BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Case Report

Lepidic-predominant adenocarcinoma of the lung in an elderly cat with kidney failure

Odette Urquiza-Bravo[1] ⓘ, Nestor Ledesma[1] ⓘ, Elizabeth Morales[2,*] ⓘ

[1]Departamento de Medicina y Zootecnia de Aves. Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. Av. Universidad 3000, Ciudad Universitaria 04510, Ciudad de México, Mexico
[2]Departamento de Patología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. Av. Universidad 3000, Ciudad Universitaria 04510, Ciudad de México, Mexico

*Corresponding author: moraless@unam.mx

Abstract

A long-haired, male, neutered domestic cat was referred to a veterinary clinic for the first time at 13 years of age due to anorexia, vomiting, dehydration, and depression. Blood biochemistry revealed renal azotemia. The cat was only given food for animals with kidney failure, and no treatment was given. Three weeks before its death at 16 years of age, the clinical signs returned, becoming more frequent and intense. The cat was referred to the veterinary clinic again, and also severe hypertension and mild dyspnea as the unique respiratory signs were detected. Blood biochemistry again revealed renal azotemia. At necropsy, the lungs exhibited a nodule in the right caudal lobe with a 3-cm-long axis and another nodule in the left caudal lobe with a 2-cm long axis, which histologically corresponded to a lepidic-predominant adenocarcinoma. The bronchioalveolar origin of the neoplasms was corroborated by immunohistochemistry with specific biomarkers, namely Thyroid Transcription Factor-1 (TTF-1), Napsin A, Surfactant Protein B (SP-B), Pancytokeratin and Vimentin, with the neoplastic tissue testing positive for all biomarkers. Both kidneys presented macroscopic and microscopic lesions consistent with nephritis and severe fibrosis, which was deemed to be the cause of death. Primary lung neoplasms in cats are rare and difficult to detect clinically due to clinic signs that may be nonspecific.

Keywords: cat, adenocarcinoma, lung, kidney failure

Introduction

Primary lung neoplasms are uncommon in cats, with an estimated prevalence ranging from 0.69–0.75% in necropsied animals (10, 21, 27). Adenocarcinomas are the most common feline primary lung neoplasms; neoplasms, such as squamous cell carcinoma and adenosquamous carcinoma, are uncommon (2, 10, 15, 27), and mesenchymal neoplasms are rarely observed (3, 13, 15). The average age of most affected cats is 12 to 13 years, and Persian cats seem overrepresented (2, 9, 10, 21). Cats are often diagnosed late in the course of the disease due to nonspecific clinical signs, such as lethargy, weight loss, cough, or vomiting (12, 19). Given the important and rapid progress in the genetic and molecular knowledge of the pathogenic mechanisms underlying lung cancer and its considerable relevance in the treatment of this disease in humans, according to the World Health Organization (WHO), its classification has significantly evolved from purely morphological to the most recent classification (2015) combining histological, immunophenotypic, molecular genetics, clinical and radiological data, thereby improving the evaluation and therapeutic management of humans patients (4, 24, 25) and also this new classification has been adapted to feline lung tumors (21, 27).

Case Description

A 16-year-old male neutered domestic cat with long yellow hair was referred to a veterinary clinic at 13 years of age due to anorexia, frequent vomiting of only saliva or gastric juice, and depression. Upon clinical examination, the cat weighed 4.3 kg and presented with mild dehydration; respiratory signs were not detected. The kidneys were observed to be small on ultrasound, which was the most relevant feature.

Hematology revealed non-relevant thrombocytopenia (279 X10⁹/L blood platelets; 300–700 interquartile range (IQR)) and hyperproteinemia associated with chronic inflammation (84 g/L blood proteins; 60–81 IQR). Blood biochemistry revealed mild hyperglycemia due to stress (8.3 mmol/L blood glucose; 3.8–7.9 IQR), renal azotemia (16.8 mmol/L urea; 4.1–10.8 IQR, 228 mmol/L creatinine; 56–176 IQR), protein changes associated with chronic inflammation (84 g/L total protein; 59–81 IQR, 57g/L globulins; 29–47 IQR), hypernatremia due to hypertonic dehydration (169 mmol/L; 150–165 IQR), and mixed acid-base imbalance (38 mmol/L calculated anion gap; 10–27 IQR, 49 mmol/L strong ion difference; 30–40 IQR).

Physical examination of the urine revealed that urinary density was lower than the critical point (1.020 refractometry), and on chemical examination, proteinuria was associated with kidney failure (0.3 g/L).

