UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE VETERINÁRIA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS VETERINÁRIAS

CARACTERIZAÇÃO OFTALMOPATOLÓGICA DE NEOPLASMAS METASTÁTICOS EXTRAOCULARES OU MULTICÊNTRICOS EM CÃES E GATOS.

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Orientador: Prof. Dr. Saulo Petinatti Pavarini

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CARACTERIZAÇÃO OFTALMOPATOLÓGICA DE NEOPLASMAS METASTÁTICOS EXTRAOCULARES OU MULTICÊNTRICOS EM CÃES E GATOS.

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RESUMO

Este trabalho pretende caracterizar a frequência e a distribuição do acometimento ocular de cães e gatos mortos em decorrência de neoplasias metastáticas de origem extraocular ou multicêntricas por meio de exame de necropsia. Para tanto, os arquivos do Setor de Patologia Veterinária da Universidade Federal do Rio Grande do Sul foram revisados e compilados entre janeiro de 2015 e janeiro de 2019. A população amostral obtida foi de 333 animais, destes 233 eram cães e 100 gatos e 40 apresentaram metástase (s) ocular (es), o que correspondeu a 11,6% nos cães e a 13% nos gatos. O linfoma foi a neoplasia mais comumente diagnosticada em ambas as espécies. Nos cães, o linfoma difuso de grandes células B (DLBCL) (5/14), linfoma linfoblástico de células T (LBL) (4/14), linfoma de células T periféricas (PTCL) (3/14) e linfoma linfocítico B (2/14) acometeram os olhos de forma bilateral e predominantemente em úvea anterior. Nos gatos, o linfoma T associado ao Vírus da Leucemia Felina foi o mais frequente e com envolvimento majoritário do corpo ciliar. O carcinoma de glândula mamária em cadelas foi o segundo neoplasma que mais acometeu os olhos, com distribuição unilateral, multifocal e obliterante em vasos sanguíneos da úvea. Nos gatos, depois do linfoma, o carcinoma pulmonar e o carcinoma de células escamosas (CCE) foram os que mais acometeram o globo ocular. Carcinomatose meningeal em nervo óptico foi demonstrada em dois gatos com CCE e duas cadelas com carcinoma anaplásico mamário. Observou-se ainda metástases oculares de colangiocarcinoma, hemangiossarcoma e quimiodectoma nos cães, e de carcinoma cribriforme de glândula mamária, de carcinoma de glândula salivar mandibular e de sarcoma histiocítico disseminado nos gatos. Dado o exposto, o globo ocular em cães e gatos configurou sítio metastático ou multicêntrico em 12% dos animais deste estudo. Tanto em cães quanto em gatos, o linfoma e os carcinomas foram as neoplasias, com maior implicação ocular. No conhecimento dos autores, pela primeira vez são demonstradas metástases intraoculares de colangiocarcinoma e quimiodectoma em cães, bem como carcinoma de glândula salivar em gato.

Palavras chaves: metástase, globo ocular, neoplasia extraocular, patologia ocular.

ABSTRACT

This study aims to characterize the frequency and distribution of ocular involvement in dogs and cats who died due to metastatic neoplasms from extraocular or multicentric origin established through necropsy examination. Therefore, archives from the Setor de Patologia Veterinária of Universidade Federal do Rio Grande do Sul were revised and compiled from January 2015 to January 2019. The sampled population consisted of 333 animals, 233 dogs and 100 cats, 40 of which presented ocular metastasis, corresponding to 11,6% of dogs and 13% of cats. Lymphoma was the most commonly diagnosed neoplasia for both species. For dogs, diffuse large B-cell lymphoma (DLBCL) (5/14), lymphoblastic T-cell lymphoma (LBL) (4/14), peripheral T-cell lymphoma (PTCL) (3/14) and lymphocytic B cell lymphoma (2/14) involved the eyes bilaterally and predominantly in the anterior uvea. For cats, FeLV-associated T-cell lymphoma was the most frequent, involving mainly the ciliary body. Carcinoma of the mammary gland in bitches was the second most important neoplasm involving the eyes, distributed unilaterally, multifocally and obliterating blood vessels of the uvea. For cats, following lymphomas, pulmonary carcinoma and squamous cell carcinoma (SCC) were the most prevalent in the eyeball. Meningeal carcinomatosis in the optic nerve was demonstrated in two cats with SCC and two dogs with anaplastic carcinoma of the mammary gland. Additionally, ocular metastasis of cholangiocarcinoma, hemangiosarcoma and chemodectoma in dogs and cribriform carcinoma of the mammary gland, carcinoma of the mandibular salivary gland and disseminated histiocytic sarcoma in cats were observed. Given the above, the ocular globe of dogs and cats was demonstrated to be a site for metastasis or multicentric neoplasia in 12% of the studied animals. For both dogs and cats, lymphoma and carcinoma were the main neoplasia with major implication in the eye. To the author's knowledge, intraocular metastasis of cholangiocarcinoma and chemodectoma in dogs, and carcinoma of the mandibular salivary gland in cats were first reported in this study.

Palavras chaves: metastasis, eyeball, extraocular neoplasm, ocular pathology.

SUMÁRIO

1. INTRODUÇÃO

A oftalmopatologia é um ramo da patologia anatômica destinada às patologias do globo ocular e seus anexos. Dentre as enfermidades que acometem os olhos de cães e gatos estão as doenças neoplásicas. Elas podem ser tanto primárias - consideradas mais comuns, quanto secundárias; contudo ambas as apresentações são ainda pouco usuais quando comparadas às neoplasias que envolvem outros sistemas dos animais de companhia (MILLER; DUBIELZIG, 2013).

Em relação ao globo ocular como sítio primário, os tumores melanocíticos e iridociliares são os mais frequentes em caninos e felinos domésticos. Já os neoplasmas secundários, segundo dados de Dubielzig (2017), os principais em cães são: o linfoma (42%), sarcoma histiocítico (24%), carcinoma (10%), melanoma (7%), hemangiossarcoma (5%), osteossarcoma (3%) e outros tipos tumorais. No que se refere aos felinos, o mesmo autor afirma que os carcinomas são os mais frequentes nessa espécie. Tais dados são propostos a partir de relatos de caso presentes na literatura, experiência pessoal do autor baseada em dados de um importante centro de patologia ocular internacional e escassas pesquisas de revisão sobre o tema (DUBIELZIG *et al*., 2010; LABELLE; LABELLE, 2013; OTA-KUROKI *et al.*, 2014; TEIXEIRA, DUBIELZIG, 2016).

Como a coleta dos globos oculares não é sistemática durante os exames de necropsia nos laboratórios de patologia nacionais, levantou-se a hipótese de que o seu real acometimento possa estar subestimado. Além disso, há na literatura veterinária, consultada pela autora, estudos de revisão baseados em resultados necroscópicos do acometimento ocular dos pacientes oncológicos que morrem em decorrência de doença metastática.

Deste modo, este estudo pretende caracterizar e gerar dados sobre a frequência e distribuição das lesões envolvendo o globo ocular de cães e gatos nas neoplasias metastáticas ou multicêntricas de origem extraocular.

2. REVISÃO DE LITERATURA

2.1. Embriologia e anatomia do globo ocular

O desenvolvimento ocular embrionário em diferentes espécies de mamíferos possui uma sequência de eventos similares. No cão, por volta do 13º dia de gestação, ocorre o primeiro sinal de seu desenvolvimento com o aparecimento dos sulcos ópticos - originários de invaginações da neuroectoderma. Durante o fechamento do tubo neural, por volta do 15º dia gestacional, os sulcos ópticos sofrem evaginações e originam as vesículas ópticas (COOK, 2013). Tais vesículas desenvolver-se-ão lateralmente (antímeros) e à medida que isso ocorrer sua conexão com o prosencéfalo será mantida por um pedículo óptico; e a ectoderma, superficial às vesículas, sofrerá um espessamento e formará o placoide da lente. Tais eventos serão sucedidos por invaginações concomitantes das vesículas ópticas e das placas da lente. Essas invaginações resultarão na formação do cálice óptico, o qual, por sua vez, resultará na retina neural (camada interna do cálice óptico) e no epitélio pigmentar da retina (ERP) (camada externa do cálice óptico). O desenvolvimento do cálice óptico originará também o corpo ciliar e a íris. A invaginação central do placoide da lente resultará nas vesículas da lente, as quais ao se destacarem do ectoderma superficial promoverão um novo espessamento no local e a formação do epitélio corneal (PERSAUD, 2004). O estroma e o endotélio corneal serão formados a partir do mesoderma. Essa sequência de espessamentos e destacamentos dos folhetos germinativos (ectoderma, mesoderma e neuroectoderma) culminarão com o desenvolvimento completo do globo ocular e de suas estruturas anexas (COOK, 2013).

Já o desenvolvimento vascular ocorrerá pelas fissuras corioides por volta do 25º dia de gestação ao longo de cada cálice e pedículos ópticos. Por meio dessas fissuras (sulcos) a artéria hialoide, que é a terminação da artéria oftálmica interna, alcançará a câmara interna do olho e seus ramos irão suprir a cápsula posterior e anterior da lente (na porção anterior ocorrerá a formação da membrana pupilar – anastomoses vasculares). Desse modo, ocorrerá a nutrição da lente e do segmento anterior durante o período de diferenciação celular (COOK, 2013). Por volta do 45º dia de gestação com o desenvolvimento do corpo ciliar e a produção de humor aquoso, a artéria hialoide e sua rede vascular, bem como a membrana pupilar regredirão. A atrofia dessas estruturas ocorre inicialmente intrauterinamente e estará completa por volta do 14º dia pós-natal do cão. Durante esse período pós-natal também ocorrerá a abertura das fendas palpebrais, já

que tanto canídeos como felídeos apresentam anquilobléfaro fisiológico (fendas palpebrais fechadas) ao nascimento. Contudo, o término do desenvolvimento ocular ocorrerá somente por volta do 40º dia após o nascimento, com o desenvolvimento completo das camadas da retina (COOK, 2013).

Uma vez desenvolvido, o globo ocular será uma estrutura esférica formada por três eixos principais: anteroposterior, horizontal (equatorial) e vertical (meridional) e composto por três camadas ou túnicas, dispostas concentricamente: a camada externa (fibrosa), a camada média (vascular) e a camada interna (nervosa) (COOK, 2013). A camada mais externa é constituída pela esclera que confere proteção, sustentação e forma ao globo ocular e pela córnea, cuja transparência permite que ocorra a refração da luz. A túnica média ou vascular é representada pela úvea anterior (íris e corpo ciliar) e posterior (coroide) e é intensamente pigmentada e vascularizada. A terceira túnica é a nervosa, composta pela retina e pelo nervo óptico, os quais captam a luz e a transmitem na forma de impulsos nervosos sensoriais ao cérebro. O cristalino é uma lente biconvexa e transparente que é mantida em posição equatorial pelo ligamento zonular e está envolvido, assim como a córnea, na refração da luz (SAMUELSON, 2013). Essas estruturas estão compartimentalizadas em câmaras anterior e posterior (segmento anterior) e câmara vítrea (segmento posterior), preenchidas pelo humor aquoso e vítreo, respectivamente (LABELLE, 2017).

A órbita é um arcabouço ósseo formado pelos ossos do crânio: frontal, lacrimal, esfenoide, zigomático, palatino e maxilar que alojam os globos oculares e possuem variações de tamanho e profundidade de acordo com os padrões raciais. Essas alterações no formato da órbita acarretam alterações diretas no campo de visão dos animais. Nos cães e gatos a parede dorsal da órbita é formada pelo ligamento supraorbital, que se estende do osso frontal ao osso zigomático, tornando a órbita nessas espécies incompleta. Além do globo ocular, tecido muscular, nervoso e vascular estão abrigados nessa fossa óssea, a qual em sua face posterior possui numerosos forames por onde vasos sanguíneos e nervos penetram e deixam a órbita (SAMUELSON, 2013).

