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Original Article
Small Animal Diseases

Jaundice in cats: Causes and *post-mortem* findings in 44 cases[1]

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ABSTRACT.- Silva A.C.R., Lopes C.E.B., Fonseca C.S., Baêta S.A.F., Oliveira J.B.S., Lopes M.C., Araujo A.C., Silveira J.A.G., Santos I.R., Driemeier D. & Ecco R. 2024. ***Jaundice in cats: Causes and post-mortem findings in 44 cases***. *Pesquisa Veterinária Brasileira 44:e07454, 2024.* Setor de Patologia e MULTILAB**,** Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais, Av. Antônio Carlos 6627, Belo Horizonte, MG 31270-901, Brazil. E-mail: ecco@vet.ufmg.br

The aim of this study was to describe the pathological findings and causes of jaundice in 44 cats (*Felis catus*) over a six-year period. The cats were from two Brazilian metropolitan areas: 34.1% were female, 56.8% were male, and 9.1% had no information regarding their sex. Their ages ranged from 6 months to 13 years. Most of the cats examined were of a mixed breed (40/44), whereas the others were Angora (2/44), Oriental Short Hair (1/44) and Persian (1/44). All animals had mild to marked jaundice, and 39 were diagnosed with mild to marked anemia. The classification of icterus types (pre-hepatic, hepatic and post-hepatic) was based on gross and microscopic findings. Of the 44 animals, 10 were classified as pre-hepatic icterus, 33 with hepatic icterus and seven with post-hepatic icterus. In some cats, two types of icterus were found, of which five were classified as pre-hepatic and hepatic icterus, and one case was hepatic and post-hepatic icterus. According to the gross and microscopic findings, the cause of pre-hepatic icterus was idiopathic hemolytic anemia. The most frequent cause of hepatic icterus was hepatic lipidosis (26/44), followed by perihepatitis and hepatitis compatible with feline infectious peritonitis, lymphoma, glycogenic degeneration, cholangiocarcinoma and metastatic myeloid leukemia. In animals with post-hepatic icterus, the causes included cholangitis due *to Platynosomum* spp. infection, cholangioma of the common hepatic duct, and chronic cholangitis. Understanding the etiopathogenesis of jaundice requires an accurate clinic-pathological study and concomitant causes of the disease in cats should be considered.

INDEX TERMS: Feline, idiopathic hemolytic anemia, hepatic lipidosis, feline infectious peritonitis virus, hemopathogens.

RESUMO.- [**Icterícia em gatos: causas e resultados *post-mortem* em 44 casos.**] O objetivo deste estudo foi descrever os achados patológicos e as causas da icterícia em 44 gatos (*Felis catus*), durante um período de seis anos. Os gatos eram provenientes de duas regiões metropolitanas brasileiras; 34,1% eram fêmeas, 56,8% eram machos e 9,1% não tinham informação sobre o sexo. A idade variou de 6 meses a 13 anos. A maioria dos gatos examinados era de raça mista (40/44), enquanto os restantes eram Angorá (2/44), Oriental de pelo curto (1/44) e Persa (1/44). Todos os gatos apresentavam icterícia leve a acentuada e 39 foram

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diagnosticados com anemia discreta a grave. A classificação dos tipos de icterícia (pré-hepática, hepática e pós-hepática) baseou-se em achados macroscópicos e microscópicos. Dos 44 animais, 10 foram classificados como icterícia pré-hepática, 33 com icterícia hepática e sete com icterícia pós-hepática. Contudo, em alguns gatos, foram encontrados dois tipos de icterícia, cinco dos quais foram classificados como icterícia pré-hepática e hepática e um caso como icterícia hepática e pós-hepática. De acordo com os achados macroscópicos e microscópicos, a causa da icterícia pré-hepática foi anemia hemolítica idiopática. A causa mais frequente de ícterícia hepática foi a lipidose hepática (26/44), seguida de peri-hepatite e hepatite compatível com peritonite infecciosa felina, linfoma, degeneração glicogênica, colangiocarcinoma e leucemia mieloide metastática. Nos gatos com icterícia pós-hepática, as causas incluíram colangite devida a infecção por *Platynosomum* spp., colangioma do ducto hepático comum e colangite crônica. Atualmente, a compreensão da etiopatogenia da icterícia requer um estudo clínico-patológico preciso e causas concomitantes da doença em gatos devem ser consideradas.

TERMOS DE INDEXAÇÃO: Felino, anemia hemolítica idiopática, lipidose hepática, vírus da peritonite infecciosa felina, hemopatógenos.

INTRODUCTION

Jaundice or icterus is defined as an increase in bilirubin levels in the blood (hyperbilirubinemia) and its deposition in tissues, identified grossly by the yellow color of the mucous membranes, skin, sclera, and various internal tissues (Cullen & Stalker 2016). Jaundice occurs when serum bilirubin levels are detected five to ten times higher than normal. Hyperbilirubinemia is highly specific for most hepatobiliary diseases and/or acute hemolysis, although less than 50% of cats with jaundice have liver disease. The accumulation of this endogenous pigment is related to pre-hepatic disorders (destruction of intra- or extravascular red blood cells), hepatic disorders (deficits in hepatocellular bile uptake, conjugation, or excretion), and post-hepatic disorders (impaired bile flow) (Sherding 2000).

Clinical signs, such as vomiting, inappetence, and weight loss, are indicators of hepatic or post-hepatic icterus. Signs of hemolytic anemia, together with jaundice, may be related to pre-hepatic icterus (Sherding 2000, Harvey 2009). However, several diseases can affect bilirubin metabolism and cause jaundice, either alone or in combination. Lipidosis, necrosis, hepatitis, cholangitis and neoplasia are examples of some liver diseases commonly reported in cats (Cullen 2009). Considering the various diseases that are associated with jaundice in cats and the lack of previous studies on this subject, the aim of this study was to determine the types of icterus, as well as to describe the causes of its occurrence in 44 cats, emphasizing the anatomopathological and etiological findings.

MATERIALS AND METHODS

Animal Ethics. This study was approved by the Ethics Committee on Animal Use of the "Universidade Federal of Minas Gerais" (CEUA – 61/2017).

