



Case Report

Clinical, histopathological and immunohistochemical features of a thymoma in a domestic rabbit (*Oryctolagus cuniculus*) – Case report

Isabella O. Almeida¹, Rebeca R. Alves¹, Leonardo L. Gorza^{2*}, Geovanni D. Cassali³, Mayra C. Flecher¹, Rodrigo S. Horta²

¹ Department of Veterinary Medicine Universidade Vila Velha, Vila Velha, ES, Brasil

² Department of Veterinary Medicine and Surgery, Veterinary School, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

³ Department of General Pathology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

*Corresponding author: Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais, Pres. Antônio Carlos Ave., 6627- CEP 30161-970, Belo Horizonte, MG, Brazil. E-mail: Leonardo_limagorza@hotmail.com

Submitted April, 24th 2020, Accepted June, 22th 2020

Abstract

Thymoma is a neoplasm originating from epithelial cells of the thymus. It represents the most common tumor in the mediastinal region of rabbits, followed by lymphoma. This study aims to report a case of *post mortem* diagnosis of thymoma in a rabbit (*Oryctolagus cuniculus*), with the purpose to contribute to the understanding of this disease and its diagnosis in this specie. A six-year-old male mixed breed pet rabbit (*O. cuniculus*), weighing 2.3 kg, was referred to necropsy exam. The previous clinical history included prostration, lethargy, weight loss, dysorexia and respiratory distress, evidenced mainly on the expiratory phase. Radiographs revealed pleural effusion and the presence of a mass involving the cranial and middle mediastinum, confirmed by ultrasound. In the cytological examination, it was diagnosed as a low-grade lymphoma and chemotherapy was performed with COP (cyclophosphamide, vincristine – Oncovin®, prednisolone). However, after 145 days, euthanasia was performed. At necropsy, a well delimited mass was observed in the mediastinal region, adhered to the pleura, with firm consistency and pale coloration. Histopathological analysis of the mass showed the proliferation of epithelial neoplastic cells, arranged in trabeculas and with infiltration of small lymphocytes. The immunohistochemical findings included cytoplasmic immunolabeling for cytokeratin AE1/AE3 in 90% of epithelial neoplastic cells, while CD3 was evidenced in a small number of lymphocytes (T-lymphocytes) and CD79a in B-lymphocytes localized on the neoplasia periphery. The growth fraction was estimated at 30% by Ki-67. According to the histopathological criteria for thymoma classification proposed by the World Health Organization, 2015, it was made the diagnosis of lymphocyte-rich predominantly cortical thymoma (B1 type).

Key words: lagomorph, oncology, neoplasm, thymus.

Introduction

The domestic rabbit (*Oryctolagus cuniculus*) is a mammal of the lagomorphic order and leporidea family, that stands out among non-conventional domestic animals due to its docile temperament and ease to raise, even in small spaces (9).

The incidence of spontaneous neoplasms in this specie is difficult to determine, once they are rarely maintained through all their natural lifespan (between seven and eight years), for being mainly used in researches (*in vivo* experimental models) and in breeding colonies (25). Several studies (22, 25, 29, 30, 31) have shown an increase in the occurrence of neoplasms in younger/adult and older rabbits (between two and 10 years old). The

incidence of some tumors may vary according to breed and gender, such as uterine adenocarcinoma in females. The most frequent tumors in laboratory rabbits are uterine adenocarcinoma, lymphoma, embryonal nephroma and bile duct adenoma, while in pet rabbits the uterine adenocarcinoma continues to be the most common, followed by lymphoma/lymphoid leukemia, mammary tumors (such as papilloma and adenocarcinoma), trichoblastomas and collagenous hamartomas (25).

The thymus is located in the cranial mediastinum (27), and tumors are infrequently found in this organ, in rabbits, however thymoma and lymphoma are overrepresented (19, 25). Thymoma is a neoplasm developed from the thymic epithelial cells, although it may also present a benign lymphocytic infiltration (27). In rabbits, thymoma is more frequent in aged animals, as from six years old, but it was already diagnosed in rabbits from one to 10 years old (26). It represents approximately 8% of all rabbit neoplasms and is a relatively common necropsy finding (7). However, once this specie does not present complete thymic remission with age, the gross differentiation between hyperplastic process, frequent in domestic rabbits (25) and mediastinal lymphoma thymic (or nodal) (19) can be difficult.