Os principais anexos oftálmicos são a pálpebra, a conjuntiva, a terceira pálpebra e o aparelho lacrimal, cujas funções baseiam-se direta ou indiretamente na proteção da superfície ocular (COOK, 2013). Ambas as espécies não apresentam cílios nas pálpebras

inferiores; já nas pálpebras superiores, os cães apresentam cílios verdadeiros e os gatos não (SAMUELSON, 2013).

Em relação a irrigação do olho e da órbita a principal artéria é a oftálmica externa, localizada ventralmente a órbita e derivada de um ramo da artéria maxilar interna, ramo por sua vez da artéria carótida externa. O ramo da artéria maxilar interna torna-se artéria oftálmica externa quando atravessa o canal alar. Em primatas a artéria oftálmica interna, ramo da carótida interna, é a artéria mais importante no suprimento sanguíneo ocular e orbital. Nos cães e gatos a artéria oftálmica interna é relativamente pequena e fornece suprimento ao nervo óptico conjuntamente com anastomoses da artéria oftálmica externa. Os vasos da retina e da coroide são oriundos das arteriais ciliares posteriores (curta e longa), contudo na retina a artéria ciliar curta origina as cilioretinais que irão se distribuir de forma praticamente difusa em toda a neuroretina. Esse padrão de vasculatura retiniana é denominada de holangiótica. Nos seres humanos ela também é holangiótica, porém as arteríolas são ramos diretos da artéria central retiniana. As demais estruturas orbitárias e do bulbo ocular serão irrigadas por ramos da artéria oftálmica externa, como a artéria lacrimal, artéria supraorbital, etc. A drenagem acompanha a irrigação (SAMUELSON, 2013).

A inervação do globo ocular e seus anexos é feita por seis nervos cranianos: nervo óptico (II par), nervo oculomotor (III par), nervo troclear (IV par), nervo trigêmeo (V par), nervo abducente (VI par) e nervo facial (VII par). A via visual inclui o nervo óptico, o quiasma óptico, os núcleos geniculados laterais, as radiações ópticas e o lobo occipital do córtex cerebral. Setenta e cinco por cento das fibras do nervo óptico cruzam o quiasma óptico em cães e 65%, nos gatos. Sendo assim, a maior parte da sensação visual tem uma representação contralateral no córtex cerebral (SAMUELSON, 2013).

2.2. Disseminação tumoral

O câncer é uma doença complexa que envolve um grupo heterogêneo de desordens proliferativas celulares de cunho maligno que acometem os seres vivos, decorrente de alterações no DNA que desregulam a estrutura ou função do gene, oriundos por sua vez, do acúmulo progressivo de alterações genéticas e epigenéticas (CULLEN; BREEN, 2017). Hanahan e Weinberg (2011), na tentativa de nortear os fenômenos complexos que caracterizam a doença, definiram marcadores biológicos necessários para a carcinogênese: crescimento autossuficiente, insensibilidade a sinais anti-crescimento, evasão da morte celular programada (apoptose), potencial replicativo ilimitado, angiogênese sustentada, reprogramação do metabolismo energético, evasão da destruição imunológica, promoção da invasão tecidual e metástase. Subjacente a essas marcas estão a instabilidade do genoma, a inflamação crônica e o microambiente tumoral, que sustentam o processo de seleção e a expansão clonal das células cancerígenas.

Metástase é definida como a disseminação de células tumorais para sítios distantes do tumor primário, para proliferação e colonização local. Por conseguinte, trata-se de característica exclusiva de neoplasias malignas e o desenvolvimento de metástases está intimamente relacionado a sua capacidade e habilidade em se desenvolver longe do sítio primário. Tal processo exige uma sequência de eventos coordenados que envolvem interações célula-célula e célula-matriz, motilidade e invasividade que tendem a tornar o processo metastático abstruso e pouco efetivo (CULLEN; BREEN, 2017).

As vias clássicas de disseminação tumoral incluem a transcelomática, linfática e hematógena. Entretanto o fato dos vasos linfáticos comunicarem-se intimamente com o sistema vascular, a distinção real entre a rota linfática e a hematógena de disseminação, tornam-se artificiais. Atualmente estudos comprovam que a densidade linfovascular tumoral e peritumoral estão diretamente associadas a uma melhor capacidade de disseminação sistêmica, especialmente, no que tange as neoplasias epiteliais. Além disso, a neoangiogênese e linfangênese promovidas pelo microambiente tumoral alteram e podem tornar anômalas as vias de drenagem da área tumoral como demonstrados em neoplasias mamárias da espécie canina (BESERRA *et al*. 2016; BIANCHI *et al*., 2018). Deste modo, a disseminação linfática não ocorre de maneira ordenada e o acometimento do (s) linfonodo (s) regionais configuram doença metastática sistêmica (NEWKIRK; BRANNICK; KUSEWITT; 2017).

Didaticamente a cascata metastática é representada por uma veia sofrendo embolização tumoral até o momento de seu extravasamento e sua implantação tumoral em um novo local (NEWKIRK; BRANNICK; KUSEWITT; 2017). Uma vez que esses êmbolos tumorais atinjam a circulação sistêmica ou pulmonar, diferentes órgãos tornam-se susceptíveis ao desenvolvimento de metástases. Nesse contexto órgãos como fígado e pulmões são irrefutavelmente os sítios mais frequentemente envolvidos (NEWKIRK; BRANNICK; KUSEWITT; 2017, CULLEN; BREEN, 2017). A veia cava e a veia porta são responsáveis pelas drenagens da circulação geral e abdominal, respectivamente, e estão envolvidas no sistema de disseminação venosa dos êmbolos tumorais e permitem que essas células atinjam os dois principais órgãos envolvidos nas doenças metastáticas (NEWKIRK; BRANNICK; KUSEWITT; 2017). Embora menos frequentes em relação à embolização venosa, a embolização arterial também ocorre (NEWKIRK; BRANNICK; KUSEWITT; 2017). Outros padrões metastáticos característicos são reconhecidos, como os carcinomas prostáticos de cães que em 22% dos casos irão metastizar para os ossos (CORNELL *et al*., 2000) e os tumores pulmonares, cujas metástases para os dígitos em falanges distais ocorrem exclusivamente na espécie felina e configuram a Síndrome dígito pulmonar felina (GOLDFINCH; ARGYLE, 2012).

No tocante dos globos oculares, eles são considerados sítios incomuns de metástase em cães gatos (WILCOCK; DUBIELZIG; RENDER., 1999; LABELLE, LABELLE, 2013; MILLER; DUBIELZIG, 2013; DUBIELZIG, 2017; LABELLE, 2017), mas com alguma frequência relatos de caso demonstram o seu envolvimento em neoplasias metastáticas (RENDER *et al.,* 1982; CASSOTIS *et al.*, 1999; MOWAT *et al*., 2012; NARANJO; DUBIELZIG; FRIEDRICHS, 2007; YOSHIKAWA *et al.,* 2008, GRADER. *et al.*, 2016; DUBIELZIG, 2017). Assim como em seres humanos, a via hematógena é proposta como primordial para a disseminação da maioria dos neoplasmas para o olho e o trato uveal o local mais acometido (SHIELDS *et al.,* 1997; DUBIELZIG, 1990; SHIELDS *et al.*, 2000; NARANJO; DUBIELZIG; FRIEDRICHS, 2007; DUBIELZIG, 2010; MILLER; DUBIELZIG, 2013; DUBIELZIG, 2017). Ainda que seu real papel como sítio metastático não esteja totalmente caracterizado em medicina veterinária, em medicina cerca de 39 a 49% de todas as neoplasias uveais metastáticas são de origem mamária (carcinoma) e a incidência dessas metástases variam de 9 a 37% de acordo com o estudo (MEWIS; YOUNG, 1982; BLOCH; GARTNER, 1971,

DEMIRCI *et al*., 2003). Depois dos carcinomas de glândula mamária, os carcinomas pulmonares e do trato gastrointestinal são os com maior implicação ocular em humanos (SHIELDS *et al*., 1997; SHIELDS *et al*., 2000).

2.3. Neoplasmas oculares

As neoplasias oculares primárias em cães e gatos incluem o globo ocular e seus anexos e representam respectivamente 0,87% e 0,34% dos tumores nessas espécies (MILLER; DUBIELZIG, 2013). Os neoplasmas primários que envolvem especificamente o globo ocular, se originam de qualquer uma das três túnicas (fibrosa, vascular e nervosa). As neoplasias melanocíticas como o melanoma difuso de íris em felinos e os melanomas/melanocitomas de úvea anterior e epibulbares em cães são os mais frequentes. Em relação ao comportamento biológico dos melanomas oculares, eles possuem baixo potencial metastático nos cães, mas são localmente agressivos (WILCOCK; PEFIFER, 1986); já nos felinos, metástases distantes são frequentes quando o tumor está em estágio avançado (PATNAIK; MOONE, 1988; DUBIELZIG, 1990; KALISHMAN *et al*., 1998). O segundo tipo tumoral mais frequente nessas espécies são os tumores iridociliares, com ocorrência maior em cães que em gatos. Esses são tumores normalmente de comportamento biológico benigno, entretanto podem causar alterações na arquitetura ocular que acarretam desconforto, algia e prejuízo à acuidade visual. Independentemente da natureza benigna ou maligna da neoplasia a enucleação é medida terapêutica usual (DUBIELZIG *et al.*, 2010).

Em virtude do globo ocular ser considerado um sítio incomum de metástase em animais domésticos, são escassas as pesquisas de revisão sobre o tema (DUBIELZIG, 1990, NARANJO; DUBIELZIG; FRIEDRICHS, 2007; LABELLE; LABELLE, 2013; OTA-KUROKI *et al.*, 2014; TEIXEIRA; DUBIELZIG, 2016; LANZA, 2018). Ainda assim, inúmeros relatos de caso demonstram seu envolvimento (RENDER *et al*., 1982; CASSOTIS *et al*., 1999; MOWAT *et al*., 2012; NARANJO; DUBIELZIG; FRIEDRICHS, 2007; YOSHIKAWA *et al*., 2008, GRADER. *et al*., 2016; DUBIELZIG, 2017).

Em cães e gatos o linfoma é considerado a neoplasia secundária ocular mais prevalente (DUBIELZIG, 1990; WILCOCK; DUBIELZIG; RENDER, 1999; DUBIELZIG, 2010; LABELLE; LABELLE, 20013; MILLER; DUBIELZIG, 2013; DUBIELZIG, 2017; LABELLE, 2017). Na espécie canina além do linfoma, o sarcoma histiocítico também é descrito como frequente, seguido pelo carcinoma de glândula mamária (NARANJO; DUBIELZIG; FRIEDRICHS, 2007; LABELLE; LABELLE, 2013). Além deles, osteossarcoma (RENDER *et al.*, 1982; YOSHIKAWA *et al.*, 2008),

hemangiopericitoma (PUCKET *et al*., 2017), seminoma (HOGENESCH *et al.,* 1987), tumor venéreo transmissível (BOSCOS *et al*., 1998), condrossarcoma (RODRIGUES *et al*, 2009) hemangiossarcoma (SZYMANSKI, 1972), adenocarcinoma de glândula parótida (HABIN; ELSE, 1995) e melanoma oral (DUBIELZIG, 1990; DUBIELZIG, 2017) são descritos. Já em felinos os carcinomas pulmonares e mamários são relatados como os de maior ocorrência (SANDMEYER; COSFORD; GRAHN, 2009; DUBIELZIG, 2017; LABELLE, 2017), mas há relatos de fibrossarcoma subcutâneo (MOWAT *et al*., 2012), carcinoma de células escamosas (HAYDEN, 1976), carcinoma de glândula sudorípara (MOISES; RIIS; ALLISON, 1982) e carcinoma de células transicionais renal (GRADER *et al.,* 2016).