Sampling method. Domestic cats (*Felis catus*) with jaundice sent for necropsy were obtained through a retrospective study at the "Setor de Patologia, Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária" (Sector of Animal Pathology in the Department of Veterinary Clinic and Surgery of the Veterinary School) of "Universidade Federal de Minas Gerais" (UFMG) (n=31) and the "Setor de Anatomia Patológica" (Sector of Animal Pathology) of "Universidade Federal do Piauí" (n=13), totaling 44 cats. The inclusion of cats from a second institution was performed to increase the number of cases. The sampling period was from June 2014 to December 2019. The main criterion for including cats in the study was jaundice on gross examination, regardless of its intensity and histopathology. The criterion for defining the intensity of jaundice was subjective, determined by differences in the intensity of the yellow color in the mucous membranes, subcutaneous tissue, skin, tunica intima of the vessels, serosae, and joint capsules.

Gross findings and histopathology. During the *post-mortem* examination, samples were collected from several organs (especially the liver, spleen, kidney, lymph nodes, intestines, bone marrow and brain) for histopathological analysis. Samples were fixed in 10% neutral-buffered formalin. Four-micrometer tissue sections were stained with hematoxylin and eosin (HE) (Luna 1968) and examined under a light microscope. Additional sections of the spleen, liver, and bone marrow were stained with Giemsa (Luna 1968) to visualize hemotropic agents in the red blood cells when prehepatic icterus was suspected. The type of jaundice (pre-hepatic, hepatic, and post-hepatic) was defined based on gross and microscopic findings.

Immunohistochemistry. Organ samples from three cats with lesions characteristic of feline infectious peritonitis (FIP) were subjected to immunohistochemistry (IHC) to identify the FIP viral antigen. Samples from two other cats with lymphoma were subjected to IHC for feline leukemia virus (FeLV). Samples from a single cat diagnosed with multicentric lymphoma were subjected to concomitant IHC for FeLV and feline immunodeficiency virus (FIV). Information regarding the IHC is shown in Table 1.

Molecular tests. For the molecular detection of hemopathogens, DNA was extracted from liver, kidney, lymph node, and spleen samples of 10 cats (10/44), from which frozen samples were available for examination. DNA was extracted using silica and sodium iodide (NaI) methods (Vogelstein & Gillespie 1979). PCR (Polymerase Chain Reaction) was carried out for hemoplasmas (16S rRNA region), *Mycoplasma* spp., *Mycoplasma haemofelis*, 'Candidatus *Mycoplasma haemominutum*', and '*Candidatus Mycoplasma turicensis*' (Criado-Fornelio et al. 2003, Watanabe et al. 2003, Peters et al. 2008); *Anaplasma platys* (16S rRNA region); *Anaplasma phagocytophilum* (gene msp4) (De La Fuente et al. 2005, Bown et al. 2007, Ramos et al. 2009); Anaplasmataceae monocyte agents (16S rRNA region) (Kawahara et al. 2009); *Ehrlichia canis* (partial gene VirB9) (Kledmanee et al. 2009); genus *Babesia*/*Theileria*/*Cytauxzoon* (18S rRNA region) (Zahler et al. 2000, Da Silveira et al. 2011); *Babesia vogeli* (18S rRNA) (Kledmanee et al. 2009); and *Cytauxzoon felis* (Birkenheuer et al. 2006) (Table 2). PCR products from samples positive for the 16S rRNA gene of *Mycoplasma* spp. were purified using a commercial QIAquick PCR Purification Kit (Qiagen Biotecnologia Brasil, São Paulo, Brazil) according to the manufacturer's instructions. The purified products were sequenced using the dideoxynucleotide method (Sanger et al. 1977) on an Applied Biosystems ABI3130 Genetic Analyzer automatic capillary sequencer (Life Technologies, Carlsbad/CA, USA).

The electrochromatograms were evaluated for quality and edited using ChromasPro 2.0.6 (Technelysium Pty Ltd., Helensvale, Australia). The identities of the obtained partial DNA sequences were determined by comparison with sequences available in GenBank using BLASTn (Altschul et al. 1990). The sequences were registered in GenBank under accession numbers OQ397116, OQ397117, OQ397118, and OQ397119.

RESULTS

Epidemiology

Among the 44 cats examined, 15 (34.1%) were female and 25 (56.8%) were male, and there was no information on the sex of four cats (9.1%). Their ages ranged from 6 months to 13 years, and most animals did not have a particular breed (35/44). The specified breeds were Turkish Angora (2/44), Oriental Shorthair (1/44), and Persian (1/44).

Classification of icterus type and frequency

Jaundice was classified based on the anatomopathological findings and established diagnoses (Table 3). Of the 44 cats, the intensity (mild, moderate, or severe) of jaundice was determined in 39 cats. The intensity was not recorded in the remaining cats because of the lack of this information in the gross description of these cases. The icterus grade was determined according to the intensity of the yellow discoloration of the body tissue. Twelve (27.3%) cats presented mild jaundice, 12 (27.3%) moderate jaundice, and 16 (36.4%) severe jaundice. The cats were also classified according to the icterus type based on gross and histopathological findings: pre-hepatic icterus in 10 (22.7%) cats, hepatic icterus in 33 (79.5%) cats, and post-hepatic icterus in seven (15.9%) animals. One cat (6.8 %) was diagnosed with both hepatic and post-hepatic icterus, and five cats (11.3%) were diagnosed with pre-hepatic and hepatic icterus. For pre-hepatic icterus, moderate intensity was recorded in three cats (3/5) and severe in two cats (2/5). For hepatic icterus, a mild intensity was recorded in 11 cats (11/27), moderate in seven cats (7/27) and severe in four cats (4/27). The intensity was not recorded in five cats with hepatic icterus. For post-hepatic icterus, mild intensity was recorded in one cat (1/6) and severe intensity in five cats (5/6). In cats with concomitant pre-hepatic and hepatic icterus, the intensity was moderate in one cat (1/5) and severe in four cats (1/4). Only one cat had concomitant hepatic and post-hepatic icterus, which was recorded as severe. Note that in 44 animals, there are cats that have been diagnosed with more than one type of icterus based on the pathological findings (Table 3).

Pre-hepatic icterus-related diseases

Pre-hepatic icterus resulting from extravascular idiopathic hemolytic anemia was identified in 10 cats (10/44).