Although the differentiation degree might influence thymoma's invasiveness and metastatic potential, the thymoma's biological behavior is usually defined by its invasiveness and respectability, and not to its histopathological features, therefore, all tumors are considered potentially malignant. Usually, thymoma present a slow growth rate, although it can cause pleural, thoracic, and/or abdominal organs invasion (17).

The main clinical signs are exercise intolerance, dyspnea, cough, bilateral exophthalmos and/or third eyelid protrusion (31). Diagnosis is made by clinical history and physical exam, associated with imaging evaluation, such as radiographic, ultrasound and thoracic computed tomography, that confirm the presence of a mass into the cranial mediastinum (26), but ultimately fine needle aspiration cytology of the mass and/or pleural effusion and/or histopathological examination, sometimes, associated with immunohistochemistry (15). Surgical resection and/or radiotherapy accounts for the standard treatment (17).

This study aims to report a case of *post mortem* diagnosis of a thymoma, in a pet rabbit (*O. cuniculus*), with the purpose to contribute to the understanding of this disease and its diagnosis in this specie.

Case Report

A six-year-old male mixed breed pet rabbit (*O. cuniculus*), weighing 2.3kg, was referred to *post mortem* exam. The previous clinical history included prostration, lethargy, weight loss, dysorexia and respiratory distress, evidenced mainly on the expiratory phase. At physical

examination, it was observed a good body condition score, however apathy, respiratory frequency of 60 mov/min, normal colored oral mucosa but hyperemic ocular mucosa. Cardiopulmonary auscultation revealed hypophonesis in the ventral thoracic region with muffling of cardiac and respiratory sounds. In addition, it was observed multifocal areas of alopecia in the flank, thorax, tail, neck, thoracic and pelvic limbs, with the presence of scabs, hypotrichosis, mild pruritus, dryness and desquamation of the skin (Fig. 1). Complementary exams included complete blood count, thorax radiography and ultrasound-guided fine-needle aspiration of the mediastinal mass for cytological evaluation. Complete blood count revealed leukocytosis ($21\,200/\text{mm}^3$; Ref: $5\,000 - 12\,000/\text{mm}^3$) by lymphocytosis ($10\,600/\text{mm}^3$; Ref: $3\,360 - 7\,000/\text{mm}^3$), segmented neutrophilia ($9\,900/\text{mm}^3$; Ref: $1\,490 - 3\,210/\text{mm}^3$) and monocytosis ($700/\text{mm}^3$; Ref: $50 - 450/\text{mm}^3$). The thoracic radiographs (ventro-dorsal, left and right laterals projections), showed an increased radiopacity in the cranial and middle mediastinum, dorsal displacement of the trachea, and opacification of pulmonary fields, along with bronchial pattern (bronchial walls enlargement) (Fig. 2). The material obtained for cytology was stained with Diff-Quick and it was suggestive of mediastinal low-grade lymphoma, due the large number of small lymphocytes. Thus, the clinician chose to begin chemotherapy with the association of cyclophosphamide, vincristine (Oncovin®) and prednisolone (COP) (Table 1). However, 21 weeks after the beginning of the treatment, the animal showed worsening of the respiratory condition besides ataxia. Due to the poor patient's clinical condition, the pet's owner decided for euthanasia, resulting in a survival time of 145 days from the diagnosis.



Figure 1. A six-year-old male mixed breed pet rabbit, weighing 2.3kg, diagnosed with thymoma. Note multifocal areas of alopecia in the flank, thorax, tail, neck, thoracic and pelvic limbs, associated with desquamation of the skin.

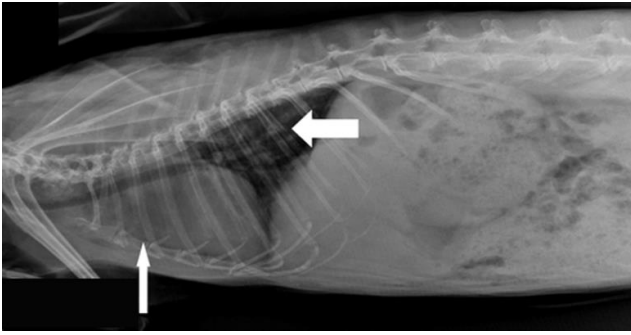


Figure 2. Radiographic of a six-year-old male mixed breed pet rabbit, diagnosed with mediastinal thymoma. Thoracic radiographs (lateral projection), showing an increased in radiopacity in the cranial and middle mediastinum (thin arrow), dorsal displacement of the trachea and opacification of pulmonary fields along with bronchial pattern (large arrow).

