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# HISTOPATHOLOGICAL EVALUATION OF SUBMANDIBULAR LYMPH NODES AND SPLEEN OF CATS FROM THE ANIMAL PATHOLOGY LAB — UFU

Natasha Rodrigues Pontes[1]*, Heloísa Cristina Teixeira de Carvalho[2], Lígia Assunção Oliveira[3], Márcio de Barros Bandarra[4]

[1,2,3,4] Faculdade de Medicina Veterinária. Universidade Federal de Uberlândia. Uberlândia, Minas Gerais, Brasil.

*Corresponding author: natasharodriguesp@gmail.com

ABSTRACT

Lymph nodes and spleen are essential lymphoid organs, which are in strategic positions in the body of the animals. A histopathological evaluation of submandibular lymph nodes and spleen of cats received at the Animal Pathology Sector of the Veterinary Hospital of the Federal University of Uberlândia was carried out to observe and document the histological patterns found at each organ in this population of cats. Tissue fragments were collected from 30 cats immediately after the animals entered the Animal Pathology Department. These fragments were placed in a 10% formalin solution for at least 24 hours, submitted to histological processing, and slides were made for evaluation under optical microscopy. The changes found were red pulp hyperplasia (0.3%), white pulp hyperplasia (5.4%), lymphoplasmacytic capsular inflammatory infiltrate (1.2%; 1.2%), congestion (1.2%; 0.9%; 2.4%), lymphoid follicular atrophy (0.6%; 1.2%; 0.6%), hemorrhage (1.5%; 0.3%), lymphoid follicular hyperplasia (3.6% e 3.3%) and hemosiderosis (0.3%). The present work indicates the importance of microscopic evaluation of these lymphoid organs in cats because, with it, we allow for a better understanding and elucidation of the lymphoid responses shown by these animals.

**KEYWORDS:** histology, lymphoid organ, feline, *Felis catus*.

## INTRODUCTION

The secondary lymphoid organs are essential for the mobilization and activation

## ORCID ID

1 https://orcid.org/0000-0003-3390-0171
2 https://orcid.org/0000-0002-7868-0224
3 https://orcid.org/0000-0002-1162-0542
4 https://orcid.org/0000-0002-8122-2865

of defense cells during an immune response in domestic animals. Furthermore, they are also crucial in the cell drainage of their peripheric regions. The cascade of events triggered by a stimulus leads to changes in these tissues, which can be observed under microscopy (ABRAHAMSOHN; JUNQUEIRA; CARNEIRO, 2018).

Submandibular lymph nodes are located at a strategic anatomic region that enables lymph drainage from regions such as the mouth and the subcutaneous tissue of the face. The spleen is an essential organ of the hemocateretic system in animals, in addition to being an important site for removing microorganisms from the blood and local lymphoid response (SUGIMURA, 1962; FIGHERA; GRAÇA, 2016; BOES; DURHAM, 2017).

Tissues may adapt to injuries positively or negatively, depending on the nature of the injurious stimulus and the cell type. Some changes, like the increased size (hypertrophy) or the number of cells (hyperplasia), can increase the function of the organ or tissue, at least temporarily, and are considered positive adaptations. In other cases, cells can reduce in size (atrophy), and the organ or tissue has its function decreased, but this negative adaptation can have a beneficial effect in avoiding cellular death (VAN DER VALK; MEIJER, 1987; OHTAKE; SHINGAKI; NAKAJIMA, 1993), and some alterations that can be observed in lymph nodes and spleen are lymphoid hyperplasia, lymphoid atrophy, congestion, pigment accumulation and neoplasia (JONES; HUNT; KING, 2000a; JONES; HUNT; KING, 2000b; HERRING; SMITH; ROBERTSON, 2002; MILLER; ZACHARY, 2017).

Reactive lymphoid proliferations are seen in multiple infectious diseases, especially those of viral origin (FIGUERA; GRAÇA, 2016). The feline leukemia virus (FeLV) and the feline immunodeficiency virus (FIV) are two of the most common infectious diseases in cats (LEVY et al., 2008) and have a worldwide prevalence (HOSIE et al., 2009).

