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Clinical presentation and treatment of lymphoma in companion rats (*Rattus norvegicus*; 2008–2020)

Sarah Faye-Fierman[1]; Sara Gardhouse, DVM[2]*; Julianne E. McCready, DVM[1]; Ryan Appleby, DVM[1]; Samuel E. Hocker, DVM[2]

[1]Department of Clinical Studies, Ontario Veterinary College Health Sciences Centre, University of Guelph, Guelph, ON, Canada
[2]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS

*Corresponding author: Dr. Gardhouse (sgardhous@vet.k-state.edu)

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OBJECTIVE
To describe the clinical presentation, treatment, and treatment outcomes for companion rats (*Rattus norvegicus*) diagnosed with lymphoma.

ANIMALS
All rats that presented to the exotics service and underwent postmortem examination during the time period of 2008 through 2020 were evaluated.

PROCEDURES
The medical records of 35 rats were evaluated for an ante- or postmortem diagnosis of lymphoma. Cases with a diagnosis of lymphoma were further reviewed for signalment, presenting complaint, clinical signs observed on physical exam, diagnostic testing performed, and treatments administered. Postmortem gross and histologic findings were reviewed.

RESULTS
7 out of 35 rats were diagnosed with lymphoma, either ante-mortem or postmortem. The most common presenting complaint that was present in all rats with lymphoma was respiratory abnormalities. Five out of 7 rats had radiographs performed, all of which had abnormalities noted in the thoracic cavity including pulmonary nodules, cranial mediastinal widening, or alteration to the cardiac silhouette. Diagnosis via cytologic aspirates was performed in 2 cases and each was diagnostic for lymphoma; however, even with treatment, survival time following initiation of chemotherapy was short (less than or equal to 24 days). The definitive diagnosis in the remainder of the cases was via necropsy.

CLINICAL RELEVANCE
Results suggest that lymphoma is a common neoplastic disease in rats and a thorough diagnostic work-up is indicated in any rat that presents for general malaise or respiratory signs.

An AVMA survey reported that zoological companion animal ownership in the United States increased by 25% from 2011 to 2016, with pet rats (*Rattus norvegicus*) representing an expanding proportion.[1] With rats becoming more popular as pets, owners are seeking veterinary care more frequently with the demand for higher quality diagnostic and treatment options.[1] Some of the most common clinical presentations in pet rats include respiratory signs and various neoplastic processes.[2] Although infectious disease is the most common cause of respiratory signs, neoplasia and cardiac disease are additional causes of dyspnea in rats.[2–4]

While more common in the mouse,[5,6] lymphoblastic lymphoma is less commonly reported in the laboratory rat.[7–13] Lymphoma is a common neoplasm of most domestic mammals including dogs, cats, and ferrets; however, there are few documented case reports discussing hematopoietic neoplasms and lymphoma in pet rats.[14–16] The incidence of neoplasia in rats varies dramatically depending on the age, diet, genetic strain, and environmental settings of the population that is being examined.[17] One study looking at disease morbidity in 375 pet rat cases did not report any cases of lymphoma.[18] Lymphoma in the domestic pet rat is a potentially important but underreported disease, as rats that present with respiratory signs are often empirically started on antibiotics without diagnostics to confirm the underlying cause.

The objectives of the study reported here were to describe the prevalence, clinical presentation, diagnostics, and treatment of lymphoma in companion rats.

Materials and Methods

Case selection

The medical record database at the Ontario Veterinary College Health Sciences Centre at the University of Guelph was searched for records of companion rats that presented to the Avian and Exotics service between 2008 and 2020. The inclusion criteria included any domestic rat that presented to the service and also had a necropsy performed in that time period. Once all rat records were identified, search terms included "neoplasia," "lymphoma," "lymphosarcoma," "mass," "neoplasm," "leukemia," "lymphoid," and "tumor." Postmortem findings were then reviewed for any diagnosis of lymphoid leukemia or lymphoma, regardless of origin, as reported on postmortem.

Medical records review

For each rat that was diagnosed with lymphoma, data extracted from the medical record included the signalment of the rat including breed if known, presenting complaint, date of onset of clinical signs, body weight, physical examination abnormalities, diagnostic tests performed, treatments administered, date of death, gross necropsy findings, histopathological evaluation, and diagnosis.