The cat was not administered any medication and was only fed commercial food for cats with chronic kidney failure. The cat showed improvement, and the clinical signs decreased without worsening for three years. However, three weeks before its death at 16 years of age, the signs intensified, again manifesting as anorexia and vomiting once or twice a week. By the last week of life, the cat also presented with marked depression and was taken to a veterinarian, who diagnosed the cat with severe hypertension (200 mmHg; 120–140 IQR) and mild dyspnea as the unique respiratory sign.

On hematological examination, no abnormalities were detected. Blood biochemistry revealed renal azotemia (urea 43.00 mmol/L; 4.1–10.8 IQR and 356 mmol/L creatinine; 56–176 IQR), hyperphosphatemia due to renal hypoperfusion (4.28 mmol/L inorganic phosphorus; 0.96–1.96 IQR), hyponatremia (136.0 mmol/L sodium; 150–165 IQR) and hypochloremia (106.0 mmol/L chloride; 112–129 IQR) possibly due to vomiting. On physical examination, the urine was cloudy, and urinary density was lower than the critical point (1.028 refractometry); additionally, chemical examination revealed proteinuria associated with kidney failure (5 g/L protein). Ultrasound was not performed in this medical review. Notably, the cat died with these clinical manifestations and was sent for a post-mortem study at the School of Veterinary Medicine and Zootechnics, National Autonomous University of Mexico (*Universidad Nacional Autónoma de México* – UNAM).

The body condition of the corpse was 2/5 (weight: 3.8 Kg). Macroscopically, two pulmonary nodules were found, one in the right caudal lobe, with a 3-cm-long axis, and another in the left caudal lobe, with a 2-cm-long axis, both of which had irregular, firm, white-yellow edges protruding from the surface and extending into the interior of the lung parenchyma. On sections, they showed a solid and coalescent multinodular appearance (Fig. 1). Both kidneys were firm and white-yellow, presenting an irregular surface with marked depressions in the renal cortex, changes consistent with fibrosis (Fig. 2). Hydrothorax and ascites were also found, which were characterized by being clear, transparent fluids, with protein content of 2.3 g/dl, absence of fibrin, triglycerides, bacteria and specific weight of 1.012 (pure transudate). During necropsy, samples of all organs were taken, fixed in 10% neutral buffered formalin, processed using a routine histological technique, and embedded in paraffin. Sections (4 µm) were stained with hematoxylin and eosin.

Histopathologically, the pulmonary nodules were composed of non-encapsulated neoplastic tissue consisting of monolayers of uniform, cuboidal epithelial cells, consistent with pneumocytes, lining fibrovascular spaces resembling alveolar walls (Fig. 1). The nuclei were round to oval, with extended chromatin, and scant cytoplasm. The mitotic count ranged from 0 to 1 under a high-magnification field (X 400). According to the 2015 WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart (4, 11, 24, 25), neoplastic tissue in both lung lobes is classified as lepidic-predominant adenocarcinoma of the lung – a primary pulmonary adenocarcinoma of the lepidic subtype without stromal invasion (*in situ*).

Microscopic lesions in both kidneys were similar, characterized by multifocal cysts, with severe multifocal lymphoplasmacytic interstitial nephritis, moderate multifocal glomerulosclerosis, severe generalized interstitial fibrosis, severe generalized tubular degeneration, and moderate multifocal mineralization (Fig. 2).

An immunohistochemical (IHC) analysis was performed using the streptavidin-biotin-peroxidase complex method and diaminobenzidine as chromogen to confirm the histopathological diagnosis of lung neoplastic tissue. According to the criteria of Wang *et al*. (26), immunostaining is considered weak when less than 25% (+) neoplastic cells were stained, intermediate when 25 to 75% (+++) cells were stained, and strong when more than 75% (+++) cells were stained. The primary antibodies, dilutions, positive control tissues, immunopositivity sites in neoplastic epithelial cells, and the interpretation of the results are summarized in Table 1 (Fig. 3).