Hemolytic anemia

Ten cats were identified as having jaundice associated with extravascular hemolytic anemia. Splenomegaly because of expansion of the red pulp (Fig.1) was a frequent finding among carriers of this condition, and hyperplasia of the white pulp was observed in three (3/10) cats. In nine (9/10), the bone marrow was pale red. Microscopically, the most relevant findings in cats with hemolytic anemia were splenic (Fig.2) and hepatic erythrophagocytosis. The livers of these animals showed bile stasis (probably with conjugated bilirubin) and vacuolar degeneration, with individual necrosis of the centrilobular hepatocytes. In the kidneys, bile pigments are present in the lumen and the epithelial cells of the tubules. The bone marrow of one cat showed marked erythroid hyperplasia. Giemsa staining of the spleen, liver, and bone marrow did not reveal infectious agents.

Hepatic icterus-related diseases

Hepatic icterus was identified in 33 cats (33/44) and was associated with various conditions, including metabolic, infectious, and neoplastic diseases.

Fatty degeneration

Twenty-six (26/33) cats were diagnosed with lipidosis (fatty degeneration). Grossly, the liver was diffusely yellow and enlarged (Fig.3) with rounded edges and evidence of a lobular pattern (mottled liver). The organ was diffusely friable and greasy when cut open. Microscopically, the

Table 1. Immunohistochemical protocol for feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and feline coronavirus (FCoV) antigens

	Virus		
	FeLV	FIV	FIP
Blocking endogenous peroxidase	Hydrogen peroxide for 20 minutes	Hydrogen peroxide for 20 minutes	Hydrogen peroxide for 15 minutes
Antigen retrieval	Tris EDTA Buffer pH 9.0, in a pressure cooker (96°C) for 40 minutes	Citrate Buffer pH 6.0, in a pressure cooker (96°C) for 40 minutes	Tris EDTA Buffer pH 9.0, in a pressure cooker (96°C) for 40 minutes
Primary antibody	Anti-feline leukemia virus mouse monoclonal (gp 70) (Bio-rad, Kidlington, UK), at 1:200 dilution, for 14-16 hours, room temperature	Anti-feline immunodeficiency vírus mouse monoclonal (p24 gag) (Bio-rad, Kidlington, UK), at 1:600 dilution, for 14-16 hours, room temperature	Anti-coronavirus mouse monoclonal (FIPV3-70) (Santa Cruz Biotechnology, Dallas, Texas, USA), at 1:250 dilution, for 14-16 hours, room temperature
Blocking nonspecific activities	Skimmed milk (5%) for 15 minutes	Skimmed milk (5%) for 15 minutes	Skimmed milk (5%) for 20 minutes
Second antibody	Universal MACH 4-HRP polymer kit, Biocare Medical, Concord, USA	Universal MACH 4-HRP polymer kit, Biocare Medical, Concord, USA	Universal MACH 4-HRP polymer kit, Biocare Medical, Concord, USA
Chromogen	3,3'-Diaminobenzidine (DAB), Sigma, St. Louis, USA	3,3'-Diaminobenzidine (DAB), Sigma, St. Louis, USA	3,3'-Diaminobenzidine (DAB), Sigma, St. Louis, USA
Counterstain	Harris Hematoxylin	Harris Hematoxylin	Harris Hematoxylin
Negative control	Universal Negative Control Serum (Biocare Medical, Concord, USA)	Universal Negative Control Serum (Biocare Medical, Concord, USA)	Universal Negative Control Serum (Biocare Medical, Concord, USA)
Positive control*	Lymph nodes	Lymph nodes	Small intestine

* Tissues from cats known to be positive for the antigens tested.

hepatocytes were enlarged as a result of an accumulation of well-demarcated large clear vacuoles, often displacing the nucleus to the periphery. In these cats, there was an accumulation of green pigment (bile) in the lumen of the bile ducts and the cytoplasm of the hepatocytes (Fig.4). Among cats diagnosed with hepatic lipidosis, 15/26 had exclusively lipidosis lesions. At the same time, 11/26 also had gross lesions related to infectious inflammatory processes. In the last of these, different cases of hepatitis and perihepatitis were variably observed. Of the animals diagnosed with hepatic lipidosis, jaundice was classified as severe in eight (8/26) cats, moderate in seven (7/26), and mild in eight (8/26). In one (1/26) cat with hepatic lipidosis, there were also poorly delimited intracytoplasmic vacuoles, consistent

Table 2. Oligonucleotide primer sequences, gene region for PCR assays for hemopathogens

Hemopathogen	Oligonucleotide primer sequences (5'-3')		Gene region	Amplicon size (bp)	Reference
Mycoplasma spp.	ATACGGCCCATATTCCT ACGTGCTCCACCACTTGTTCA	HBTF5 HBTR5	*16S rRNA*	595	Criado-Fornelio et al. (2003)
Mycoplasma haemofelis	CGTGGAAACTAGAGCTTCGCGAGC ATGGTATTGCTCCATCAGACTTTCG	OH-OK 00CB-r1	*16S rRNA*	274	Watanabe et al. (2003)
'*Candidatus Mycoplasma haemominutum*'	ATGCCCCTCTGTGGGGGATAGCCG ATGGTATTGCTCCATCAGACTTTCG	CA-B2f 00CB-r1	*16S rRNA*	202	Watanabe et al. (2003)
'*Candidatus Mycoplasma turicensis*'	AGAGGCGAAGGCGAAAACT CTACAACGCCGAAACACAAA	CMt-F CMt-R	*16S rRNA*	138	Peters et al. (2008)
Anaplasma platys					
1st reaction	AGTTTGATCATGGCTCAG CCATGGCGTGACGGGCAGTGT	8-F 1448-R	*16S rRNA*		Ramos et al. (2009)
2nd reaction	GATTTTTGTCGTAGCTTGCTATG TAGCACTCATCGTTTACAGC	PLATYS-F EHR16S-R		678	
Anaplasma phagocytophilum					
1st reaction	ATGAATTACAGAGAATTGCTTGTAGG TTAATTGAAAGCAAATCTTGCTCCTATG	MSP4AP5 MSP4AP3	*msp4*	849	De La Fuente et al. (2005)
2nd reaction	CTATTGGYGGNGCYAGAGT GTTCATCGAAAATTCCGTGGTA	msp4f msp4r		381	Bown et al. (2007)
Anaplasmataceae monocyte					
1st reaction	ACGGACAATTGCTTATAGCCTTACAACTTTT ATGGATTAGCTAAAT	NS16SCH1F NS16SCH1R	*16S rRNA*	1195	Kawahara et al. (2009)
2nd reaction	GGGCACGTAGGTGGACTAG CCTGTTAGGAGGGATACGAC	NS16SCH2F NS16SCH2R		443	
Ehrlichia canis	CCATAAGCATAGCTGATAACCCTGTTAC TGGATAATAAAACCGTACTATGTATGCT	Ehr1401 F Ehr1780 R	*VirB19 parcial*	377	Kledmanee et al. (2009)
Babesia spp./*Theileria* spp./*Cytauxzoon* spp.					
1st reaction	CGGGATCCAACCTGGTTGATCCTGC CCGAATTCCTTGTTACGACTTCTC	RIB-19 RIB-20	*18S rRNA*	1700	Zahler et al. (2000)
2nd reaction	ACCTCACCAGGTCCAGACAG GTACAAAGGGCAGGGACGTA	BAB-rumF BABrumR	*18S rRNA*	430	Da Silveira et al. (2011)
Babesia vogeli	CCAATCCTGACACAGGGAGGTAGTGACA CCCCAGAACCCAAAGACTTTGATTTCTCTCAAG	Ba103F Ba721R	*18S rRNA*	619	Kledmanee et al. (2009)
Cytauxzoon felis	CGAATCGCATTGCTTTATGCTCCAA TTGATACTCCGGAAAGAG	Cytaux F Cytaux R	*18S rRNA*	284	Birkenheuer et al. (2006)