Results

Rats

A total of 148 rats were admitted from 2008 to 2020. Some rats had multiple visits, but each rat was only included once in the total number for rat patients that were seen. A total of 35 rats met the inclusion criteria for this study. Of these 35 cases, 7 rats had a diagnosis of lymphoma, and these records were reviewed in detail. The overall prevalence of lymphoma in this population of rats was 4.73%.

Signalment

For the 7 cases examined in the present study, records of weight, age, and sex are described **(Table 1)**.

Table 1—Descriptive data (age, weight, gender) at death of 7 cases of lymphoma in pet rats presented to the Ontario Veterinary College, Avian and Exotics Service from 2008 to 2020.

Case	Weight (g)	Age (y)	Sex
1	366	2.08	Male
2	300	2.03	Male
3	426	1.8	Male castrated
4	607	2.2	Male castrated
5	707	1.7	Male castrated
6	515	2.3	Female spayed
7	421	2.6	Female

At the time of death, the median age of the rats was 2.08 years (range, 1.7 to 2.6 years). Not all breeds were reported in the medical record, but of those that were, breeds included 2 Dumbo (cases 2 and 6), 1 Rex (case 1), and 1 Siamese (case 5). With respect to sex distribution, 2 were intact males (cases 1 and 2), 3 were castrated males (cases 3, 4, and 5), 1 was an intact female (case 7), and 1 was an ovariectomized female (case 6). Four biologically unrelated rats in the study came from the same household (cases 4, 5, 6, and 7), and an additional 2 rats in the study (cases 1 and 2) had the same owner but the biological relationship was unknown.

Clinical signs and physical examination findings

All 7 rats presented with clinical signs of respiratory compromise of varying severity noted by the owner at home and confirmed on physical examination. In all cases, progression of respiratory compromise was also noted either at home by the owner or on subsequent physical examinations at the veterinary hospital, often many months before a definitive diagnosis was achieved. Two cases presented with owner concerns for weight loss (cases 1 and 3). On physical examination, 1 case had palpable splenomegaly and a firm irregular swelling in the left axillary area (case 3). None of the rats that were examined were free from clinical signs on presentation. A summary of the clinical signs and physical examination findings can be found online **(Supplementary Table S1)**.

Diagnostic findings

Blood smears were performed in 4 of the 7 cases. In 3 cases, the blood smears were unremarkable. In one of these cases in which chemotherapy was administered (case 3), a blood smear was repeated 16 days after diagnosis to evaluate for evidence of cytopenia secondary to chemotherapy. The blood smear revealed adequate numbers of neutrophils. However, there were low numbers of atypical large lymphocytes present, which exhibited a finely granular chromatin pattern, occasional nuclear convolution, and a rim of deeply basophilic cytoplasm which contained occasional evidence of small, punctate vacuoles. These lymphocytes were concerning for a leukemic phase of lymphoma. One rat had a blood sample collected for a blood smear while anesthetized just prior to euthanasia due to declining quality of life (case 6). The blood smear was submitted along with the postmortem, and revealed a marked lymphocytosis comprised of mainly small to intermediate sized lymphocytes **(Figure 1)**. The lymphocytes contained low amounts of basophilic cytoplasm, frequent pink cytoplasmic granules, and a peripheral round to amoeboid to lobulated nucleus with finely clumped chromatin. The blood smear was consistent with lymphoid leukemia. Radiographs were performed in 5 of the 7 cases. Case 2 and 5 demonstrated evidence of multifocal pulmonary masses, cases 3, 4, and 6 demonstrated solitary pulmonary masses. Additionally, case 4 demonstrated cranial mediastinal widening, and case 3 demonstrated an enlarged cardiac silhouette with an abnormal shape. For case 5, despite improvement of the pulmonary soft tissue opacities, the