At necropsy, a well delimited mass was observed in the mediastinal region, measuring 1.4x0.8x0.2cm, with firm consistency, pale coloration (Fig. 3) and diffusely red at cut surface.

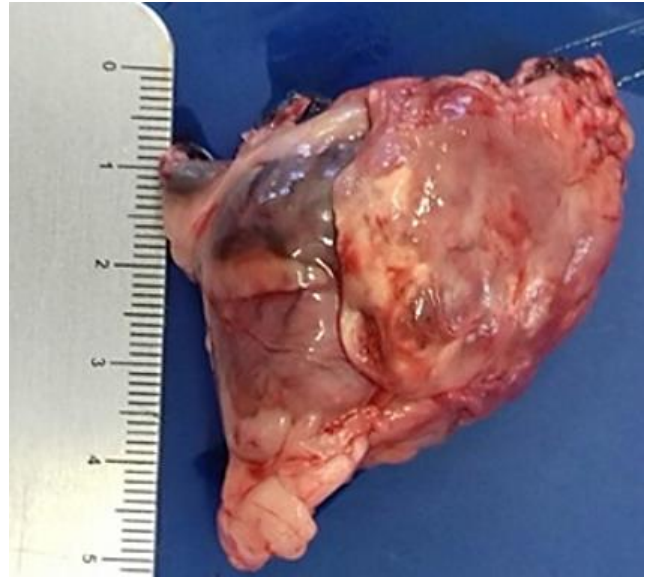


Figure 3. Pleura, heart and mediastinal thymoma, at necropsy of a six-year-old male mixed breed pet rabbit. Mediastinal mass, outside the thoracic cavity, adhered to the pleura, with firm consistency and pale coloration.

Table 1. COP Protocole (Cyclophosphamide, Vincristine and Prednisolone) adapted from Teske (2002).

Week	1	2	3	4	5	6	7	8	9	10	13	16	19
Vincristine (0,5 mg/m ² IP)	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyclophosphamide (100 mg/m ² PO)	X			X			X			X	X	X	X

IP –Intraperitoneal route; PO –Oral route; A- Body surface area (BSA) was calculated using the follow equation: $ASC = W \times (\text{weight in grams})^{2/3} / 10$. $W = 12$ in rabbits. The prednisolone was administered at a dosage of 1mg/kg every 24 hours, through the treatment. From the 20th week, vincristine and cyclophosphamide are administered every 21 days, up to one year of treatment.

Others *postmortem* findings included subcutaneous edema in the ventral region of the abdomen, large quantity of red foam fluid flowing from the trachea and pulmonary lobes (at cut section), suggesting pulmonary edema, besides hepatic congestion. Samples of the mediastinal mass were fixed in 10% buffered formalin and submitted to routine histological processing. Sections of 3µm were stained with hematoxylin and eosin and observed under light microscopy. Microscopically, it was observed an epithelial neoplastic cell proliferation,

arranged in trabeculas, showing eosinophilic cytoplasm, vesicular nuclei, moderate nuclei pleomorphism, thin chromatin, single and prominent nucleoli (Fig. 4A). There were four mitotic figures in 10 high power-fields (40x) and a diffuse infiltrate of small lymphocytes between neoplastic cells (Fig. 4B). Thus, according to the World Health Organization (WHO), it was diagnosed as a lymphocyte-rich predominantly cortical thymoma (B1 type).

