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NEOPLASTIC DISEASE

Diffuse Pulmonary Adenocarcinoma with Micropapillary Growth Pattern in a Cat

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Summary

A 12-year-old female European shorthair cat was presented with severe dyspnoea. Echocardiography revealed hypertrophic cardiomyopathy and pleural effusion. The cat died from acute decompensated left heart failure. At necropsy examination, the lungs were diffusely congested and firm, with multifocal grey areas and sparse haemorrhages. No solid masses were detected. Histopathology revealed a diffuse neoplastic proliferation characterized by irregular growth along alveolar walls with a micropapillary pattern. Tumour cells were large, highly pleomorphic and intensely positive for pan-cytokeratin and CAM 5.2. Tumour growth was obscured by simultaneous lesions related to chronic pulmonary congestion and interstitial lung disease. Histological features were consistent with a diffuse invasive pulmonary adenocarcinoma with a micropapillary pattern of tumour growth. Differential diagnosis included large cell carcinoma, which is usually characterized by rosettes or solid clusters of cells occupying alveolar lumen. Extensive cytokeratin immunolabelling was helpful in the differentiation from histiocytic proliferative disease.

Keywords: adenocarcinoma; cat; lung; micropapillary growth

Pulmonary carcinomas may occasionally occur in a diffuse form involving most or all of the lung parenchyma. This form does not produce large neoplastic masses, since it spreads via airways, maintaining the gross appearance of the lung (Bertazzolo *et al.*, 2002). It can also mimic other more common diffuse interstitial lung diseases in both man and animals (Sestini *et al.*, 1985; Ballegeer *et al.*, 2002; Bertazzolo *et al.*, 2002; Yagil-Kelmer *et al.*, 2005).

Pulmonary adenocarcinoma is a relatively common neoplasm of older cats (Caswell and Williams, 2016), although its occurrence in a diffuse fashion is very rare in this species (Moulton *et al.*, 1981).

In the veterinary literature, bronchioloalveolar carcinoma was reported to be the most common histological type of lung tumour occurring with a diffuse distribution (Dungworth *et al.*, 1999; Bertazzolo *et al.*, 2002; Yagil-Kelmer *et al.*, 2005). In this respect, the classification of human pulmonary carcinomas has undergone extensive revision since the last consensus on classification of these tumours in domestic animals. Important changes include abandoning the term 'bronchioloalveolar carcinoma' and introducing the concept of lepidic growth (Travis *et al.*, 2011; Caswell and Williams, 2016), which refers to the growth of atypical, cuboidal, adenoid cells along alveolar walls. Although lung tumours of animals follow similar patterns when compared with the human counterpart, application of the classification system used for human lung carcinomas to animals is premature pending further studies. Some of the subtypes recognized in man have not been reported in animals (Caswell and Williams, 2016). This report describes the unusual gross and histopathological findings and differential diagnosis of a case of diffuse

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pulmonary adenocarcinoma with a micropapillary growth pattern in a cat.

A 12-year-old neutered female European shorthair cat was presented to the Veterinary Teaching Hospital, University of Teramo, with severe dyspnoea. FAST-T ultrasound performed during emergency assessments revealed multifocal, well-marginated, hypoechoic structures, associated with ultrasound signs of pulmonary oedema ('ultrasound lung rockets'), and severe pleural effusion. Thoracocentesis was performed and analysis of pleural effusion revealed a modified transudate. Echocardiography also showed hypertrophic cardiomyopathy, with marked left atrial dilation. Thoracic radiographs were avoided because of the severe respiratory distress. Despite supportive treatment, the cat died from acute decompensated heart failure a few hours after hospitalization. The owner gave consent for necropsy examination, which revealed diffusely congested and firm lungs, with multifocal to coalescing, irregular grey areas and sparse haemorrhages (Fig. 1). No solid masses were detected. Heart examination confirmed the concentric hypertrophy of the left ventricle with marked left atrial dilation.

