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HISTOPATHOLOGICAL PATTERNS OF CHRONIC LIVER DISEASES IN DOGS AND CATS: CORRELATION WITH LABORATORY TESTS

PADRÕES HISTOPATOLÓGICOS DE DOENÇAS HEPÁTICAS CRÔNICAS EM CÃES E GATOS: CORRELAÇÃO COM EXAMES LABORATORIAIS

PATRONES HISTOPATOLÓGICOS DE ENFERMEDADES HEPÁTICAS CRÓNICAS EN PERROS Y GATOS: CORRELACIÓN CON EXÁMENES DE LABORATORIO

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Iasmim Cristiane Sena da Silva[1], Apolônia Agnes Vilar de Carvalho Bulhões[2], Isabella Silva Borges[3], Ygor Cesar Amador de Lima[4], Fernanda Laura Gil Marques[5], Daniella Cristina Menezes Mota[6], Andreia Oliveira Santos[7], Aline Bittencourt de Souza[8], Artur Carmisin Duarte da Silva[9], Kelly Patrícia da Costa Camelo[10], Lizane Paula de Farias e Silva[11], João Paulo Yoshio Prado Cerqueira

[1]Undergraduate student in Veterinary Medicine
Mauritius University Center of Nassau
E-mail: iasmimsenas4@gmail.com
[2]Graduated in Veterinary Medicine; Dr. in Veterinary Science
Federal Rural University of Pernambuco
E-mail: agnes.carvalho.14@gmail.com
[3]Graduated in Veterinary Medicine; Master's student in Animal Science
Federal University of Goiás
E-mail: isabella_borges2@discente.ufg.br
[4]Undergraduate student in Veterinary Medicine
Estácio de Sá College
E-mail: ygorexpert@gmail.com
[5]Undergraduate student in Veterinary Medicine
State University of Ceará
Email: fernanda.marques1502@gmail.com
[6]Graduated in Veterinary Medicine
University Center of Patos de Minas
E-mail: daniella.menezesm@gmail.com
[7]Undergraduate student in Veterinary Medicine
Veiga de Almeida University
E-mail: andreia_oliversantos@yahoo.com.br
[8]Undergraduate student in Veterinary Medicine
Castelo Branco University
Email: medvetalinebitt@gmail.com
[9]Graduated in Veterinary Medicine
University of Southern Santa Catarina
Email: artur_carmisin@hotmail.com
[10]Graduated in Veterinary Medicine
Integrated Colleges of the Educational Union of the Central Plateau
Email: vetcamelokpcc@gmail.com
[11]Undergraduate student in Veterinary Medicine
Brazilian University Center
E-mail: lifasil@hotmail.com

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Kubota[12], Amanda Ferreira de Jesus[13], Bruna Araújo Marinho[14] and Mateus de Melo Lima Waterloo[15]

ABSTRACT

Objective: To evaluate the main histopathological patterns found in chronic liver disease (CLD) in dogs and cats and correlate them with laboratory findings, emphasizing the importance of histopathological examination for definitive diagnosis and prognosis. Chronic liver disease in small animals has diverse etiologies and slow progression, and is often diagnosed at advanced stages. This literature review analyzed national and international studies on the prevalence, morphological patterns, and clinical and laboratory implications of CHD in dogs and cats. The data show that microvascular dysplasia, chronic hepatitis, and cholangitis are among the most frequent diagnoses. The association between laboratory abnormalities, such as elevated ALT and FA, and histological findings such as fibrosis, portal inflammation, and hepatocellular degeneration, allows for better clinical management. Liver biopsy techniques (Tru-Cut®) remain essential, although complementary methods such as serum biomarkers and digital analysis are expanding. It is concluded that the integration of clinical, laboratory, and histopathological findings is indispensable for the early diagnosis and effective management of CHD in small animals.

Keywords: Liver biopsy. Liver fibrosis. Portal inflammation. Hepatocellular injury. Animal pathology.