Discussion

Adenocarcinomas account for more than 50% of primary pulmonary neoplasms in senior cats (> ten years), more commonly in females, and Persian cats seem to be overrepresented (2, 9, 10, 21). In cats, these neoplasms can
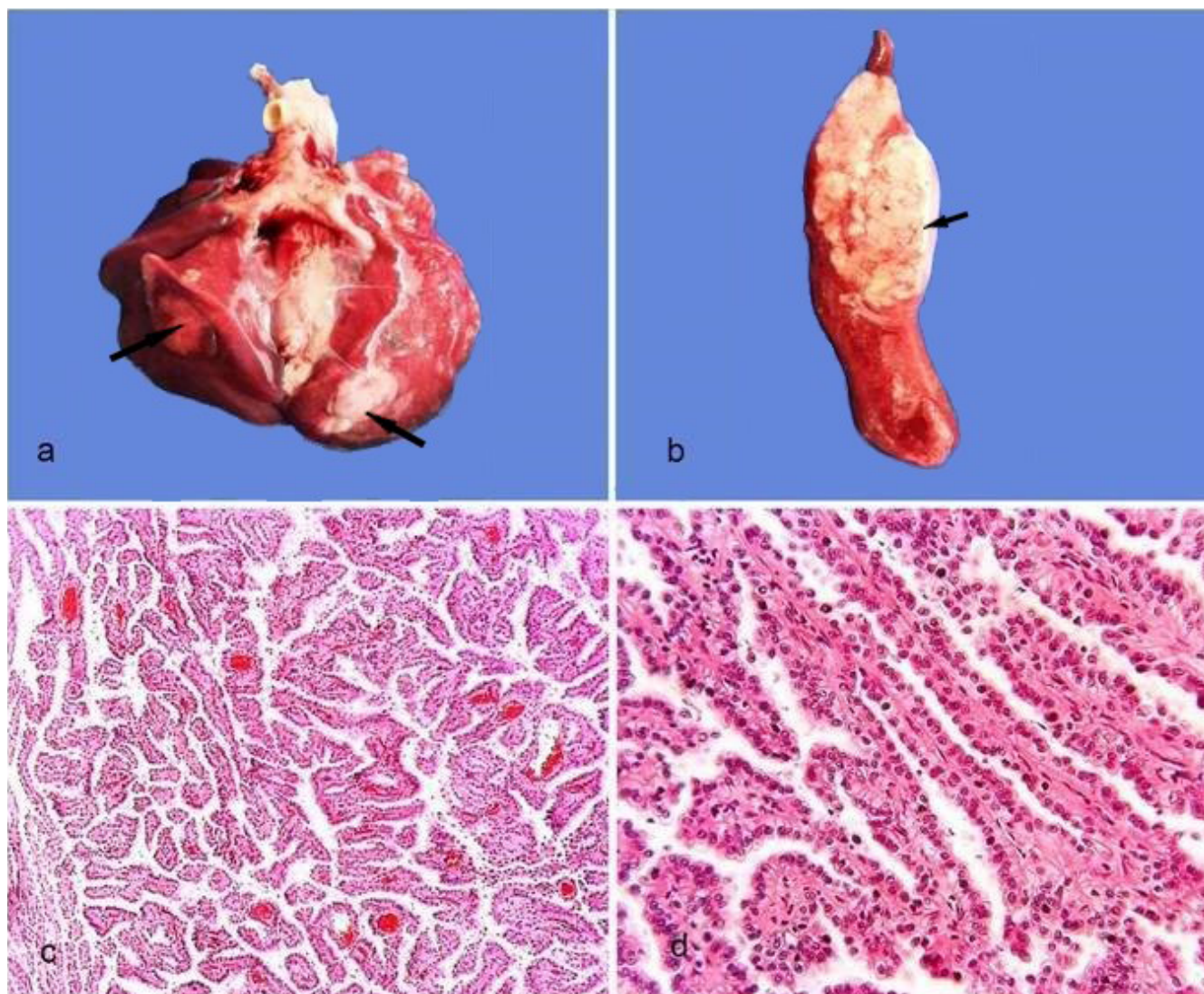
Figure 1. A- Ventrocaudal view of the lung showing neoplastic nodules in both caudal lobes (arrows). B- Lung section showing a close-up of a neoplastic nodule (arrow). C- Histological appearance of a lepidic-predominant adenocarcinoma (H&E, 50X). D- Detail of an adenocarcinoma, characterized by alveolar septa covered by a single layer of neoplastic epithelial cells that do not invade the connective tissue (H&E, 200X).

be either single or multiple and commonly occur in the caudal pulmonary lobes; this location has been reported in up to 79% of the cases, thus matching the location of the adenocarcinomas in this case report (1, 2, 18, 21, 27).