Samples of the lungs and representative tissues of all major organs were fixed in 10% neutral buffered formalin, processed routinely and embedded in paraffin wax. Sections were stained with haematoxylin and eosin (HE). Additional sections of the lungs were also stained with periodic acid–Schiff (PAS) and subjected to immunohistochemistry (IHC) using primary antibodies directed against pan-cytokeratin (CK; 1 in 100 dilution, AE1/AE3, mouse monoclonal; Dako, Glostrup, Denmark), CAM 5.2 (ready to use, mouse monoclonal; BD Biosciences, San Jose, California, USA), vimentin (1 in 100 dilution, V9, mouse monoclonal; Dako), CD3 (1 in 100 dilution, polyclonal rabbit; Dako), myeloid/histiocyte antigen (1 in 50 dilution, MAC387, mouse monoclonal; Dako) and Ki67 (1 in 50 dilution, MIB-1, mouse monoclonal; Dako). Immune complexes were treated with secondary biotinylated goat anti-mouse or anti-rabbit antibody (1 in 200 dilution; Vector Laboratories, Burlingame, California, USA) and subsequently detected using an avidin–biotin complex (ABC) method (Vectastain® ABC Kit, Vector Laboratories). Peroxidase activity was detected using 0.1% H_2O_2 with 3, 3′-diaminobenzidine solution (Sigma–Aldrich, St. Louis, Missouri, USA) as chromogen. Sections were counterstained with Mayer's haematoxylin (Merck, Darmstadt, Germany).

Lung histopathology revealed a diffuse neoplastic proliferation characterized by irregular growth along alveolar walls, with multifocal micropapillary formations (Fig. 2). Tumour cells were large, predominantly cuboidal in shape, with marked nuclear pleomorphism, prominent nucleoli, multifocal binucleated elements and 2–4 mitoses per high-power (×400) field. Neoplastic cells had a high Ki67 proliferative index (>30%) and showed intense positivity for pan-cytokeratin (Fig. 3) and CAM 5.2 (Fig. 3, inset) immunohistochemically. No intracytoplasmic mucin was detected by PAS stain. Stromal and pleural invasion was present multifocally (Fig. 3), but metastases to tracheobronchial lymph nodes or

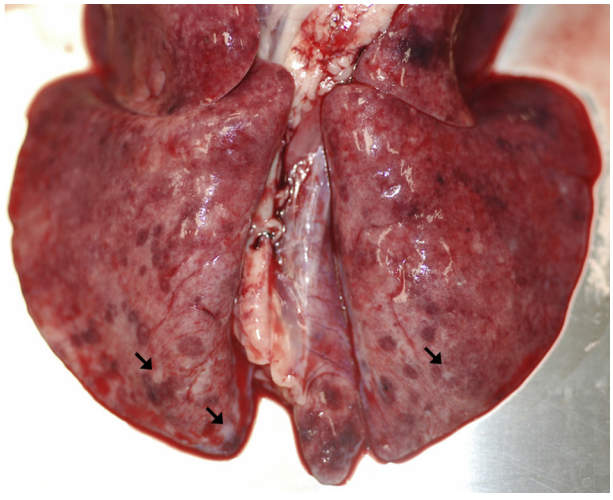

Fig. 1. Diffuse pulmonary congestion with multifocal to coalescing, irregular grey areas (arrows) and sparse haemorrhages. No solid masses are visible.

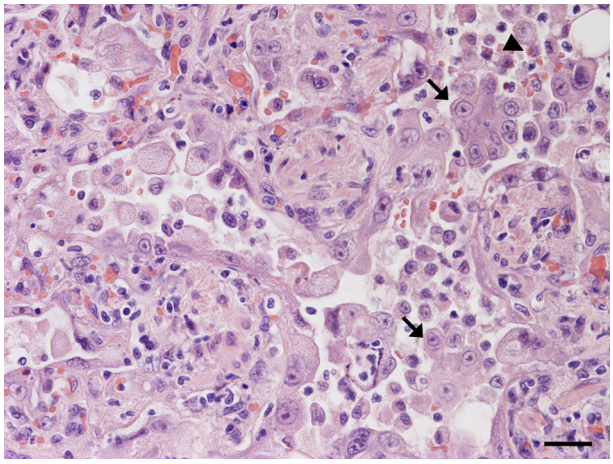

Fig. 2. Large, pleomorphic tumour cells growing along the alveolar surfaces, with multifocal micropapillary formation (arrows). Neoplastic proliferation is obscured by concomitant lesions related to chronic left heart failure, including congestion of alveolar capillaries, moderate interstitial fibrosis and increased number of alveolar macrophages with multifocal erythrophagocytosis (arrowhead). HE. Bar, 25 μm.