia was thickened and had a 7-cm-diameter cystic lesion containing yellow viscous fluid. The spleen was attached to the omentum and contained a 2.5-cm round nodule near the attachment site. The caudal pole of the left kidney contained multiple raised, gray to brown nodules extending to the renal cortex and appeared to be cystic on cross sections. 

Formulate differential diagnoses, then continue reading.

Cytological, Histopathologic, and Immunohistochemical Findings

Cytology of postmortem imprint from the pulmonary lesions revealed aggregates of pleomorphic epithelial cells, many of which were elongated and had high nuclear-to-cytoplasmic ratios, prominent nucleoli, and dark vacuolated cytoplasm (Figure 1). Findings were interpreted as epithelial proliferation exhibiting malignant criteria and glandular features. On histopathology following the routine H&E processing, the pulmonary mass consisted of an infiltrative epithelial neoplasm forming islands, cords, and acinar structures and loss of polarity with intraluminal papillary projections, supported by a prominent stroma, admixed with areas of necrosis and inflammation. The neoplastic cells were pleomorphic (columnar to polyhedral) and lined the remnant of pulmonary airways with round to oval and basal nuclei (Figure 2). Mitotic count was 14 cells/2.37 mm² with atypical mitotic figures. Satellite neoplastic cell clusters were also present in the airways, suggestive of intra-airway spread, and lymphovascular invasion was also seen. Following decalcification and H&E processing of metatarsal bones, microscopic examination revealed that extending from the cortical surface and elevating the periosteum there were bone trabeculae, with irregular, scalloped margins and many osteocytes within lacunae and many reactive osteoclasts. Periosteum was expanded by abundant fibrous connective tissue. Blocks of lung tissue were sent to the Purdue University Animal Disease Diagnostic Laboratory for immunohistochemistry for cytokeratin, thyroid transcription factor 1 (TTF-1), and napsin A, all of which are routine assays and validated at the laboratory. On immunohistochemistry
(Figure 3). The neoplastic cells showed immunoreactivity to cytokeratin (80% to 90% of cells), TTF-1 (approx 60% to 75% of cells), and napsin A (approx 40% of cells). Very few neoplastic cells were identified in the pleura, and the pulmonary visceral pleura was expanded 2 to 3 mm by granulation tissue admixed with lymphocytes, plasma cells, and macrophages, consistent with fibrous pleuritis. Pericardial and esophageal nodules contained neoplastic invasion and a prominent desmoplastic response. The left kidney contained areas of metastasis, and histology revealed a similar morphology to the pulmonary neoplasm, with evidence of lymphovascular invasion within renal blood vessels. More than 75% of the kidney showed signs of severe chronic renal disease with interstitial fibrosis, lymphoplasmacytic interstitial nephritis, and tubulointerstitial nephritis. Histopathologic examination of a core bone marrow sample revealed diffused hyperplasia with an increased myeloid-to-erythroid ratio. Focal to multifocal nodular hyperplasia was also noted in the pancreas and adrenal cortices, interpreted as age-related changes.

**Morphological Diagnoses and Case Summary**

- Morphologic diagnosis: (1) pulmonary adenocarcinoma, acinar and papillary type, with metastasis in the pericardium, esophagus, and left kidney; (2) fibrous pleuritis, severe diffuse; (3) multiple long bones and digits: periosteal new bone formation (hyperostosis) compatible with hypertrophic osteopathy.

**Comments**

Respiratory distress in dogs can be associated with a variety of conditions, including congested heart failure, upper airway obstruction, and pulmonary tumors. A multimodal approach is often required to investigate the cause of a dyspneic dog. Besides clinical history and physical examination, thoracic radiography is considered the most important diagnostic test for pets with lung disease because imaging studies can provide a wealth of information on the presence, location, and intensity of the abnormality to guide differential diagnosis and diagnostic plans. Although fine-needle aspiration of the pulmonary parenchyma can be viewed as a relatively invasive technique, it is inexpensive, it is safe, and its turnaround period for results is fast, so it should be considered when evaluating animals with a nodular lung pattern noted on imaging studies.

Primary lung tumors are considered relatively uncommon in domestic animals, and pulmonary adenocarcinoma is the most commonly diagnosed primary pulmonary tumor in dogs. The most frequent clinical signs associated with pulmonary carcinoma in dogs are coughing (52%), dyspnea (24%), lethargy (18%), and weight loss (12%). However, in the same survey, 25% of the pulmonary carcinoma cases were incidental findings with no evident clinical signs of respiratory disease before diagnosis.

The lung is also a frequent site for tumor metastasis, and it can sometimes be difficult to differentiate primary pulmonary neoplasms from metastatic neoplasms originating from another location. Immunohistochemistry using TTF-1 and napsin A has proved to be highly sensitive for detecting canine pulmonary carcinoma in previous studies. Although both markers have been reported exhibiting reactivity to cells of thyroid origin, no thyroid-related abnormality was observed in this dog. Therefore, using this combination as a marker for canine primary pulmonary carcinoma was deemed adequate. However, an ectopic thyroid carcinoma cannot be completely ruled out, and this lack of a more specific marker for canine lung cancer can be viewed as a potential deficiency in this study.

In the present case, within the lungs, the primary pulmonary adenocarcinoma had spread through bronchial invasion and reaspiration with intra-airway seeding in other lobes and lymphovascular invasion. The neoplasm also disseminated to the pericardium and esophageal serosa, most likely through direct extension. The fibrous pleuritis was thought to be from the rubbing effects of the neoplasm between the pulmonary and parietal pleura. The hypertrophic osteopathy demonstrated by the thickening of cortical bones is a common paraneoplastic syndrome associated with thoracic space-occupying lesions. Although the exact mechanism of hypertrophic osteopathy secondary to pulmonary tumor is still unknown, it has been postulated that the hypoxic microenvironment created by the lung tumor leads to elevation of plasma vascular endothelial growth factor, which in turn contributes...
Leg swelling and lameness are common findings of hypertrophic osteopathy. These were not described in our case, maybe overshadowed by other clinical signs from the neoplasm. The combination of hyperglycemia and mild mature neutrophilia supports that the patient was under stress and, in combination with the mild nonregenerative anemia, likely represented a result of chronic disease, such as neoplasia.

Treatment of pulmonary carcinomas is mainly by surgical excision alone or with adjuvant chemotherapy. In a retrospective study of 278 dogs with pulmonary carcinoma, the mean survival time was 399 days, in which adjuvant chemotherapy did not benefit the survival outcome. Shorter survival times have been associated with primary tumor size (largest diameter, > 5 cm), presence of pleural effusion, high mitotic count, distant metastasis, and lymph node status (N1 or N2). Out of these prognostic factors, lymph node metastasis and the differentiation state of the tumor are thought to be the best predictors of survival time. Additionally, lymph node metastasis was identified histologically in 28.1% of pulmonary adenocarcinoma dogs with normal-appearing lymph nodes on preoperative CT. The lack of analysis of the thoracic serosanguineous fluid and microscopic investigation of lymph nodes are potential limitations of the present study. Interestingly, despite being the most common clinical sign associated with pulmonary tumors, the presence of coughing was not significantly associated with survival time in 1 study.

In the present case, the dog had multiple negative prognostic factors, including a large primary tumor size (largest diameter, about 10 cm), the presence of pleural effusion, high mitotic count, and distal metastasis (renal), suggesting a surgical treatment would have likely been unrewarding.

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References