with glycogenic degeneration; in four (4/26) cats, there was an association of lipidosis with fibrinous and necrotizing and/or pyogranulomatous hepatitis/perihepatitis owing to FIP; and one cat (1/26) was diagnosed with hepatic lipidosis and lymphoma.

Glycogenic degeneration

Two cats (2/33) were diagnosed with degenerative liver lesions compatible with glycogen accumulation. Grossly, the liver was diffusely pale red to yellow, intensely enlarged, and showed a lobular pattern. The parenchyma was diffusely friable. Both cats had mild jaundice. Microscopically, poorly demarcated microvacuoles accumulated in the cytoplasm of the hepatocytes in the absence of compression and nuclear displacement. Green pigment accumulation was observed in the cytoplasm of several hepatocytes and bile ducts. In one (1/2) of these cats, there was also a variable accumulation of lipid vacuoles in the cytoplasm of the hepatocytes (hepatic lipidosis). No other changes that could explain jaundice were found in these cats.

Feline infectious peritonitis

In four cats (4/33) with hepatic icterus, the lesions were compatible with the effusive form of FIP. In one (1/5) of these animals, there was severe jaundice, whereas moderate jaundice was found in another cat (1/5), and in the other three cats (3/5), the jaundice was mild. In the livers of these cats, gross lesions consisted of prominent millimetric white nodules (granuloma) on the surface and parenchyma. These lesions were also present in the intestinal serosa, spleen, and kidneys. In one (1/5) of these animals, nodules were also seen in the pleura, along with fibrin deposits. One cat (1/5) had fibrin deposits in the liver capsule. Microscopically, different animals show multifocal infiltrates of macrophages, neutrophils, lymphocytes, and plasma cells in the aforementioned organs, as well as thrombosis, phlebitis, and perivascular fibrin accumulation. Hepatic lipidosis was observed variably in three (3/5) of these cats with lesions compatible with FIP.

Intrahepatic bile duct carcinoma

In one (1/44) of the cats, there was severe jaundice associated with primary hepatic neoplasia. Grossly, the liver was markedly enlarged with multifocal to coalescent five-centimeter yellowish-white nodules prominent on the subcapsular surface and deep in the parenchyma of all lobes. Microscopically, the neoplasm was poorly delimited, expansive, infiltrative, and composed of epithelial cells organized in ducts and acini with one or two cell layers (cholangiocarcinoma), supported by an abundant fibrovascular stroma. The cells were cuboidal to columnar and closely juxtaposed, with scant and granular cytoplasm and a round central nucleus with coarse chromatin and prominent nucleoli. Anisocytosis and anisokaryosis were moderate, and 15 mitotic figures were seen in 10 400x fields (2.37mm^2). There were extensive areas of fibrosis and compressive necrosis throughout the neoplasm with loss of the hepatic parenchyma.

Lymphoma

In four cats (4/33), gross lesions were compatible with multicentric lymphoma. In these animals, the liver was enlarged with white, flat, and multifocal to coalescent, millimeter-sized areas. Lymphoma-like lesions were also identified in the spleen and gastric and pancreatic lymph nodes. In one animal (1/4), the spleen was markedly enlarged with an irregular surface and capsular thickening. Jaundice was mild in these four animals, and the lymphoma was classified as multicentric. Microscopically, the neoplasm was infiltrative, non-encapsulated, and poorly demarcated. It was composed of round cells organized in mantles and supported by a fine fibrovascular stroma. The cells had a scant eosinophilic cytoplasm with indistinct cell borders, a

Table 3. Classification of icterus in 44 cats according to type, frequency, and causes

Icterus type % (n/total)	Diagnosis	n	(%)
Pre-hepatic 11.36% (5/44)	Hemolytic anemia	5	100
	TOTAL	5	100
Hepatic 61.36% (27/44)	Hepatic lipidosis	15	55.56
	Lipidosis and hepatitis/FIP perihepatitis	3	11.11
	FIP perihepatitis	1	3.70
	Lymphoma	3	11.11
	Glycogenic degeneration	1	3.70
	Lipidosis and glycogenic degeneration	1	3.70
	Myeloid leukemia	1	3.70
	Intrahepatic bile duct carcinoma	1	3.70
	Lipidosis and lymphoma	1	3.70
	TOTAL	27	100.0
Post-hepatic 13.63% (6/44)	Platynosomiasis	4	66.6
	Proliferative cholangitis	1	16.7
	Common bile duct cholangioma	1	16.7
	TOTAL	6	100.0
Pre-hepatic and hepatic 11.36% (5/44)	Hemolytic anemia/lipidosis	4	80.0
	Hemolytic anemia/lipidosis and hepatitis/FIP perihepatitis	1	20.0
	TOTAL	5	100.0
Hepatic and post-hepatic 2.27% (1/44)	Lipidosis and platynosomiasis	1	100.0
	TOTAL		100.0