The behavior of these tissues to different stimuli of the organism and its respective histological findings allows the pathologist to better observe how these organs respond to these stimulations. Therefore, the objective of this paper was to evaluate the histological pattern of submandibular lymph nodes and spleen of cats, regardless of their clinical history, received in the Animal Pathology Sector of the Federal University of Uberlândia (UFU), aiming at elucidating the histological patterns found, reporting which histopathological alterations were found and contributing to the data bank for future investigations involving these organs.

## METHODOLOGY

Spleen and left and right submandibular lymph nodes were collected from 30 cats, ranging in age from 45 days to 19 years old, primarily mixed breed, of both sexes, regardless of their clinical history, antemortem physiological stage, and cause of death, which referred to the Animal Pathology Sector of the Veterinary Hospital of the Federal University of Uberlândia for histopathological evaluation, totaling 60 fragments of right and left submandibular lymph nodes and 30 fragments of the spleen. Submandibular lymph nodes were chosen because of their anatomical proximity to the oral cavity, a well-known means of entry for animal pathogens. The necroscopic examination was not performed in its entirety in this stu-

dy; only the organs of interest for the study were collected.

The animals were divided and gathered into three age groups: cubs (45 days to 11 months old), adults (1 to 6 years old), and elderly (7 to 19 years old).

Organ fragments were chosen from random locations in the spleen, and lymph nodes were collected in their entirety and placed in wide-mouth flasks containing a 10% neutral buffered formalin solution. After being fixed for at least 24 hours, they underwent histological processing. These fragments were dehydrated in solutions of decreasing alcohol concentration, cleared in xylol, and embedded in paraffin to make the histological blocks. For each animal, three blocks were made: the left submandibular lymph node, spleen fragment, and the right submandibular lymph node. Sections of the blocks were made at a 5 μm thickness with a microtome to make the histological slides, totaling two slides per animal, each containing two cuts of organ fragments. Subsequently, they were stained with hematoxylin-eosin. When finished, the slides were evaluated under an optical microscope, and the alterations found were documented.

## RESULTS

The most found alteration in the submandibular lymph nodes of the animals under study was lymphoid follicular hyperplasia (figure 1D), observed in 12/30 fragments of the right lymph node and 11/30 fragments of the left lymph node. Lymphoid follicular atrophy was found in 2/30 fragments of the right submandibular lymph node (figure 1A), both in animals belonging to the cub age group (animals between 45 days and 11 months old), and in 4/30 fragments of the left submandibular lymph node, belonging to two animals from the cub age group and two animals from the elderly age group (aged between 7 and 19 years old). The cases in which capsular lymphoplasmacytic inflammatory infiltrates were observed (figure 1C) were 4/30, both in right and left submandibular lymph nodes. Hemorrhage was observed only in the right lymph node, corresponding to 5/30, and its location varied between medullary sinuses and subcapsular sinuses. Hemosiderosis was found only in one animal's right submandibular lymph node, which concomitantly presented congestion in this organ. Congestion (figure 1B) was observed in 4/30 in the right submandibular lymph node and in 3/30 fragments in the left submandibular lymph node.

In the spleens of the animals under study, the most observed alteration was white pulp hyperplasia (figure 1C), present in 18/30 of the fragments of this tissue. The second most frequent alteration in these animals' spleen was splenic congestion (figure 2B), observed in 8/30 of the fragments of this organ. The finding of lymphoid follicular atrophy in the spleen (figure 2A) was observed in 2/30 animals, and both belonged to the elderly age group (animals between 7 and 19 years old). Splenic hemorrhage was found in only one animal, as well as red pulp hyperplasia. The animal that presented red pulp hyperplasia concomitantly presented splenic lymphoid follicular atrophy (figure 1D). All data are presented in Table 1.

The age of the animals varied from 45 days to 19 years old, and the number of animals in each age group was 8/30 cubs, 13/30 adults, and 9/30 elderly.

