UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE VETERINÁRIA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS VETERINÁRIAS

ASPECTOS CLÍNICO-PATOLÓGICOS DOS SARCOMAS NÃO-LINFOIDES METASTÁTICOS OU MULTICÊNTRICOS EM GATOS

RAFAEL BIONDO ROSA

PORTO ALEGRE

2023

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Dissertação apresentada como requisito parcial para obtenção de grau de Mestre em Ciências Veterinárias na área de concentração em Patologia Animal e Patologia Clínica

Orientadora: Luciana Sonne

PORTO ALEGRE

2023

O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Código de Financiamento 001

CIP - Catalogação na Publicação

Rosa, Rafael Biondo
Aspectos clínico-patológicos dos sarcomas não-linfoides metastáticos ou multicêntricos em gatos / Rafael Biondo Rosa. -- 2023.
56 f.
Orientadora: Luciana Sonne.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Veterinária, Programa de Pós-Graduação em Ciências Veterinárias, Porto Alegre, BR-RS, 2023.

1. Patologia. 2. Oncopatologia. 3. Sarcoma. 4. Não-linfoide. 5. Gato. I. Sonne, Luciana, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

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ASPECTOS PATOLÓGICOS DOS SARCOMAS NÃO-LINFÁTICOS METASTÁTICOS OU MULTICÊNTRICOS EM GATOS

Aprovado em 14 de março de 2023

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AGRADECIMENTOS

Aos meus pais e minha irmã que sempre me apoiaram incondicionalmente. Aos professores que tão habilmente passaram todo seu conhecimento e oportunizaram inúmeras experiências. A todos os tutores e pacientes que me proporcionaram amadurecer e crescer profissionalmente e pessoalmente. Aos meus amigos, que tornaram tudo mais fácil.

RESUMO

Sarcomas metastáticos ou multicêntricos não-linfáticos são incomumente reportados em gatos domésticos. Os registros de necropsia do Setor de Patologia da Universidade Federal do Rio Grande do Sul foram acessados com o intuito de obter casos compatíveis com sarcomas metastáticos ou multicêntricos entre os anos de 2012 e 2022, dos quais 12 casos foram selecionados. Comportamento metastático ou multicêntrico dos sarcomas não linfáticos levou a sobrevidas baixas. A mediana do tempo de sobrevida (MST) (n=11) foi de 40 dias (variando de 2–240 dias). Os diagnósticos incluíram sarcomas de aplicação (4 casos, 33,3%), sarcomas histiocíticos (3 casos, 25%), sarcomas viscerais fusocelulares sem envolvimento cutâneo (3 casos, 25%) e hemangiossarcomas (2 casos, 16,6%). A maioria dos sarcomas de aplicação (3/4, 75%) foram classificados morfologicamente como fibrossarcomas e 1/4 (25%) como osteossarcoma. A origem mais provável dos sarcomas viscerais fusocelulares foi o esôfago em dois casos (mixossarcoma e sarcoma indiferenciado) e a bexiga em um caso (sarcoma indiferenciado). As alterações macroscópicas reportadas em 10 casos (83%) consistiram em massas brancas acastanhadas com exceção dos dois hemangiossarcomas caracterizados por massas multifocais vermelho-escuras em múltiplos órgãos. Houve envolvimento pulmonar em quase todos os casos (11/12, 91,6%), seguido por rins e pele (6/12, 50% cada) e fígado (4/12, 33,3%). As células neoplásicas dos sarcomas histiocíticos expressaram IBA-1 e não expressaram anti-macrófago-humano (MAC 387) e E-caderina. Sarcomas multicêntricos ou metastáticos não-linfáticos constituíram um grupo heterogêneo de doenças com manifestações clínicas distintas, com exceção dos sarcomas de aplicação que tiveram como manifestação clínica inicial massas grandes no subcutâneo em locais de aplicação.

Palavras-chave: *gatos, metástase, sarcomas, não-linfático, histiocítico.*

ABSTRACT

Nonlymphoid metastatic or multicentric sarcomas are uncommonly reported in domestic cats. The database from Setor de Patologia Veterinária of Universidade Federal do Rio Grande do Sul was searched for necropsy reports compatible with metastatic sarcomas submitted between 2012 and 2022 and 12 cases were selected. Metastasis or multicentric involvement yielded poor overall survival in patients with non-lymphoid sarcomas, in which the median survival time (MST) (n=10) was 40 days (range, 2–240 days). The diagnoses included feline injection site sarcomas (FISS) (4 cases, 33,3%), histiocytic sarcomas (3 cases, 25%), visceral spindle cell sarcomas without skin involvement (3 cases, 25%) and hemangiosarcomas (2 cases, 16,6%). Most FISS (3/4, 75%) were classified morphologically as fibrosarcoma and 1/4 (25%) as osteosarcoma. The most likely primary site of visceral spindle cell sarcomas was the esophagus in 2 cases (myxosarcoma and undifferentiated sarcoma) and the urinary bladder in one case (undifferentiated sarcoma). Gross changes reported in 10 cases consisted of white-to-tan masses except for the two cases of hemangiosarcomas that appeared as multifocal dark red-purple masses in multiple organs. The lungs were affected in almost all cases (11/12, 91,6 %), followed by the kidneys and skin (6/13, 50% each) and liver (4/12, 33,3%). Neoplastic cells of the histiocytic sarcomas immunohistochemically stained for IBA-1 and did not expressed anti-human-macrophage (MAC 387) and E-cadherin. Metastatic/multicentric nonlymphoid sarcomas comprised a group of heterogeneous diseases with many clinical manifestations except for metastatic FISS, in which the first clinical manifestation was large masses at vaccine injection sites in four cats.

Keywords: cats, metastasis, sarcomas, nonlymphoid, histiocytic.