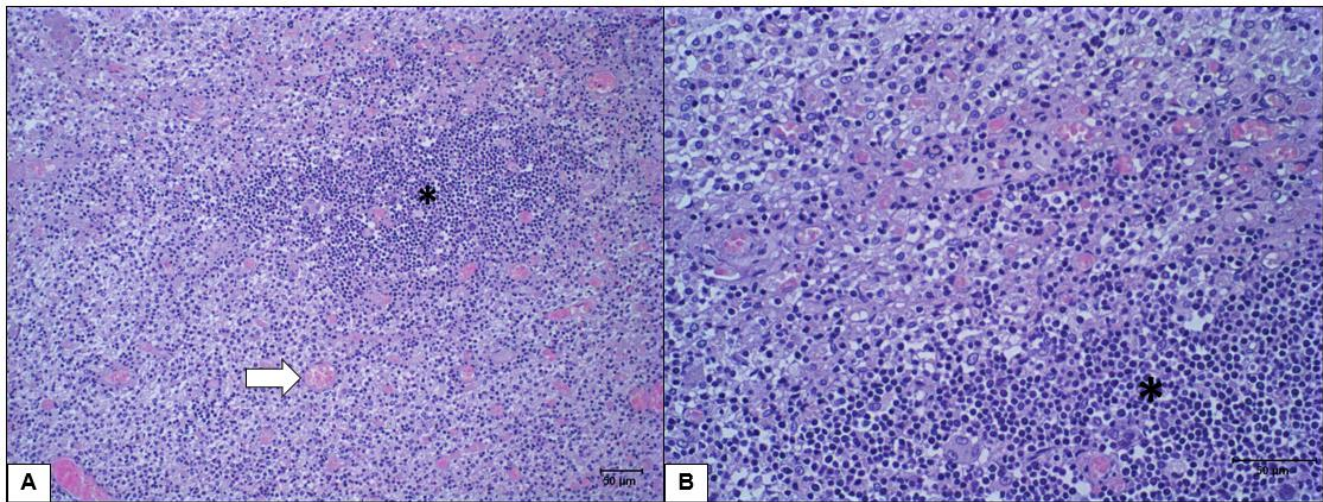


Figure 4. Histopathological findings of a thymoma from a pet rabbit. **A.** Epithelial neoplastic cells proliferation (E), arranged in trabeculas, with infiltration of small lymphocytes (*) and blood vessels (arrow). **B.** Epithelial neoplastic cells (E) showing eosinophilic cytoplasm, vesicular nuclei, moderate nuclear pleomorphism, thin chromatin, besides single and prominent nucleoli. Note between the neoplastic cells, a high diffuse infiltrate of predominant small lymphocytes, characterizing a lymphocyte-rich predominantly cortical thymoma (B1 type), according to World Health Organization, 2015.

To the best elucidation of the case, immunohistochemistry was performed. The paraffin-embedded-blocks containing samples from the mediastinal mass were sectioned at 3µm with a manual microtome and mounted on silanized slides. Antigenic recovery was performed with citrate (pH=6.0) in pressurized heat (125°C for 3 min). The primary antibodies were incubated for 18 hours and included cytokeratin AE1/AE3 (Dako, at dilution 1:100, semi-quantitative evaluation), for confirming the presence of epithelial cells, CD79a (PBS, at dilution 1:500, semi-quantitative evaluation) and CD3 (CL

Davis, at dilution 1:300, semi-quantitative evaluation) to characterize the small lymphocyte infiltrate and Ki-67 (Dako, at 1:800 dilution, semi-quantitative evaluation) to determine the cellular proliferation index. In addition to the internal controls, it was used as a positive control of the reactions a sample of canine lymph node and as a negative control the same tumor, with suppression of primary antibody. Cytoplasmic immunolabeling for cytokeratin AE1/AE3 was observed in 90% of epithelial neoplastic cells, while CD3 was evidenced in a small number of lymphocytes (T-lymphocytes) and CD79a in B-lymphocytes localized on the neoplasia periphery. The growth fraction was estimated at 30% by Ki-67 (Fig. 5).