A aparência e os sinais clínicos das neoplasias metastáticas são bastante variáveis e incluem formação de massas tumorais focais, multifocais ou difusas; além de hifema, uveíte anterior e glaucoma (DUBIELZIG, 1990; CASSOTIS *et al.*, 1999, DUBIELZIG, 2013; LABELLE; LABELLE, 2013). Em cães elas envolvem, majoritariamente, a úvea anterior (íris e corpo ciliar) e apresentam dois padrões: um difuso e com crescimento expansivo e obliterante e outro focal ou multifocal. O linfoma e o sarcoma histiocítico tipicamente apresentam-se infiltrando e obscurecendo a úvea anterior de forma difusa, enquanto os carcinomas tendem a obliterar vasos sanguíneos e formarem massas multifocais (NARANJO *et al*., 2007; LABELLE; LABELLE, 2013; LABELLE, 2017)

Em felinos a maior parte das metástases intraoculares envolve a úvea posterior, igualmente, como em seres humanos (MILLER; DUBIELZIG, 2013). Em ambas as espécies, os carcinomas mamários e pulmonares fazem metástases com frequência para a coroide (SHIELDS *et al*. 1997; CASSOTIS *et al*., 1999; MILLER; DUBIELZIG, 2013; DUBIELZIG, 2017). Shields *et al*. (1997) demonstraram em seu estudo retrospectivo após avaliação de 520 globos oculares de mulheres com neoplasia mamária e metástase no trato uveal a seguinte distribuição: coroide (81%), íris (9%) e corpo ciliar (2%). Em outro estudo Demirci e colaboradores (2003) avaliaram o globo ocular de 264 mulheres com neoplasia mamaria metastática e a distribuição observada foi similar com o envolvimento da coroide em 85%. Em relação ao globo ocular como sítio metastático único ou como parte de doença sistêmica metastática em mulheres com neoplasia mamária, o envolvimento ocular normalmente ocorre após o desenvolvimento de metástase pulmonar e cerebral (DEMIRCI *et al*., 2003).

O linfoma é a neoplasia hematopoiética mais comum em cães e gatos e sua implicação ocular secundária é descrita em cerca de 37% dos cães com linfoma multicêntrico e o trato uveal anterior como o local usual (KHRONE *et al*., 1994*;* OTA-KUROKI *et al.,* 2014; DUBIELZIG, 2017). Em seres humanos o linfoma intraocular primário (PIOL) é considerado um subtipo do linfoma do sistema nervoso central e trata-se majoritariamente de um linfoma não-Hodgkin, difuso de grandes células B. Em humanos a localização anatômica corrobora o diagnóstico de PIOL uma vez que eles permanecem confinados às estruturas neurais oculares – retina, câmara vítrea e cabeça do nervo óptico (SAGOO *et al*., 2014). Na doença sistêmica, o trato uveal e as estruturas orbitárias tendem a ser afetados. Em medicina veterinária Lanza *et al*., (2018) diferenciaram e classificaram o PIOL canino do envolvimento secundário ocular, baseados na ausência de doença sistêmica clínica síncrona ao momento do diagnóstico dos globos oculares enucleados. Eles não estabeleceram correlação com os locais anatômicos acometidos como descrito por SAGOO *et al*., (2014) em humanos, entre os linfomas primários e secundários do estudo.

3. RESULTADOS E DISCUSSÃO

3.1. Artigo

Neste item será apresentado o artigo "Ophtalmopathologic characterization of extraocular metastatic or multicentric neoplasms in dogs and cats", que será submetido à publicação na revista Veterinary Ophthalmology".

ORIGINAL ARTICLE

Ophthalmopathologic characterization of extraocular metastatic or multicentric neoplasms in dogs and cats.

ABSTRACT

Objective: To characterize the frequency and distribution of the ocular involvement in dogs and cats by metastatic or multicentric neoplasms, which were concomitantly identified as the main cause of death in these animals.

Methods: A retrospective analysis of the necropsy records was conducted between 2015 to 2019, and cases with extraocular metastatic or multicentric neoplasms in dogs and cats involving the eyes were selected.

Results: In the period analysed, a total of 233 dogs and 100 cats had metastatic or multicentric neoplasms. Of these, 40 animals had ocular metastatic disease (11.6% in dogs (27/233), and 13% in cats (13/100)). Lymphoma was the most common metastatic neoplasm involving the eyes of dogs and cats. In dogs, these neoplasms occurred bilaterally, predominantly in the anterior uvea, and were diffuse large B-cell (5/14), T-lymphoblastic (4/14), peripheral T-cell (3/14), and lymphocytic B-cell lymphomas (2/14). In cats, T-cell lymphoma associated with Feline Leukemia virus (FeLV) was the most common. Mammary carcinoma was the second most common ocular metastatic neoplasm occurring in bitches, with a predominantly unilateral involvement of the uveal tract blood vessels. In cats, following lymphoma, pulmonary carcinoma and squamous cell carcinoma were the most common eye metastatic neoplasms identified. Additional findings included individual cases of cholangiocarcinoma, hemangiosarcoma, and chemodectoma in dogs, as well as mammary gland cribriform carcinoma, salivary gland carcinoma, and histiocytic sarcoma in cats.

Conclusions: The eyeball was identified as a site for the occurrence of metastatic or multicentric neoplasms in 12% of the dogs and cats with a concomitant metastatic or multicentric neoplastic disease. The eyes of dogs were mostly affected by lymphoma and mammary gland carcinoma, while the eyes of cats had mostly lymphoma, pulmonary carcinoma, and squamous cell carcinoma as the main metastatic/multicentric neoplasms. By the author's knowledge, this is the first study that identified intraocular metastatic cholangiocarcinoma and chemodectoma in dogs, aside from salivary gland carcinoma in a cat.

KEYWORDS: metastasis, eyeball, extraocular neoplasms, ocular pathology.

1. INTRODUCTION

Ophthalmopathology is an anatomical pathology field with a focus on the diseases that affect the eyeball and its annexes. Neoplasms are among the diseases that affect the eyes of dogs and cats, with primary neoplasms making up to 0.87% and 0.34% of the cases, respectively, and any of the layers (fibrous, vascular, and nervous) may be equally affected (MILLER, DUBIELZIG, 2013). Melanocytic neoplasms, as diffuse iris melanoma in cats, and canine anterior uveal and epibulbar melanoma/melanocytoma, are most commonly identified, followed by iridociliary tumors, with a major occurrence in dogs when compared to cats (DUBIELZIG, 1990). Independently of the benign or malignant behavior of the neoplasm involving the eye, enucleation is a routine therapy employed in these cases, due to severe abnormalities in the ocular arrangement, which may lead to deformities, pain, and/or possible visual deficits (LABELLE, LABELLE, 2013).

The eyes are considered uncommon metastatic sites in dogs and cats (DUBIELZIG, 1990; WILCOCK, DUBIELZIG, RENDER, 1999; LABELLE, LABELLE, 2013; MILLER, DUBIELZIG, 2013; DUBIELZIG, 2017; LABELLE, 2017); however, numerous studies in these species have reported cases with an involvement of the eye in metastatic neoplastic diseases (RENDER et al., 1982; CASSOTIS et al., 1999; MOWAT et al., 2012; NARANJO, DUBIELZIG, FRIEDRICHS, 2007; YOSHIKAWA et al., 2008, GRADER. et al., 2016; DUBIELZIG, 2017). Furthermore, as in humans, the metastatic cells reach the eye mostly through the hematogenous route, and, thus, the uveal tract is usually affected (SHIELDS et al, 1997; DUBIELZIG, 1990; NARANJO, DUBIELZIG, FRIEDRICHS, 2007; MILLER, DUBIELZIG, 2013; DUBIELZIG, 2017).

Lymphoma is the most prevalent hematopoietic neoplasm in dogs and cats (DUBIELZIG, 1990; WILCOCK, DUBIELZIG, RENDER., 1999; MILLER, DUBIELZIG, 2013; LABELLE, 2017). In dogs, despite secondary eye involvement by lymphoma, histiocytic sarcoma is the most common metastatic neoplasm affecting the eyeball, followed by mammary gland carcinoma (NARANJO, DUBIELZIG, FRIEDRICHS, 2007; LABELLE, LABELLE, 2013). Nevertheless, cats are most commonly affected by metastatic pulmonary and mammary neoplasms involving the eyeball (SANDMEYER, COSFORD, GRAHN, 2009; DUBIELZIG, 2017; LABELLE, 2017).

Retrospective or prospective studies with a special focus on the eye as a metastatic site or as part of a multicentric disease are sparse (DUBIELZIG, 1990, NARANJO, DUBIELZIG, FRIEDRICHS, 2007; LABELLE, LABELLE, 2013; OTA-KUROKI et al., 2014; TEIXEIRA, DUBIELZIG, 2016; LANZA, 2018). Therefore, this work aimed to characterize the frequency and distribution of ocular involvement in dogs and cats affected concomitantly by extraocular metastatic or multicentric neoplasms, which were identified as the cause of death through a complete necropsy exam.

2. MATHERIALS AND METHOD

A retrospective study of the necropsy database was conducted from January 2015 to January 2019 in search of dogs and cats with extraocular neoplastic metastatic or multicentric disease diagnosed grossly at the necropsy examination at the veterinary pathology laboratory. All dogs included in this study were housed at the metropolitan area of the Porto Alegre city, Rio Grande do Sul state, Brazil. Epidemiological data, regarding sex, age and breed, as well as the histological classification of the primary neoplasm, and location of the metastatic sites were retrieved from the necropsy protocols and later grouped. Samples of multiple organs were collected at necropsy, identified, and fixed in 10% neutral buffered formalin for 24h. According to the size of the eyeball, 0.5 to 1 mL of 10% neutral buffered formalin was instilled within the vitreous employing a 26g hypodermic needle in a parallel line to the posterior ciliary artery, and the eyeballs were identified as right (RE) and left eyes (LE) (GRAHAN, PEIFFER, WILCOCK, 2019). These tissues were fixed for 24h, and trimmed through a vertical and perpendicular to the posterior ciliary artery cut section, and placed on Tissue-Tek Mega-Cassettes (Sakura Finetek, USA). These tissues were then routinely processed for histology, and embedded in paraffin. Paraffin-embedded tissues were cut at 3 µm, and later stained by hematoxylin and eosin (H&E). When lymphoma was diagnosed through histopathology, histological characterization was according to the World Health Organization (WHO), as applied for use in animals (VALLI et al., 2011), and the immunophenotype was determined through immunohistochemistry employing a monoclonal mouse CD79α (Bio-Rad®) and a polyclonal rabbit CD3 antibodies (Dako®) at a dilution of 1:15 and 1:250, respectively. Antigenic retrieval for CD79α antibody was obtained by boiling the sections in Tris-EDTA pH 9.0 with a digital pressure cooker (Dakocitomaker®) for 20 min at 99ºC; while for CD3 it was obtained by the enzymatic method employing Protease type XIV (Sigma®) for 15min at 24ºC at room temperature. The amplification signal was obtained with MACH4 universal HRP polymer (Biocare®), and the reactions were revealed with the chromogen AEC (3-amino-9-ethylcarbazole; Biocare®).

Cases in which the eyeballs were not collected at the necropsy, as well as those that presented primary ocular neoplasms and/or extraocular neoplasm in a single site without metastatic disease were excluded from this study.