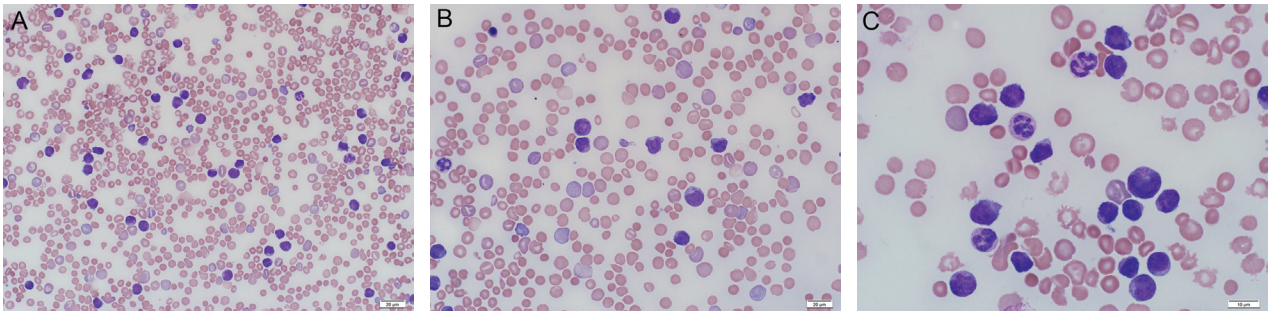

Figure 1—Photomicrographs of blood smears from a rat (case 6) with lymphoid leukemia at 40X (A), 60X (B), and 100X (C). Images demonstrate a marked lymphocytosis comprised of mainly small to intermediate-sized lymphocytes. The lymphocytes are characterized by low amounts of basophilic cytoplasm, frequent pink cytoplasmic granules, and a peripheral round to amoeboid to lobulated nucleus with finely clumped chromatin.

mediastinal shift persisted when radiographs were repeated 1 month later following a course of antimicrobial and non-steroidal anti-inflammatory drugs for a suspected infectious cause of the respiratory clinical signs **(Figure 2)**.

A CT scan was performed in 2 cases. For case 3, radiographs were initially performed when the rat presented with mildly increased respiratory effort; however, 1 month later, the rat presented in severe respiratory distress, and a CT scan was pursued which demonstrated a mediastinal mass. In case 4, radiographs were initially performed for mild respiratory signs and a CT scan was pursued 6 months following the initial radiographs when the rat had worsening signs. In case 4, CT demonstrated moderate to severe multifocal right-sided pulmonary consolidation **(Figure 3)**.

Thoracic ultrasound was performed in 3 cases. In case 3 and case 5, a large mediastinal mass was identified with ultrasound. In case 4, an irregular pulmonary surface was noted.

Abdominal ultrasound was performed in 2 cases and demonstrated hyperechoic hepatopathy in case 5, and hy-