SUMÁRIO

1. INTRODUÇÃO

A incidência de câncer em animais de companhia vem crescendo nos últimos anos, sobretudo devido ao aumento na expectativa de vida dessa população (BALDUCCI 2018). A transição demográfica que ocorre, principalmente, nos países desenvolvidos é resultado do avanço tecnológico no diagnóstico e terapêutica das doenças e da maior preocupação dos tutores com a saúde dos seus animais de estimação (TEDARDI *et al.* 2016). O Brasil ocupa a segunda posição no número de gatos domiciliados, com 24 milhões de animais, com perspectivas de crescimento (ABINPET 2018). Esse cenário impacta diretamente no aparecimento de doenças crônicas como o câncer. Muitas vezes extrapolam-se os dados internacionais que dizem respeito à epidemiologia do câncer em cães e gatos, entretanto, deve-se ter cuidado já que o ambiente, estado reprodutivo, perfil racial e genético dessas populações pode variar entre os países (TEDARDI *et al.* 2016).

O câncer em cães e gatos é uma doença espontânea que se desenvolve naturalmente e compartilha muitas características com sua contraparte em humanos (VAIL & MACEVEN 2000). A incidência de algumas neoplasias é maior em animais do que em humanos, com curso clínico mais rápido, o que permite prever os desdobramentos antecipadamente nessa população, como metástases, recorrência local e sobrevida (VAIL; THAMM; LIPTAK 2020). Cães e gatos compartilham o mesmo ambiente que os seus tutores, funcionando como sentinelas etiológicos e epidemiológicos do desenvolvimento tumoral visto em humanos (TEDARDI *et al.* 2016). Os tumores espontâneos nessas espécies compartilham uma variedade de características epidemiológicas, biológicas e clínicas com os humanos, e, portanto, são modelos naturais atrativos na pesquisa oncológica (PINHO *et al.* 2012).

2. DESORDENS HISTIOCÍTICAS EM GATOS

Desordens histiocíticas em gatos são incomuns. Três entidades são descritas na espécie: histiocitose progressiva felina (HPF), histiocitose pulmonar de células de Langerhans (HCL) e sarcoma histiocítico (SH) localizado ou disseminado.

2.1 Histiocitose progressiva felina

HPF é considerada a desordem histiocítica mais frequente em gatos cuja origem é atribuída às células dendríticas (CD) da pele e o curso inicial da doença é semelhante a um sarcoma histiocítico de baixo grau (MOORE 2017). A apresentação clínica é caracterizada por nódulos cutâneos únicos ou múltiplos, pápulas ou placas ulceradas e alopécicas predominantemente localizados nas extremidades distais dos membros, na cabeça e no tronco (MOORE 2017; COSTE *et al*. 2019). Essas lesões podem aumentar e diminuir de tamanho, mas a regressão espontânea não acontece (MOORE 2017; COSTE *et al*. 2019). Com a progressão da doença alguns gatos podem desenvolver metástases a distância em linfonodo, pulmão, rim, pâncreas, baço, fígado, coração, adrenal e mediastino (AFFOLTER & MOORE 2006; COSTE *et al*. 2019).

Histologicamente, na fase inicial da doença, nota-se na derme um infiltrado de histiócitos com baixa atipia celular (MOORE 2017). Em 42% dos casos há epiteliotropismo, além de ocasionais agregados dessas células no interior de vasos linfáticos (MOORE 2017; COSTE *et al*. 2019). Em fases tardias da doença, nos casos em que já há confirmação de envolvimento múltiplo de órgãos, geralmente observa-se um aumento substancial do pleomorfismo celular caracterizado por acentuada anisocitose e anisocariose, aumento no número de células gigantes multinucleadas e no número de mitoses atípicas (MOORE 2017; AFFOLTER & MOORE 2006). Nesses casos a diferenciação macroscópica e microscópica entre SH e HPF em fase final é difícil e reside na velocidade do curso clínico da doença (AFFOLTER & MOORE 2006).

Os histiócitos na HPF imunoexpressam CD18, CD1, MHCII e Iba1 o que é consistente com um fenótipo de CD (AFFOLTER & MOORE 2006). Há controvérsias quanto a origem dessas células dendríticas. Em um estudo com 26 gatos diagnosticados com HPF, 24 expressaram E-caderina, sendo que os epiteliotrópicos tiveram porcentagens de células marcadas estatisticamente maiores do que os não-epiteliotrópicos. Esse achado sugere que estas CD sejam células de Langerhans (CL) (COSTE *et al*. 2019). No entanto, em outro estudo, nos 13 casos em que as células exibiam epiteliotropismo, apenas três imunoexpressaram E-caderina (AFFOLTER & MOORE 2006). Nesses casos, os resultados sugerem um fenótipo de CD, no entanto não se pode descartar o fenótipo de CL uma vez que essas células quando migram para a derme diminuem a expressão dessa proteína (TANG *et al*. 1993; BORKOWSKI *et al*. 1994). Os grânulos intracitoplasmáticos de Birbeck, indicativos de CL, não foram evidenciados nos 3 casos de HPF em que se realizou essa avaliação ultra estrutural por meio da microscopia eletrônica (DA CUNHA *et al*. 2014; MOORE 2014).

2.2 Histiocitose pulmonar de células de Langerhans

HCL é uma doença que acomete gatos idosos (7-15 anos) e é caracterizada por dispneia grave e prognóstico desfavorável (BUSCH *et al*. 2008; MOORE 2017; ARGENTA *et al*. 2020). No exame radiográfico os padrões pulmonares variam e podem ser intersticial, alveolar e bronco-intersticial (BUSCH *et al*. 2008; ARGENTA *et al*. 2020). Macroscopicamente, à necropsia, esses pulmões são firmes, não colabados e exibem múltiplos nódulos firmes, brancos e bem delimitados, que por vezes coalescem e invadem o parênquima (ARGENTA *et al*. 2020). Microscopicamente observa-se infiltrado de histiócitos arranjados em grupos coesos no interior de brônquios, bronquíolos e espaços alveolares. Essas células são redondas a levemente alongadas e exibem moderada anisocitose e anisocariose (ARGENTA *et al*. 2020). Não há consenso quanto a natureza dessa enfermidade. O fato dessa doença poder acometer múltiplos órgãos além do pulmão, caracterizado por infiltrados no esôfago, pâncreas, baço, rim, fígado, linfonodo, tireoide e paratireoide associado a um certo grau de atipia celular, favorecem o diagnóstico de um processo neoplásico em detrimento de um processo reativo (BUSCH *et al*. 2008; BELLAMY *et al*. 2019; ARGENTA *et al*. 2020). A demonstração de grânulos de Birbeck no citoplasma dessas células associada à imunoexpressão de E-caderina e CD18 confirmam o fenótipo de CL (BUSCH *et al*. 2008; ARGENTA *et al*. 2020).