3. RESULTS

A total of 333 animals with metastatic or multicentric neoplastic disease was analyzed in this study, accounting for 666 eyeballs. Of these, 233/333 were dogs (142/233 females and 91/233 males) and 100/333 were cats (53/100 females and 47/100 males). Mixed breed animals were more frequently affected, corresponding to 52% of the dogs (121/233) and 93% of the cats (93/100). The cats had an average age of 8.9 years-old, and a median age of 8 years-old, while the dogs had 10.8 and 10 years-old, respectively. Among the 333 animals analyzed, 40 also had metastatic ocular disease, which corresponded to 11.6% (27/233) and 13% (13/100) of the cases in the dogs and cats, respectively.

Table 1 summarizes the findings related to the metastatic or multicentric extraocular neoplasms diagnosed in dogs, with a special focus to the neoplasms involving the eyeballs. Among these neoplasms, the findings have been subdivided into distinct categories: mammary carcinomas (**Table 2**), lymphomas (**Table 3**), and other neoplasms (**Table 4**). Moreover, the findings related to the metastatic or multicentric extraocular neoplasms diagnosed in cats are shown in **Table 5**, with a focus on the ocular metastatic neoplasms involving the eyeballs. The epidemiological and ophthalmopathologic findings related to these neoplasms are further described in **Table 6**.

Table 1. Extraocular metastatic or multicentric neoplasms diagnosed through necropsy in 233 dogs, and ocular metastasis detected in 27 dogs.

DIAGNOSIS	Frequency of extraocular metastatic or multicentric neoplasms	Ocular metastasis
Mammary gland carcinoma	58	10
Multicentric lymphoma	35	14
Hemangiosarcoma	28	1
High-grade mast cell tumor	17	0
Melanoma	14	0
Pulmonary carcinoma/adenocarcinoma	9	0
Skeletal osteosarcoma	9	0
Cholangiocarcinoma	8	1
Fibrosarcoma	7	0
Squamous cell carcinoma	7	0
Malignant chemodectoma	6	1
Carcinoma of the prostate	4	0
Chondrosarcoma	3	0
Ectopic thyroid carcinoma	2	0
Exocrine pancreatic carcinoma	2	0
Intestinal adenocarcinoma	2	0
Malignant peripheral nerve sheath tumor	2	0
Urethral transitional cell carcinoma	2	0
Adrenal cortical carcinoma	1	0
Apocrine ductal carcinoma	1	0
Carcinoma of unknown origin	1	0
Endocrine pancreatic carcinoma	1	0
Gastric adenocarcinoma	1	0
Hemophagocytic histiocytic sarcoma	1	0
Histiocytic sarcoma	1	0
Mammary gland osteosarcoma	1	0
Multilobular tumor of bone	1	0
Nasal transitional cell carcinoma	1	0
Ovarian granulosa cell tumor	1	0
Ovarian papillary adenocarcinoma	1	0
Perianal gland carcinoma	1	0
Pheochromocytoma	1	0
Pleomorphic rhabdomyosarcoma	1	0
Thyroid carcinoma	1	0
Mammary gland carcinoma	58	10
Multicentric lymphoma	35	14
TOTAL	***233***	***27***

Table 2. Secondary involvement of the eyeballs by metastatic mammary neoplasms in dogs.

N	Sex	Age (years)	BREED	DIAGNOSIS	DISTRIBUTION	LOCATION
1	F	9	Rottweiler	Anaplastic carcinoma	Unilateral	LE: sclera and optic nerve meninges
2	F	7	English bulldog	Anaplastic carcinoma	Unilateral	LE: sclera and optic nerve meninges
3	F	11	German sheperd	Anaplastic carcinoma	Unilateral	LE: ciliary body (NE)
4	F	9	Mixed breed	Anaplastic carcinoma	Bilateral	LE: uveal tract (NE) / RE: ciliary body (NE)
5	F	14	Lhasa Apso	Adenosquamous carcinoma	Unilateral	RE: iris
6	F	10	Poodle	Carcinoma complex-type	Unilateral	LE: choroid
7	F	12	Dachshund	Carcinoma arising in a mixed tumor	Bilateral	LE: sclera / RE: choroid
8	F	10	Rottweiler	Carcinoma arising in a mixed tumor	Unilateral	LE: ciliary body
9	F	8	Mixed breed	Micropapillary invasive carcinoma	Unilateral	LE: choroid and meninges (NE).
10	F	14	Mixed breed	Micropapillary invasive carcinoma	Bilateral	LE and RE: ciliary body

N: number of identification of the animal; F: female; LE: left eye; RE: right eye; NE: neoplastic emboli.

Table 3. Secondary involvement of the eyeballs by multicentric lymphomas in dogs.

N	SEX	AGE (YEARS)	BREED	DIAGNOSIS	DISTRIBUTION	LOCATION
1	M	10	Mixed breed	T-lymphoblastic lymphoma	Bilateral	Uveal tract
2	F	7	Golden Retriever	Peripheral T-cell lymphoma (extranodal)	Bilateral	Cornea, limbus, and sclera
3	F	10	Mixed breed	T-lymphoblastic lymphoma	Bilateral	Limbus, iris, iridocorneal angle, and ciliary body
4	F	10	Rottweiler	Lymphocytic B-cell lymphoma	Bilateral	Sclera, limbus, iris, and ciliary body
5	F	14	Mixed breed	Diffuse large B-cell lymphoma (centroblastic)	Bilateral	Fibrous, vascular and nervous layers
6	M	NA	Mixed breed	Diffuse large B-cell lymphoma (centroblastic)	Bilateral	Sclera, limbus, iris, and choroid
7	M	11	Mixed breed	Diffuse large B-cell lymphoma (immunoblastic)	Bilateral	Sclera, limbus, and ciliary body
8	F	9	Mixed breed	Diffuse large B-cell lymphoma (anaplastic)	Bilateral	Sclera and optic nerve meninges
9	F	5	Dobermann	Peripheral T-cell lymphoma (nodal)	Bilateral	Fibrous, vascular and nervous layers
10	M	18	Pitbull	T-lymphoblastic lymphoma	Bilateral	Iris and ciliary body
11	M	8	Rottweiler	Lymphocytic B-cell lymphoma	Bilateral	Iris and ciliary body
12	F	19	Pinscher	Peripheral T-cell lymphoma (extranodal)	Bilateral	Iris and ciliary body
13	F	2	Mixed breed	Diffuse large B-cell lymphoma (immunoblastic)	Bilateral	RE: iris / LE: iris and ciliary body
14	M	NA	Mixed breed	T-lymphoblastic lymphoma	Bilateral	Choroid

N: number of identification of the animal; F: female; M: male; NA: not available; LE: left eye; RE: right eye; NE: neoplastic emboli.

Table 4. Secondary involvement of the eyeballs by other metastatic neoplasms in dogs.

N	SEX	AGE (years)	BREED	DIAGNOSIS	DISTRIBUTION	LOCATION
1	F	11	MB	Cholangiocarcinoma	Unilateral	RE: sclera, uveal tract, and optic nerve
2	F	7	MB	Hemangiosarcoma	Unilateral	RE: posterior uvea posterior
3	F	13	MB	Chemodectoma	Bilateral	Sclera and uveal tract

N: number of identification of the animal; F: female; MB: Mixed breed; RE: right eye.

Table 5. Extraocular metastatic or multicentric neoplasms diagnosed through necropsy in 100 cats, and ocular metastasis detected in 13 cats.

Diagnosis	Frequency of extraocular metastatic or multicentric neoplasms	Ocular metastasis
Lymphoma	63	6
Cholangiocarcinoma	7	0
Mammary gland cribriform carcinoma	6	1
Exocrine pancreatic carcinoma	6	0
Squamous cell carcinoma	5	2
Pulmonary carcinoma	5	2
Tracheal adenocarcinoma	1	0
Salivary gland adenosquamous carcinoma	1	1
Nasal adenosquamous carcinoma	1	0
Sublingual carcinoma	1	0
Hemangiosarcoma	1	0
Urinary bladder fibrosarcoma	1	0
Spinal cord anaplastic meningioma	1	0
Disseminated histiocytic sarcoma	1	1
Total	**100**	**13**

Table 6. Secondary involvement of the eyeballs by extraocular metastatic or multicentric neoplasms in cats.

N	SEX	AGE (years)	DIAGNOSIS	DISTRIBUTION	LOCATION
1	F	18	Pulmonary acinar adenocarcinoma	Unilateral	LE: uveal tract
2	F	10	Pulmonary acinar adenocarcinoma	Unilateral	RE: uveal tract
3	F	11	Salivary gland adenosquamous carcinoma	Unilateral	LE: uveal tract
4	F	12	Mammary gland cribriform carcinoma	Unilateral	RE: ciliary body and choroid
5	F	5	Auricular squamous cell carcinoma	Unilateral	RE: optic nerve meninges and sclera
6	F	NI	Nasal squamous cell carcinoma	Unilateral	LE: optic nerve meninges and sclera
7	F	1,6	Peripheral T-cell lymphoma associated to FeLV	Bilateral	Choroid
8	F	1,8	Peripheral T-cell lymphoma associated to FeLV	Bilateral	Uveal tract
9	M	10	Enteropathy-associated T-cell lymphoma (type 1)	Unilateral	LE: iris and ciliary body
10	F	2	T-cell rich diffuse large B-cell associated to FeLV	Unilateral	LE: ciliary body and choroid
11	F	10	T-lymphoblastic lymphoma	Bilateral	Ciliary body
12	M	1	T-lymphoblastic lymphoma associated to FeLV	Unilateral	RE: iris and ciliary body
13	M	15	Disseminated histiocytic sarcoma	Unilateral	RE: iris and ciliary body

N: number of identification of the animal; F: female; M: male; LE: left eye; RE: right eye

Lymphoma was the most frequent extraocular metastatic/multicentric neoplasm diagnosed in cats, with ocular involvement in 9,5% of the cases both unilaterally (3/6) and bilaterally (3/6), with a predominance of the phenotype T (5/6). Most of these cats were young adults (less than 3 years-old) and positive for FeLV (4/6). Grossly, one of these cats (**Cat #12**) had a nodular unencapsulated whitish soft mass involving the iris and ciliary body of the right eyeball. This mass measured 0.3 cm in diameter and was located at the dorsal nasal region (Figure 1A). Microscopically, the uveal tract was focally extensive to diffusely affected, with the involvement of the ciliary body in 5/6 cases (one of the cases this was the only location), while it was also associated to the iris in 2/5, and to the choroid and the complete uveal tract in 1/5 each. Moreover, the posterior uvea was involved as the only location in 1/6 cases.

The dogs with metastatic or multicentric ocular neoplasms were mostly affected by lymphoma (14/35; 40%), with bilateral involvement as a major finding (13/14). Two dogs presented gross lesions, which were characterized by a marked and diffuse corneal opaque thickening, besides conjunctival and episcleral blood vessels hyperemia, hyphema, and retinal displacement (Figure 1B and 1C). The **Dog #2** had, in addition, a severe vitreous hemorrhage (Figure 1D). Microscopically, all eye layers were affected either with a single to combined pattern of neoplastic distribution. These were characterized by a diffuse distribution in the sclera (Figure 2A), corneal stroma (Figure 2B), sclera, limbus and anterior uvea (Figure 2C), anterior uvea (Figure 2D), posterior uvea (Figure 2E), and retina (Figure 2F).