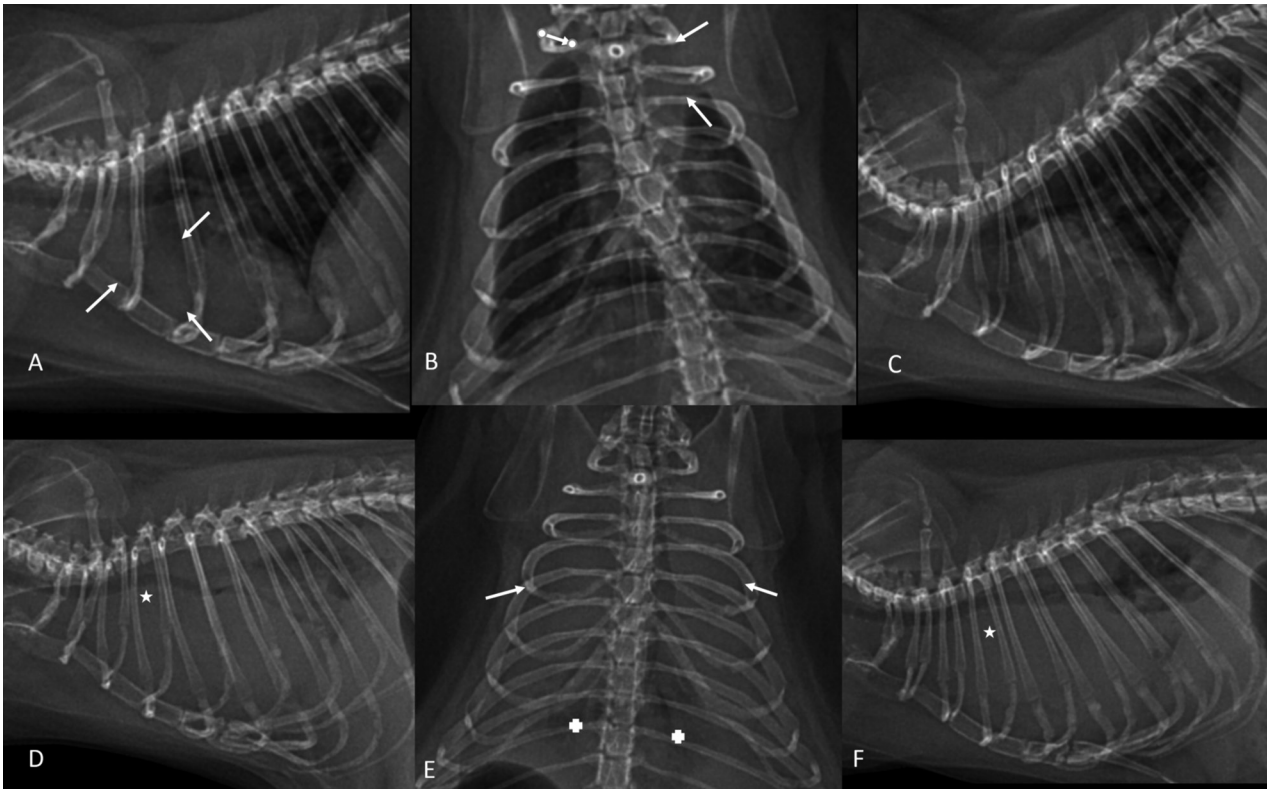

Figure 2—Right lateral (A, E), left lateral (B, F), and dorsoventral (C, D) radiographs of case 5. While initially diagnosed as pulmonary consolidation, the images are consistent with a mediastinal mass. The mass (arrows) progresses from initial diagnosis (A, B, C) until recheck 4 weeks later (D, E, F). In the initial radiographs, the mass occupies the left cranial thorax and displaces the left lung lobe caudally. The mass progresses and occupies a majority of the thorax in the follow-up images, completely silhouetting with the cardiac silhouette and causing caudal displacement of lung lobes (plus signs). At this time point there is focal dorsal displacement of the trachea in the lateral projections (stars) and a possible component of pleural effusion causing the diffuse increase in thoracic opacity.