2.3 Sarcomas histiocíticos

A frequência de SH em gatos é muito menor do que em cães. SH primários localizados já foram descritos no mediastino, tarso, globo ocular, cavidade nasal e boca (SMOLIGA *et al*. 2005; PINARD *et al*. 2006; SCURRELL *et al*. 2013; SANTIFORT *et al*. 2018; NÉČOVÁ *et al*. 2020). Quando os SH se disseminam para além do linfonodo regional, ele passa a ser chamado de SH disseminado (sinonímia antiga: histiocitose maligna) (MOORE 2017). Rim, traqueia, mediastino, pulmão, estômago, baço, fígado, cérebro, medula espinhal, região periarticular, coração, vértebra, medula óssea e bexiga já foram descritos participando de quadros disseminados da doença (PINARD e*t al*. 2006; REED *et al*. 2006; TROST *et al*. 2008; BISSON *et al*. 2017; CHALFON *et al*. 2021; MONTEIRO *et al*. 2021). SH em felinos apresentam prognósticos ruins e na maioria dos casos há indicação de eutanásia (MOORE 2017). Histologicamente, as alterações são semelhantes aos SH caninos, caracterizadas por proliferações de histiócitos neoplásicos malignos entremeados por discreta quantidade de células fusiformes. Estas células exibem acentuadas anisocitose e anisocariose, multinucleação, e grande número de mitoses incluindo figuras atípicas (MOORE 2017). O principal diagnóstico

diferencial para SH quando há envolvimento do subcutâneo em regiões de aplicação é o sarcoma pleomórfico indiferenciado, e nesses casos o histórico clínico associado a exame imuno-histoquímico é mandatório para a discriminação (MOORE 2017; KIUPEL 2018).

Sarcomas histiocíticos hemofagocíticos (SHH) em gatos são restritos a poucos relatos de casos muitas vezes sem confirmação fenotípica da origem macrofágica das células neoplásicas (KRAJE; PATTON; EDWARDS 2001; FRIEDRICHS & YOUNG 2008; IDE *et al*. 2009; HUBER & LELEONNNEC 2020). Em um estudo, dois gatos tiveram alterações clínico-patológicas semelhantes à doença em cães (KRAJE; PATTON; EDWARDS 2001). Eles apresentaram esplenomegalia, anemia, trombocitopenia e, no exame histopatológico *post mortem*, histiócitos neoplásicos exibindo atividade eritrofagocítica em múltiplos órgãos. Por outro lado, a formação de múltiplos nódulos no fígado, rim e baço, nesses dois casos, sugere um SH disseminado em detrimento de um SHH. Em um único relato de caso, os autores utilizaram imuno-histoquímicas específicas e o diagnóstico final de SHH foi dado em função dos sinais clínico-patológicos associado a um fenótipo $CD1c^{-}/CD11b^{+}$ dos histiócitos neoplásicos (FRIEDRICHS; YOUNG 2008). Acredita-se que gatos não expressam CD11d e, portanto, o anticorpo utilizado para confirmar a doença em cães não é específico para gatos (FRIEDRICHS & YOUNG 2008). Nesses casos, a confirmação da origem macrofágica da polpa vermelha do baço representa um desafio. Discute-se ainda, o fato de que SHH exibiriam baixo pleomorfismo celular comparado ao SH. No entanto, os relatos de SHH em gatos são contraditórios entre si quanto a esse critério (FRIEDRICHS & YOUNG 2008; HUBER & LELEONNNEC 2020). Há ainda um relato de sarcoma histiocítico intranasal envolvendo a medula óssea com características celulares sugestivas de origem macrofágica-mieloide ($CD1a^{-}/CD1b^{+}$/CD11c) (WONG *et al*. 2012). Apesar de exibirem ocasionalmente eritrocitose, outros achados clínico-patológicos característicos de SHH em cães, como envolvimento esplênico e hepático além de anemia e trombocitopenia não foram identificados nesse caso (WONG *et al*. 2012).

3. SARCOMAS DE TECIDOS MOLES EM GATOS

Sarcomas de tecidos moles (STM) são neoplasias oriundas de células mesenquimais do tecido conjuntivo (KIUEPEL 2021). STM podem originar-se em qualquer sítio anatômico, no entanto a pele e o subcutâneo são os locais mais comuns (DOBROMYLSKYJ; RICHARDS; SMITH 2021). Esses tumores possuem origens celulares distintas, porém apresentam

características histológicas e comportamentos biológicos semelhantes. São eles: fibrossarcoma, mixossarcoma, tumor de bainha de nervo periférico, tumor de parede perivascular, sarcoma indiferenciado e lipossarcoma (DENNIS *et al*. 2011). Em gatos, há ainda os sarcomas de aplicação (SA) que ocorrem em sítios de aplicação de medicamentos, vacinas, *microchips*, fios de sutura não absorvíveis e placas metálicas (BURACCO *et al*. 2002; DALY *et al*. 2008; MARTANO *et al*. 2012; HARTMANN *et al*. 2015; DE CECCO *et al*. 2019). Acredita-se que as células mesenquimais pluripotentes presentes no processo inflamatório e reparativo nestes sítios pós-aplicação sofram transformação maligna e deem origem aos sarcomas de aplicação (KIUPEL 2018). A inflamação crônica associada à superexpressão de fatores de crescimento, superexpressão ou mutação de oncogenes e de genes supressores tumorais parecem desempenhar um papel importante na transformação neoplásica dessas células (HENDRICK 1998; NIETO *et al*. 2003; WOOWARD 2011). Ainda, sugere-se uma predisposição genética individual no desenvolvimento desses sarcomas (WOOWARD 2011).