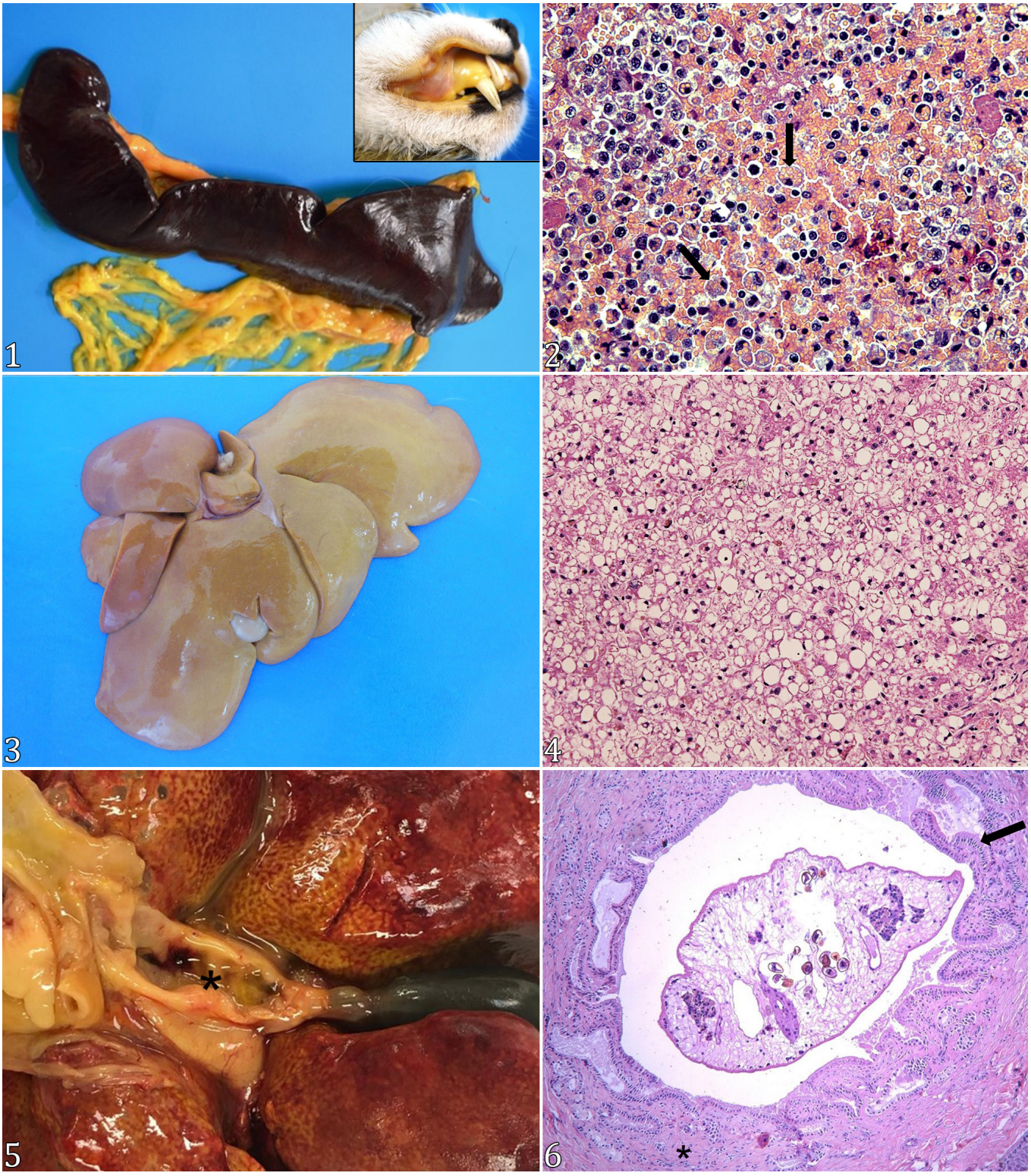

Fig.1-6. Pathological findings in cats with jaundice of various causes. (**1**-**2**) Pre-hepatic icterus caused by hemolytic anemia. (**1**) Cat, mixed breed, male, 3-year-old, spleen. The organ was markedly enlarged, with rounded edges and diffusely dark red, and omentum marked yellow. Inset: oral mucous membrane with icterus. (**2**) Cat, mixed breed, female, 7-month-old, spleen. Marked erythrophagocytosis (arrows). Giemsa, obj.40x. (**3**-**4**) Hepatic icterus caused by fatty degeneration. (**3**) Cat, mixed breed, male, 2-year-old, liver. Liver enlarged and diffusely yellow. (**4**) Cat, mixed breed, female, liver. Well-demarcated vacuoles in the cytoplasm of the hepatocytes with displacement of the nucleus to the periphery (lipidosis). HE, obj.40x. (**5**) Post-hepatic icterus due to *Platynosomum* spp. cholangitis. Cat, mixed breed, male, liver. Cut surface with intense dilation and thickening of bile ducts (asterisk), and accumulation of intraluminal mucus. (**6**) Markedly dilated intrahepatic bile duct, with intraluminal adult trematode (center), epithelial hyperplasia (arrow), and abundant mural fibrosis (asterisk). HE, obj.10x.

central round nucleus with stippled chromatin, and prominent nucleoli. Anisocytosis and anisokaryosis were moderate, and there were 12 mitotic figures in 10 400x fields (2.37mm^2). The remnant hepatic parenchyma was compressed and partially lost. Similar neoplastic cells were found in the spleen, gastric, and pancreatic lymph nodes, whereas kidney metastases were observed in only one cat (1/4). Hepatic lipidosis was also present in one (1/4) cat.

Myeloid leukemia

One cat (1/33) with hepatic icterus was diagnosed with myeloid leukemia (undifferentiated blast cells) with metastases to the liver, lymph nodes, and spleen. Grossly, the liver was diffusely orange with an accentuated lobular pattern. The animal had moderate jaundice and petechiae in its pleura and cecal mucosa. The mesenteric lymph nodes were moderately enlarged and diffusely yellow-to-white upon cutting. The bone marrow of all bones was light red to white. Microscopically, there was an evident distortion of the hepatic architecture, with numerous neoplastic cells displaying myeloid characteristics found along the sinusoids, leading to compression and hepatocyte loss. Neoplastic cells with morphology similar to that described above were present in the mesenteric lymph nodes and spleen. In the bone marrow, undifferentiated blast cells were predominant, and granulocytes, rubricytes and megakaryocytes were rare.