Early detection of lung tumors in cats is difficult because clinical signs, such as lethargy, hyporexia, regurgitation, vomiting, and diarrhea, are often nonspecific. Respiratory signs, such as cough and dyspnea, generally do not present until lung neoplasms have grown sufficiently to impair the health of the animals or these produce abundant pleural effusion (3, 9, 15, 19). In this case, anorexia, vomiting, weight loss, hydrothorax, and ascites were mainly associated with chronic kidney failure, lasting approximately three years, which was corroborated by blood biochemistry and a post-mortem study, based on which kidney failure was identified as the cause

of death and lung neoplasms as incidental findings. On the other hand, hematologic and biochemical profile changes in cats with lung neoplasm as unique lesions are not common. However, they may occur in some cases, including anemia or neutrophilic leucocytosis as described in cats with metastasis pulmonary carcinomas ("feline lung-digit syndrome") (14, 16, 23).

The extent and stage of lung tumors in humans are clinically determined using the primary tumor, lymph nodes, and metastases (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) and the International Association for the Study of Cancer (IASLC) published in 2017 (20). According to this proposal, pulmonary adenocarcinomas found in this cat in the post-mortem study would have been clinically classified as low grade: Tis (*in situ*)
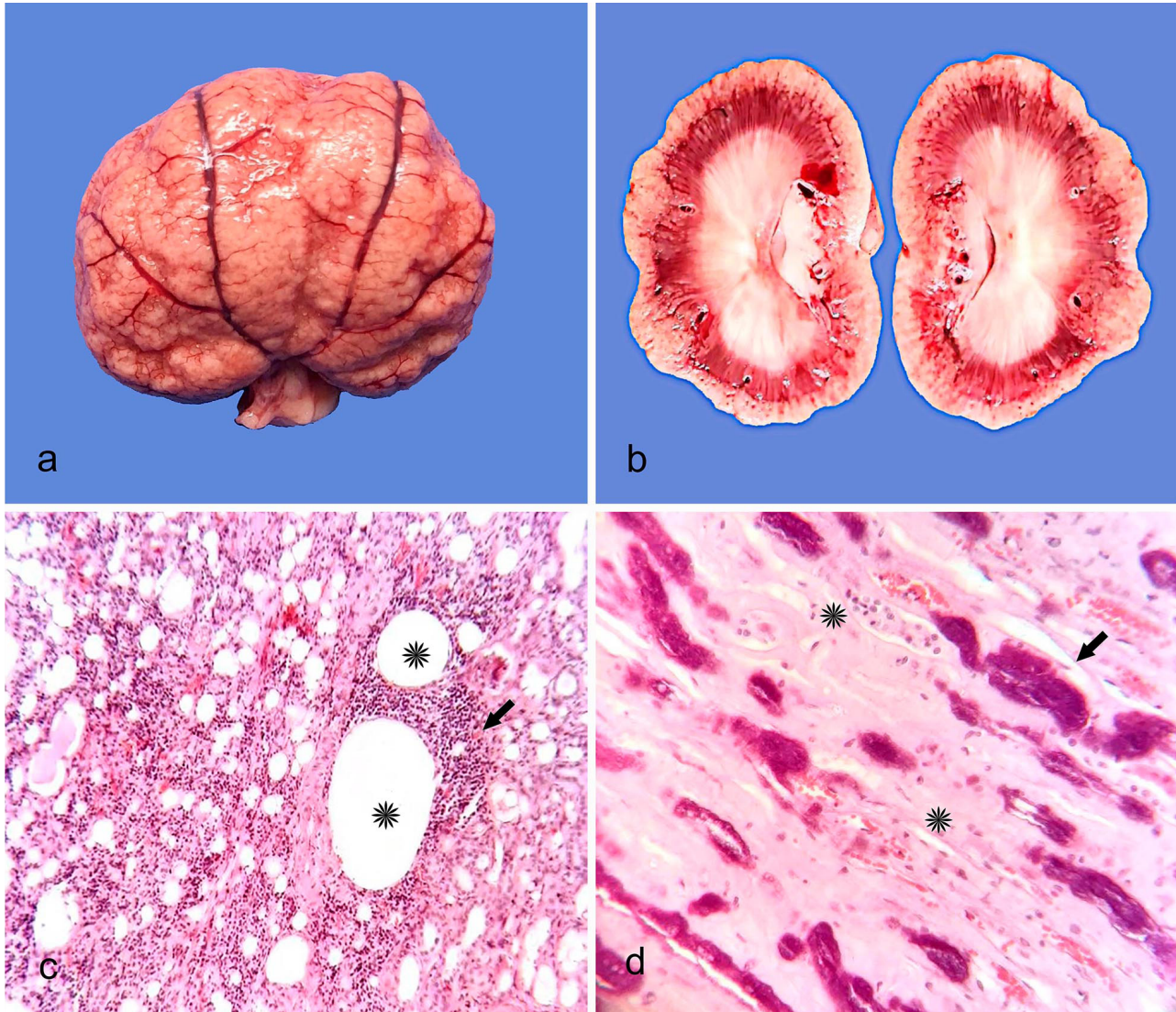
Figure 2. A- Gross appearance of a kidney showing an irregular surface and depressions in the renal cortex. B- Longitudinal section of the kidney; note the depressions in the renal cortex. C- Histological appearance of the kidney, showing cysts (asterisks) and inflammatory infiltrate with mononuclear cells in the interstitium (arrow) (H&E, 100X). D- Renal medulla showing fibrosis (asterisk) and calcification of renal tubules (arrow) (H&E, 400X).

