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COMPARISON BETWEEN THORACIC RADIOGRAPHIC FINDINGS AND POSTMORTEM DIAGNOSIS OF THORACIC DISEASES IN DYSPNEIC COMPANION RATS (*RATTUS NORVEGICUS*)

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Companion rats are often presented to veterinarians for respiratory difficulties. Dyspnea in rats is most commonly due to infectious pneumonia, and thoracic neoplasia can go undiagnosed ante mortem due to a mistaken interpretation of pneumonia. In domestic carnivores, pulmonary nodular patterns have been shown to correlate with lung neoplastic diseases and infectious diseases. The main objective of this retrospective case series study was to determine whether certain radiographic criteria could be correlated with the presence of thoracic infectious disease and neoplastic disease in companion rats. A secondary objective was to determine whether the patient's sex and age were different between rats diagnosed with infectious versus neoplastic disease. Medical records and thoracic radiographs of dyspneic companion rats presented to the University of California at Davis, William R. Pritchard Veterinary Medical Teaching Hospital during the time period from January 2000 to December 2014 were reviewed. Rats with postmortem confirmation of thoracic lesions were included in the study. Thoracic radiographs were evaluated for positioning, lesion distribution, lung lobe involved, pulmonary pattern, mediastinal and pleural lesions by three observers blinded to diagnosis. Thirty rats were included in the study, including 23 rats with an infectious disease and seven with neoplasia. Mediastinal lesions were significantly more prevalent in the group diagnosed with thoracic neoplasia ($P = 0.031$), in particular cranially ($P = 0.048$). Although there was an overlap between the two groups, findings indicated that the presence of cranial mediastinal lesions may be helpful for differentiating neoplastic from infectious disease in rats.

Key words: bronchopneumonia, lung, mycoplasmosis, rat, radiographs, tumor.

Introduction

RESPIRATORY INFECTION IS ONE OF THE MOST COMMON diseases in companion rats.[1,2] Pneumonia may be associated with *Mycoplasma pulmonis*, ciliary associated respiratory bacteria, *Streptococcus pneumoniae*, *Corynebacterium kutscheri*, the fungus *Pneumocystis carinii*, sialodacryoadenitis coronavirus, Sendai virus, murine pneumonia virus, and paramyxoviruses among others.[3,4] Laboratory rats are typically tested for these infectious diseases[5] but systematic testing is not performed in companion rodents[4] and these agents are often present concomitantly and may act synergistically.[2,6] Thoracic lesions due to infectious agents can lead to dyspnea, which is a common cause of presentation of rats to exotic practitioners.[1,7] Conversely, spontaneous thoracic neoplasms are rare[7,8] and may be misdiagnosed.[9] Rats are used as model for carcinogen-induced pulmonary tumors in humans,[10] and the most common primary pulmonary tumors of rats are alveolar adenomas and carcinomas arising from type II pneumocytes[7,8,10–12] and Clara cells.[7] Spontaneous pulmonary hemangiosarcoma[9] and thoracic rhabdomyosarcoma[13] have also been described. Secondary thoracic neoplasms of rats include mesotheliomas, lymphomas,[14,15] histiocytic sarcomas,[3,16] and metastatic mammary adenocarcinomas among others.[3] Some authors have postulated that thoracic radiographs may be useful for differentiating mycoplasmosis from thoracic neoplasms in companion rats.[1] In dogs, the distribution of lesions among lobes may give an indication of the possible nature of pulmonary neoplasms.[17] In addition,

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in domestic carnivores, a solitary well-defined pulmonary nodule and multiple circumscribed nodules or masses are considered imaging signs of pulmonary neoplastic diseases.[17–21] However, a nodular pattern has also been related to infectious diseases.[22–25] Some textbooks have suggested that radiographic interpretation of rodents may be extrapolated from domestic animals.[26]

Rats have two lungs. The right lung is divided into cranial, middle, caudal, and accessory lung lobes while the left lung is composed of a single lung lobe.[7,27] This is different from cats and dogs that have a cranial left lobe, further divided into cranial and caudal parts, and a caudal left lobe. Histologically, rodents display Clara cells in their bronchial epithelium,[7] which are considered precursor cells.[28] Three cell types have been described in the rat alveolar epithelium: type I and type II pneumocytes, and a third cell type specific to rodents, which is considered as a chemoreceptor cell.[29] The rat normal radiographic anatomy has been previously described.[26,30] To the authors' knowledge, radiographic characteristics of pulmonary lesions have not been described in companion rats; while radiographic techniques[11] and more advanced imaging techniques, such as microcomputed tomography[31] and scintigraphy,[32] have been described in laboratory rats.

The main objective of this study was to compare radiographic findings and postmortem diagnosis in companion rats with thoracic diseases and determine whether these criteria could distinguish between infectious and neoplastic disease. A secondary objective was to determine whether the patient's sex and age was significantly different between rats diagnosed with infectious versus neoplastic disease. We hypothesized (1) that we could identify characteristic radiographic features of pulmonary neoplasms that could help differentiate between infectious and neoplastic lesions, and (2) that signalment would not be a predictor of the nature of thoracic lesions in companion rats.

Materials and Methods

This study was a retrospective case series design. Medical records of rodents presented to the University of California at Davis, William R. Pritchard Veterinary Medical Teaching Hospital during the time period from January 2000 to December 2014 were searched for the following criteria: rats presented for dyspnea with two orthogonal thoracic radiographs performed within a month prior to death or euthanasia and available necropsy report. Normal thoracic radiographs from rats retrospectively confirmed to be free of thoracic disease based on postmortem examination were also retrieved. Case exclusion was decided collectively by three of the authors (V.F.-L., C.V.-G., A.L.Z.), including a faculty in zoological medicine and in radiology. If any animal was found to not meet all inclusion criteria by one of the authors, it was excluded.