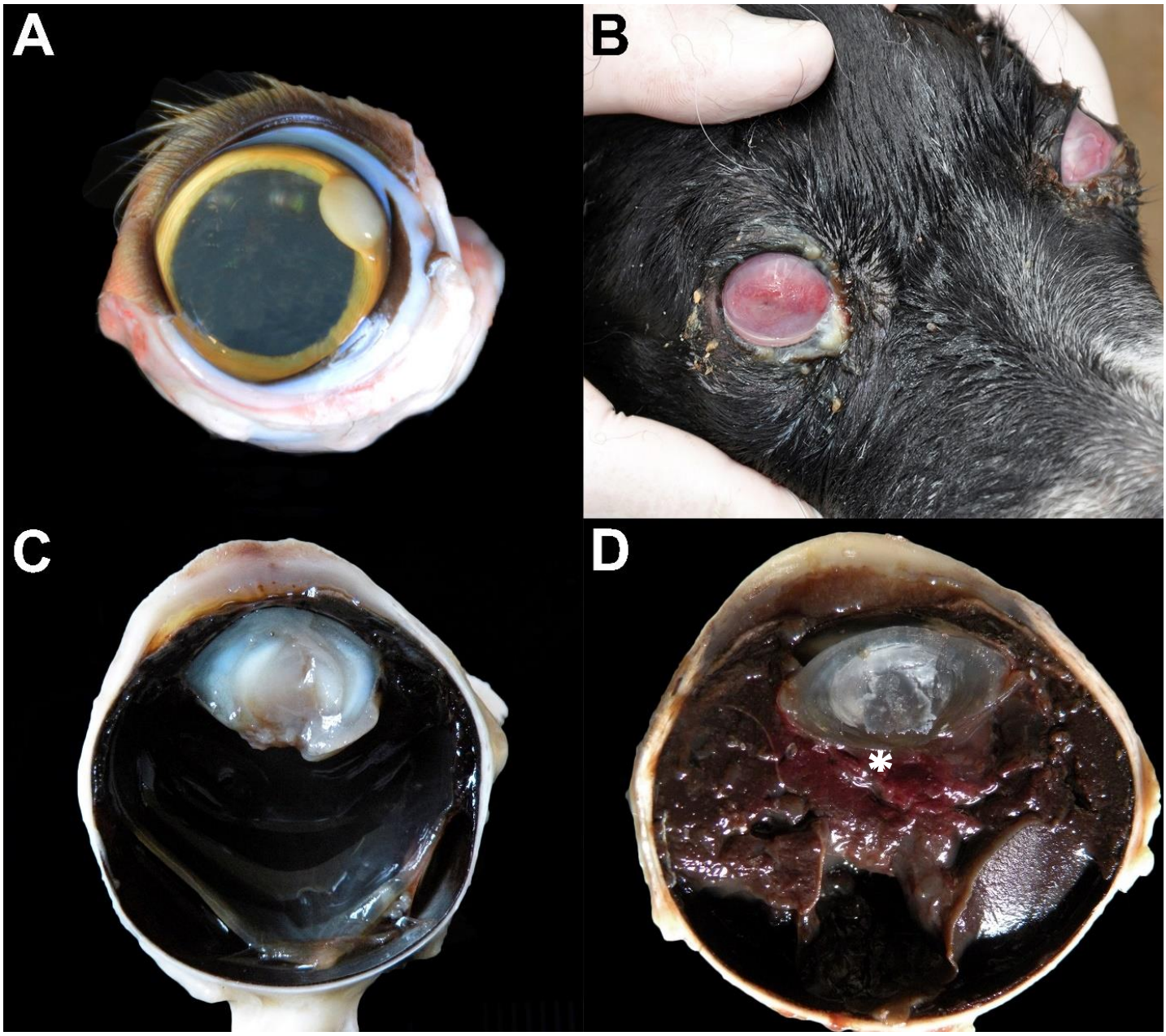

Figure 1. Secondary involvement of the eyeballs by multicentric lymphoma**.** (a) Cat 12. T-lymphoblastic lymphoma associated to FeLV. Nodular whitish lesion involving the iris at the dorsal and medial region of the right eye. (b and c) Dog 5 - Diffuse large B-cell lymphoma (centroblastic). (b) right lateral view of the eyeballs shows the opaque rosy and irregular aspect of the corneal surface due to the neoplastic infiltrates obliterating the corneal stroma, as well as a purulent discharge at the medial angle. (c) Vertical section (meridional) of the eyeball shows a severe diffuse thickening of the corneal stroma, as well as hyphema and retinal displacement. (d) Dog 2. Peripheral T-cell lymphoma. Vertical section (meridional) of the eyeball shows severe hemorrhage involving the anterior and posterior segments, in addition to retinal displacement and subretinal hemorrhage (asterisk).

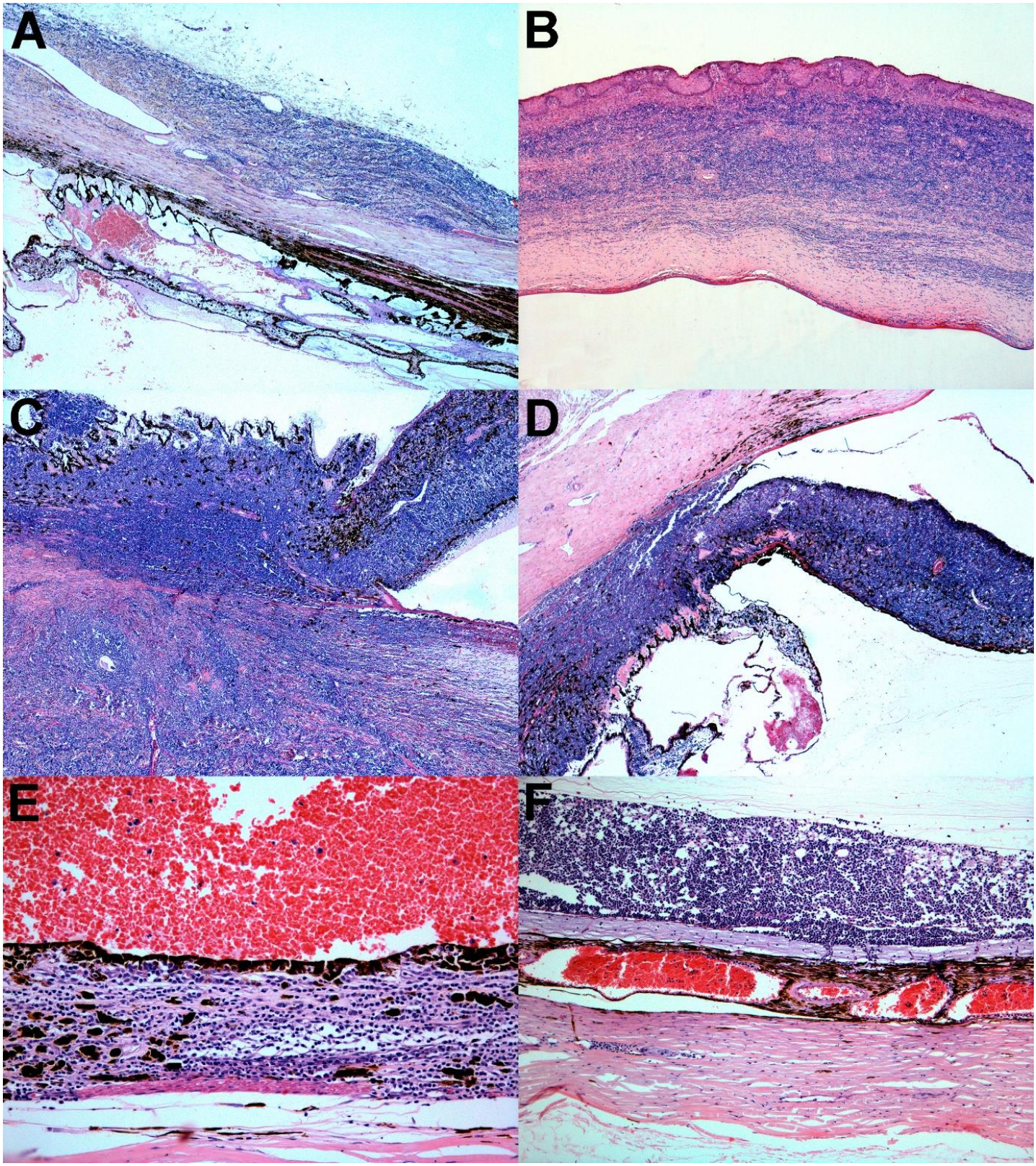

Figure 2. Canine multicentric lymphoma with secondary eye involvement. (a) Diffuse and moderate neoplastic infiltrate of lymphocytes in the sclera. Obj. 4x, Hematoxylin and Eosin (HE). (b) The corneal stroma is obliterated by a severe and diffuse infiltrate of neoplastic lymphocytes, which are associated to neovascularization and acanthosis of the epithelium. Obj. 4x, HE. (c) The sclera, corneal limbus, iris and ciliary body are replaced by large amounts of neoplastic lymphocytes, which are obliterating the iridociliary drainage angle. Obj. 4x, HE. (d) The anterior uvea and the iridocorneal angle are diffusely obliterated by similar neoplastic cells. Obj. 4x, HE. (e) The posterior uvea is diffusely and severely occupied by

similar neoplastic cells, which are replacing the choriocapillaries. There is also retinal displacement which is associated to a severe vitreous hemorrhage. Obj. 20x, HE. (f) Severe neoplastic infiltrate of lymphocytes in the tapetum retina, replacing the retinal layers. Obj. 10x, HE.

Mammary gland carcinoma was the most frequent metastatic extraocular neoplasm involving dogs (58 cases), while it was the second most common metastatic neoplasm with eye involvement (17.2% of the cases; 10/58). Gross intraocular metastasis was observed in two bitches: one of these was affected by a mixed tumor (**Dog #8**) with a grossly nodular well-limited whitish lesion at the *pars plana* of the ciliary body, measuring 0.5 cm in diameter, which was associated to a focal area of hemorrhage in the anterior uvea (**Figure 3A)**. The other bitch (**Dog #5**) had an adenosquamous mammary gland carcinoma metastasis at the anterior chamber of the right eye at the dorsal-temporal region, measuring 0.3 cm in diameter, which was whitish and friable. Histologically, it was loosely adhered to the corneal endothelium and to the anterior epithelium of the iris (**Figure 3B**). Mammary gland anaplastic carcinoma was the most common histological subtype involving the eye (40% of the cases; 4/10) (**Figure 3C**), followed by micropapillary invasive carcinoma (2/10) (**Figure 3D**), carcinoma arising in a mixed tumor (2/10) (**Figure 3E**), adenosquamous carcinoma (1/10) and carcinoma-complex type (1/10). Unilateral involvement was the predominant pattern of distribution (7/10) with embolic or obliterating dissemination within uveal tract blood vessels, mainly in the ciliary body. Mammary gland cribriform carcinoma in one of the cats (**Cat #4**) also had a similar pattern of marked obliterating involvement of the blood vessels of the ciliary body and the choroid with a multifocal distribution of the right eye (**Figure 3F**).