Post-hepatic icterus-related diseases

Post-hepatic icterus was identified in seven (7/44) cats and was associated with inflammatory and neoplastic diseases of the intra- or extrahepatic bile ducts.

Cholangitis

In this study, six cats (6/44) had cholangitis as the predominant lesion. In one animal (1/6), the cause of cholangitis could not be determined, whereas, in the other five (5/6), cholangitis was attributed to platynosomiasis, confirmed by the visualization of intralesional trematodes or parasitic eggs by direct examination of the bile. Three cats were from Teresina, Piauí. In the cat diagnosed with idiopathic cholangitis, jaundice was moderate, and the liver was diffusely yellow and enlarged with evidence of a lobular pattern. Microscopically, there was a moderate proliferation of ducts in the portal spaces with periductal fibrosis, which was sometimes associated with moderate amounts of lymphocytes, plasma cells, macrophages, and neutrophils. There was an intraluminal accumulation of green pigment (bilirubin) in the lumen of the ducts and bile ducts. The same animal was also diagnosed with fibrinonecrotic pancreatitis. Grossly, animals infected with *Platynosomum* spp. exhibit severe jaundice. The liver was enlarged and diffusely yellow. When cut, the intrahepatic bile ducts were dilated, and the mucus flowed slightly to marked volumes (Fig.5). One cat also had cystic mucinous hyperplasia of the gallbladder and post-hepatic/obstructive jaundice owing to complete obstruction of bile flow. Microscopically, operculated eggs and adult trematodes accumulated in the lumen of some ducts. The bile ducts were proliferated and dilated (duct ectasia), with intraluminal accumulation of mucus and deposits of fibrous connective tissue throughout the wall (proliferative and sclerosing cholangitis). Moderate numbers of lymphocytes, plasma cells, histiocytes, rare neutrophils, and eosinophils were clumped around the bile ducts. In two (2/5) cases, adult forms of trematodes were observed (Fig.6), with compression and loss of hepatocytes in extensive areas of the liver parenchyma resulting from bile duct fibrosis. In two animals (2/5), no adult forms of the parasite or trematode eggs were observed, although areas of marked ectasia and bile duct proliferation were identified. In one (1/5) of these animals, parasite eggs were found upon direct examination of the bile contents.

Cholangioma of the common hepatic duct

Bile flow obstruction of the extrahepatic ducts was diagnosed in one of the seven cats with post-hepatic icterus owing to cholangioma of the common hepatic duct. In this animal, the liver was diffusely red-orange and moderately enlarged with an increased lobular pattern. A white, firm nodule in the common hepatic duct impaired the extrahepatic bile flow, resulting in severe post-hepatic icterus. Marked retention of bile flow causes bilirubin accumulation and deposition in various tissues, including the brain (moderate multifocal kernicterus). Microscopically, the neoplasm was non-encapsulated, well-demarcated, and expansive, compressing the common hepatic duct, composed of cuboidal cells organized into well-differentiated ducts and acini. Moderate amounts of multifocal yellowish pigments were observed within the cytoplasm of hepatocytes and bile duct cells (moderate multifocal cholestasis).

Immunohistochemical analysis

Five cats had characteristic FIP lesions (Fig.7), and immunolabelling for the FcoV antigen was performed in three cats (3/5), all three with positive results (Fig.8). Hepatic lipidosis was a common finding in these cats. Of the three cats diagnosed with lymphoma and tested for FeLV, two (2/3) tested positive for the virus alone. One of these cats was also diagnosed with lipidosis. Lymphoma was a major comorbidity in these cats. One cat with multicentric lymphoma had double-positive results (FeLV and FIV) (Fig.9 and 10).

Detection and molecular characterization of hemopathogens by conventional PCR

Only two of the 10 cats tested by PCR were positive for hemoparasites, as confirmed by gene sequencing. Only one cat that tested positive for both mycoplasmas (*Mycoplasma haemofelis* and *Candidatus M. haemominutum*) in the liver, lymph node, and kidney samples was diagnosed with anemia. However, there was no histological evidence of infection (erythrophagocytosis and visualization of infectious agents in red blood cells by histochemical staining). One cat that was positive only for *Candidatus M. haemominutum* in a lymph node was diagnosed with post-hepatic icterus due to cholangioma of the common hepatic duct. BLASTn analysis of the sequences obtained in this study revealed 100% identity with *M. haemofelis* detected in a fishing cat (*Prionailurus viverrinus*) from Thailand (GenBank KM275257.1) and *Candidatus M. haemominutum* from domestic cats in Distrito Federal (GenBank KC331024.1) and Cuiabá/MT, Brazil (GenBank KC331024.1). All DNA samples were negative for *A. platys* (16S rRNA gene), *A. phagocytophilum* (*msp4 gene*), piroplasms, based on the 18S rRNA genes of *Babesia/Theileria* and *Babesia* spp. and the 18S rRNA gene of *C. felis*.

DISCUSSION

In comparison, hepatic icterus was found more frequently in cats in the present study, whereas post-hepatic icterus was observed in a smaller number of animals, followed by cases that showed different types of icterus simultaneously. These findings were similar to those reported in studies on dogs, in which hepatic icterus was also the most frequent type of jaundice (Andrade et al. 2020, Brough et al. 2022).