3.1 Fibrossarcoma

Os fibrossarcomas são compostos por feixes de células fusiformes sustentadas por quantidades variáveis de tecido conjuntivo. Há três variantes descritas: fibrossarcoma convencional, queloidal e miofibroblástico (KIUPEL 2018). Eles se apresentam na maioria das vezes como massas focais localmente infiltrativas e com baixo potencial metastático (MARTANO; MORELLO; BURACCO 2011). Uma exceção é o fibrossarcoma induzido pelo sarcoma vírus felino (FeSV) cuja apresentação é multicêntrica, tem maior potencial metastático e acomete gatos mais jovens, com idade média de três anos (HARTMANN 2012). FeSV é um vírus recombinante que se desenvolve *de novo* em gatos infectados com FELV-A através da recombinação do genoma viral com oncogenes celulares do hospedeiro (HARTMANN 2012);

3.2 Mixossarcoma

Mixossarcomas são tumores de fibroblastos caracterizados por produzir uma matriz mixoide rica em mucopolissacarídeo positiva no *Alcian Blue* (HENDRICK 2017). É a contraparte maligna do mixoma e se origina, principalmente, no subcutâneo (KIUPEL 2018). São compostos por células fusiformes a estreladas arranjadas de maneira frouxa (HENDRICK 2017). É considerado um tumor localmente invasivo com potencial metastático baixo, sendo o pulmão o principal sítio (KIUEPEL 2018). Em gatos, há duas descrições de mixossarcomas, em que um deles é visceral acometendo unicamente um dos rins (MANFREDI *et al*. 2015) e o

outro de subcutâneo associado à colocação de implantes metálicos para correção de uma fratura femoral (MADERE *et al*. 2020).

3.3 Sarcoma de aplicação

Morfologicamente, sarcomas de aplicação (SA) podem assumir várias linhas de diferenciação como fibrossarcoma, osteossarcoma, condrossarcoma, rabdomiossarcoma e sarcoma pleomórfico indiferenciado (DUBIELZIG; HAWKINS; MILLER 1993; HELDMANN; ANDERSON; WAGNER-MANN 2000; DE CECCO *et al*. 2019; KIUPEL 2018). Recorrência é comum nos SA e muitas vezes há necessidade de mais de uma intervenção cirúrgica em um curto espaço de tempo (HENDRICK & GOLDSCHMIDT 1991). No curso inicial da doença, o potencial metastático é baixo, no entanto aumenta com o desenvolvimento da doença (MARTANO; MORELLO; BURACCO 2011). Metástases já foram reportadas em linfonodo, mediastino e pulmão (ESPLIN & JAFFE 1996; RUDMANN *et al*. 1996);

Muitas vezes, diferenciar um sarcoma de tecido mole espontâneo de um associado à aplicação em gatos é difícil e deve-se lançar mão de alguns critérios. Os principais envolvem: (1) localização compatível com aplicação de vacinas ou medicamentos; (2) histórico de aplicação de vacinas ou medicamentos; (3) à avaliação histológica, presença de necrose e infiltrado inflamatório mononuclear na periferia do tumor são mais comuns e em maior quantidade nos sarcomas relacionados à aplicação (ABERDEIN *et al*. 2007; DE CECCO *et al*. 2019). O número de mitoses é controverso. Segundo CECCO *et al*. 2019, a maioria dos sarcomas de aplicação apresentam atividade mitótica baixa, enquanto ABERDEIN *et al*. 2007 e DODDY *et al*. 1996 reportam SA com atividade mitótica estatisticamente superior aos não-relacionados a aplicação. Metade dos casos de SA apresentaram mais de 20 mitoses em dez campos de maior aumento (ABERDEIN *et al*. 2007). SA são macroscopicamente maiores, acometem gatos mais jovens (DODDY *et al*. 1996) e recidivam com maior frequência do que os sarcomas de tecidos moles oriundos de sítios anatômicos não relacionados à aplicação (HENDRICK *et al*. 1994). Ainda, localização no subcutâneo, grau de inflamação e grau de necrose são associados mais aos SA do que aos não associados à aplicação (DODDY *et al*. 1996).

Nos STM em cães, o grau histológico associado à condição da margem histológica são fatores prenunciadores de recorrência local (DENNIS *et al*. 2011). A classificação em graus histológicos leva em consideração o grau de diferenciação tumoral, número de mitoses e

quantidade de necrose (DENNIS *et al*. 2011). Em gatos, há uma proposta semelhante de graduação dos sarcomas cutâneos e subcutâneos em que o grau de diferenciação tumoral é substituído pelo grau de inflamação (DOBROMYLSKYJ; RICHARDS; SMITH 2021). Esse estudo não distingue os SA dos não relacionados à aplicação e, portanto, devido ao grau de necrose e inflamação comumente observadas nos SA, estes receberiam graus altos, trazendo poucas informações quanto a uma possível diferença biológica entre eles (DOBROMYLSKYJ; RICHARDS; SMITH 2021).

4 SARCOMAS COM DIFERENCIAÇÃO INCERTA

4.1 Sarcoma pleomórfico indiferenciado

Sarcoma pleomórfico indiferenciado (SPI) (sinonímia antiga: fibrohistiocitoma maligno) normalmente se origina no subcutâneo em sítios de aplicação (GARMA-AVIÑA 1987; HARTMANN *et al*. 2015) e apresenta três componentes celulares: células fusiformes, células gigantes multinucleadas (CGM) e histiócitos (DE CECCO *et al*. 2021). As células fusiformes são arranjadas em um padrão estoriforme exibindo anisocitose e anisocariose variadas e ocasionais citomegalia e cariomegalia (KIUPEL 2018). Essas células expressam consistentemente vimentina e marcação variável para actina de músculo liso e desmina, o que sugere um fenótipo fibroblástico/miofibroblástico (DE CECCO *et al*. 2021). As células gigantes são caracterizadas por grande quantidade de núcleos (GLEISER *et al*. 1979; DE CECCO *et al*. 2021; KIUPEL 2018) e por exibem fenótipos semelhantes à das células fusiformes (KIUPEL 2018). No entanto as CGM podem exibir diferenciação histiocítica (DE CECCO *et al*. 2021). A expressão de marcadores histiocíticos como CD18 e CD204 pelas células fusiformes e multinucleadas leva invariavelmente a um diagnóstico de sarcoma histiocítico em detrimento de SPI. Não está claro se estas células gigantes multinucleadas e histiócitos intratumorais são células reativas ou neoplásicas (MADEWELL *et al*. 2001). Pleomorfismo celular acentuado sugere origem neoplásica (MADEWELL *et al*. 2001).