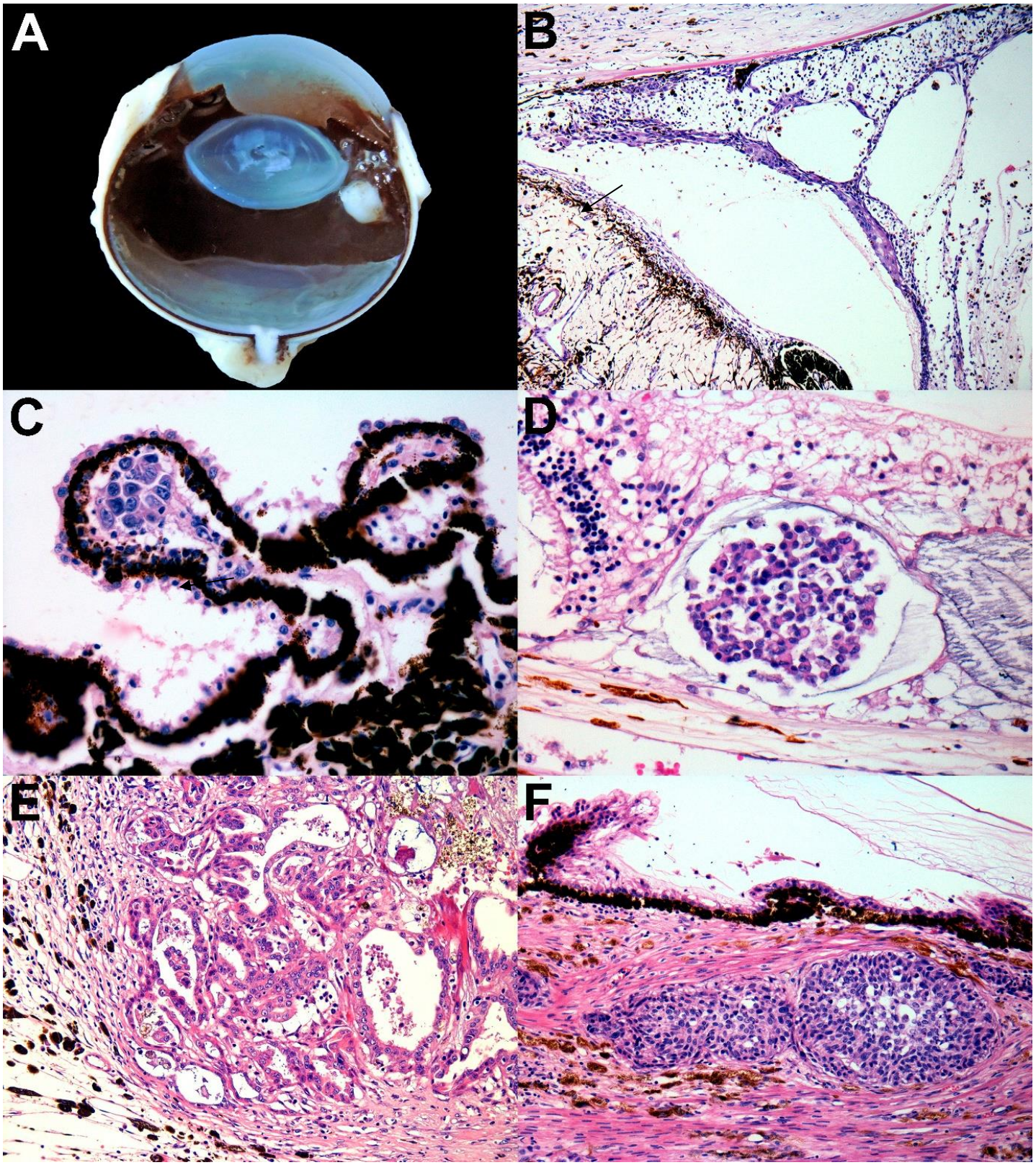

Figure 3. Mammary gland carcinoma with metastasis to eyeballs in dogs and cats. (a) Dog 8, mammary gland carcinoma arising in a mixed tumor with focal involvement of the ciliary body. (b) Dog 5, mammary gland adenosquamous carcinoma with anterior chamber metastasis, which was poorly adhered to the corneal endothelium, and was forming a pre-iridal fibrovascular membrane (arrow). Obj. 10x, Hematoxylin and eosin (HE). (c) Dog 4, metastatic mammary gland anaplastic carcinoma within blood vessels of the *pars plana* region of the ciliary body. Obj. 40x, HE. (d) Dog 14, micropapillary invasive carcinoma with metastasis to a blood vessel in the choroid (non-obliterating neoplastic emboli). Obj. 40x, HE. (e)

Dog 8, mammary gland carcinoma arising in a mixed tumor with tubular arrangement in the ciliary body. Obj. 10x, HE. (f) Cat 4, mammary gland cribriform carcinoma in a cat with multifocal metastasis in the ciliary body. Obj. 20x, HE.

Squamous cell carcinoma with metastatic lesions was observed in five cases, while in two it involved secondarily the eyeballs. Grossly, one of these cats (**Cat#6**) had a yellow to whitish firm, focally extensive, poorly limited and irregular mass involving the posterior region of the right eye, in addition to the sclera and the optic nerve (**Figure 4A**). This mass also extended into the ipsilateral optic chiasm (**Figure 4B**). Histologically, the optic nerve meninges in both cases were unilaterally infiltrated by epithelial neoplastic cells (**Figure 4C and 4D**).

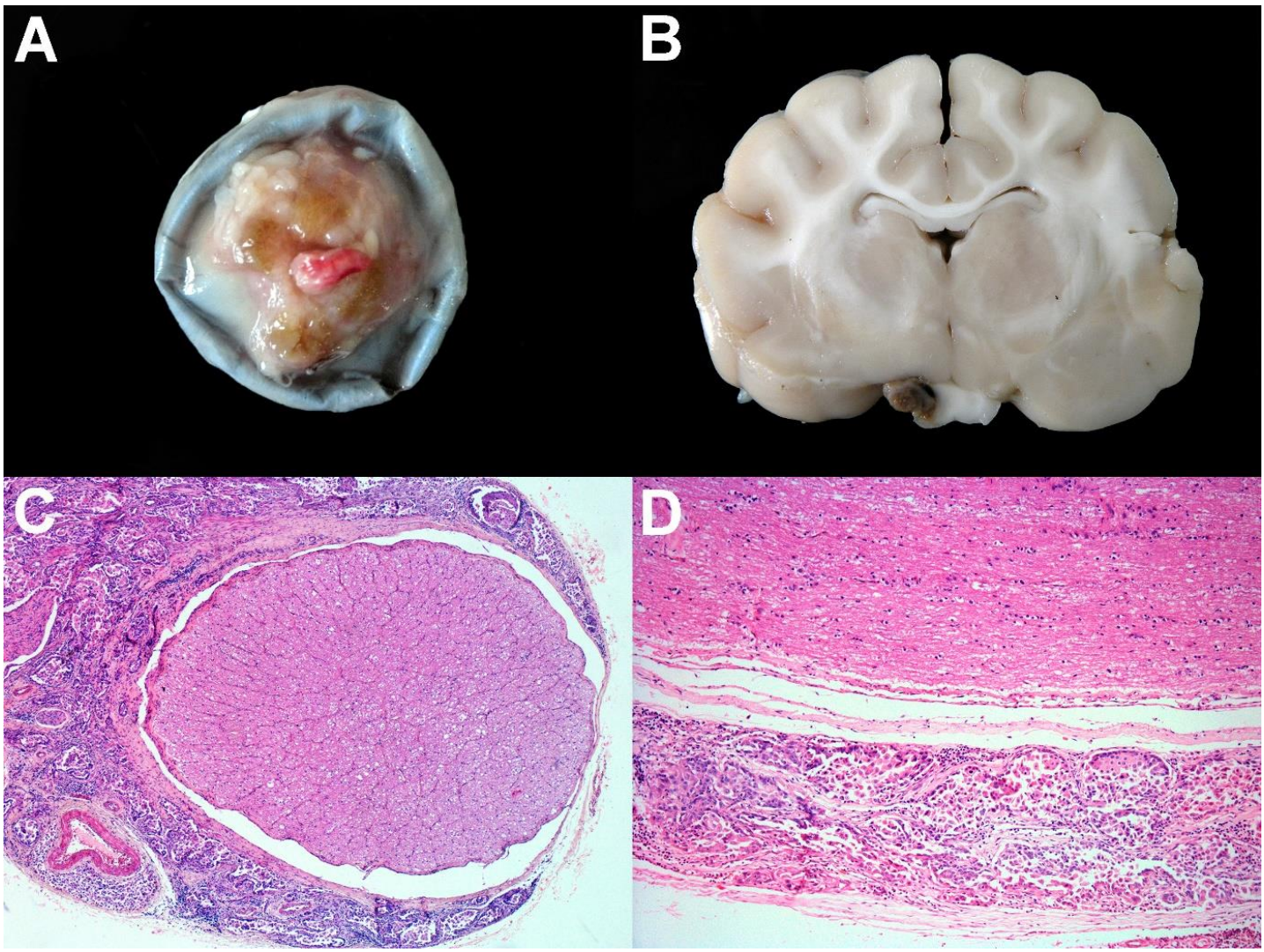

Figure 4. Metastatic squamous cell carcinoma. Cat 6 (a-c). (a) Posterior view of the right eyeball showed a yellowish irregular tumoral lesion involving the sclera and surrounding the optic nerve. (b) Coronal cut section of the brain at the optic chiasm level, anterior view. Focal partially limited black area at the right optic chiasm of neoplastic infiltrate. (c) Transversal section of the right optic nerve highlighted a diffuse and severe neoplastic infiltrate involving the dura-mater and blood vessels. Obj. 4x, HE. (d) Cat 5, Longitudinal section of the optic nerve showed a diffuse and severe metastasis of epithelial cells involving the dura-mater. Obj. 10x, HE.

Pulmonary carcinoma with metastasis was observed in five cats, of which two had ocular involvement. Grossly, **Cat #1** had a mild thickening at the left eye anterior uvea (iris and ciliary body), while **Cat #2** had, on the vertical section of the right eye, a diffuse and irregular thickening of the iris, which was most pronounced at the dorsal region, where a nodular soft black lesion was observed at the anterior uvea (hemorrhage). This was not limited, measured 1 cm in diameter, and displaced laterally the lens (**Figure 5A**). Histologically, the uveal tract blood vessels were multifocally obliterated by this neoplasm, as well as multiple nodular lesions were observed at the *pars plana* and *pars plicata* of the ciliary body, while infiltrative lesions were affecting the choroid (**Figure 5B**).

Cat #3 had an adenosquamous salivary gland carcinoma with secondary involvement of the right eyeball as part of a metastatic disease. Microscopically, the uveal tract had multifocal areas with marked neoplastic proliferation of similar epithelial cells (**Figure 5C**).

Furthermore, **Cat #13** had a disseminated histiocytic sarcoma with an initial lesion at the subcutaneous tissue of the abdominal region, involving the caudal abdominal and inguinal mammary glands, with secondary involvement of the right eye. This was characterized by embolic non-obliterating multifocal neoplastic cells located at the blood vessels of the ciliary body (**Figure 5D**).