In the present study, the hepatic icterus-associated lesions were caused by degenerative processes (fatty and glycogenic degeneration), perihepatitis, hepatitis (caused by FIP virus), primary hepatic neoplasms (intrahepatic duct cholangiocarcinoma), multicentric lymphoma, and metastasis of myeloid leukemia. Jaundice is usually present in approximately 30-40% of cats with liver disease (Ettinger & Feldman 2004). Hepatic icterus occurs because of acute or chronic, extensive, and severe hepatic injury, with significant damage to hepatocytes and consequent reduction or prevention of bilirubin uptake, excretion, and elimination processes (Barros & Giaretta 2023). The causes of liver disease in cats generally include feline hepatic lipidosis, primary liver neoplasms, feline cholangiohepatitis complex, feline triaditis (Zoran 2015), and infectious hepatitis, such as FIP (Sills & Howerth 2018), disseminated toxoplasmosis, (Nagel et al. 2013) and salmonellosis (Riker et al. 2023). In the present study, severe diffuse lipidosis was the most common lesion causing hepatic icterus. In cats, the causes of lipidosis are multifactorial (Cullen & Stalker 2016, Barros & Giaretta 2023) and can occur as a result of obesity, endocrine diseases such as diabetes mellitus (Zawie & Garvey 1984, Barros & Giaretta 2023), acute pancreatitis, cholangiohepatitis, inflammatory diseases that cause anorexia, such as enteritis (Center et al. 1993, Cullen & Stalker 2016, Barros & Giaretta 2023) and nephritis (Cullen & Stalker 2016), neoplasms (Center et al. 1993, Cullen & Stalker 2016, Barros & Giaretta 2023), hyperthyroidism (Cullen & Stalker 2016, Barros & Giaretta 2023). In this study, severe cases of hepatic lipidosis were associated with certain

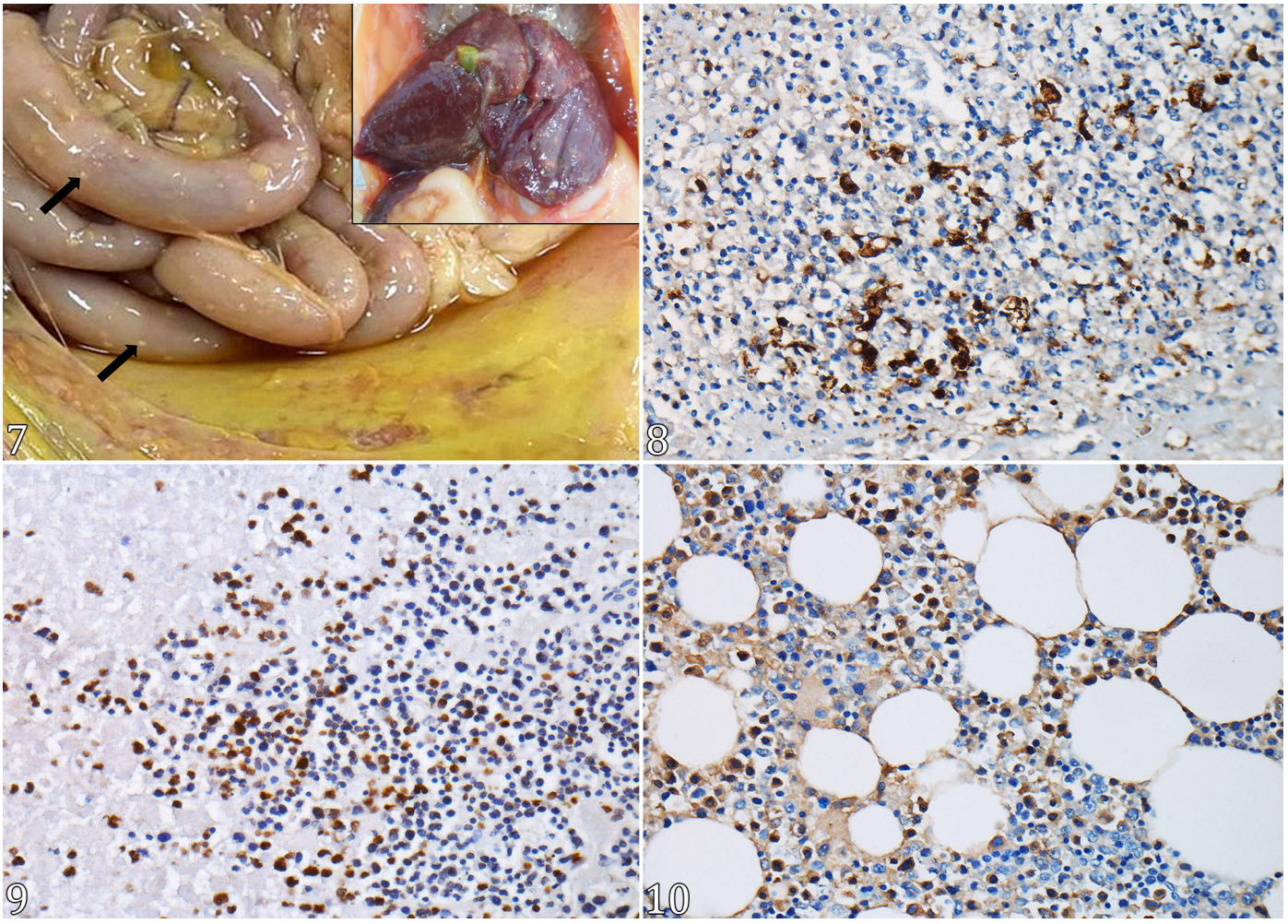

Fig.7-10. Cat with hepatic icterus due to FIP. (**7**) Abdominal cavity. Randomly distributed fibrin deposits over the peritoneal surface and intestinal serosa. Note multifocal small nodules in the intestinal serosa (arrows) and mild cavitary effusion. Inset: fibrin deposition and multifocal small nodules in the subcapsular surface of the liver. (**8-9**) Viral immunolabeling panel. (**8**) Intestinal serosa immunohistochemistry. Positive multifocal cytoplasmic immunolabeling in mononuclear inflammatory infiltrate. Anti-Fcov, obj.40x. (**9**) Cat, mixed breed, female, 6-year-old, liver. Positive multifocal cytoplasmic immunolabeling in neoplastic lymphoid cells. Anti-FeLV, obj.40x. (**10**) Cat, mixed breed, female, 6-year-old, bone marrow. Positive multifocal cytoplasmic immunolabeling in myeloid cells. Anti-FIV, hematoxylin counterstain, obj.40x.

infectious, parasitic, and neoplastic diseases, possibly owing to impairment of the complex process of lipid metabolism and secretion of low-density lipoproteins (LDL) resulting from hepatocyte injury, reduced protein intake in malnourished animals (Cullen & Stalker 2016), or an increase in fatty acid income to the liver resulting from the mobilization of lipid reserves in inappetent and anorexic cats (Blanchard et al. 2002).