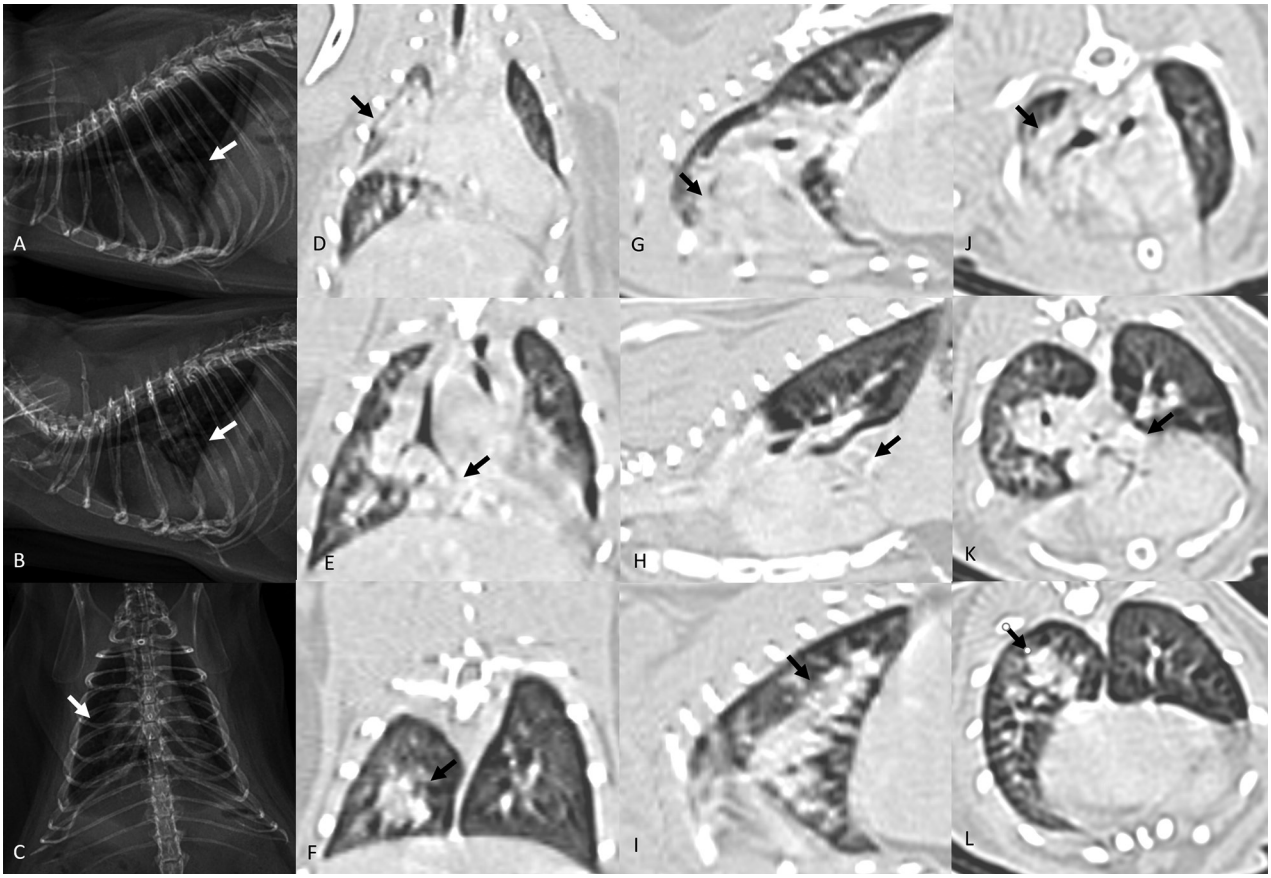

Figure 3—Right lateral (A), left lateral (B), and dorsoventral (C) radiographs of case 4 demonstrating a left caudal lung nodule (lateral radiographs) and mild increase in right pulmonary opacity (dorsoventral projection). At the time there was thought to be cranial mediastinal widening. Two months later, CT of the thorax in a lung window shown in the dorsal (D, E, F), sagittal (G, H, I), and transverse (J, K, L) planes demonstrate various lesions. Regions of increased attenuation (alveolar pattern) were seen in the right cranial and middle lung lobes. A linear increase in attenuation tracking along the lobar bronchus of the right caudal lung lobe as well as complete consolidation of the accessory lobe were seen. No changes were noted in the left lung lobe and the mediastinum was normal. The left lobar nodule seen radiographically was likely due to the accessory lung lobe lesion and the apex of the cardiac silhouette in the dorsoventral projection.

perechoic hepatic nodules, mild to moderate splenomegaly, and bilateral central renal mineralization in case 6.

Ultrasound-guided fine-needle aspirates and cytology were performed on the 2 cases with cranial mediastinal masses (case 3 and 5). For case 3, the majority of cellular material was composed of moderate to marked numbers of large lymphocytes. The lymphocytes had a loosely clumped chromatin pattern with evidence of single, to multiple, variably sized nucleoli and frequent atypical mitotic figures were noted. The cytoplasm was described as scant and deeply basophilic. For case 5, cytology identified a monotypic population of large lymphocytes with features of immaturity and evidence of increased mitotic activity. For both cases, the final interpretation based on the microscopic findings was lymphoma. Case 6 had mild to moderate splenomegaly noted on abdominal ultrasound. Ultrasound-guided fine-needle aspirates of the spleen were performed, and cytology was unremarkable. The spleen displayed a focal infarct on postmortem but there was no neoplastic infiltration into this organ. A summary of the diagnostic results can be found online **(Supplementary Table S2)**.