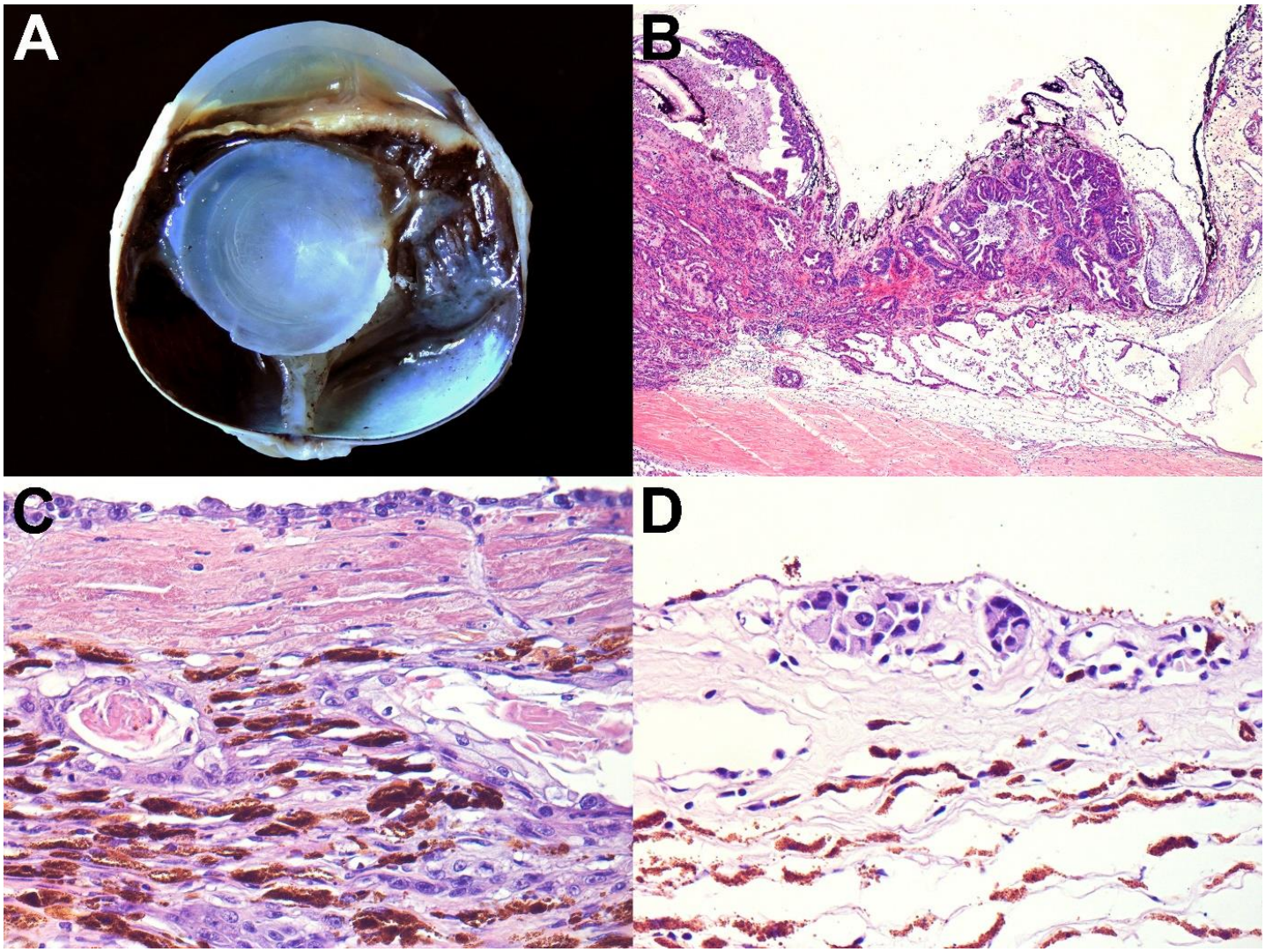

Figure 5. Solid metastatic tumors involving the eyeballs of cats. (a) Cat 2, metastatic pulmonary carcinoma involving the ciliary body was associated to severe peritumoral hemorrhage. (b) Cat 1, Pulmonary carcinoma metastatic cells replaced most of the ciliary stroma. A tubular pattern is observed within this metastasis. Hematoxylin and eosin (HE), obj. 4x. (c) Cat 3, mandibular salivary gland adenosquamous carcinoma with multifocal obliterating metastasis within choroidal and supra-tapetal blood vessels. HE, obj. 40x. (d) Cat 4, multifocal and mildly, blood vessels of the *pars plana* region of the ciliary body were obliterated by a disseminated histiocytic sarcoma neoplastic cells. HE, obj. 40x.

Metastatic cholangiocarcinoma was observed in a dog, which presented a nodular whitish to reddish lesion involving and dissecting the sclera and the complete uveal tract. This lesion was associated to retinal displacement, hyphema, and vitreous hemorrhage (**Figure 6A**). Microscopically, the sclera, uveal tract (anterior and posterior uvea) and the optic nerve had a marked poorly differentiated neoplastic infiltrate of epithelial cells (**Figure 6B**), and the optic nerve a severe Wallerian degeneration associated.

Although dogs with metastatic chemodectoma and hemangiosarcoma did not present any ocular gross lesions, microscopic lesions were evident. Chemodectoma metastatic ocular lesions had two histological patterns:

diffusely throughout the uveal tract (**Figure 6C**), and focally in the sclera and in the meninges of the optic nerve. On the other hand, hemangiosarcoma metastasis involved the choroid focally, causing a local hemorrhage (**Figure 6D**).

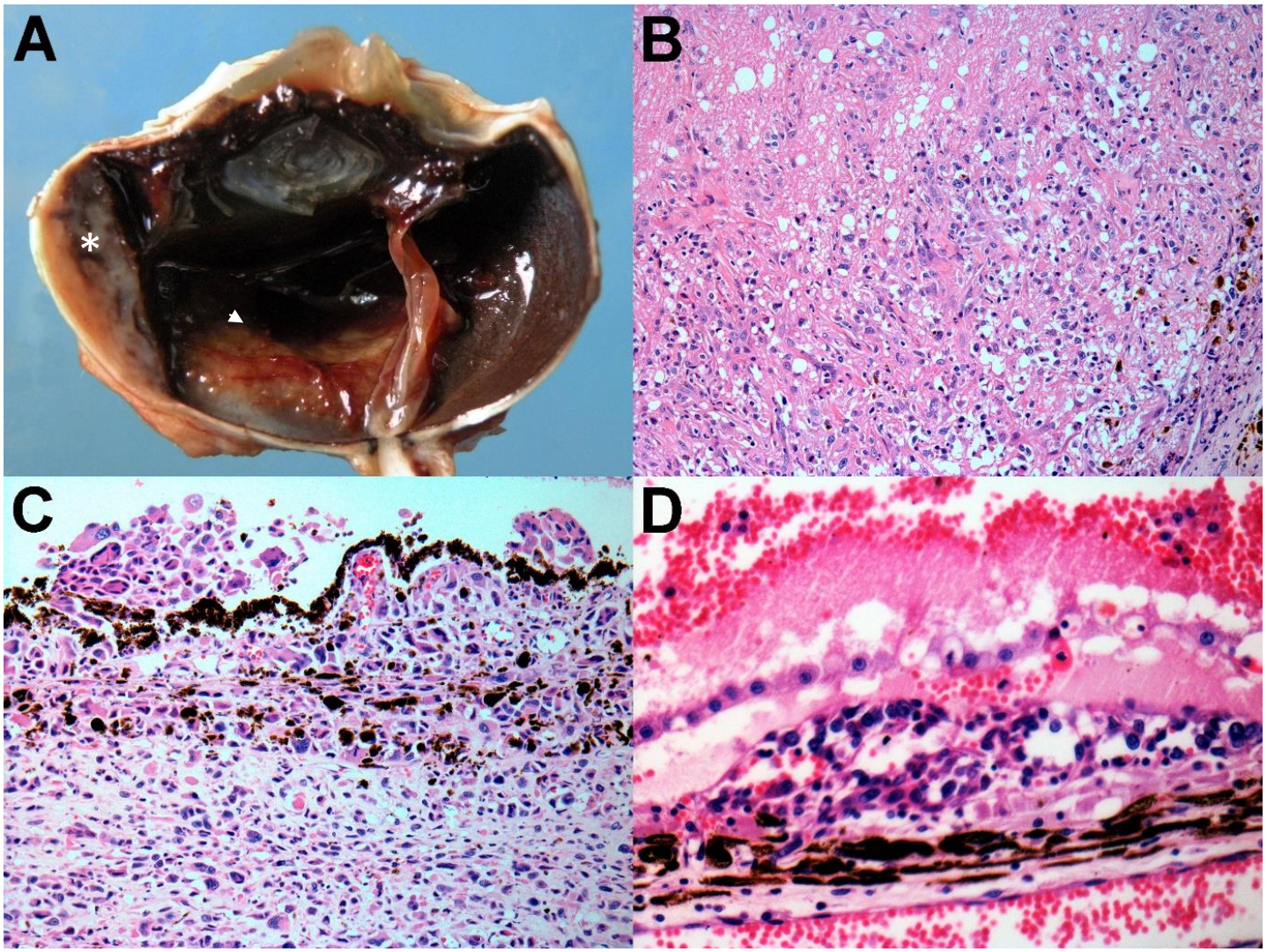

Figure 6. Others metastatic neoplasms involving the eyeballs of dogs. (a) Metastatic cholangiocarcinoma involving the right eye. The vertical cut section shows a nodular mass with a whitish aspect involving the sclera and uveal tract (asterisk). The neoplasm is also evident as an whitish focally extensive area at the subretinal space (arrowhead). (b) The cholangiocarcinoma infiltrated the optic nerve and caused a severe Wallerian degeneration. Hematoxylin and eosin (HE), obj. 20x. (c) Malignant and infiltrative chemodectoma at the choroid and sclera. HE, obj. 20x. (d) Hemangiosarcoma neoplastic cells involved focally the choroid, while were associated to hemorrhage and release of the retinal pigmentary epithelium. HE, obj. 40x.

4. DISCUSSION

The hematogenous route is proposed as an essential via to neoplastic dissemination affecting the eyes, and, therefore, the uveal tract is the most common location of ocular metastasis (SHIELDS et al, 1997; NARANJO, DUBIELZIG, FRIEDRICHS, 2007; MILLER, DUBIELZIG, 2013; DUBIELZIG, 2017), as observed in the present study. In dogs and cats, the eye and orbit are supplied mainly by the external ophthalmic artery, which is located ventrally to the orbit. This is a branch of the internal maxillary artery, which is, further, a branch from the external carotid artery. On the other hand, the internal ophthalmic artery in dogs and cats is relatively small, and provides mainly, along with anastomosis of the external ophthalmic artery, blood supply to the optic nerve (SAMUELSON, 2013). Thus, extraocular systemic neoplasms may have primarily to reach the general circulation in order to affect the eyes (KHRONE et al., 1994 VALLI et al., 2002).

In this study, the main neoplasms affecting secondarily the eyes of dogs were lymphoma and mammary gland carcinoma, respectively. Dubielzig (1990) showed in a previous study a similar distribution of secondary neoplasms in the eye; yet, most of the recent publications have regarded histiocytic sarcoma (HS) as the most common secondary eyeball neoplasm, followed by lymphoma (DUBIELZIG, 2016; LABELLE, LABELLE, 2013). Nevertheless, in the present study, HS was not detected in any dog with metastatic or multicentric neoplasms involving the eyeballs, which may have occurred due to the low frequency of HS occurrence in the analyzed population, as observed with two cases diagnosed in a time course of four years, even though breeds predisposed to this condition, such as Rottweiler, Golden Retriever and Labrador Retriever were also composing the analyzed population.

Lymphoma is the most common hematopoietic tumor of dogs and cats, while secondary ocular involvement is described in at least 37% of the dogs with multicentric lymphoma, usually affecting the anterior uvea (KHRONE et al., 1994*;* LABELLE, LABELLE, 2013; OTA-KUROKI et al*.*, 2014; DUBIELZIG, 2017, LABELLE, 2017). This study has observed a similar frequency of lymphomas affecting the eyeballs (40%), as well as in the majority of the cases the anterior uvea was affected bilaterally. In addition, the limbus, sclera, and cornea were also frequently affected. For instance, the cornea was diffusely affected in approximately 20% of the

cases. Sclerocorneal involvement is recurrent in dogs with multicentric lymphoma (DUBIELZIG, 2010; LABELLE, LABELLE, 2013; KANG, JEONG, SEO et al., 2019), since the limbic sclerocorneal and conjunctival regions have a high vascular density. These vessels are essential to the corneal peripheral nutrition, and, thus, they assume an important function in the corneal repair processes (DUBIELZIG, 2010), as well as these vessels are probably essential to the neoplastic dissemination observed in the present study. In addition, the corneal stroma has pro and anti-angiogenic factors, which, in homeostasis, ensure its avascular condition (DUBIELZIG, 2010). The corneal involvement by lymphoma strengthens the hypothesis that hematogenous dissemination occurs through the limbic sclerocorneal region vessels, since there is an absence of involvement of the anterior segment of the eyeballs in some of the dogs as well.