For each case included in the study, signalment (sex and age) and medical records (including the radiographic report and necropsy report) were reviewed. Results of additional tests, such as microbiology tests and additional histopathologic stains, were also recorded. When available, findings were also recorded from bacteriologic cultures and *Mycoplasma* Polymerase Chain Reaction (PCR) (Comparative Pathology Laboratory, University of California, Davis, MGSO & GPO-1 primers) using a 715 base-pair portion of the 16S rRNA gene of several *Mycoplasma* species.[33] Rats were classified in two thoracic lesion groups based on postmortem examination: infectious and neoplastic.

For each case, radiographs acquired prior to necropsy, including a minimum of two orthogonal thoracic radiographs (right-lateral, left-lateral, dorsoventral [DV], and/or ventrodorsal [VD] projections), were reviewed by three authors blinded to diagnosis and in a randomized order (to minimize interpretation bias), using a DICOM images viewer (Osirix 64 bit v. 5.8.2, Pixmeo, Bernex, Switzerland) and a light box for radiographic films. Images were analyzed for the overall quality, including evaluation of positioning. If no rotation or a very slight rotation was noted based on superimposed origin of contralateral ribs on the lateral view, and superimposition of the sternum and thoracic spine on the DV/VD view, it was attributed a 1 score. If positioning partially impaired radiographic interpretation, such as thoracic limbs not being pulled sufficiently cranially and being superimposed on the cranial aspect of the thorax, it was scored as 3. All radiographs between these two descriptions were scored as 2. Radiographs with a poor positioning were discarded.

Normal thoracic radiographs from rats retrospectively confirmed to be free of thoracic disease based on postmortem examination were used as reference images for affected patients. Distribution of thoracic lesions (craniventral, caudodorsal, hilar, lobar, generalized) and location within the affected lung lobe (right cranial, right middle, right caudal, right accessory, left) were recorded as present or absent with dichotomic coding. Abnormal pulmonary patterns were noted and defined as vascular, bronchial, alveolar, unstructured interstitial, and nodular.[34] Additional thoracic lesions such as mediastinal involvement (cranial, central or caudal mediastinal widening, or mediastinal shift), pleural lesion (pleural effusion or pneumothorax), evidence of mineralization, and extra-thoracic lesions were also documented if present. None of the lesions were mutually exclusive; hence multiple thoracic lesions could be described for a single patient if observed. If some lesions prevented evaluation of other characteristics (for instance a severe pleural effusion preventing evaluation of pulmonary parenchyma), the nonevaluated category was classified as not observed. For views that were only partially interpretable due to suboptimal quality of positioning, nonevaluated criteria were classified as

missing. A consensus was reached between the three observers for presence or absence of each radiographic lesion.

Statistical tests were selected and performed by two authors (C.V.-G., P.H.K.). Exact logistic regression compared groups of rats with and without neoplastic disease regarding lesion distribution type, presence or absence of lesions in each lobe, pulmonary pattern, and other types of radiographic lesions (pleural effusion, pneumothorax, mineralization) with commercially available statistics software (Stata IC/13.1, StataCorp LP, College Station, TX). To compare the sex distribution between the two groups of rats, a Fisher's exact test was performed with statistics freeware (R 2015, R Foundation for Statistical Computing, Vienna, Austria). The Shapiro-Wilk test was performed with the same software to evaluate age distribution, which was nonnormally distributed. Therefore, the Wilcoxon rank sum test was performed to compare age between rats with and without neoplastic lesions. For all tests, $P < 0.05$ was considered significant.

Results

A hundred and fifty-one cases of dyspneic rats were found, out of which 53 had thoracic or full body radiographs within a month prior to death or euthanasia. Among those 53 selected records, cases were excluded if necropsy was declined by the owner ($n = 16$), if necropsy was performed more than a month after radiographs ($n = 1$), if necropsy did not confirm thoracic lesions ($n = 2$), if only one radiographic view was available due to patients being severely dyspneic ($n = 2$), or if radiographic films could not be located in the database ($n = 2$). Finally, 30 cases matched all inclusion criteria. Overall, in 18/30 cases included in the study, time between radiographs and death was less than 4 days and out of these, 11/30 cases died on the day radiographs were obtained.

Among the 30 dyspneic companion rats included in the study, there were 15 females and 15 males. A summary of sampled animals, by group, is presented in Table 1. Thirteen female and 10 males were included in the infectious group, two females and five males in the neoplastic group. Sex distribution was not significantly different in both groups ($P = 0.25$). Median age was 24 months of age, with standard deviation of 10 months (range 6–44). Median age of the rats was not significantly different between groups ($P = 0.93$) and was 24 months of age for each group (infectious and neoplasia). Histologic diagnosis was infectious pneumonia in 23/30 rats (77%) and neoplastic lesions in 7/30 rats (23%). Among rats diagnosed with mycoplasmosis (8/23; 35%), diagnosis was achieved via postmortem PCR in seven cases. *Mycoplasma* culture of the lungs was submitted in 15 cases and the result was positive in one case. Four rats had a negative *Mycoplasma* culture with a concomitant positive *Mycoplasma* PCR and PCR was not submitted in the single case with a positive *Mycoplasma* culture result. A Warthin-Starry stain was submitted in eight cases and the result was positive in four cases (4/23; 17%), this was considered indicative of ciliary associated respiratory bacteria.[3] Other pneumonia infectious agents included *Streptococcus* spp. (4/23; 17%) and *C. kutscheri* (2/23; 9%), each cultured postmortem from pulmonary lesions. The etiology of the remaining bronchopneumonia cases (5/23; 22%) was not determined. The seven thoracic neoplasms were as follows: lymphoma (5/7; 72%), histiocytic sarcoma (1/7; 14%), and undifferentiated round cell neoplasm (1/7; 14%).