Discussion

Thymoma is the most common mediastinal neoplasm in the rabbit, however mediastinal lymphoma (nodal or thymic) is an important differential diagnosis, mainly in cases with lymphocytic infiltration (15). Apparently, the tumor development has no relationship

with the rabbit's breed or gender, differently from lymphoma, predisposed in breeds such as New Zealand White, Multicoloured English type, Japanese White and Dutch Dwarf (8). However, most cases of thymoma in rabbits are reported in older animals, with an average age of six years old (7), corroborating with the reported case. Although lymphoma may occur in all life stages, it is most often reported in rabbits with less than two years old (26). Weight loss, apathy and inappetence are unspecific clinical signs, although they may occur in association with neoplastic diseases. The ventral pulmonary hypophonesis was compatible with pleural effusion, confirmed by thoracic radiographs, which also revealed the mediastinal mass (17). Exophthalmos, jugular vein dilation, head, neck, and thoracic limbs oedema might occur due to the compression of the cranial cava vein, which results in an increased intrathoracic pressure (14). Exophthalmos may be transitory and identified after patient's head ventroflexion (29). It can also occur in cases of extra-nodal lymphoma. However, these clinical features were not reported in this case.

Many paraneoplastic syndromes are associated with thymoma, such as lymphocytosis, thrombocytopenia, anemia, hypercalcemia, myasthenia gravis, megaesophagus and exfoliative dermatitis (4, 10, 27, 29). All animal's species with reported thymomas, including rabbit, dog, cat, goat, sheep, swine, horse and cattle are predisposed to the development of the described paraneoplastic syndromes (27). However, myasthenia gravis and hypercalcemia are mostly associated with thymoma in dogs and cats (5, 10, 27) and the exfoliative dermatitis only in cats (5, 27).