Treatment and case outcome

Five out of the 7 cases were diagnosed on postmortem alone. The 2 cases with an antemortem diagnosis via cytology underwent a chemotherapy protocol in addition to supportive treatments. Both rats were treated with antimicrobial therapy due to the immunosuppression and potential for unmasking of underlying infectious respiratory disease. Upon diagnosis, case 3 received 400 U/kg of L-asparaginase subcutaneously (2000 U/mL compounded medication; Wedgewood Pharmacy), 0.2 mg/kg of dexamethasone IV, (dexamethasone-SP; VetOne) and was dispensed 2 mg/kg of prednisolone (prednisolone, 5 mg/mL oral liquid, compounded medication; Ontario Veterinary College) orally, once daily, and 1 mg/kg of omeprazole (omeprazole, 2 mg/mL oral liquid, compounded medication; Ontario Veterinary College) orally, once daily. Five days following diagnosis, 5 mg/kg of lomustine (lomustine, 40 mg/mL peanut butter oil suspension, compounded medication; Chiron Compounding Pharmacy Inc) was administered orally. Seven days following diagnosis, a sec-

ond dose of 400 U/kg of L-asparaginase was given subcutaneously due to worsening in respiratory effort and the previous positive response that was seen following initial administration of the drug. Within the first 10 days following the second dose the animal was reported to have a decreased appetite and some remaining increase in respiratory effort at home; however, overall, the owner noted the rat seemed improved following the second L-asparaginase treatment. Twenty-four days following diagnosis and initiation of chemotherapy, case 3 presented to the hospital for humane euthanasia due to concerns for quality of life. At home, the owner noted that the appetite and energy had become markedly decreased. Case 3 had a survival time of 24 days following diagnosis and initiation of treatment.

One day following diagnosis, case 5 was given 2 mg/kg of diphenhydramine (diphenhydramine HCl injection USP, 50 mg/mL; Sandoz) subcutaneously and 440 U/kg of L-asparaginase. Two days following diagnosis, this animal was also given 0.2 mg/kg, IM, of dexamethasone-SP. On the third day following diagnosis, 2 mg/kg of prednisolone was initiated orally, once daily (prednisolone 25 mg/mL, oral liquid, compounded medication; Ontario Veterinary College). The delay in initiating corticosteroid therapy was due to the fact that the patient had initially been treated with an NSAID and a wash-out period was performed to reduce the risk of gastric ulceration. Four days following diagnosis, case 5 was given lomustine, 5 mg/kg, orally, once. The patient initially improved with treatment and was able to be weaned out of oxygen and discharged from the hospital. However, after a few days at home the patient began to have increasing respiratory effort again. Case 5 had a survival time of 12 days following diagnosis, 11 days following administration of L-asparaginase and 1 week following administration of lomustine. Case 5 experienced severe progression of dyspnea and underwent cardiac and respiratory arrest prior to presentation to the hospital. Many animals in this retrospective study demonstrated several months of clinical signs prior to reaching a definitive diagnosis **(Supplementary Table 3)**. It can be presumed, that at least in some of these cases, the clinical signs related to the lymphoma.

Postmortem findings

The description of organ involvement and the postmortem findings for each of the rats are presented in Table 2 and 3 **(Tables 2 and 3)**. In brief, 3 cases were diagnosed as mediastinal lymphoma with dissemination to other organs, 1 case was a multicentric lymphoma, 1 case was a lymphoid leukemia, and 2 cases were lymphoma of pulmonary origin, 1 confirmed as a T-cell lymphoma based on IHC (partial reactivity for CD3, the reactivity for other markers (CD20, CD79, Pax5) was weak/unapparent), and 1 case was diagnosed as lymphoid leukemia. Pulmonary culture demonstrated mycoplasmosis on 2 of the rats in this retrospective study.

Table 2—Necropsy findings of organ involvement in 7 cases of lymphoma in pet rats presented to the Ontario Veterinary College, Avian and Exotics Service from 2008 to 2020.

Case	Pulmonary	Mediastinal	Thymus	Lymph nodes	Hepatic	Splenic	Gastrointestinal	Cardiac or epicardial fat	Bone marrow/ blood
1	X	X	X			X			
2	X			X					
3	X	X	X	X	X	X			X
4	X	X						X*	
5		X	X				X		X
6	X				X				X
7	X								

*Epicardial fat.

Table 3—Description of relevant postmortem findings of 7 cases of lymphoma in pet rats presented to the Ontario Veterinary College, Avian and Exotics Service from 2008 to 2020.