TABLE 1. Summary of Signalment and Postmortem Diagnoses Obtained in Sampled Dyspneic Companion Rats in Each Group

Group	Infectious	Neoplasia
Number of cases	23	7
Age in months	Median: 24 Range: 6–44	Median: 24 Range: 8–35
Sex (F/M)	13/10	2/5
Postmortem diagnoses including microbiological and histopathologic results	*Mycoplasma* spp. (8/23; 35%) *Streptoccocus* spp. (4/23; 17%) *C. kutscheri* (2/23; 9%) Not determined (5/23; 22%)	Lymphoma (5/7; 72%) Histiocytic sarcoma (1/7; 14%) Undifferentiated round cell (1/7; 14%)

Patients included in this study had been either sedated for radiographic positioning, using a combination of midazolam (Midazolam, Novaplus, Irving, TX) and an opioid, or were fully anesthetized with gas anesthesia (Isoflurane, USP, Piramal Healthcare, Bethlehem, PA) when deemed necessary by the clinician. Rats were then restrained with masking tape and foam elements were used as needed to improve positioning. Radiographs were obtained with 50–60 kVp, 5–7.5 mAs, and a small focal spot. No complications were recorded during or following acquisition of radiographs. Radiographs were either analog (20 cases from 2000 to 2005, X-ray Generator, Sedecal model SHF-310, Sedecal, Buffalo Grove, IL; X-ray Tube, Toshiba Rotanode model E7239X, Toshiba America Information System Inc., Irvine, CA; Console Global, Sedecal model A-6199-01, Sedecal) or digital (10 cases from 2006 to 2014, Summit Innovet high frequency radiographic unit, Sound-Eklin DR System, Eklin Medical Systems, Santa Clara, CA). Subjectively, digital and analog radiographs were equally diagnostic.

For lateral views, nine radiographs were scored as a 1 (i.e., perfect positioning or slight rotation), 16 radiographs were scored as a 2 (i.e., mild rotation), five radiographs were scored as a 3 (i.e., major positioning abnormality partially impairing interpretation, such as superimposition of thorax and forelimb). Rotation was common on the lateral view, which was often scored as 2. A steep thoracic curve in rats