2. ARTIGO 1

Nesse item é apresentado o artigo intitulado “Feline nonlymphoid metastatic or multicentric sarcomas in 12 cats: clinicopathological features” a ser submetido ao periódico “Journal of Comparative Pathology”.

Feline nonlymphoid metastatic or multicentric sarcomas in 12 cats: clinicopathological features

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Funding information: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Word count:

Number of figures and tables:

Declaration of conflicting interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abstract

Nonlymphoid metastatic or multicentric sarcomas are uncommonly reported in domestic cats. The database from Setor de Patologia Veterinária of Universidade Federal do Rio Grande do Sul was searched for necropsy reports compatible with metastatic or multicentric sarcomas submitted between 2012 and 2022, and 12 cases were observed. Metastasis or multicentric involvement led to poor overall survival in patients with non-lymphoid sarcomas, in which the median survival time (MST) (n=10) was 40 days (range, 2–240 days). The diagnoses included feline injection site sarcomas (FISS) (4 cases, 33.3%), histiocytic sarcomas (3 cases, 25%), visceral spindle cell sarcomas without skin involvement (3 cases, 25%) and hemangiosarcomas (2 cases, 16.6%). Most FISS (3/4, 75%) were classified morphologically as fibrosarcoma and the remaining case (1/4, 25%) as osteosarcoma. The most likely primary site of visceral spindle cell sarcomas was the esophagus in 2 cases (myxosarcoma and undifferentiated sarcoma) and the urinary bladder in one case (undifferentiated sarcoma). Neoplastic cells of the histiocytic sarcomas immunohistochemically stained for IBA-1 and vimentin and did not expressed anti-human-macrophage (MAC 387) and E-cadherin. Gross changes reported in 10 cases (83%) consisted of white-to-tan masses, except for the two cases of hemangiosarcomas that appeared as multifocal dark red-purple masses in multiple organs. The lungs were affected in almost all cases (11/12, 91.6%), followed by the kidneys, skin (6/12, 50% each), and liver (4/12, 33.3%). Metastatic/multicentric nonlymphoid sarcomas comprise a group of heterogeneous diseases with many clinical manifestations except for metastatic FISS, in which the first clinical manifestation was large masses at vaccine injection sites in four cats.

Keywords: cats, metastasis, sarcomas, nonlymphoid, histiocytic

Introduction

Typically, nonlymphoid sarcomas in cats include soft tissue sarcoma (STS) not related to injection, feline injection-site sarcomas (FISS), histiocytic sarcoma and hemangiosarcoma. STS are neoplasms arising from mesenchymal cells within connective tissue at any anatomical site; nevertheless, those arising from cutaneous and subcutaneous tissues are the most common.[1,2] Even though these tumours may be of different cell origin, they have similar biological behavior and histological features, therefore, they are listed as "soft tissue sarcomas".[1]

FISS arises from the neoplastic transformation of pluripotent mesenchymal cells present in the inflammatory process, which may morphologically resemble various lines of differentiation, such as undifferentiated pleomorphic sarcoma, osteosarcoma and fibrosarcoma.[1] Unfavourable outcome seems to be associated with local recurrence since metastasis has been rarely reported.[2] However, metastatic potential appears to increase with prolonged survival, with reports of metastasis to lymph nodes, mediastinum and lungs.[3-5] Still, FeLV-induced fibrosarcomas have great metastatic potential, usually occurs in young cats on average at the 3 years of age and are often multicentric in the skin at previous sites of injection.[6]

Histiocytic sarcoma (HS) is a malignant neoplasm arising from interstitial dendritic cells (IDC) present in several organs.[7] Disseminated histiocytic sarcomas (DHS) are well recognized in purebred dogs and are characterised by systemic lesions spread to distant sites besides the local draining lymph node.[8] Typically, these neoplasms occur as multifocal masses in internal organs.[8] Clinical course of DHS is rapid and aggressive, and it carries a poor prognosis.[9] In cats, the disease has been sporadically reported involving multiple internal organs.[10-15] Clinical outcomes of DHS vary according to the affected sites, distribution and size of the masses.[9] Systemic proliferative histiocytic disorders in cats are uncommon and include Langerhans cell histiocytosis (LCH) and feline progressive histiocytosis (FPH) in the terminal phase.[7] The

distinction between DHS, LCH and FPH in the terminal phase may be difficult because of the overlap of microscopic and immunohistochemical features of these diseases.[16-18] Thus, correlating clinical data may be helpful in these circumstances.

Reports describing the clinical behaviour, pathological and immunophenotypic features of metastatic/multicentric sarcoma in cats are scarce. Here we bring new insights into the clinical course, metastatic behaviour and histiocytic cell markers for three cases of feline DHS, as well as the pathologic features of multicentric or metastatic sarcoma in cats, including injection site sarcomas, visceral spindle cell sarcomas and hemangiosarcomas.

Material and methods

Case selection

Cases of nonlymphoid metastatic or multicentric sarcomas in cats were identified retrospectively from the database of Setor de Patologia Veterinária of Universidade Federal do Rio Grande do Sul (UFRGS). The records were searched for necropsies samples based on combination of keywords such as 'cats' 'sarcoma', 'metastatic', 'metastases', and 'multicentric' on their reports and final diagnosis. "Lymphosarcoma" and lymphoma diagnosis have been excluded from the study as well as leukaemia diagnosis. Only cases that match those criteria and had evidence of metastasis at microscopic reports have been included.

Clinical details were obtained from records of Hospital de Clínicas Veterinárias of UFRGS (HCV-UFRGS) and included clinical presentation, date of the first consultation, sex, age, breed, test results for Feline leukemia virus (FeLV) antigen and (FIV) antibodies. The cats were subdivided according to age: kitten (birth up to 1 year); young adult (1-6 years); mature adult (7-10 years) and senior (>10 years).[19] Overall survival was defined as the time from the diagnosis to death. The diagnosis of FISS was based on the following criteria: tumor arising at application sites on the neck, thorax, flank, limbs and interscapular and lumbar regions,

histological characteristics including large areas of necrosis, peripheral inflammation of lymphocytes and macrophages and subcutaneous origin. [20-22] Dobromylskyj *et al.* numeric method grading system was used in those three cases of FISS. Following this classification cutaneous and subcutaneous soft tissue sarcomas in cats can be graded as grade I, II or III based on mitotic rate, degree of inflammation and presence and extend of necrosis.