Figure 1: Photomicrography of submandibular lymph node of a cat. A) Lymphoid atrophy (black arrows). B) Congestion (arrows). C) Capsular lymphoplasmacytic inflammatory infiltrate (*). D) Lymphoid follicular hyperplasia (*). H.E, 10x.

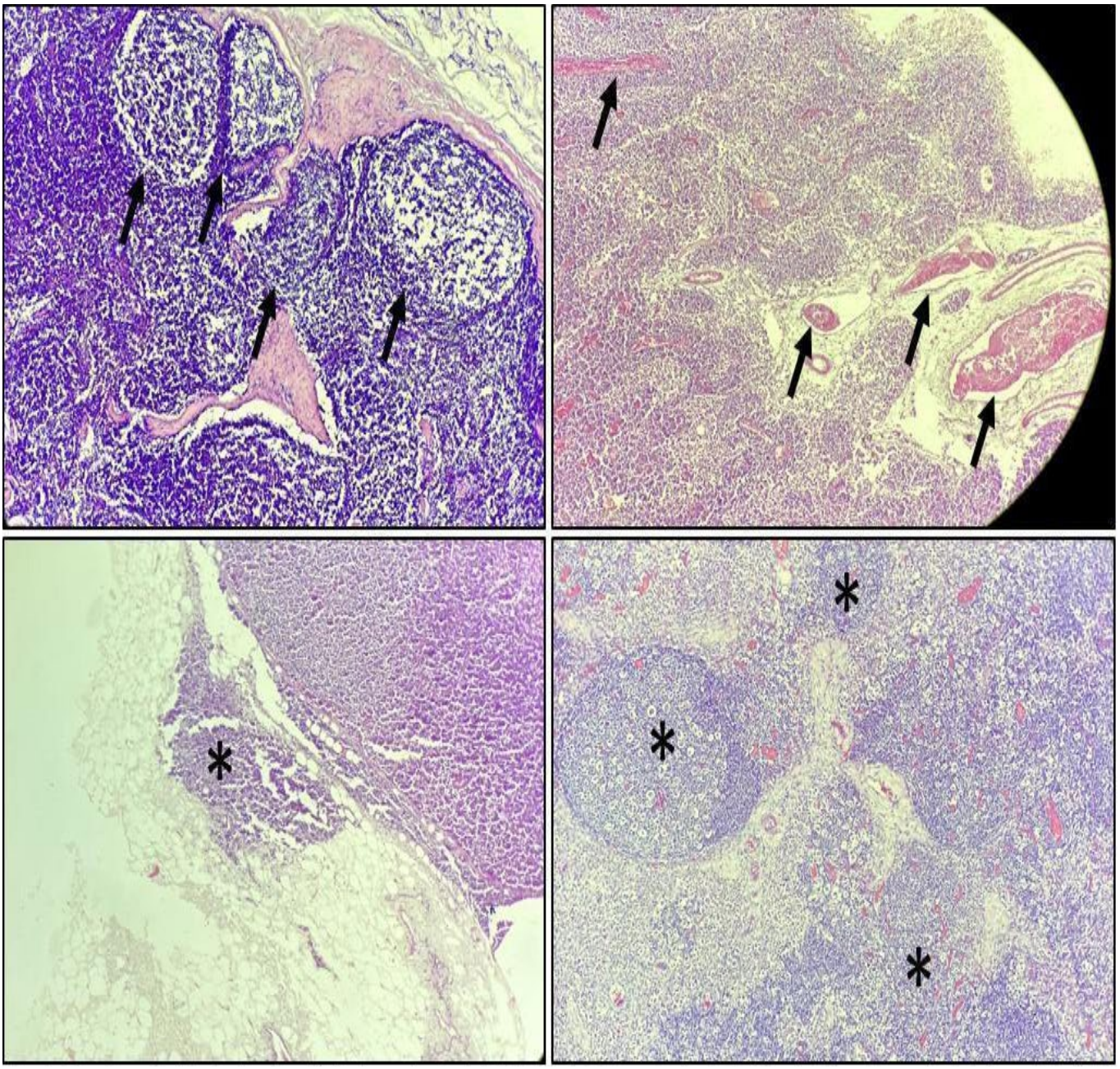

Figure 2: Photomicrography from a spleen of a cat. A) Lymphoid atrophy (arrows). B) Congestion (arrows). C) White pulp hyperplasia (*). D) Red pulp hyperplasia. H.E, 10x.