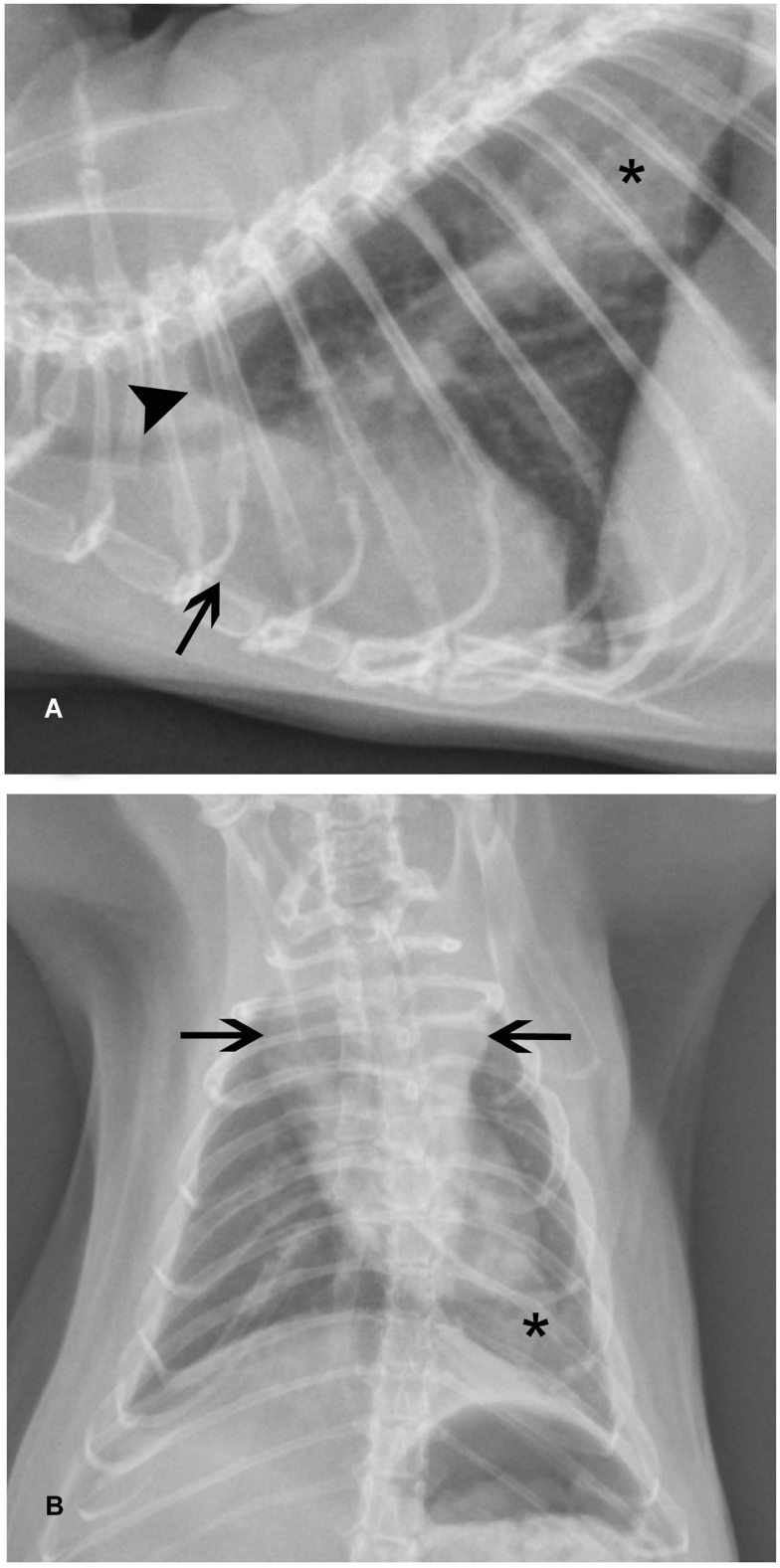

FIG. 1. Right lateral (A) and ventrodorsal (B) radiographs of a 31-month-old male neutered rat with lymphoma. (A and B) There is an alveolar pattern with partly ill-defined nodular borders in the caudal aspect of the left lung lobe (asterisk). The mediastinum is widened (arrows) causing caudal retraction of the cranial portions of the lungs (arrowhead). The mediastinal mass was caused by enlarged lymph nodes, and the caudal aspect of the left lung was infiltrated with lymphoma.

TABLE 2. Number of Rats Presenting with Each Type of Thoracic Lesion, Distribution, Pulmonary Pattern, and Exact Logistic Regression Results for Each Group

	Infectious group $N = 23$		Neoplasia group $N = 7$				
	n	(%)	*n*	(%)	Odds ratio	95% Confidence interval	*P*-value
Thoracic lesion							
No lesion	5	(22)	0	(0)	2.36	0.27–∞	0.304
Lesion detected	18	(78)	7	(100)	0.42	0–3.65	0.304
Pulmonary lesion							
No lesion	6	(26)	3	(43)	2.00	0.50–8.00	0.327
Unilateral	3	(13)	2	(29)	0.75	0.08–7.21	0.803
Bilateral lesion	14	(61)	2	(29)	3.50	0.46–26.62	0.226
Cranioventral	4	(17)	0	(0)	1.77	0.19–∞	0.548
Caudodorsal	3	(13)	2	(29)	0.39	0.03–5.84	0.565
Lung lobes involved							
Right cranial	12	(52)	2	(29)	2.64	0.34–33.16	0.399
Right middle	14	(61)	1	(14)	8.68	0.84–459.18	0.080
Right caudal	11	(48)	2	(29)	2.23	0.29–28.03	0.427
Right Accessory	10	(43)	2	(29)	1.88	0.24–23.72	0.669
Left	15	(65)	4	(57)	1.39	0.16–10.67	1.000
Pulmonary pattern							
Bronchial	1	(4)	0	(0)	0.30	0.01–∞	1.000
Vascular	0	(0)	0	(0)	N/A	N/A	N/A
Alveolar	15	(65)	3	(43)	2.42	0.32–20.92	0.391
Unstructured interstitial	0	(0)	0	(0)	N/A	N/A	N/A
Nodular	7	(30)	2	(29)	1.09	0.13 –14.10	1.000
Mediastinum							
Lesion	1	(4)	3	(43)	0.07	0.00–1.10	0.031
Cranial lesion	0	(0)	2	(29)	0.11	0.00–1.51	0.048
Central lesion	1	(4)	0	(0)	0.30	0.00–∞	1.000
Caudal lesion	0	(0)	1	(14)	0.30	0.00–11.87	0.233
Shift	6	(26)	0	(0)	3.02	0.36–∞	0.290
Pleural space							
Pleural effusion	9	(39)	3	(43)	0.86	0.11–7.31	1.000
Pneumothorax	1	(4)	0	(0)	0.30	0.01–∞	1.000

and consequently radiographic rotation precluded evaluation of tracheal deviation; hence this criterion was not used to evaluate the set of radiographs included in this study. For VD and DV views, 15 radiographs were scored as a 1, 12 radiographs were scored as a 2, and three radiographs were scored as a 3. Overall, 52 radiographic views (52/60; 87%) were found to be fully interpretable. Radiograph interpretation results are shown in Table 2. Overall radiographic lesions were detected in only 25 of 30 cases diagnosed with postmortem thoracic lesions (sensitivity = 83%). Five rats presented with infectious disease (5/23; 22%) and none of the rats presented with neoplastic disease (0/7; 0%) had normal radiographs ($P = 0.30$). The distribution of pulmonary lesions among the different lobes did not vary significantly among groups or within each group. Overall, 16 rats had bilateral pulmonary lesions (16/30; 53%), one had lesions only in the right lung lobe (1/30; 3%), and four had lesions only in the left lung lobe (4/30; 13%). The lateralization of the lesions ($P = 0.09$), type of pulmonary pattern ($P = 0.85$), and other criteria of radiographic interpretation did not differ significantly among groups. Pulmonary vessels could not be clearly visualized due to the small size of the thorax: no vascular pattern was described. One case exhibited a bronchial pattern and multiple mineral opacities with linear shapes in the right caudal lung lobe suspected to be airway associated. No unstructured interstitial pattern was described. Rats diagnosed with thoracic neoplasia in this study were significantly more likely to display mediastinal lesions ($P = 0.03$; Fig. 1). Mediastinal lesions cranial to the heart were significantly more frequent in the neoplastic group ($P = 0.05$), whereas prevalence of a mediastinal lesion caudal to the heart was not significantly different among groups ($P = 0.23$).