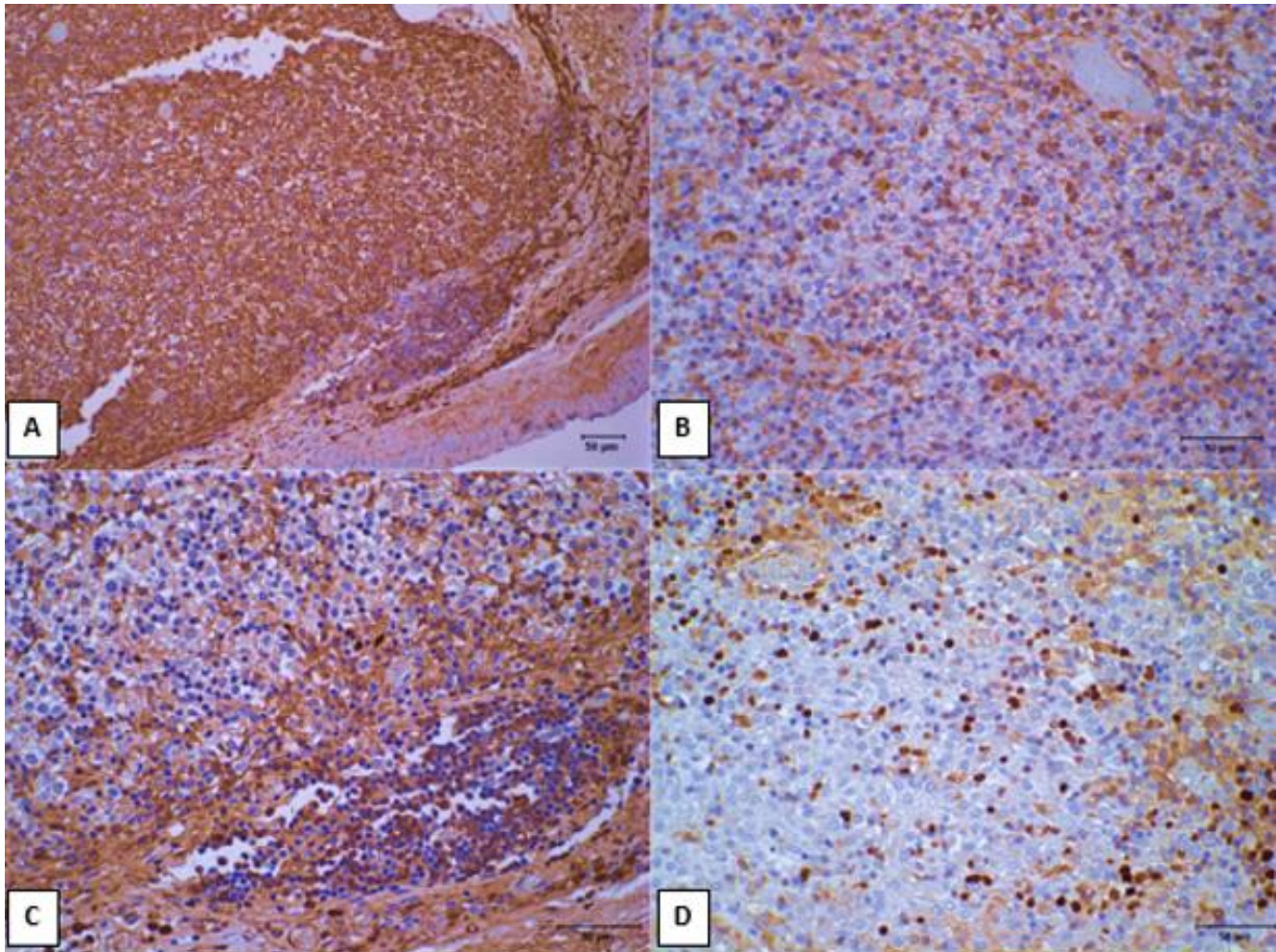


Figure 5. Immunohistochemistry of a thymoma predominantly cortical lymphocyte-rich (type B1) from a pet rabbit. **A.** Cytoplasmic immunolabeling for cytokeratin AE1/AE3 in 90% of epithelial neoplastic cells. **B.** Small number of T-lymphocytes showing a positive immunolabeling for CD3. **C.** Lymphocytes localized on the neoplastic periphery with cytoplasmic immunolabeling for CD79a (B-lymphocytes). **D.** Immunolabeling for Ki-67 in 30% of tumor cells.

Lymphocytosis is a relatively rare finding in dogs with thymoma (2), however, it was reported in 4/13 (30.7%) rabbits with thymoma (15) and also in the presented case, which also showed neutrophilia and monocytosis probably associated with inflammation (24). The mechanism for thymoma's associated lymphocytosis involves tumor's lymphopoiesis and production of polyclonal CD4+ and CD8+ T cells. In addition, there are decreased autoimmune regulators stimuli and reduced expression of the major histocompatibility complexes (MHC) molecules, resulting in export of autoreactive T lymphocytes to the periphery, particularly CD4+, that stimulate the proliferation and differentiation of B lymphocytes, which can circulate increasing its blood count (27). The thymectomy was proven an effective method for controlling these paraneoplastic syndromes, with reduction in lymphocytes counts in a dog 24 hours after surgery (2).

Anemia and thrombocytopenia are hematological abnormalities that can occur in association with thymoma due to an autoimmune response triggered by the tumor. As an immunological disorder, it can lead to bone marrow suppression and aplastic anemia (3). Hypercalcemia is reported at 1/3 of the dogs with thymoma as it occurs due to production of the parathyroid hormone-related protein (PTHrP) (27). However, these abnormalities were not observed in the reported case.

Myasthenia gravis and megaesophagus, can also occur in animals with thymoma, as dogs, cats and goats (10, 18). Myasthenia gravis occurs in up to 47% of dogs with thymoma (10), associated with the production of serum antibodies against acetylcholine receptor (27). However, according to the author's last consent it has not been reported in rabbits.

The reported rabbit showed signs of chronic cutaneous dermatitis, including alopecia, scabs and skin desquamation. Cats with thymoma may develop

exfoliative dermatitis secondary to the tumor, which is presented at microscopy as an interface dermatitis, characterized by an inflammatory infiltrate, predominantly lymphocytic, with few mast cells and plasma cells in the dermis (21). Additionally, it has been observed hyperkeratosis, hydropic degeneration, infundibular lymphocytic mural folliculitis and absence or decrease in the number of sebaceous glands (21). However, histopathological evaluation of the skin was not performed in the present case, thus it was not possible to confirm such diagnosis.