Table 1. Primary antibodies used in immunohistochemical analysis and immunostaining characteristics.

Antibody	Host (clone)	Dilution	Source	Positive control	Immunostaining site
Thyroid transcription factor-1 (TTF-1)	Mouse 8G7G3/1	1:100	Biocare Medical	Lung	++ Nucleus
Napsin A	Mouse TMU-Ad 02	1:100	Biocare Medical	Lung	+ Cytoplasm
Surfactant protein B (SP-B)	Mouse F2	1:100	Santa Cruz Biotechnology	Lung	++ Cytoplasm
Pancytokeratin	Mouse AE1/AE3	1:100	Biocare Medical	Colon	++ Cytoplasm
Vimentin	Mouse V9	1:100	Biocare Medical	Colon	+ Cytoplasm and basal membranes

Weak immunostaining, < 25% (+), intermediate immunostaining, ranging from 25–75% (++), strong immunostaining, > 75% (+++) (Wang et al. 2020)
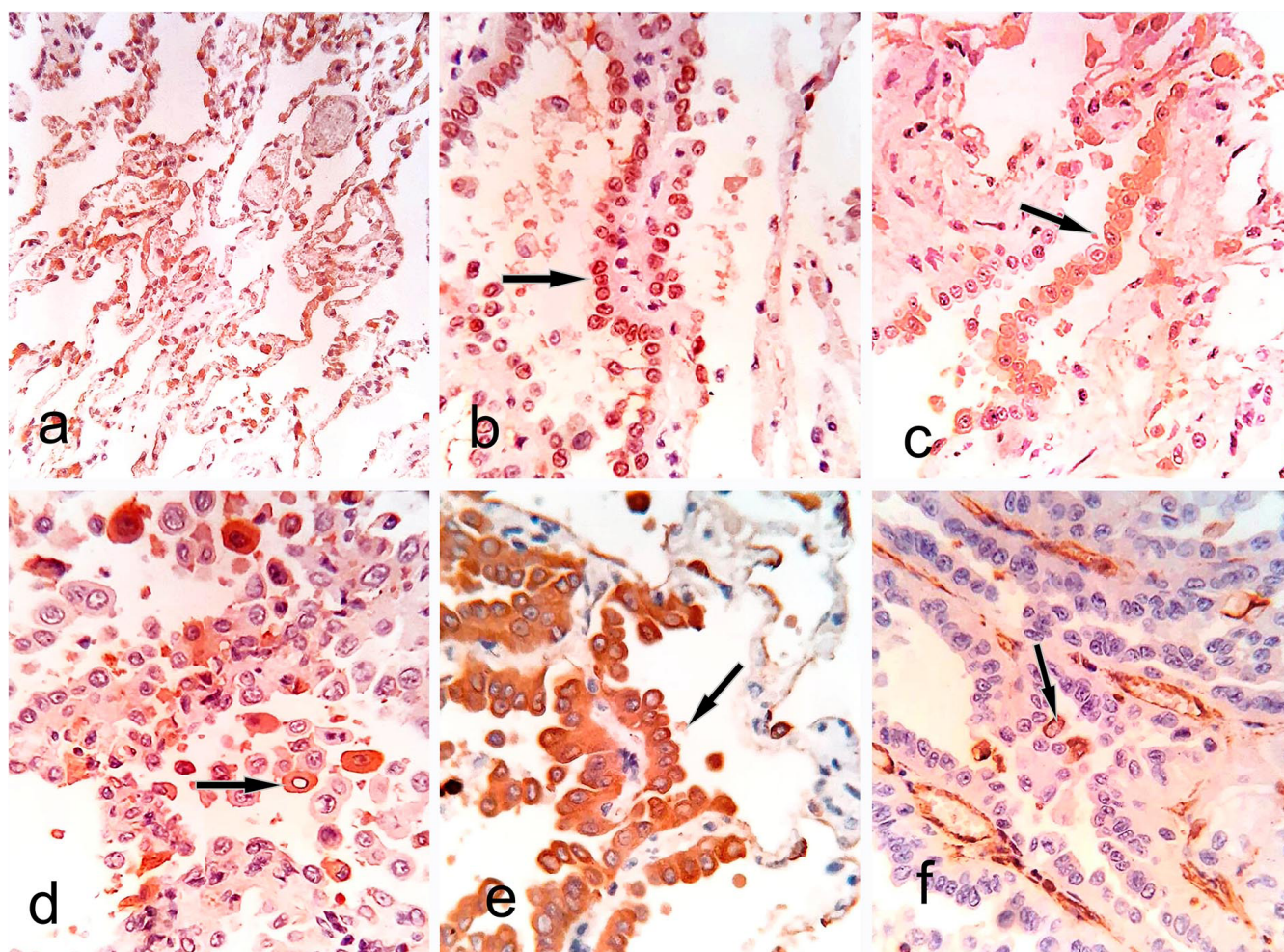
Figure 3. Immunostaining with different biomarkers for cat lepidic-predominant adenocarcinoma of the lung. A- Napsin A, positive control (lung) (200X). B- TTF-1 (400 X). C- Napsin A (400X). D- SP-B (400X). E- Pancytokeratin (400X). F- Vimentin (400X). Hematoxylin contrast.