Immunohistochemical analysis

Formalin-fixed paraffin-embedded tissues from all cases morphologically compatible with histiocytic sarcoma (cases 1–4) were submitted to immunohistochemistry (IHC) for CD3, CD20, ionized calcium binding adaptor molecule 1 (IBA-1), anti-human-macrophages, E-cadherin and vimentin. To confirm the origin and histological subtype of the other tumors IHC was performed only in the purported primary site. FISS and spindle cell visceral sarcomas (cases 6-11) were submitted to vimentin (VIM), desmin (DES), alpha smooth muscle actin (α-SMA), and S100. External positive control tissues included normal feline skin for vimentin, lymph node (CD3, CD20, and IBA-1), feline reactive histiocytosis (anti-human-macrophage, MAC 387), and small intestine (VIM, DES and α-SMA). Bronchiolar and epidermal epithelium were considered as the internal positive and external positive controls for E-cadherin, respectively. Amplification signal was obtained (Novolink -Max polymer Detection System - LEICA) and revealed with 3-amino-9-ethylcarbazole. For negative controls, phosphate buffered saline was used to replace the primary antibodies in each IHC assay. Data regarding immunohistochemistry protocol are summarized in table 1.

Table 1 – Antibodies and immunohistochemical protocols used in feline nonlymphoid metastatic and multicentric sarcomas

Antibody/code	Positive control tissue	Clone	Antigenic recovery	Dilution	Detection system	Chromogen
CD3/A0452[1]	lymph node	polyclonal	15 min protease XIV, at room temperature	1:250	Novolink -Max polymer Detection System - LEICA®	AEC
CD20/PA516701[2]	lymph node	polyclonal	Heat (microwave), 10 min in pH 9.0 Tris EDTA	1:400	Novolink -Max polymer Detection System - LEICA®	AEC
IBA-1/A1527[3]	lymph node	polyclonal (A1527)	Heat (pressure cooker), 40 mins in pH 6.0 citrate buffer at 96 ºC	1:2000	Novolink -Max polymer Detection System - LEICA®	AEC
Anti-human-macrophage/ M0747[1]	reactive histiocytosis	monoclonal (MAC387)	Heat (pressure cooker), 40 mins in pH 6.0 citrate buffer at 96 ºC	1:20	Novolink -Max polymer Detection System - LEICA®	AEC
E-Cadherin/M3612[1]	internal positive control and haired skin	monoclonal (NHC-38)	Heat (microwave), 15 mins in pH 6.0 citrate buffer	1:100	Novolink -Max polymer Detection System - LEICA®	AEC
Vimentin/18-0052	small intestine	monoclonal (V9)	Heat (pressure cooker), 40 mins in pH 6.0 citrate buffer at 96 ºC	1:200	Novolink -Max polymer Detection System - LEICA®	AEC
Desmin/M07	small	monoclonal	Heat (microwave),10	1:300	Novolink -Max	AEC

60[1]	intestine	(D33)	min in pH 9.0 Tris EDTA		polymer Detection System - LEICA®	
SMA/M0851[1]	small intestine	monoclonal (1A4)	Heat (pressure cooker), 20 mins in pH 9.0 Tris EDTA at 120ºC	1:50	Novolink -Max polymer Detection System - LEICA®	AEC
S100/IR504[1]	canine melanoma	polyclonal	Heat (pressure cooker), 20 min in pH 6.0 citrate buffer at 96ºC	Ready-to-Use	Novolink -Max polymer Detection System - LEICA®	AEC

[1] Dako, Carpinteria, California, USA; [3] ABClonal Technology, Massachusetts, USA; [2,4] Invitrogen, Carlsbad, California, USA;

AEC: 3-amino-9-ethylcarbazole (Biocare®); IBA-1: ionized calcium binding adapter molecule 1; α-SMA: alpha smooth muscle actin;

Statistical analysis

Descriptive statistical analyses were performed. Continuous variables (i.e., age and survival time) were assessed for normality by the Shapiro-Wilks test. Normally distributed variables (i.e., age) were described with mean ± standard deviation, whereas median and range were used to describe non normally distributed variables (i.e., survival time).

Results

Of the 2112 feline cases entered into Setor de Patologia Veterinária of Universidade Federal do Rio Grande do Sul between 2010 and 2022 for necropsy exam, neoplasia represented 24.28%. Among 513 feline cancer cases, nonlymphoid metastatic or multicentric sarcomas comprised 2.33%. The average age of affected cats was 11 ± 3.3 years. Most cats (11/12; 91.6%) were euthanized because of a poor prognosis after the diagnosis except for one cat (case 9) that died of the disease. Relevant information (diagnosis, age, breed, clinical presentation, survival outcome) are summarized in table 2. Retrovirus status was reported in only six cases, of which only one case (case 3) was positive for FeLV.

Table 2 – Diagnosis, first clinical presentation and overall survival of cases of feline metastatic or multicentric nonlymphoid sarcomas

Case	Diagnosis	Age (years)	Sex	Breed	Overall survival (days)	First clinical presentation
1	HS	15	male	DSH	17	Anorexia and dyspnea
2	HS	8	female	DSH	22	Anorexia and perianal subcutaneous growth

3	HS	4	male	DSH	—	Anorexia and bilateral renomegaly
4	FISS	10	male	DSH	35	Invasive local growth in SC
5	FISS	6	female	DSH	114	Invasive local growth in SC
6	FISS	10	female	DSH	93	Invasive local growth in SC
7	FISS	9	female	DSH	—	Invasive local growth in SC
8	VSCS	11	female	DSH	240	Dysuria and weight loss
9	VSCS	16	male	DSH	13	Regurgitation
10	VSCS	10	male	DSH	120	Regurgitation
11	HAS	12	female	DSH	45	Subcutaneous mass at abdominal wall
12	HAS	13	male	DSH	2	Anorexia

DSH: domestic shorthair; FISS: feline injection site sarcoma; HS: histiocytic sarcoma; HSA: hemangiosarcoma; VSCS: visceral spindle cell sarcoma. SC: subcutaneous . — missing information.