RESUMO

Objetivo: Avaliar os principais padrões histopatológicos encontrados em doenças hepáticas crônicas (DHC) em cães e gatos e correlacioná-los com achados laboratoriais, ressaltando a importância do exame histopatológico para diagnóstico definitivo e prognóstico. As doenças hepáticas crônicas em pequenos animais possuem etiologias diversas e progressão lenta, sendo frequentemente diagnosticadas em estágios avançados. Esta revisão de literatura analisou estudos nacionais e internacionais sobre a prevalência, padrões morfológicos, implicações clínicas e laboratoriais das DHC em cães e gatos. Os dados evidenciam que a displasia microvascular, as hepatites crônicas e as colangites estão entre os diagnósticos mais frequentes. A associação entre alterações laboratoriais, como elevações de ALT e FA, e os achados histológicos como fibrose, inflamação portal e degeneração hepatocelular, permite melhor condução clínica. Técnicas de biópsia hepática (Tru-Cut®) continuam sendo essenciais, embora métodos complementares como

[12]Federal University of Goiás
Graduated in Veterinary Medicine; Doctorate student in Animal Science
E-mail: jpyoshiok@gmail.com
[13]Graduated in Veterinary Medicine; Master's student in Animal Science
Federal University of Goiás
E-mail: amandaferreira@discente.ufg.br
[14]Undergraduate student in Veterinary Medicine
Instituto Master de Ensino Presidente Antônio Carlos (IMEPAC)
Email: brunaaraujo.marinho@hotmail.com
[15]Graduated in Veterinary Medicine; Doctorate student in Veterinary Medicine (Animal Clinic and Reproduction)
Fluminense Federal University
Email: mateuswaterloo@icloud.com

biomarcadores séricos e análise digital estejam em expansão. Conclui-se que a integração entre clínica, exames laboratoriais e histopatologia é indispensável para o diagnóstico precoce e manejo eficaz das DHC em pequenos animais.

Palavras-chave: Biópsia hepática. Fibrose hepática. Inflamação portal. Lesão hepatocelular. Patologia animal.

RESUMEN
Objetivo: Evaluar los principales patrones histopatológicos encontrados en las enfermedades hepáticas crónicas (EHC) en perros y gatos y correlacionarlos con los hallazgos de laboratorio, destacando la importancia del examen histopatológico para el diagnóstico definitivo y el pronóstico. Las enfermedades hepáticas crónicas en animales pequeños tienen diversas etiologías y una progresión lenta, por lo que a menudo se diagnostican en etapas avanzadas. Esta revisión bibliográfica analizó estudios nacionales e internacionales sobre la prevalencia, los patrones morfológicos y las implicaciones clínicas y de laboratorio de las DHC en perros y gatos. Los datos evidencian que la displasia microvascular, las hepatitis crónicas y las colangitis se encuentran entre los diagnósticos más frecuentes. La asociación entre alteraciones de laboratorio, como elevaciones de ALT y FA, y hallazgos histológicos como fibrosis, inflamación portal y degeneración hepatocelular, permite una mejor conducción clínica. Las técnicas de biopsia hepática (Tru-Cut®) siguen siendo esenciales, aunque los métodos complementarios como los biomarcadores séricos y el análisis digital están en expansión. Se concluye que la integración entre la clínica, los exámenes de laboratorio y la histopatología es indispensable para el diagnóstico precoz y el manejo eficaz de las DHC en animales pequeños.

Palabras clave: Biopsia hepática. Fibrosis hepática. Inflamación portal. Lesión hepatocelular. Patología animal.

INTRODUCTION

Chronic liver diseases (CLD) in dogs and cats represent an important diagnostic and therapeutic challenge in veterinary clinical practice. These diseases encompass a large number of progressive morphofunctional alterations, often silent in the early stages. They are marked by the persistence of liver damage, inflammation, recovery and, especially, deposition of extracellular matrix, liver fibrosis, which can progress to cirrhosis and irreversible liver failure (Cullen; Stalker, 2016; Van Sprundel *et al*., 2020).

In recent years, the standardization of histopathological criteria proposed by the Liver Standardization Group of the *World Small Animal Veterinary Association* (WSAVA) has provided a more uniform classification of liver lesions, with emphasis on categories such as chronic hepatitis, vascular dysplasia, cholangitis, and primary or metastatic tumors (Andrews *et al.,* 2019). These advances have facilitated the correlation between the clinical and laboratory fields, especially with the use of liver-specific biochemical markers, such as ALT, AST, GGT, bilirubins, in addition to the measurement of hepatic copper and serum biomarkers of fibrosis (Webb *et al*., 2021).

The pathophysiology of liver fibrosis in pets has been widely studied. It is known that continuous stimuli activate stellate liver cells, resulting in the deposition of collagen in the portal and centrilobular spaces, resulting in a distortion of the liver structure (Ramaiah *et al*., 2022). In addition, dog breeds such as Doberman Pinscher, Labrador Retriever, Cocker Spaniel, and Bedlington Terrier have a genetic predisposition to specific forms of chronic hepatitis, usually linked to excessive copper accumulation (Poldervaart *et al*., 2009; Speeti *et al.,* 2021).