Correlating radiographs with histopathology, 5/23 (22%) of animals with thoracic disease of infectious etiology had normal radiographs. The only bronchial pattern reported was related to bronchiectasis with luminal obstruction secondary to mucosal proliferation and secretions causing the chronic atelectasis of the lung. Infectious agents associated with this severe bronchopneumonia were not determined in this case. The nodular lesions and lobar consolidation were pulmonary abscesses and lobar necrosis. Mediastinal lesions were confirmed to be related to lymphoma in three rats and to a very large abscess of the tracheobronchial lymph nodes in one rat. Pleural effusion was detected in 12/30 (40%) rats on radiographs and was

TABLE 3. Combination of Radiographic Signs for Each Group of Dyspneic Companion Rats

Pulmonary lesion		Mediastinum			Infectious group ($N = 23$)		Neoplasia group ($N = 7$)		
Without alveolar pattern	With alveolar pattern	Lesion	Shift	Pleural space	*n*	(%)	*n*	(%)	*P*-value
−	−	−	−	−	5	(22)	0	(0)	0.30
−	−	−	−	+	1	(4)	2	(29)	0.13
−	−	+	−	−	0	(0)	1	(14)	0.23
+	−	−	−	−	1	(4)	1	(14)	0.42
+	−	−	+	+	1	(4)	0	(0)	1.00
−	+	−	−	−	4	(17)	0	(0)	0.55
−	+	−	−	+	5	(22)	1	(14)	1.00
−	+	−	+	−	3	(13)	0	(0)	1.00
−	+	−	+	+	2	(9)	0	(0)	1.00
−	+	+	−	−	1	(4)	2	(29)	0.13

+, observed; −, not observed.

present in both groups. Necropsy confirmed pleural effusion was related to infectious diseases in 9/12 (75%) of those cases.

To determine other relevant radiographic signs allowing group differentiation, we studied combinations of lesions. Results are shown in Table 3. No combinations of lesions were significantly different between groups though there were some trends. Four rats with an infectious disease (4/23; 17%) and none with neoplastic disease demonstrated only an alveolar pattern ($P = 0.55$). One rat with infectious disease (1/23; 4%) had pulmonary nodules, slight mediastinal shift, and pleural effusion ($P = 1.00$). A combination of pulmonary nodules and alveolar lesions, mediastinal shift secondary to volume loss, and pleural disease was found only in the group with infectious pneumonia (2/23; 9%; $P = 1.00$). Representative radiographs of rats with infectious disease are illustrated in Figs. 2 and 3. In one rat with neoplastic disease (1/7; 14%), the only abnormality identified was a mediastinal lesion whereas all rats with infectious disease also had other abnormalities ($P = 0.23$). One rat with infectious disease (1/23; 4%), and one rat with neoplastic disease (1/7; 14%) had only a pulmonary lesion ($P = 0.42$). One rat with infectious disease (1/23; 4%) and two rats with neoplastic disease (2/7; 29%) had only pleural effusion ($P = 0.13$). One rat with an infectious disease (1/23; 4%) and two with a neoplastic disease (2/7; 29%) demonstrated an alveolar pattern and enlarged mediastinum without pleural lesions ($P = 0.13$). Three rats with infectious disease (3/23; 13%) and none with neoplastic disease had concomitant alveolar pattern, a mediastinal shift without pleural effusion ($P = 1.00$). Five rats with infectious disease (5/23; 22%) and only one rat with neoplastic disease (1/7; 14%) had a combination of a pulmonary lesion consisting of an alveolar pattern, a pleural abnormality without a mediastinal involvement (lesion or shift; $P = 1.00$).

Discussion

For the dyspneic companion rats sampled in the current study, diagnosis was not affected by rat's sex or age. Both thoracic infectious and neoplastic conditions mostly occurred in older rats, although rats as young as 9 months of age were also represented in both groups. Therefore, when evaluating a younger rat, clinicians should not rule out neoplastic disease from their differential diagnosis.

Rat positioning for radiographic acquisition is complicated by the small size of the patient. Lateral thoracic radiographs positioning involves applying gentle cranial traction on the forelimbs of the patient without causing the trunk to be twisted, so that the sternum lies in the same horizontal plane as the spine.[26] The forelimbs should be drawn as cranially as possible to prevent summation onto the cranial lung field.[26] Radiolucent foam wedges may be used to prevent rotation.[26] In ventro-dorsal and dorso-ventral thoracic radiographs, the patient positioning should be such that the sternum is projected precisely over the spine.[26] The spine is placed under slight traction by gently pulling on the fore- and hindlimbs with tapes placed on each of the limbs.[26] Collimation should allow visualization of the caudal contour of the diaphragm and the caudal quarter of the neck to be able to follow the course of the trachea.[26] In the present study, a majority of radiographs were scored as a 2 (i.e., mild rotation), or a 3 (i.e., major positioning abnormality partially impairing interpretation, such as superimposition of thorax and forelimb), illustrating the difficulty for obtaining perfect radiographs in dyspneic rats. However, the notation used in the present study was conservative and interpretation was not jeopardized when scoring radiographs as a 2. In domestic carnivores, ventro-dorsal thoracic views allow a better visualization of the accessory lobe, caudal mediastinum and pleural effusion, while the appearance of the cardiac silhouette is more constant on dorso-ventral views,[35,36] and caudal lobar pulmonary