Pathological findings

A complete necropsy was conducted in all cases. The main affected sites in feline nonlymphoid metastatic or multicentric sarcomas are summarized in table 3.

Table 3 – Main affected sites in feline nonlymphoid metastatic and multicentric sarcomas

Case	Diagnosis	Affected organs
1	HS	Lungs, kidneys, skin, heart, liver, pancreas, adrenal, spleen, lymph nodes
2	HS	Lungs, kidneys, skin, esophagus, lymph nodes
3	HS	Lungs, kidneys, heart, ureter, bone marrow, thyroid,

		ocular globe, intercostal musculature, lymph nodes
4	FISS	Lungs, skin
5	FISS	Lungs, skin
6	FISS	Lungs, skin
7	FISS	Lungs, kidneys, skin, central nervous system, intercostal musculature
8	VSCS	Lungs, kidneys, skin, bladder, liver, adrenal, lymph nodes
9	VSCS	Lungs, esophagus
10	VSCS	Lungs, esophagus
11	HSA	Lungs, kidneys, skin, liver, heart, pancreas, heart, central nervous system, lymph nodes
12	HSA	Colon, liver, lymph nodes

FISS: feline injection site sarcoma; HS: histiocytic sarcoma; HSA: hemangiosarcoma; VSCS: visceral spindle cell sarcoma.

Histiocytic sarcomas

In cases 1 and 3, a locally invasive subcutaneous mass growing was observed in the inguinal and perianal regions, respectively. In case 1, the lesions consisted of multiple, tan-white, flat nodules with invasion of adjacent parenchyma and affected lungs, liver, pancreas, heart, adrenals, and kidneys (Figure 1A). The spleen had 4-10 mm, multifocal, elevated, tan-white, growths (Figure 1B) on the capsular surface. On the cut surface, these were well demarcated and bulged from the capsular surface. The inguinal, tracheobronchial and iliac lymph nodes were enlarged, firm and had loss of corticomedullary distinction.

Gross changes in case 2 consisted of a white solid mass (6,0 x 4,0 x 1,0 cm) located in the caudal portion of the esophagus with invasion of the mediastinum, and affecting mostly the caudal lung lobes (Figure 1C). The adjacent tracheobronchial lymph nodes were enlarged and firm, as well as the iliac lymph nodes. Multiple white nodules of 2 to

3 cm in the cortex of both kidneys were observed (Figure 1D). Case 3 had involvement of both kidneys, heart, ureter, eyes, thyroid, and lungs (Figure 2E). Both the right and left kidney were enlarged with irregular capsular surfaces, and on the cut surface, multiple white masses that coalesced and extended from the cortex to the medulla were observed. Unilateral hydronephrosis developed secondary to a nodule of 2.5 cm in diameter in the proximal left ureter, which protruded into the lumen and obstructed the urinary flow. On vertical sections of the eyes, a white to rede solid mass effaced the uvea and extended into the anterior chamber (Figure 2F). Moreover, the lungs and epicardium had multiple well demarcated white nodules of up to 0.5 cm. Similar lesions were found in the parietal pleura mostly in the intercostal muscles.

Histologically, all lesions observed at necropsy corresponded to neoplastic histiocytic cells proliferation. Bone marrow infiltration by neoplastic histiocytes was observed only in case 3. In all cases, the neoplastic cells were round and markedly anaplastic (Figures 1A-1D), with abundant eosinophilic cytoplasm and indented hyperchromatic nuclei. Multinucleate neoplastic cells and karyomegaly were observed in all three cases. Numerous mitotic figures were observed and included bizarre ones (Mitotic figures: case 1-3: 12, 15 and 11/2.37mm^2, respectively).

The neoplastic cells expressed marked and multifocal membranous to cytoplasmic immunolabeling for IBA-1 (Figure 2E-F) and vimentin. The other immunomarkers (MAC 387, CD3 and CD20) were negative.

Feline injection site sarcomas

The most common histologic diagnosis in these cases was fibrosarcoma (cases 4, 5 and 7; 3/4; 75%), but a case of osteosarcoma was also observed in this study (case 6; 1/4; 25%). White firm masses in the subcutis were observed in all cases. Cat 4 had a large

18 x 13 x 7 cm invasive subcutaneous mass in the cervical and interscapular region (Figure 3A). Pulmonary metastasis involved multiple lung lobes and was characterised by pinpoint, multiple, firm, white nodules of 0.5 x 1 cm. Case 5 had an 8 x 6 x 0.2 cm ulcerated soft tissue tumor that expanded the subcutaneous tissues of the lumbar region and extended along the left thoracic wall. On the cut surface, large, friable areas of necrosis were observed. Pulmonary metastases were characterised by pinpoint, multiple, firm, white nodules of 1 to 1.5 cm in multiple lung lobes. Case 6 had a poorly defined mass in the subcutis in the right scapular region, which involved the adjacent connective tissue and skeletal muscle. The lesion measured 10 x 8 x 6 cm without bone infiltration. On the cut surface, it was white with a cystic center containing mucinous fluid. Pulmonary metastasis appeared as multiple round white pinpoint areas in all lung lobes. Right hindlimb amputation was performed in case 7 to treat a sarcoma previously diagnosed by cytology. At necropsy, metastatic sites included intercostal musculature, cerebellum, spinal cord, both kidneys, and lungs (Figures 3B-D).

Histologically, cases 4, 5 and 7 had a histologic pattern of fibrosarcomas, which was well-differentiated and composed of spindle-cells arranged in multiple interwoven bundles on primary and metastatic sites (Figure 3E-3F). Peripheral inflammation of lymphocytes and zones of necrosis were consistently present. Mitotic count was high in all three cases (12, 11 and 8/2.37mm^2, respectively). Based on these histologic criteria, the three cases were considered grade III. At IHC, these cases were all negative for desmin and α smooth muscle actin, which excluded a myofibroblastic phenotype. Case 6 revealed spindle-shaped neoplastic cells arranged in interwoven bundles, which occasionally produced osteoid matrix mineralization. Adjacent inflammation and zones of necrosis were present as well, yelling a grade III tumor. Mitotic figures were 7 in 2.37mm^2. In all four cases, the neoplastic cells expressed marked, multifocal, cytoplasmic

immunolabeling for vimentin and did not expressed IBA-1 which excluded feline giant-cell pleomorphic sarcoma.