In felines, cholangitis (neutrophilic and lymphocytic) and hepatic lipid are the most common chronic conditions, presenting nonspecific clinical symptoms such as anorexia, weight loss, vomiting, and jaundice. The role of the gut microbiota and the enterohepatic pathway are increasingly being identified as modulators of chronic liver inflammation in felines (Strombeck *et al*., 2020; Barrs *et al*., 2023).

Despite the advances, histopathological evaluation remains the most reliable method for defining the etiology, extent of fibrosis, and monitoring the therapeutic response. Complementary techniques, such as special stains (Masson's trichrome, Sirius Red), immunohistochemistry and digital morphometric analysis, have increased diagnostic accuracy (Tostes, 1998; Tani *et al*., 2023). Thus, this study aims to review the main histopathological patterns of chronic liver diseases in dogs and cats,

correlating them with clinical and laboratory findings, in order to assist in diagnostic and therapeutic decision-making in a more accurate way.

METHODOLOGY

This study is a narrative literature review, based on the analysis of primary and secondary sources. Three studies were used as a basis: the dissertation by Silva (2005), which evaluated chronic liver lesions in dogs through necropsies; the article by Hirose *et al*. (2014), which compiled data from canine and feline liver biopsies performed at the University of Tokyo; and the dissertation of Tostes (1998), which compared liver biopsy techniques and their results in relation to post-mortem diagnosis.

In addition, a search was carried out for scientific articles published between 2016 and 2023, through the PubMed, ScienceDirect, and Scopus databases. The following descriptors were used: "canine chronic hepatitis", "feline liver disease", "histopathology", "hepatic fibrosis", "bile duct proliferation", "copper-associated hepatitis", "biopsy liver veterinary", "liver biomarkers in dogs and cats".

Studies focusing on chronic hepatic histological lesions, histopathological diagnostic approaches, and laboratory correlations were included. The choice of sources prioritized studies with significant casuistry, methodological standardization (preferably following WSAVA guidelines), use of histological staining techniques, biomarkers or digital analyses, and veterinary clinical applicability. However, studies that addressed only acute liver diseases, experimental models with species other than dogs or cats, studies with a sample size of less than 10, duplicate texts or without access to full content, and articles published in languages other than Portuguese, English, or Spanish were excluded.

The information extracted was organized and discussed in a thematic way, divided into topics that address prevalence, histopathological patterns, clinical-laboratory correlation and diagnostic techniques, including recent innovations in the field.

RESULTS AND DISCUSSIONS

PREVALENCE AND CLASSIFICATION OF CHRONIC LIVER DISEASES IN DOGS AND CATS

DHC in small animals encompasses a variety of alterations with different histological patterns and clinical implications. Retrospective studies in dogs indicate that these diseases correspond to 6% to 10% of the liver alterations identified through necropsy or liver biopsy (Silva, 2005; Hirose et al., 2014).

According to Hirose et al. (2014), among 4,755 canine biopsies performed at the University of Tokyo between 2006 and 2012, 463 (9.7%) involved the liver. The classification of diseases followed the criteria of the *Liver Standardization Group* of the World Small Animal Veterinary Association (WSAVA), grouping the conditions into: nonproliferative diseases (such as microvascular dysplasia, hepatitis, and fibrosis) and proliferative diseases (such as adenomas, carcinomas, and nodular hyperplasia). The most frequent condition (29.4%) was microvascular dysplasia (MVD), which includes portal hypoplasia, followed by hepatitis (23.5%) and primary liver tumors (21%).

In felines, DHC is most commonly represented by hepatitis (45.1%), especially neutrophilic cholangitis (23.9%) and lymphocytic cholangitis (14.1%), as well as degeneration (14.1%) and dysplasia (12.7%) (Hirose et al., 2014). These patterns are in line with recent literature, which indicates cholangiohepatitis as the main causes of chronic liver inflammation in felines (Barrs *et al*., 2023; WSAVA Liver Standardization Group, 2019).

HISTOPATHOLOGICAL PATTERNS AND FREQUENT MORPHOLOGICAL CHANGES

Histological patterns change according to the origin of the disease and the species affected. Liver cirrhosis, in dogs, is a frequent terminal condition, characterized by generalized fibrosis, nodular regeneration, and change in architecture (Andrews *et al*., 2019). Silva (2005) thoroughly studied 14 cases of canine cirrhosis, identifying mild fibrosis in 57.2% of the cases, moderate fibrosis in 28.6% and severe fibrosis in 14.2%. These situations presented predominant histological alterations, such as fatty degeneration (71.4%), lymphoplasmacytic inflammatory infiltrate (71.4%), hemosiderosis (64.3%), proliferation of bile ducts (50%) and intrahepatic biestasis (42.8%).