adenocarcinoma, N0 (no regional lymph node metastasis) and M0 (no distant metastasis). Approximately 75–80% of cats with primary lung cancer present with metastasis (10, 15, 9), which did not occur in this cat, possibly due to the low grade of the adenocarcinoma, which would also explain why the cat did not show evidence of severe respiratory disease. Although this subtype of adenocarcinoma has good clinical prognoses when detected early, had this cat not died of chronic kidney failure, the adenocarcinoma would have likely become invasive, with the potential for metastasis.

Lepidic-predominant adenocarcinoma of the lung (previously known as bronchioloalveolar carcinoma), as in the present case, is characterized by preexisting alveoli, whose septa were covered by a single layer of neoplastic epithelial cells, corresponding to type II pneumocytes, similar to a row of butterflies perched on a branch, without extending to the stroma, blood vessels, or pleura (*in situ* adenocarcinoma) and preserving lung architecture (8, 27). Human studies have shown that lepidic-predominant adenocarcinomas are usually low-grade tumors. Therefore, they have a good clinical prognosis after surgical

resection (8, 30). Of the lung adenocarcinomas in cats, the subtype lepidic seems to be one the least common. In this regard, in a recent histopathological study of 39 lung adenocarcinomas in cats, only 2 (5.1%) were classified as subtype lepidic (21).

Lung adenocarcinomas are usually positive for Thyroid Transcription Factor-1 (TTF-1). This biomarker is expressed in type II pneumocytes, Club cells, and bronchial basal cells (10, 22). Napsin A is an aspartic protein involved in the maturation of surfactant protein B, which is expressed in type II pneumocytes. Cytoplasmic positivity has been described in more than 90% of primary lung adenocarcinomas (5). Conversely, Surfactant Protein B (SP-B) is found in the pulmonary surfactant, which is also produced by type II pneumocytes (29). Although Pancytokeratin (AE1/AE3 clone) is not specific to lung cells, this biomarker helped to determine the epithelial origin of the neoplasm (7). As in the present case, immunopositivity for Vimentin has been described in the cytoplasm of lung adenocarcinoma cells (7, 8). The absence of neoplasms in other organs or lymphoid nodes, the histological characteristics of the lung neoplasms,

and the positive TTF-1, Napsin A, and SP-A immunostaining supported the bronchioalveolar origin of the neoplasms.