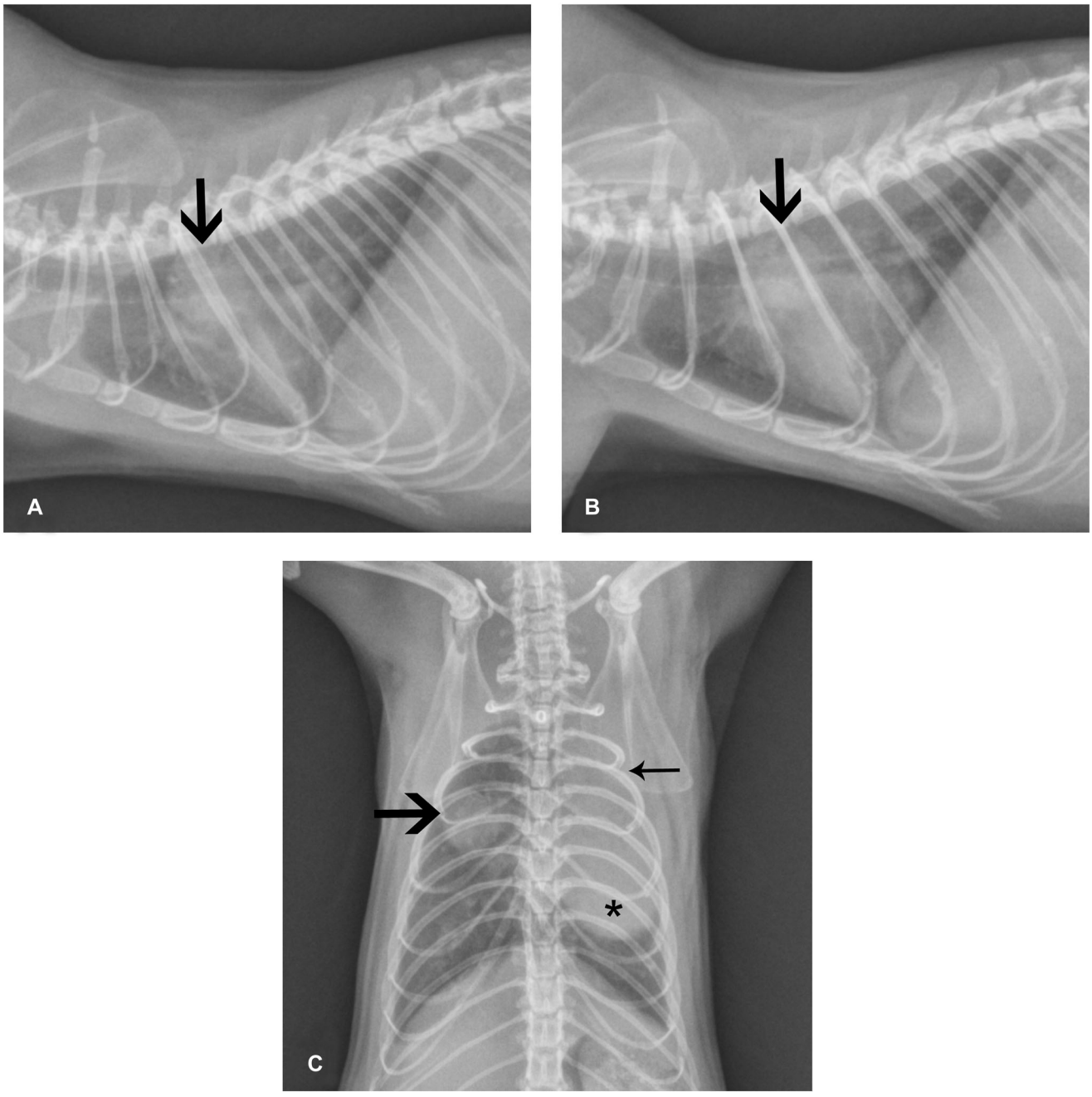

FIG. 2. Three-view thoracic radiographs of an 18-month-old female rat with dyspnea. There is a round soft tissue opacity nodule in the right cranial lung lobe (arrow) seen on the left lateral (A), right lateral (B), and dorsoventral (C) projections. The left lung has an alveolar pattern with volume loss (C, small arrow) resulting in a mediastinal shift of the cardiac silhouette (C, asterisk) to the left, contacting the thoracic wall. The nodule is equally visible on both lateral projections due to the compensatory hyperinflation of the right lung lobes. The pulmonary nodule represented an abscess, and the left lung atelectasis was caused by pneumonia and bronchial obstruction with volume loss. Ciliary associated respiratory bacteria were highlighted by Warthin-Starry stain in this case and histopathologic lesions were compatible with pulmonary mycoplasmosis although the *Mycoplasma* culture was negative.

arteries are more easily identified.[37] Although certain ventro-dorsal and dorso-ventral views were evaluated in this study, comparing the advantages of each view was beyond the scope of this study as both views were rarely available for a single patient. In domestic carnivores, a right lateral view will allow a better visualization of the left hemithorax due to right lung potential atelectesis and the opposite is true for the left lateral view.[38] Similarly, comparing right lateral and left lateral views was beyond the scope of this study and sensitivity of each lateral view for detecting thoracic lesions is likely to vary depending on lesion distribution.