In summary, clinical suspicious of mediastinal neoplasm can be obtained by history, physical exam, haematological abnormalities, as well as imaging exams, as thorax radiographs, abdominal and thoracic ultrasound, for evidences of tumor infiltration in different tissues, contributing for disease's clinical staging. Although metastasis was not detected in this case, imaging exam allowed identification of the mediastinal mass and pleural effusion (23, 32). The thoracic radiograph is the initial complementary exam for thorax's evaluation in patients showing dyspnea and exercise intolerance or abnormalities in pulmonary auscultation (1). Mediastinal masses can be identified with variable size and they can also cause displacement of the trachea as observed in this case. The suggestive diagnosis may be performed by cytological analysis of the tumor, but must be confirmed by histopathological exam, in which the samples can be initially obtained by biopsy with tru-cut needle, thoracoscopy or thoracotomy followed by mass extirpation (22). However, immunohistochemistry may be required to confirm the diagnosis, mainly in cases with lymphocytic infiltration which makes thymic lymphoma an important differential diagnosis (19). Ki-67 might have been overestimated once it is difficult to differentiate neoplastic epithelial cells from lymphoid cells without an immunohistochemistry double staining technique, nevertheless, care was taken using serial cuts with immunolabeling comparison. The cytology can be helpful, especially in cases with adequate cellularity and scarce inflammatory cells (17). In a retrospective study (15), it was revised the medical records of 13 domestic rabbits with mediastinal masses, in a period of three years. All cases were compatible with thymoma and there was a positive correlation between cytological and histopathological diagnosis in all cases (15). However, lymphocytic infiltration may favor a wrong diagnosis of small cell mediastinal lymphoma (27), as occurred in the present report, and mislead the therapeutic decision. In 2015, it was published the 4th edition of the World Health Organization (WHO) Classification of tumors of the lungs, pleura, thymus and heart (16). In this classification, the thymoma subtypes were differentiated by letters and numbers (A, AB, B1, B2, B3) (16). The obligatory histopathological criteria for each subtype are summarized in table 2. In a study done in 13 domestic rabbits diagnosed

with mediastinal thymoma, the lymphocyte-rich (type B1) was the most frequent type, representing six cases (6/13), followed by mixed lymphoepithelial (type AB) (4/13) and epithelial predominant (type B3) (1 /13) (15). In this same study, immunostaining was performed for cytokeratin on the lymphocyte-rich tumors, to confirm the diagnosis, since the histopathological differentiation between thymoma and lymphoma can be difficult in such cases (15).

In cases of thymoma in rabbits, surgery must be considered the treatment of choice (17), because these tumors, in most cases, are not invasive and offers a great probability of cure, despite the risks in the pre and post-operative periods. The association between surgery and radiotherapy is recommended, choosing mainly hypofractionated protocols, to avoid excessive anesthetic procedures (17, 22). This therapy can result in side effects such as fibrosis in the local organs including lungs, heart and blood vessels. For lymphoma, surgery and radiotherapy can offer an effective loco-regional control, however, considering the systemic behavior of the disease, it does not result in lifespan's increase (6, 17). Previously, the reported animal has been incorrectly diagnosed with lymphoma and associated with the limitations related to surgery in cases of lymphoma, chemotherapeutic treatment was performed. Chemotherapy, as the COP protocol, is the most indicated treatment in cases of mediastinal lymphoma. However, satisfactory results are unlikely for thymomas in rabbits, dogs and cats, with available protocols. In humans, the treatment is performed according to tumor stage (I, II, III and IV), and other factors, such as involvement of the great vessels and arteries, pericardium, trachea, mediastinum and metastases to extrathoracic organs (13). For patients in stages I and II, the complete surgical resection is highly indicated, with a careful exploration of the entire mediastinum and saving the phrenic nerve (13). The indication of neoadjuvant chemotherapy, using combinations such as cisplatin, doxorubicin and cyclophosphamide, associated or not with prednisone, are recommended for stages III and IV (13). Nevertheless, this therapeutic modality for invasible and/or metastatic thymomas, has not been reported in rabbits (17). Studies of rabbits' sensibility to chemotherapeutic agents and glucocorticoids are scarce. Nevertheless, severe side effects are reported in rabbits after chemotherapy, including collapse (28), inappetence, weight loss, gastrointestinal stasis (15) and infectious disease manifestation, by *Encephalitozoon cuniculi* and *Pasteurella multocida*, once rabbits may be carriers of such agents which may emerge in a consequence to the immunosuppression, caused by chemotherapeutic drugs (20). In rabbits, before chemotherapy, it might be recommended bacterial culture and antibiogram from "nasal swab", and also prophylactic therapy for encephalitozoonosis and pasteurellosis, with administration of sulfonamide-trimethoprim (15mg/kg PO