Case	Postmortem findings
Case 1	Thymic and splenic lymphoma with focal pulmonary spread
Case 2	Multicentric lymphoma involving the mesenteric and mediastinal lymph nodes *Mycoplasma pulmonis* bronchopneumonia
Case 3	Thymic origin lymphoma Involvement of lungs, liver, spleen, and lymph nodes
Case 4	Round cell neoplasm (lymphoma) affecting lungs, mediastinal, and epicardial fat
Case 5	Lymphoma (suspect thymic) with peripheral invasion of heart and spread to colon High suspicion of large cell lymphoma based on size of neoplastic lymphocytes
Case 6	Bone marrow exam showed trilineage hyperplasia with increased lymphocytes – consistent with lymphoid leukemia with pulmonary and hepatic involvement *Mycoplasma pulmonis* neutrophilic bronchopneumonia
Case 7	Pulmonary T-cell lymphoma, large cell, intermediate grade

Discussion

The results of the present study demonstrate that lymphoma is a common neoplasm of companion rats (prevalence 4.73%) and should be considered as a differential diagnosis in rats that present with respiratory signs as well as nonspecific clinical signs. The rats in this case series varied in some aspects of clinical presentation, but overall, a respiratory component, multicentric presentation, and poor prognosis were key clinical features in all cases. Of the 35 rats evaluated, 17 (48.57%) presented with respiratory distress, 7 (7/17, 41.18%) of which were diagnosed with lymphoma. The number of rats with lymphoma in the present study might have been artificially increased relative to the number of rats with lymphoma in the general population because rats examined at a referral hospital likely have more advanced disease and clinical signs compared to those that are examined at primary care hospitals. In addition, rats that fail to respond to standard antibiotic treatment for respiratory signs are more likely to present to a specialty hospital for more advanced diagnostics. Additional bias in the population was provided by including only those that had necropsy.

Of the 7 cases in the present study, there was a varied sex distribution for the development of lymphoma, with 2 intact males, 1 intact female, 1 ovariectomized female, and 3 castrated males. Previous studies that discussed morphology of hematopoietic neoplasms in rats as well as imaging methods for dyspneic rats have not demonstrated an apparent sex predilection for rats with hematopoietic neoplasia, including lymphoma and leukemia.[19,20] With the current numbers in this study, it is difficult to draw conclusions if the disease may be more common in males or females at this time.

For the seven cases in the present study, the median age at death was 2.08 years old, with the youngest rat being 1.7 years and the oldest rat being 2.6 years. The average lifespan of rats is 2.1 to 3.3 years, with the maximum reported life span as 4.6 years.[5] With the average age of this study's cases being close to that of the average lifespan of a pet rat, this is consistent with reports that document the incidence of lymphoblastic lymphoma increases with age in rats.[19]

The most common presenting complaint for the rats in this study was evidence of respiratory compromise, seen in all 7 rats in the present study both by the owner at home, and confirmed on physical examination. While the primary differential for rats with respiratory disease is typically infectious pneumonia,[21] this study demonstrates that it is important to consider lymphoma as a differential diagnosis, as 7 out of the 17 rats with respiratory compromise were found to have lymphoma. Infectious respiratory disease in rats is most commonly the result of a bacterial pneumonia with a secondary viral component and resultant chronic respiratory disease.[5,21] In a study evaluating rat thoracic radiographs in comparison with the postmortem diagnosis, lymphoma represented 72% of the neoplastic group, with lesions most commonly located in the cranial mediastinum.[22] In this study, the radiographic interpretation was challenging and there were some difficulties differentiating pulmonary changes, cardiac changes, and mediastinal changes on radiographs. Additionally, some of the cases had evidence of suspected mediastinal change, such as widening, but no distinct mass noted. In this study, solitary to multifocal intrathoracic nodules were noted in five cases and a distinct cranial mediastinal lesion was noted in 1 case. Additionally, one rat was initially interpreted to have pulmonary changes on radiographs, but later was discovered to have a mediastinal mass on thoracic ultrasound (case 5). It is known that thoracic radiographs present limitations regarding the ability to differentiate between infection and neoplasia.[22] A previous study indicated that the presence of cranial mediastinal lesions on radiographs may be helpful to differentiate neoplastic from infectious disease in rats, although mediastinal lesions were often difficult to detect on radiographs in this study.[22] In case 6, a blood smear was obtained just prior to euthanasia, which would have resulted in antemortem diagnosis of lymphoid leukemia had the animal not been euthanized. This demonstrates the importance of hematologic assessment in ill rats.