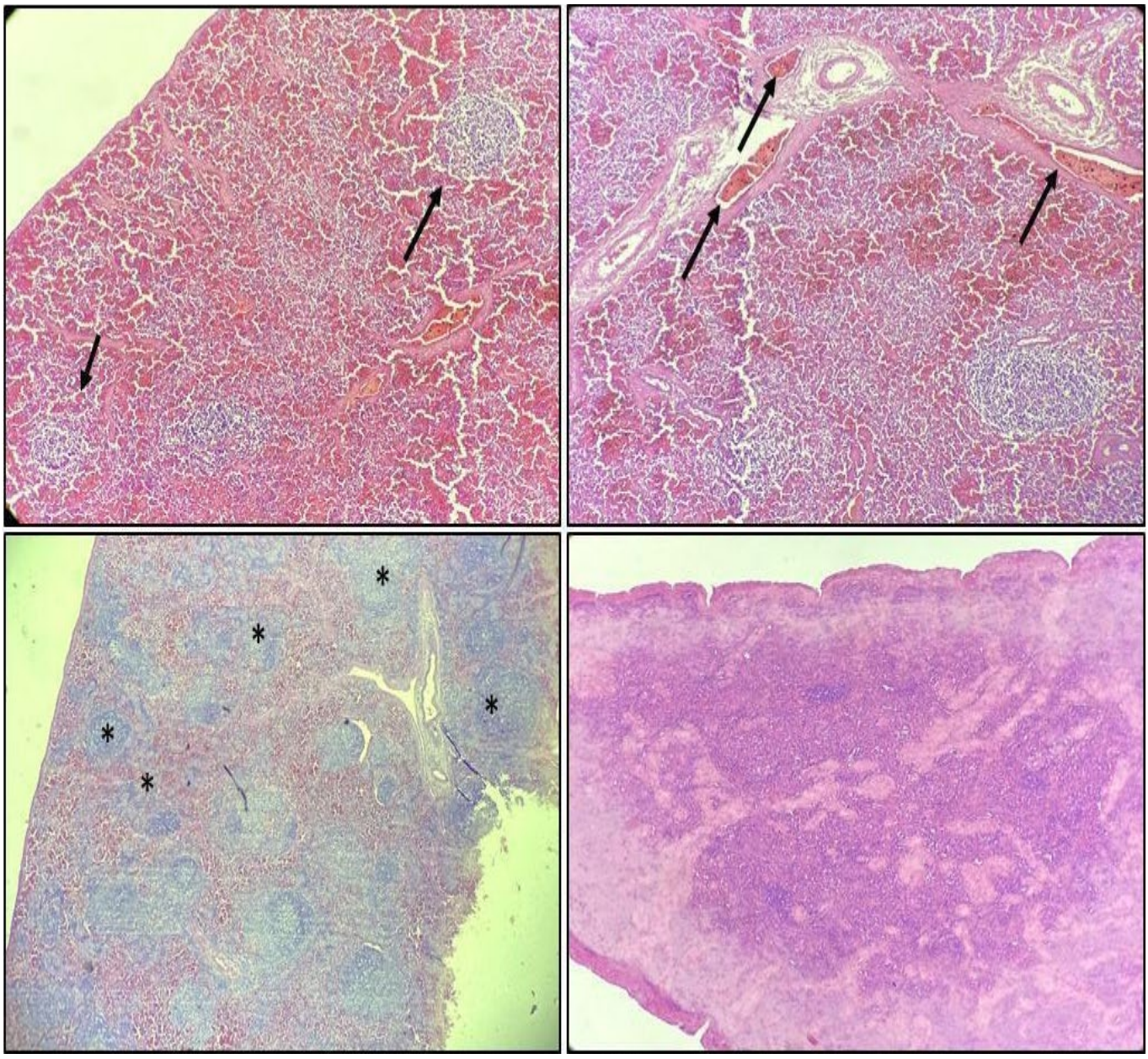

Table 1. Histopathological alterations found in submandibular lymph nodes and spleen of cats received in the Animal Pathology Sector, HV/UFU.