every 12 hours, for seven days) and febendazole (20mg/kg PO every 24 hours, for 28 days). The reported rabbit was treated with COP protocol and showed worsening in the clinical condition after 21 weeks, however, it was not possible to correlate the clinical worsening with the chemotherapeutic treatment. The clinical condition deterioration can be associated with the ventricular compliance impairs, due to the cardiac compression caused by the mediastinal mass, resulting in organs congestion and pulmonary edema, explaining the respiratory distress

evidenced. About the neurological signs, the animal may have developed encephalitozoonosis, due to the immunosuppressive effects of chemotherapy. Yet, histopathological analysis of the brain was not performed in the present case due to autolysis. A prevalence of 52% of the disease was demonstrated in rabbits from the United Kingdom, however, only 6% of animals showed clinical signs (12). However, there are no studies about its prevalence in Brazil.

Table 2. Histological criteria of thymoma classification according to World Health Organization, 2015 (adapted from Travis et al., 2004).

Thymoma subtype	Histological criteria
Type A (medullary)	Presence of spindle shaped epithelial cells with few or absence of immature T-cells. Atypical type A variant show in addition comedo-type tumor necrosis and increased mitotic count ($>4/2\text{mm}^2$).
Type AB (mixed)	Presence of spindle shaped epithelial cells and abundance of immature T lymphocytes
Type B1 (predominantly cortical)	Abundance of immature T lymphocytes, areas of medullary differentiation and paucity of polygonal or dendritic epithelial cells. This type has the thymus-like-architecture
Type B2 (cortical)	Increased number of polygonal or dendritic epithelial cells with abundance of immature T lymphocytes
Type B3 (well-diferentiated thymic carcinoma)	Tumor has a lobular growth pattern. Clusters of polygonal epithelial cells slightly to moderately atypical and scarces or absent intermingled T lymphocytes
Type micronodular with lymphoid stroma (MNT)	Multiple, discrete or focally confluent nodules formed by bland spindle or oval epithelial cells, surrounded by a cell-free lymphoid stroma
Type metaplastic	Tumor consisting by solid areas of epithelial cells in a background of bland-looking spindle cells and absence of immature T lymphocytes
Type microscopic	Marked heterogeneity and can be composed of bland-looking or more pleomorphic cells. Sometimes without intraepithelial immature T-cells. Preferentially occur in myasthenia gravis-associated thymomas
Type sclerosing	Presence of features of a conventional thymoma, with respect to epithelial cell morphology and lymphocyte content. However, additionally has a exuberante collagen-rich stroma
Type lipofibroadenoma	Paucity of lymphocytes and the extended narrow strands of epithelial cells into account. Occurs the predominance of stroma over the epithelial componente (ex, rare Hassall corpuscles)
Type C (thymic carcinoma)	Proliferation of malignant epithelial cells with marked cytological atypia, almost invariable invasiveness and lack of thymus like features. Other histological features will depend on the carcinoma type (squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, etc.)

The outcome for thymoma in rabbits is poor and most deaths are related to postpone surgery, post-operative complications and tumor recurrence (7, 8). However, in dogs and cats, it is estimated that for every 10% increase in the lymphocyte's tumor infiltrate there is a reduction of 35% of mortality, improving its prognosis (32). However, this information cannot be extrapolated for the reported specie.

Veterinary medicine of wildlife, exotic or unconventional domestic animals is expanding, however, in most cases the animal's owners are still reluctant for veterinary assistance, which makes difficult the studies in this field. Advances in the medical care of those patients

will be obtained from the association between veterinary specialists. The opinion of a veterinary specialist in wild animals could have prevented the risks of immunosuppressive treatment as well as the prevention of opportunistic diseases. In association with a veterinary diagnostic imaging specialist, an oncologist, surgeon and a pathologist, it would be reasonable to set the list of differential diagnoses for this case and to obtain the definitive diagnosis from histopathologic and immunohistochemistry analysis, from a tissue sample obtained in vivo. Thymectomy might have been performed, after adequate planning with computed tomography evaluation, and it would probably have

increased the patient's life expectancy and quality. In the presented case there was no agreement between cytological and histopathological diagnosis, and the differentiation between lymphoma and lymphocyte-rich thymoma can be difficult without immunohistochemistry assistance.

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