According to the histological characteristics, lepidic-predominant adenocarcinoma of the lung should be differentiated from other subtypes of adenocarcinomas, such as acinar, papillary, solid, and micropapillary adenocarcinomas; however, the particularities and cellular arrangements of these subtypes suffice to differentiate them from each other (8, 27). In addition to adenocarcinomas and their subtypes, differential diagnoses also identify other epithelial neoplasms of the lung, which are histologically classified as non-small cell carcinomas, including squamous (SCC), large (LCC), and adenosquamous (ACC) cell carcinomas. However, they markedly differ from adenocarcinomas histologically (8, 27). SCC exhibits varying degrees of keratinization, concentric layered keratin sheets (keratin pearls), and intracellular desmosomes (intercellular bridges). LCC is a neoplasm consisting of large tumor cells with marked anisocytosis, anisokaryosis, pleomorphism, and binucleate cells. ACC has a glandular and squamous component (8, 27). Additionally, possible renal or colon adenocarcinoma metastases, among others, should be ruled out, thereby requiring IHC with specific biomarkers for type II pneumocytes and surfactants (TTF-1, Napsin A and SP-B) (17, 28). In addition to IHC, molecular markers should be used to identify genetic mutations for specific treatments against lung cancer, as applied in humans (25).

Chronic kidney disease is highly common in geriatric domestic cats older than 12 years (6). Often, no specific cause is found; however, this condition has been associated with polycystic kidneys, renal lymphomas, bacterial nephritis, feline infectious peritonitis, and urolithiasis. Cats may manifest weakness, fatigue, anorexia, vomiting, diarrhea, polydipsia, polyuria, weight loss, dehydration, and abdominal pain, which are some signs detected in this cat (6).

Conflict of Interest

The authors declare no competing interests.

Acknowledgements

References

1. Aarsvold S, Reetz JA, Reichle JK, Jones ID, Lamb CR, Evola MG, Keyerleber MA, Marolf AJ. Computed tomographic findings in 57 cats with primary pulmonary neoplasia. Vet Radiol Ultrasound. 2015;56(3):272-277.

2. Ambrosini YM, Johnson KA, Matthews M, Sato AF. Unusual invasion of primary pulmonary adenocarcinoma in a cat. JFMS Open Rep. 2018; 4(2):2055116918810897.

3. Barr F, Gruffyd-Jones TJ, Brown PJ, Gibbs C. Primary lung tumours in the cat. J Small Anim Pract. 1987;28(12):1115-1125.

4. Barrionuevo CC, Dueñas HD. Clasificación actual del carcinoma de pulmón. Consideraciones histológicas, inmunofenotípicas, moleculares y clínicas. Horiz Med. 2019; 19(4):74-83.

5. Bishop JA, Sharma R, Illei PB. Napsin A and thyroid transcription factor-1 expression in carcinomas of the lung, breast, pancreas, colon, kidney, thyroid, and malignant mesothelioma. Hum Pathol. 2010;41(1):20-25.

6. Brown CA, Elliott A, Schmiedt CW, Brown SA. Chronic kidney disease in aged cats: clinical features, morphology, and proposed pathogeneses. Vet Pathol. 2016;53(2):309-326.

7. Caprioli RA, Argenta FF, Hammerschmitt MA, Pereira PR, de Lorenzo C, Pavarini SP, Driemeier D, Sonne L. Achados patológicos e imuno-histoquímicos de neoplasmas pulmonares primários em caninos na região metropolitana de Porto Alegre, Rio Grande do Sul. Pesq Vet Bras. 2018;38(6):1151-1158.

8. Caswel JL, Williams KJ. Respiratory System. In: Maxie MG, editor. Jubb, Kennedy, and Palmer's. Pathology of domestic animals. 6th ed. St. Lous: Elsevier; 2016. p 495-500.

9. Culp WTN, Rebhun RB. Pulmonary neoplasia. In: Vail DM, Thamm DH, Liptak JM, editors. Withrow & MacEwens Small animal clinical oncology. 6th ed. Edinburgh: Elsevier; 2020.p. 507-523.

10. D'Costa S, Yoon BI, Kim DY, Motsinger-Reif AA, Williams M, Kim Y. Morphologic and molecular analysis of 39 spontaneous feline pulmonary carcinomas. Vet Pathol. 2012;49(6):971-978.

11. Eguchi T, Kadota K, Park BJ, Travis WD, Jones DR, Adusumilli PS. The new IASLC/ATS/ERS lung adenocarcinoma classification: what the surgeon should know. Semin Thorac Cardiovasc Surg. 2014; 26(3):210-222.