| | RSL (n=30)(%) | LSL (n=30)(%) | S (n=30)(%) |
|---|---|---|---|
| Capsular lymphoplasmacytic inflammatory infiltrate | 4 – 1.2% | 4 – 1.2% | - |
| Lymphoid follicular hyperplasia | 12 – 3.6% | 11 – 3.3% | - |
| Congestion | 4 – 1.2% | 3 – 0.9% | 8 – 2.4% |
| Follicular lymphoid atrophy | 2 – 0.6% | 4 – 1.2% | 2 – 0.6% |
| Hemorrhage | 5 – 1.5% | - | 1 – 0.3% |
| Hemosiderosis | 1 – 0.3% | - | - |
| White pulp hyperplasia | - | - | 18 – 5.4% |
| Red pulp hyperplasia | - | - | 1 – 0.3% |

RSL: right submandibular lymph nodes; LSL: left submandibular lymph nodes; S: spleen; Source: the author.

## DISCUSSION

Lymphoid follicular hyperplasia occurs when there is a multiplication of B lymphocytes in lymphoid follicles, leading to an increase in the size of the follicles and the appearance of lighter zones called germinal centers (WILLARD-MACK, 2006; BOES; DURHAM, 2017). This is the proliferative lymphoid alteration observed most frequently in lymph nodes of animals and is commonly seen in cases where the animal has an infectious disease, mainly due to viral agents but also caused by *rickettsiae* or protozoa. In this study, it was impossible to relate such alterations to possible pathogenic agents in the animals' bodies. When led by viral causes, histologically, the lymphoid follicular hyperplasia triggered in lymph nodes and spleen in the early stages of the viral infection is notable, but in later stages, it may vary according to the age and state of immunological stimulation of the animal and lead for example to lymphoid atrophy (ANDERSON; MCKEATING, 1970; ROGERS et al. 1975; RIDEOUT et al. 1992; BACH et al. 1994; PARODI et al. 1994; FIGHERA; GRAÇA, 2016). This hyperplasia is considered compensatory, and, in many cases, the exact nature of the stimulus for the elicited response may not be known for sure (MOORE et al., 1986; JONES; HUNT; KING, 2000a).

A distinct pattern of lymphoid follicular hyperplasia, characterized by the presence of large, irregular, partially united germinal centers, has been described in cats and is termed atypical lymphoid follicular hyperplasia. This lesion has been associated with the feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infection and is considered borderline between lymphoid hyperplasia and lymphoma (ANDERSON; MCKEATING, 1970; PARODI et al., 1994; YAMAMOTO et al. 1997; FIGUERA; GRAÇA, 2016). This finding was not observed in the animals of this study.

The cause of lymphoid atrophy in animals may be due to a normal physiological phenomenon, an idiopathic cause, or in res-

ponse to a pathological process that leads to the autoimmune destruction of follicular cells. The correlation of this finding with a specific disease in the animals cannot be elucidated. These cells within the organ may be fewer than expected due to the death of part of these cells, characterizing numerical atrophy, or they may appear in regular numbers but with reduced cell size (JONES; HUNT; KING, 2000a; MILLER; ZACHARY, 2017).

This type of atrophy can be observed in lymph nodes of individuals who survive episodes of lymphoid necrosis for a few days and may be reversible depending on the intensity and cause. At microscopy, the lymphoid follicles and the paracortex are rarefied, and macrophages full of stainable corpuscles can also be observed amidst the small population of residual lymphocytes. Some causes for lymphoid atrophy include cachexia and infection with immunosuppressive viruses, such as the feline immunodeficiency virus and feline leukemia virus. Occasionally, it can be found, in cats and some other animals, moderate atrophy of the superficial and deep lymph nodes distributed diffusely in the tissue in elderly animals, which is called senile nodal atrophy, of commonly idiopathic cause (ANDERSON et al. 1971; SCHULLER□LEVIS et al. 1990; RIDEOUT et al. 1992; BACH et al. 1994; ROOF-WAGES et al. 2015; FIGUERA; GRAÇA, 2016).