These findings are in accordance with the criteria for chronic hepatitis established by Cullen and Stalker (2016), which include hepatocellular necrosis, chronic portal inflammation, and progressive fibrosis. The diagnosis of advanced chronic liver lesions

is supported by the presence of random coagulation necrosis, positive staining for collagen with Sirius Red or Masson, and lobular disorganization (Hirose *et al*., 2014).

In cats, cholangitis is the main manifestation of chronic inflammation of the liver. Neutrophilic cholangitis is linked to bacterial infections of ascending course and manifests histologically as a neutrophilic infiltrate concentrated in the bile ducts. On the other hand, lymphocytic cholangitis, which probably has an immune-mediated origin, exhibits a continuous portal lymphocytic infiltrate and a mild periductal fibrosis (Strombeck *et al.,* 2020; Barrs *et al.,* 2023).

CORRELATION WITH LABORATORY TESTS AND CLINICAL SIGNS

The connection between histopathological findings and clinical and laboratory information is important for diagnostic suspicion and prognostic evaluation (Hirose *et al*., 2014). Silva (2005), in his studies, noted a uniform increase in the enzyme alanine aminotransferase (ALT) in dogs with cirrhosis, along with the presence of ascites with pure transudate in all evaluations, indicating hypoalbuminemia and portal hypertension. In addition, in 23.7% of the cases, there was a report of jaundice, usually linked to the bilestasis identified on the histological slides.

According to Webb et al. (2021), increased ALT signals liver damage, while elevated levels of alkaline phosphatase (AF) and gamma-glutamyl transferase (GGT) are more linked to cholestasis or biliary impairment. In chronic canine liver diseases, particularly those linked to copper accumulation, there is ongoing inflammation, fibrosis, and related biochemical changes. Hirose et al. (2014) detected copper deposits in approximately one-third of dogs with chronic hepatitis, particularly in Doberman Pinscher and Labrador Retriever. In addition, the genetic research carried out by Speeti et al. (2021) emphasizes that copper accumulation may play a causal and aggravating role in chronic liver disease in certain breeds, needing to be examined through specific stains (such as rubealic) and liver quantification.

In cats, the elevation of ALT is also noticed in cholangitis, although less intensely. For example, neutrophilic cholangitis manifests with moderate elevation of ALT and AF, which can lead to mild hyperbilirubinemia. On the other hand, feline liver lipidosis is marked by significant ALT elevations and generalized hepatocellular vacuolation, playing a crucial role in differential diagnosis (Strombeck *et al.,* 2020).

DIAGNOSTIC EVALUATION: BIOPSY METHODS AND LIMITATIONS

Liver biopsy is the most reliable method for diagnosing CVD, allowing the definition of the type of lesion, the evaluation of the extent of fibrosis, and the identification of neoplastic or infectious changes (Hirose *et al*., 2014). However, the collection method has a direct impact on the representativeness of the sample. In a comparative study, Tostes (1998) revealed that liver biopsy performed with a Tru-Cut® needle (cutting) showed a higher diagnostic accuracy (88.3%) in relation to the Menghini® needle aspiration technique, which was not successful especially in situations of fibrosis.

Currently, in addition to traditional stains, technological advances such as digital morphometric analysis, quantitative stains, and immunohistochemistry that use stellate cell activation markers, such as α-SMA and desmin, have helped in a more accurate diagnosis of fibrosis (Tani *et al*., 2023). Noninvasive serum biomarkers, such as hyaluronic acid, type IV collagen, and laminin, have been investigated as options for biopsy. However, its application in small animals is still experimental and restricted to research centers (Ramaiah *et al*., 2022).

Therefore, liver biopsy remains essential for definitive diagnosis, particularly in cases of chronic liver disease of undefined etiology, and its interpretation requires integration with clinical signs and laboratory tests.

FINAL CONSIDERATIONS

Chronic liver diseases in dogs and cats have unique histopathological characteristics that, when associated with clinical and laboratory results, allow for more accurate diagnoses. Histopathological examination, particularly by laser biopsy, remains the safest diagnostic technique. It is essential to understand morphological patterns, such as fibrosis, portal inflammation, ductal proliferation, and copper deposition, in order to establish prognosis and management. Despite the advancement of modern techniques such as digital morphometric analysis and blood biomarkers, liver biopsy is still indispensable in clinical practice. Early detection requires a combination of clinical, laboratory tests, and histopathology.

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