Neoplastic cells occupying the anterior uvea may also have a metastatic behavior, both by direct tumoral extension, as well as by direct exfoliation to the aqueous humor (DUBIELZIG, 1990). In humans, individuals presenting some tumors are not recommended as corneal donors, such as in hematopoietic neoplasms (leukemia, myeloma, and lymphoma), malignant neoplasms involving the anterior segment of the eyeball (melanoma, squamous cell carcinoma, etc.), retinoblastoma, and concomitant extraocular metastatic disease (EEBA, 2019). Similarly, this study suggests that dogs presenting a systemic metastatic disease should not be eligible to corneal donation.

Diffuse large B-cell lymphoma (DLBCL) is considered the main histological subtype in dogs and cats, and it is associated to the classical lymphadenomegaly clinical presentation in dogs (VALLI et al., 2011; VALLI et al., 2017). Likewise, in the present study it was the main subtype detected with ocular involvement, followed by T-lymphoblastic (LBL) and peripheral T-cell lymphomas (PTCL). Other authors have investigated eyeballs of dogs with systemic diseases (LANZA et al., 2018), and the results were similar to the present study, with a mild preponderance of B cell phenotype, when compared to T cell phenotype, and with the subtypes DLBCL and PTCL as the most prevalent (OTA-KUROKI et al., 2013; LANZA et al., 2018).

Cats were less commonly affected by lymphoma when compared to dogs, but equally the anterior uvea was mostly affected, mainly within the ciliary body. Similarly, a diffuse involvement of the ciliary body by

lymphomas in cats has been previously observed by others authors (DUBIELZIG, 2010; TEIXEIRA, DUBIELZIG, 2016). Most of the cats of the present study had T cell phenotypes lymphomas (67%), which may have occurred due to the fact that most of these animals were young adults (less than 3 years-old) and positive for FeLV. FeLV associated lymphomas are predominantly multicentric, and the literature presents conflicting results with regards to the neoplastic lymphocytes phenotypes (HARDY, ZUCKERMAN, MACEWEN, 1977; JACKSON et al., 1996; LOUWERENS, 2005, OTA-KUROKI et al., 2013). Even though, recent studies have shown a decrease in lymphomas associated to FeLV due to efficient vaccination protocols targeting this virus (LOUWERENS, 2005), other studies conducted in Brazil through serological, molecular, immunohistochemistry analysis have established a higher prevalence of FeLV, and this was further associated to a greater occurrence of lymphomas (ALMEIDA, 2012; BIEZUS et al, 2019; CRISTO et al., 2019).

When lymphomas affecting the eyeballs of dogs are excluded from this analysis, in this perspective, the mammary gland carcinoma would be the major metastatic ocular disease of female dogs, as it is observed in women (MEWIS, YOUNG, 1982; BLOCH, GARTNER, 1971, SHIELDS et al., 1997; SHIELDS et al., 2000, DEMIRCI et al., 2003) and in female cats (CASSOTIS et al., 1999; SANDMEYER et al., 2009; DUBIELZIG, 2017). Mammary gland carcinoma is the most common neoplasm of female dogs (GOLDSCHIMIDT et al., 2011), and in Brazil it is the main cause of death of bitches presenting neoplasms. In addition, it has been described as the main metastatic neoplasm involving the central nervous system of dogs (HECK et al., 2018), similarly to the present study. Thereby, 17.2% of the female dogs of the present study had its eyeballs involved in some sort of systemic metastatic disease, with a multifocal obliterating distribution within blood vessels of the uveal tract, and mainly with a mild predominance of involvement of the anterior uvea. In cats, a single case of mammary gland cribriform carcinoma with metastasis to the eyeballs was detected, which involved the ciliary body and the choroid with a multifocal obliterating pattern. Such metastatic distribution, with multifocal masses or obliterating blood vessels, have been previously described, with a propensity of involvement of the anterior and posterior uvea in dogs and cats, respectively (NARANJO et al., 2007; LABELLE, LABELLE, 2013; LABELLE, 2017).

Among the histological subtypes of mammary neoplasms, anaplastic, micropapillary invasive, and adenosquamous carcinomas accounted for more than half of the cases with eye metastasis in dogs of the present study. These are referred as the worst prognosis subtypes (RASOTTO et al., 2017); however, in this study, other less aggressive subtypes, as complex-type and carcinoma arising in a mixed tumor were also detected as metastatic eye diseases. All these female dogs with metastatic mammary carcinomas from the present study had disseminated neoplasms, with the involvement of the lungs as well. Similarly in humans affected by mammary metastatic neoplasms, the ocular involvement is usually preceded by pulmonary and brain involvement (DEMIRCI et al., 2003).

The involvement of the optic nerve as part of a metastatic disease, such as observed in two cats affected by squamous cell carcinoma and in two bitches affected by anaplastic mammary carcinoma, is uncommon in veterinary medicine. Nevertheless, in humans these metastasis involving solely the optic nerve and its meninges are referred to occur in 1.3-4.5% of the cases (FERRY, FONT, 1974; SHIELDS, SHIELDS, 2000), which are mainly related to carcinomas, especially pulmonary, mammary, and gastrointestinal tumors (DEMIRCI, 2003; SHIELDS et al., 1997, SHIELDS et al., 2000). Moreover, other metastatic neoplasms are also reported to involve this location, such as squamous cells carcinomas, pancreatic and prostatic carcinomas, sarcomas, primary central nervous system tumors, melanoma, and carcinoids (MACK, JAKOBIEC, 1997). Furthermore, multiple reports have described the involvement of the optic nerve by uterine cervix squamous cell carcinomas metastasis (HERTZANU et al., 1987, PORTERA et al. 2006, BALAJI et al., 2007, TUNIO et al., 2015), of which in one case the pachymeninges were affected (BALAJI et al., 2007) similarly to the two cats of the present study. Besides these, two female dogs affected by anaplastic mammary carcinoma also presented optic nerve meningeal involvement. Similarly, in humans a previous study has found 11 metastatic mammary carcinomas involving exclusively this nerve and/or its meninges, mainly unilaterally (FOX et al., 2005).

Some dissemination routes for neoplastic cells to reach the meninges are proposed: hematogenous, direct extension, through centripetal migration by the perineural and perivascular spaces (GONZALEZ-VITALE, GARCIA-BUNUEL, 1976; CHAMBERLAIN, 2008). Among these, meningeal carcinomatosis, as well as

perineural invasion support these hypotheses. Perineural invasion is a distinct metastatic dissemination process, which is characterized by the involvement of the nerves without lymphatics or vascular invasion (LIEBIG et al., 2009). In veterinary medicine, an anal sac carcinoma with medial iliac metastasis in a cat with a similar behavior of neurotropic involvement is reported to occur in nerves roots and sacrococcygeal nerves (S3-Cd4) (RALEIG, LANZA, PERRY, 2018), while in a cow (*Bos taurus*) affected by an ocular squamous cell carcinoma, intracranial metastasis occurred through the cranial nerves (BARROS, 2006). Supporting these theories, a previous study showed that perineural spaces have a propensity for neoplastic dissemination due to the absence of lymphatic vessels, as well as due to its minor resistence (RODIN et al., 1967). The molecular mechanisms expressed by the neoplastic cells are not completely elucidated; however it is believed that neurotrophins play a major role in this metastatic route, as it has been shown in prostate cancer patients (AYALA et al., 2004). Still, in the present study, since there was an exclusive involvement of the optic nerve meninges, we believe that metastasis occurred through hematogenous dissemination, and are, indeed, cases of meningeal carcinomatosis.

Pulmonary carcinoma is considered an uncommon neoplasm of cats, making up less than 1% of all the neoplasms of this species (D'COSTA et al., 2012). However, the literature has conflicting results, since this neoplasm has been shown to be, along with mammary tumors, as the most common to affect the eyes in metastatic diseases (SANDMEYER, COSFORD, GRAHN, 2009; MILLER, DUBIELZIG, 2013; DUBIELZIG, 2017). In the present study, pulmonary acinar carcinoma was the second most common neoplasm that affected the eyes, with a marked multifocal pattern of distribution involving blood vessels of the uveal tract and forming multifocal masses in the anterior uvea in both cases.

Other metastatic tumors occurred individually in the eyeballs of dogs and cats, such as chemodectoma, cholangiocarcinoma, and hemangiosarcoma in dogs. Among these, hemangiosarcoma may cause an ocular neoplastic dissemination in at least 7% of the dogs (DUBIELZIG, 2017), while malignant chemodectomas and cholangiocarcinomas have not been, by the author's knowledge, yet reported to involve the eyeballs. Moreover, in cats isolates cases of mandibular salivary gland adenosquamous carcinoma, mammary gland carcinoma, and histiocytic sarcoma occurred. Previous studies have reported that carcinomas are the main metastatic neoplasms

to the eyeballs of cats; however, no case of primary salivary gland neoplasm causing ocular metastasis has yet been reported. Furthermore, histiocytic sarcomas in cats are uncommon (MOORE, 2017), while the primary ocular involvement has only been reported in a British blue cat affected by a disseminated disease (SCURRELL et al., 2013).

5. CONCLUSION

Dogs and cats had metastatic eye neoplasms in 11.6% and 13% of the cases, respectively, in which extraocular metastatic or multicentric diseases were detected through a necropsy exam. Lymphomas were the most common neoplasms observed in dogs and cats of the present study. Dogs were affected similarly by T and B phenotypes, while in cats T phenotype related to FeLV was the most common. In both species, the anterior uvea was mostly affected with a diffuse pattern in cases of lymphoma. Mammary gland carcinoma was, after lymphoma, the second most common ocular metastatic neoplasm in female dogs, with 60% of the cases corresponding to more aggressive subtypes. The uveal tract was multifocally affected with an obliterating blood vessel pattern, and mainly affecting the anterior uvea of dogs. By the author's knowledge, chemodectoma and cholangiocarcinoma in dogs and salivary gland carcinoma ocular metastasis are reported for the first time.

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4. CONCLUSÃO

- De forma geral cães e gatos que morrem de doenças metastáticas ou multicêntricas extraoculares primárias tem seus olhos como sítio metastático em 12% dos casos.

- O linfoma e o carcinoma de glândula mamária perfazem 86% das neoplasias que afetam o globo ocular nos cães.

- O linfoma é a neoplasia mais frequentemente diagnosticada na população onde o laboratório do Setor de Patologia Veterinária está inserido. E destes, 40% dos cães tem seus globos oculares envolvidos como parte da doença multicêntrica, com ou sem macrometástases e 6% dos gatos.

- Ambas as espécies apresentam a úvea anterior como o local de predileção e com padrão de distribuição difuso nos linfomas.

- O carcinoma de glândula mamária é a segunda neoplasia mais diagnosticada na espécie canina em fêmeas e 17,2% tiveram seus olhos envolvidos como parte de doença metastática sistêmica. O subtipo histológico anaplásico foi o mais observado e a úvea anterior foi o local mais implicado como sítio secundário nos carcinomas de mama.

- O carcinoma pulmonar e de células escamosas em gatos corresponderam a 31% das neoplasias que metastizaram para o globo ocular (4/13). Ambas as neoplasias apresentaram lesões macroscópicas nos globos oculares.

- O carcinoma de células escamosas nos felinos e o carcinoma anaplásico de glândula mamária canino apresentaram carcinomatose meningeal no nervo óptico.

- Quimiodectoma e colangiocarcinoma em cães e carcinoma adenoescamoso de glândula salivar mandibular são descritos pela primeira vez acometendo o globo ocular nessas espécies.

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