Lymph node hemorrhages are not often seen in routine and are commonly associated with specific diseases that lead to vasculitis and disseminated intravascular coagulation. However, the drainage of erythrocytes from areas that suffered hemorrhages is a frequently seen alteration in lymph nodes. On histology, the medullary sinuses and occasionally cortical and subcapsular sinuses are filled with erythrocytes and fibrin in varying amounts. The macrophages of the medullary cords may be exercising erythrophagocytosis, which results in the accumulation of golden-brown granules in the cytoplasm of these cells, corresponding to hemosiderin (ROOF-WAGES et al. 2015; FIGUERA; GRAÇA, 2016).

In addition to draining erythrocytes, the drainage of inflamed areas may also lead to the presence of inflammatory cells in subcapsular sinus, with the cell type varying according to the nature of the inflammation. The lymphoplasmacytic inflammatory infiltrate is commonly related to viral antigenic stimulation in cats (VAN DER VALK; MEIJER, 1987; FIGUERA; GRAÇA, 2016).

Hemosiderosis can affect lymph nodes and is commonly seen in lymph nodes draining areas of hemorrhage, as well as in the presence of chronic congestion. Rarely is this pigment accumulation due to excess iron from the diet or other external sources (JONES, HUNT; KING, 2000b; MILLER; ZACHARY, 2017). In the histological evaluation of these lymph nodes, the cytoplasm of macrophages is full of golden-brown granules, being observed in variable amounts. (FIGUERA; GRAÇA, 2016).

The alterations in splenic lymphoid follicles were similar to those presented in nodal lymphoid follicles, increasing in size and quantity. After antigenic stimulation, a response is triggered in the spleen of these animals, which leads to the multiplication of B lymphocytes in the follicles. White pulp hyperplasia can initially be seen only as an expansion in the volume of periarteriolar lymphoid sheaths. However, with continued antigenic stimulation, secondary lymphoid follicles are formed, which have germinal

centers delineated by a well-defined mantle zone. This injury is nonspecific concerning the type of stimulating agent and it occurs both in chronic systemic bacterial infection and in some diseases caused by viruses, *rickettsiae*, or protozoa (ANDERSON et al. 1971; BACH et al. 1994; KIPAR et al. 2001; FIGUERA; GRAÇA, 2016; BOES; DURHAM, 2017)

Splenic congestion is among the most common alterations found in the spleen of domestic animals. It may result from portal or splenic vein hypertension, which leads to the proliferation of macrophages in the walls of red pulp vascular spaces, with the thickening of reticular walls between the vascular spaces of the red pulp being the primary response to vascular space injury. It is also seen in animals anesthetized with barbiturates or even euthanized using barbiturates. This group of drugs can relax capsular/trabecular smooth muscle, leading to blood pooling and congestion. Such alterations were not observed in the animals of this study.

In cats and some other domestic animals, the characteristic of the spleen to store blood is a function of great importance, making it sometimes challenging to determine whether the congestion ceased to be functional and started to be considered pathological. Microscopically, a large number of erythrocytes is seen inside the splenic vascular spaces, making them distended to the point of making it difficult to recognize other organ structures. The presence of low -oxygen stagnant blood causes parenchymal necrosis, which can be focal or, more often, diffuse (BLUE; WEISS, 1981; FIGUERA; GRAÇA, 2016; BOES; DURHAM, 2017).