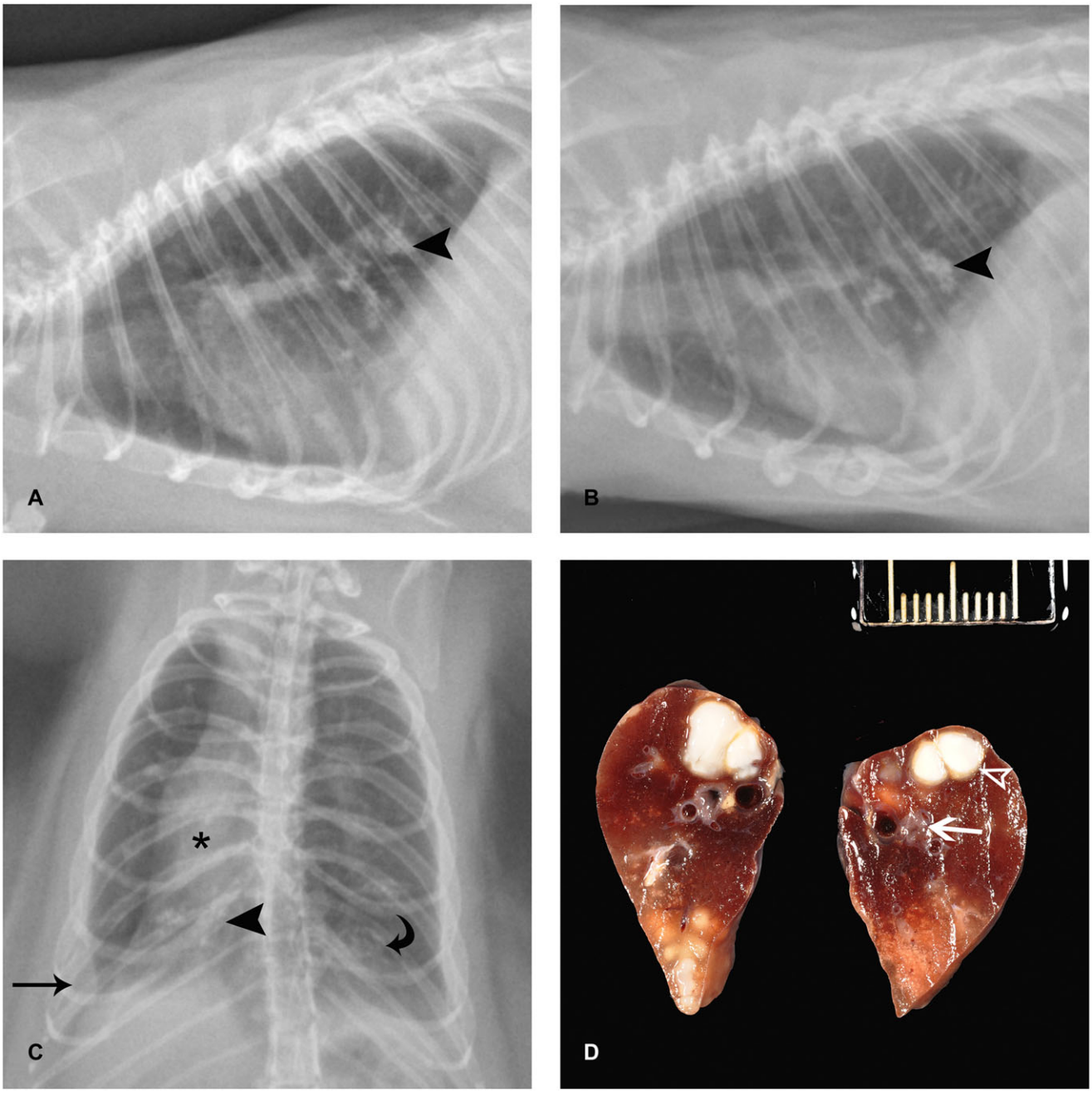

FIG. 3. Three-view thoracic radiographs of a 19-month-old female rat with dyspnea. (A) Left lateral projection, (B) right lateral projection, (C) dorsoventral projection, (D, scale 1 cm) gross photographs of the right lung lobe. There is a bronchial pattern and peribronchial, multiple, mineral opacities with linear shapes are present in the right caudal lung lobe (black arrowheads) which are suspected to be airway associated. The cardiac silhouette (C, asterisk) has a mediastinal shift to the right, indicating atelectasis of the right lung. There is retraction of the right lung from the thoracic wall (C, small arrow) with increased soft tissue opacity caused by pleural effusion. On necropsy, there was pleural effusion and atelectasis with chronic fibrosis of the right lung. Abscesses were present bilaterally (C, curved arrow; D, open arrowhead) that were not well visualized on the radiographs. There was bronchiectasis with luminal obstruction secondary to mucosal proliferation and secretions (D, white arrow) causing the chronic atelectasis of the lung. Infectious agents associated with this severe bronchopneumonia were not determined in this case.

Overall lesion distribution among pulmonary lobes was evaluated with the goal of developing recommendations regarding views that should be prioritized for dyspneic companion rats. No preferential lateralization was detected in this study. Three-view thoracic radiographs are therefore recommended to make the lesions more conspicuous in the left and right lung lobes, as either could be affected.