12. Fowler BL, Johannes CM, O'Connor A, Collins D, Lustgarten J, Yuan C, Weishaar K, Sullivan K, Hume KR, Mahoney J, Vale B, Schubert A, Ball V, Cooley-Lock K, Curran KM, Nafe L, Gedney A, Weatherford M, LeVine DN. Ecological level analysis of primary lung tumors in dogs and cats and environmental radon activity. J Vet Intern Med. 2020;34(6):2660-2670.

13. Ghisleni G, Grieco V, Mazzotti M, Caniatti M, Roccabianca P, Scanziani E. Pulmonary carcinosarcoma in a cat. J Vet Diagn Invest. 2003; 15(2):170-173.

14. Goldfinch N, Argyle DJ. Feline lung-digit síndrome: unusual metastatic patterns of primary lung tumours in cats. J. Feline Med. Surg. 2012;14(3):202-208.

15. Hahn KA, McEntee MF. Primary lung tumors in cats: 86 cases (1979-1994). J Am Vet Med Assoc. 1997;211(10):1257-1260.

16. Hanselman BA, Hall JA. Digital metastasis from a primary bronchogenic carcinoma. Can Vet J. 2004; 45(7):614-616.

17. Kadivar M, Boozarai B. Applications and limitations of immunohistochemical expression of "Napsin-A" in distinguishing lung adenocarcinoma from adenocarcinomas of other organs. Appl Immunohistochem. Mol Morphol. 2013;21(3):191-195.

18. Maritato KC, Schertel ER, Kennedy SC, Dudley R, Lamm C, Barnhart M, Kass P. Outcome and prognostic indicators in 20 cats with surgically treated primary lung tumors. J Feline Med Surg. 2014; 16(12):979-984.

19. Nunley J, Sutton J, Culp W, Wilson D, Coleman K, Demianiuk R, Schechter A, Moore G, Donovan T, Schwartz P. Primary pulmonary neoplasia in cats: assessment of computed tomography findings and survival. J Small Anim Pract. 2015;56(11):651-656.

20. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67(2):138-155.

21. Santos IR, Raiter J, Lamego ÉC, Bandinelli MB, Dal Pont TP, Siqueira KF, Almeida BA, Panzeira W, Sonne L, Driemeier D, Pavarini SP. Feline pulmonary carcinoma: Gross, histological, metastatic, and immunohistochemical aspects. Vet Pathol. 2023;60(1):8-20.

22. Stenhouse G, Fyfe N, King G, Chapman A, Kerr KM. Thyroid transcription factor 1 in pulmonary adenocarcinoma. J Clin Pathol. 2004;57(4):383-387.

23. Thrift E, Greenwell C, Turner AL, Harvey AM, Maher D, Malik R. Metastatic pulmonary carcinomas in cats ("feline lung-digit syndrome"): further variations on a theme. JFMS Open Rep. 2017;3(1): 2055116917691069.

24. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th ed. Vol.7. Lyon, France: International Agency for Research on Cancer; 2015. 412 p.

25. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I; WHO Panel. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol. 2015;10(9):1243-1260.

26. Wang J Y, Wang XM, Xu XY, Li SR, Liu XL. Expression and significance of CK5/6, P63, P40, CK7, TTF-1, NapsinA, CD56 Syn and CgA in biopsy specimen of squamous cell carcinoma, adenocarcinoma and small cell lung carcinoma. Int J Morphol. 2020;38(2):247-251.

27. Wilson DW. Tumors of the respiratory tract. In: Meuten DJ, editor. Tumors in domestic animals. 5th ed. New Jersey: john Wiley & Sons, Inc.; 2017. p. 467-498.

28. Ye J, Findeis-Hosey JJ, Yang Q, McMahon LA, Yao JL, Li F, Xu H. Combination of napsin A and TTF-1 immunohistochemistry helps in differentiating primary lung adenocarcinoma from metastatic carcinoma in the lung. Appl Immunohistochem Mol Morphol. 2011; 19(4):313-317.

29. Yokohira M, Yamakawa K, Nakano Y, Numano T, Furukawa F, Kishi S, Ninomiya F, Kanie S, Hitotsumachi H, Saoo K, Imaida K. Immunohistochemical characteristics of surfactant proteins A, B, C and D in inflammatory and tumorigenic lung lesions of F344 rats. J Toxicol Pathol. 2014;27(3-4):175-182.

30. Yoshizawa A, Motoi N, Riely GJ, Sima CS, Gerald WL, Kris MG, Park BJ, Rusch VW, Travis WD. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol. 2011;24(5)653-664.