Atrophy of splenic lymphoid follicles occurs similarly to nodal lymphoid atrophy, with follicles appearing rarefied and reduced in size, with the amount of total lymphoid tissue reduced, and possible spleen reduction. It can occur physiologically, for example, in regression after antigenic stimulation has ceased or due to pathological causes such as effects of toxins, action of infectious microorganisms, malnutrition, and debilitating/ cachectic diseases. The atrophy can also be related to the advanced age of the animals and occur idiopathically, being called senile splenic atrophy (ANDERSON et al. 1971; SCHULLER-LEVIS et al. 1990; BACH et al. 1994; KIPAR et al. 2001; FIGUERA; GRAÇA, 2016; BOES; DURHAM, 2017).

Splenic hemorrhage has a variety of causative factors, ranging from infection by specific microorganisms that cause vasculitis and disseminated intravascular coagulation to splenic infarcts and trauma. When splenic hemorrhages are subcapsular-located, this is primarily due to parenchymal rupture while maintaining the capsule. In histology, they are seen as areas with erythrocytes accumulation and necrosis in variable amounts in the parenchyma, in addition to macrophages performing erythrophagocytosis (FIGUERA; GRAÇA, 2016; CAMPOS, 2017; PARK et al. 2019).

On the other hand, red pulp hyperplasia consists of an increase in the number of macrophages in the splenic red pulp and occurs because of cases of hemolytic crisis and hypersplenism (in dogs and humans). Histologically, the sinusoids are full of erythrocytes, and large amounts of macrophages perform erythrophagocytosis in the splenic cords. This intense cell proliferation in the red pulp can lead to secondary lymphoid follicular atrophy in chronic cases, but in cases in which the hemolytic disease is infec-

tious, there may be concomitant white pulp hyperplasia (NAGEL; WILLIAMS; SCHOEMAN, 2013; FIGUERA; GRAÇA, 2016; BOES; DURHAM, 2017).

## CONCLUSION

Based on the histopathological findings in these animals' submandibular lymph nodes and spleen, it can be stated that the alterations found in the studied lymph nodes demonstrate that these organs are responding to some injury, considering that lymphoid reactivity was found in most animals. Correlating these histopathological findings with a specific cause or pathological agent was impossible. However, the lymphoid response pattern suggests an intense antigenic stimulation, which may raise suspicions about infections in these animals, perhaps due to important viral agents in cats such as FIV and FeLV. From the histological description of the microscopic patterns that these lymphoid organs can present, it is possible to broaden the vision of how the immune system of this species of animals can react to lymphoid stimulation.

# AVALIAÇÃO HISTOPATOLÓGICA DE LINFONODO SUBMANDIBULAR E BAÇO DE GATOS RECEBIDOS NO SETOR DE PATOLOGIA ANIMAL – UFU


## RESUMO

Os linfonodos e o baço são importantes órgãos linfoides, e que estão localizados em posições estratégicas no organismo dos animais. Foi realizada a avaliação histopatológica de linfonodo submandibular e baço de gatos recebidos no Setor de Patologia Animal do Hospital Veterinário da Universidade Federal de Uberlândia, com objetivo de observar e documentar quais são os padrões histológicos apresentados nesses órgãos dessa população de gatos recebidos no departamento. Foram coletados fragmentos desses tecidos de 30 gatos, imediatamente após a entrada dos animais no Setor de Patologia Animal. As amostras foram acondicionadas em solução de formol tamponado 10% por no mínimo 24 horas, sendo posteriormente submetidas a processamento histológico e confeccionadas lâminas para avaliação sob microscópio óptico. As alterações encontradas foram: hiperplasia de polpa vermelha (0,3%), hiperplasia de polpa branca (5,4%), infiltrado inflamatório capsular linfoplasmocitário (1,2%; 1,2%) , congestão (1,2%; 0,9%; 2,4%), atrofia folicular linfoide (0,6%; 1,2%; 0,6%), hemorragia (1,5%; 0,3%), hiperplasia folicular linfoide (3,6% e 3,3%) e hemossiderose (0,3%). Conclui-se, com o presente trabalho, a importância da avaliação microscópica desses órgãos linfoides em gatos pois a partir da mesma, pode-se entender e melhor elucidar as respostas linfoides apresentadas por esses animais.


**PALAVRAS-CHAVE**: Histologia, Órgão linfoide, Felino, *Felis catus*

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