Cats with concomitant pre-hepatic and hepatic icterus caused by hemolytic anemia and lipidosis, respectively, may suffer from hepatocyte hypoxia owing to their dependence on oxidative metabolism for the synthesis and transport of lipoproteins, leading to the accumulation of intracellular triglycerides and hepatic lipidosis (Cullen & Stalker 2016). In these cases, the gross and microscopic findings were compatible with cases similar to those described previously (Cullen & Stalker 2016, Barros & Giaretta 2023).

Glycogenic degeneration in cats in this study was possibly a result of a natural or iatrogenic endocrine imbalance (Cullen & Stalker 2016, Barros & Giaretta 2023). However, it was not possible to determine the hormone dosages. Although cats are considered less susceptible than dogs, glucocorticoid hepatopathy (Lowe et al. 2008), on the other hand, represents a differential diagnosis of glycogenic degeneration associated with diabetes. In the former, pathogenesis may result from the activation of glycogen synthase (resulting from the use of glucocorticoids), which induces an increase in glycogen storage in hepatocytes (Cullen & Stalker 2016), while in the latter, there is usually insulin resistance or a deficiency in its production, leading to an excessive and prolonged increase in glucose and overloading of the hepatic glycogen metabolic pathway, causing accumulation in hepatocytes (Lowe et al. 2008, Cullen & Stalker 2016).

In this study, feline coronavirus was associated with fibrinonecrotic or pyogranulomatous hepatitis/perihepatitis lesions in two cats. FIP is considered the most lethal viral disease among domestic cats (Dean et al. 2003) and mostly affects young animals (Uzal et al. 2016). Systemic polyserositis, vasculitis, and thrombosis were observed in the same cats. The mild jaundice observed in these cases might have been caused by compression and loss of hepatocytes.

Hepatocellular adenoma/carcinoma and cholangioma/cholangiocarcinoma are two of the most common primary liver neoplasms in cats (Cullen & Popp 2002). The latter may appear as multiple nodules in the hepatic lobes with centrally collapsed (umbilicated) areas of central necrosis (Cullen & Stalker 2016). Malignant neoplasms can lead to loss and compression of the liver parenchyma and consequent hepatic and/or post-hepatic icterus (Cullen & Popp 2002, Ochoa, et al. 2012, Cullen & Stalker 2016). The lymphoma in this report appears to be the most frequently occurring neoplasm, leading to jaundice of hepatic origin in four cats, highlighting the importance of this type of neoplasm associated with jaundice in domestic cats (Valli et al. 2016).

Pre-hepatic icterus associated with hemolytic anemia due to splenic, hepatic, and extravascular hemolysis was an important finding in the cats in this study. In these cats, the cause of hemolysis could not be definitively diagnosed, favoring the diagnosis of idiopathic hemolytic anemia. In cats, immune-mediated hemolytic anemia (IMHA) usually results from the interaction of red blood cells with immune complexes comprising antigen-antibody reactions with infectious agents (secondary IMHA) (McCullough 2003). To diagnose primary IMHA, all possible causes of secondary IMHA should be ruled out (Gunn-Moore et al. 1999). *Mycoplasma haemofelis* and FeLV are among the infectious agents most commonly associated with hemolytic anemia in cats (Taneno & Sacco 2009). Molecular detection of *Mycoplasma* spp. antigen (hemoplasma) was obtained in two cats in the present study. In these cases, there was no association with hemolytic anemia (Taneno & Sacco 2009). Reports on the molecular detection of *Mycoplasma haemofelis* in cats with or without clinical signs of anemia have been documented in different regions of Brazil (Braga et al. 2012, Santis et al. 2014). Another cause of pre-hepatic icterus includes hemophagocytic histiocytic sarcoma caused by phagocytosis of red blood cells by neoplastic macrophages (Sills & Howerth 2018). In this study, intravascular hemolytic anemia was not found in the cats. This type of hemolytic anemia is caused by *Babesia lengau*, which has so far only been reported in Africa and Europe (Bosman et al. 2013).

Cats with post-hepatic icterus were mainly affected by parasite-induced cholangitis. Although infectious cholangitis was suggested in one animal, it could not be confirmed based on the examinations performed (Cullen & Stalker 2016). For anatomical reasons, cholangitis or cholangiohepatitis is a relatively frequent disease in cats (Hirose et al. 2014), mainly linked to bacteria (Cullen & Stalker 2016), viruses (FIV and/or FeVL) (Argenta et al. 2018), or trematodes (Daniel 2012), and is also included as one of the elements that constitute feline triaditis (Černá et al. 2020). Histologically, three forms of presentation of the condition are known: suppurative cholangitis/cholangiohepatitis, chronic progressive non-suppurative cholangitis/cholangiohepatitis, and biliary cirrhosis or sclerosing cholangitis (Barros & Giaretta 2023). Cholangitis with multiple cysts is another presentation (Daniel 2012). In two studies, lymphocytic cholangitis (non-suppurative) was the most frequent. It was associated with changes in the extrahepatic biliary system, small intestine, or pancreas (Gagne et al. 1996, Argenta et al. 2018). In the present study, chronic non-suppurative cholangitis was observed in six animals as a consequence of parasitism by *Platynosomum* spp.

CONCLUSIONS

Hepatic icterus was the most frequent type of jaundice in this study, in contrast to post-hepatic icterus. Hepatic lipidosis was the comorbidity most frequently associated with jaundice. The causes of pre-hepatic icterus were particularly challenging in the current study, as specific ancillary tests were required to confirm its etiology. The type of jaundice was confirmed by diagnosing the underlying disease and excluding differential diagnoses.

Complementary tests are essential when considering the diversity of causes and pathological findings. Nevertheless, necropsy should not be considered optional, as it is the key to a definitive diagnosis and is necessary to confirm or refute clinical hypotheses in fatal cases.

Authors' contributions.- ACRS and RE: conceptualization, methodology, investigation, data curation, ACRS, RE and CEBL: writing-original draft, RE, ACRS, CSF, MCL, JBSO and SAFB: performed post-mortem and histologic examinations, IRS and DD: performed immunohistochemical analysis, ACA and JAGS performed molecular analysis, RE; writing – review & editing. All authors critically review the final version.

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