Two rats in this series had concurrent mycoplasmosis. The respiratory compromise noted in case 2 was likely secondary to the bronchopneumonia due to *Mycoplasma pulmonis* as well as the multicentric lymphoma reported on postmortem. Case 6 had lymphoid leukemia with lung involvement; and the antemortem respiratory distress was likely compounded by the severe neutrophilic bronchopneumonia due to *M pulmonis*. Three cases had mediastinal lymphoma, presenting a likely space occupying lesion in the cranial mediastinum that contributed to the respiratory distress.

Treatment using L-asparaginase, and chemotherapeutics including lomustine, and prednisolone was attempted in 2 cases in the present study. Case 3 was noted to have moderate but short-term improvements in respiratory effort and appetite after administration of treatments, while case 5 showed an initial improvement followed by acute worsening of clinical signs and death. In canine patients diagnosed with lymphoma, the multi-agent CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) protocol is usually the recommended first line therapy[23]; however, in rats of the present study, due to the challenges associated with intravenous catheter placement and routine blood monitoring, an oral and subcutaneous protocol was selected for safety of the patient and ease of administration. All of the drugs utilized in the treatment of these rats were extralabel and administered with owner consent and complied with provisions of the Animal Medicinal Drug Use Clarification Act. Compounded products were prepared from bulk substances due to small patient size with recognition that there may be differences in pharmacokinetic properties of compounded drugs. The only previously reported treatment of lymphoma in rats is derived from an experimental study in an inbred strain of rats.[24]

Although most rats in this study were diagnosed postmortem, treatment was attempted in 2 of the 7

rats, with each rat only living 11 and 24 days after the initial diagnosis and initiation of treatment. In canine patients with lymphoma, the prognosis is highly variable and depends on a wide variety of factors. Characteristics such as immunophenotype, WHO substage, as well as various antigen receptor expression have all been demonstrated as factors that influence the response to therapy and the duration of response to therapy.[14] In canine patients, mediastinal lymphoma has been reported to have an overall poor prognosis, with survival time improved with the use of a CHOP protocol.[25] It is not known if lymphoma behaves similarly in rats, or if these prognostic factors apply to them. More information is required to accurately determine a prognosis for lymphoma in rats.

Four rats in this study shared a household and 2 rats shared another household. This raises the possibility of an environmental component to the development of lymphoma in these animals.[26] In addition, an interesting consideration would be whether the inflammation associated with chronic respiratory disease could be involved in the development of neoplasia.[27] Two of the rats in the present study were positive for *M pulmonis*.[27]

Previous reports of lymphomas and leukemias in rat and mice laboratory populations demonstrated induction after exposure to retroviruses or chemicals[13]; however, a direct comparison cannot be easily made to pet rats.[19,20] Additionally, the genetics of domestic companion rats represent a different population than those of Wistar or Sprague-Dawley that are typically used to induce and study lymphoma and leukemia.[28] The rats in the present study came from an unknown genetic background.

Limitations to the present study include its retrospective nature, the cases being limited to 1 hospital, the fact that only rats that presented for postmortem were included, and the evaluation of the cases being reliant on what is written in the medical records. Only rats that had complete postmortem reports were included to complete case information. Additionally, due to the retrospective nature of this study, it is difficult to speculate on possible causes of these neoplasms.

In the present study, lymphoma was a common neoplasm in companion rats that underwent postmortem exam at a veterinary teaching hospital between 2008 to 2020. In contrast to what has been reported by some authors, lymphoma was common in this group of rats at this institution, found in 20% (7/35) of all rats submitted for postmortem during this time period. All of the rats in this study presented with some degree of respiratory compromise and this study highlights the challenges associated with distinguishing infectious from non-infectious respiratory disease in rats. The standard of care for rats presented to a veterinary hospital with respiratory signs, especially those that do not improve with antibiotics, should include a thorough diagnostic workup with radiographs and potentially advanced imaging with aspirates for cytology as indicated to help ruling out neoplasia. In addition, performing postmortem examinations with histopathology and immunohistochemistry on rats that die of respiratory disease will help to provide more information about the prevalence of the various subtypes of lymphoma in rats.

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Supplementary Material

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