Compared to radiographic interpretation of dogs and cats, interpretation of thoracic radiographs in rats carried some additional challenges due to the small size of the

patient and limits of spatial resolution. Pulmonary vessels were not visible in any of the studied radiographs. Additionally, due to the small size of the thorax, differentiating well-defined and ill-defined nodules was challenging when the spatial resolution did not enable clear visualization of the nodule's margin. Alveolar pattern, changes in the mediastinum and pleural abnormalities were easily identified on rat's radiographs in this study. Unstructured interstitial pattern was not diagnosed in any rat, as it may have been indistinguishable from normal lung due to spatial resolution limitations. In most cases, diffuse pulmonary interstitial opacity was considered as artifactual; therefore the prevalence of changes to the structure of the lungs without nodular or alveolar disease could have been underestimated in the present study. Although the thymus causes a characteristic widening of the cranial mediastinum in rats,[26] a radiographic diagnosis of a cranial mediastinal mass was suggestive of round cell neoplasia in four cases. However, at the individual level, mediastinal lesions could be associated with both thoracic infectious disease and neoplasia. One rat's radiographic diagnosis was in favor of neoplasia but the cranial mediastinal mass was actually diagnosed as a very large abscess on necropsy, while lymphoma was confirmed in the three other rats. Mediastinal lesions were a common feature of thoracic neoplasms in this dataset. This finding can be explained by the majority of cases being affected by round cell neoplasia causing lymphadenopathy. Hence, suspicion of a cranial mediastinal mass should prompt further diagnostic investigations such as thoracic ultrasound or computed tomography.

It was surprising that five patients from this database were diagnosed with lymphoma as spontaneous visceral lymphomas are considered uncommon in most rats strains,[3,39] with the exception of Fisher 344 rats and inbred Sprague/Dawley/Cub rats.[40,41] In Wistar rats, thymomas account for the majority of hematolymphopoietic tumors and are reported to be more common in females than in males.[42] Malignant thymic lymphomas may be induced with N-methyl-N-nitrosourea in carcinogenesis studies.[43] Contrary to what is described in some other rodents, lymphomas are not associated with oncogenic viruses in rats.[3] Conversely oncogenic retrovirus and polyomavirus are described in guinea pigs and Syrian hamsters,[44] respectively, with lymphoma being the most common neoplasm in these two species.[2] Typical lesions associated with lymphoma in rats include splenomegaly, hepatomegaly, and lymphadenopathy.[3] Thymic lymphoma has also been reported,[3] and all lymphopoietic tissues may be affected.[39] Lymphomas may be characterized via immunohistochemistry as previously described in rats,[39,40] and may be staged via bone marrow biopsy,[40,45] similar to other species. In a clinical setting, ultrasound-guided fine-needle aspirations of thoracic masses may allow antemortem diagnosis of lymphomas in rats. Characterization of the type of lymphoma detected in the enrolled patients was beyond the scope of the study.

Frequencies of radiographic lesions in this study were not significantly different between the infectious and neoplastic groups. However, presence of a combination of lesions may be helpful for differentiating infectious from neoplastic conditions. For example, a combination of nodular and/or alveolar pattern associated with mediastinal shift may suggest infectious disease. That being said, normal radiographs should not rule out infectious thoracic disease.

Limitations of this study include the low number of individuals, which may have decreased statistical power and lead to a type II error. Necropsy results were deemed necessary to rigorously assess the significance of the radiographic lesions detected and this limited the sample size. The population of companion rats enrolled in this study may also have been biased as it was collected from a referral center, included dyspneic rats that worsened despite treatment. As a necropsy was available during the following month after radiographs were obtained, it is possible that more advanced cases of respiratory disease were likely selected compared to the general rat population. The time frame between radiograph acquisition and postmortem examination was also a limitation of the study, as thoracic disease could have progressed in the interim. Some rats received antimicrobial treatments between radiograph acquisition and postmortem examination, which could have decreased the extent of their lesions in some cases and could have negated microbiologic cultures. In addition, screening for bacterial agents through microbiologic tests and special stains was not performed for all rats and testing for viral agents was beyond the scope of the study. Finally nonpathogenic *Mycoplasma* spp. were likely detected via PCR. The PCR used in these rats has a low specificity, as *M. pulmonis* is regarded as the only clinically significant *Mycoplasma* in rats[3] but other *Mycoplasma* species were detected with the primers used in the present study.[33] This could have led to erroneous conclusions regarding the cause of pneumonia in some patients. For this reason, rats with infectious bronchopneumonia were grouped together regardless of the infectious agent detected. Due to the delay between radiographic and postmortem tests, it was also not feasible to compare radiographic and histopathologic lesions in each pulmonary lobes. Patients were therefore considered as a whole entity affected by a disease.

To the authors' knowledge, this study is the first to describe thoracic and pulmonary radiographic lesions of companion rats presenting for dyspnea. Sex and age were not predictors of infectious or neoplastic diagnoses. Mediastinal lesions, especially cranial ones, were significantly more prevalent in the group diagnosed with thoracic neoplasia. Rats with mediastinal masses were most often affected by round cell neoplasia. Thoracic radiographs

obtained from rats with pneumonia might show pulmonary nodules and alveolar pattern representing abscesses, and mediastinal shift due to volume loss and necrosis. Pleural effusion was seen in both groups. Comparing combinations of radiographic lesions (alveolar lung pattern, mediastinal lesion or shift, and pleural abnormality) in a larger companion rat population may help orient diagnosis toward neoplastic or infectious disease in rats presented with dyspnea.

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