Visceral spindle cell sarcomas

Primary disease in case 8 was suspected to have arisen from the bladder based on first clinical manifestation and gross appearance at necropsy (Figure 4A). The gross findings in Case 8 included multifocal to coalescing, white nodules ranging from 2.0 to 3.0 cm in diameter that expanded the bladder mucosa, kidneys, lungs, liver, adrenal, and medial iliac lymph nodes (Figures 4B-C). The primary site in cases 9 and 10 was suspected to be the esophagus. Case 9 had a friable, white, mass in the caudal portion of the esophagus (Figure 4D). Metastases to the lungs were characterized by pinpoint, white foci ranging from 0.2 to 0.5 cm in diameter. Case 10 had a white mass of 11 x 6 cm in the caudal portion of the esophagus. Pulmonary metastasis consisted of rare white nodules up to 1 cm in diameter. Histologically, cases 8 and 9 exhibited highly pleomorphic neoplastic cells, which ranged from spindle-shaped to ovoid to polygonal and were arranged in bundles. Anisokaryosis and anisocytosis were severe and mitotic count of 10 and 7 in 2.37 mm^2, respectively. A final diagnosis of a poorly differentiated (anaplastic) sarcoma was reached (Figure 4E). Case 10 was morphologically compatible with myxosarcoma (Figure 4F) and was composed of spindle to stellate cells loosely arranged in a basophilic matrix. In all three cases, the neoplastic cells expressed marked, multifocal, cytoplasmic immunolabeling for vimentin, which proved the mesenchymal origin of these cells.

Hemangiosarcomas

Macroscopically, case 11 showed nodular masses in varying sizes from 0.1 to 3.0 cm with dark-red (or black) colour in subcutaneous tissues of abdominal mammary glands, skeletal muscles, omentum, kidneys, lungs, heart, pancreas, central nervous

system, spleen, and liver (Figure 5A). Lymph nodes (superficial cervical, axillary, inguinal, mandibular, sternal, tracheobronchial, cranial mediastinal, hepatic, gastric, pancreaticoduodenal, and medial iliac) were enlarged and red. Multifocal, red nodules involving the telencephalon, diencephalon and cerebellum were observed (Figure 5B). The primary site was considered the subcutaneous tissue in this case.

The colon was considered the primary site in case 12. There was an infiltrative, dark red, fluctuant, intramural mass, which compressed the lumen and infiltrated the mesenteric lymph node (Figure 5C). Metastasis was observed in the liver, which were characterized by dark red and white fluctuant masses up to 2 cm in diameter (Figure 5D). The lesions were also associated with a massive hemoperitoneum. Histologically, both cases exhibited neoplastic endothelial cells arranged in irregular and blood-filled spaces with adjacent areas of haemorrhage (Figures 5E-F). Cellular morphology was sufficient to provide the diagnosis and therefore immunohistochemistry was necessary to confirm the cell origin.

Discussion

The diagnosis and characterization of multicentric or metastatic nonlymphoid sarcomas were based on pathological and immunohistochemical findings. Multicentric or metastatic nonlymphoid sarcomas are rare in cats and mature adults to senior cats were most commonly affected by nonlymphoid sarcomas in our study, which suggests that age is a risk factor for these neoplasms. The low frequency of this condition (2,33% of 513 feline case cancers) is similar to the veterinary literature records which is restricted to few published reports and small cases series.[4,5,13,14] The clinical survival was highly variable in the cats ranging from 2 to 240 days, but definitive conclusions cannot be drawn from

the clinical data as almost all individuals were euthanized. Poor survival is compatible with other reports describing the same conditions. [14,15]

Histiocytic sarcomas (SH) are neoplasms of interstitial DC, which occur as multiple masses in multiple organs and most frequently affect dogs.[8] Three cats in this study had lesions similar to those described in disseminated histiocytic sarcomas well characterised in dogs, with multiple tumor masses in several organs.[8] In cats, the most commonly affected sites in this study were the lungs, kidneys, skin, and lymph nodes, which are frequently described sites in dogs [8,24] suggesting a similarity of the disease between both species. Lymph node metastasis was a significant feature in all three cases which favors metastasis by lymphatic vessels to solid organs. Besides, skin DC have distant migratory potential to paracortex of lymph nodes following contact with antigen, suggesting metastasis via lymphatic routes as a major route in SH.[24]

In cats, disseminated histiocytic sarcoma (DHS) needs to be distinguished from Langerhans cell histiocytosis (LCH) and feline progressive histiocytosis (FPH). First, FPH lesions usually remain limited to the skin for a prolonged time before evidence of organ involvement and are preferentially located on the legs and extremities.[16,25] In cats 1 and 2, skin lesions presented simultaneously with organ involvement; thus, it was not possible to determine whether skin involvement was primary or secondary. We believe that the skin was part of a disseminated disease in both cases. Moreover, inguinal and perineal skin are not commonly described sites of FPH.[16,25] Last stages of FPH can progress to histiocytic sarcomas with metastasis to several organs and may be histologically indistinguishable from a primary histiocytic sarcoma.[24] Cells tend to exhibit marked anisocytosis and anisokaryosis and multinucleated cells [24], as observed in our three cases. The absence of immunolabeling for E-cadherin suggested the diagnosis of histiocytic sarcoma and may be a useful tool to rule out FPH, since the cells in this

condition frequently do not express E-cadherin.[16] However, the literature shows controversy regarding the dendritic cell origin in FPH.[25] Absence of E-cadherin immunolabeling is not straightforward for an interstitial dendritic cells immunophenotype because lesional histiocytes at metastatic sites may have down regulated their expression of E-cadherin and therefore Langerhans cells immunophenotype cannot be ruled out.[16,17] Terminal involvement of multiple organs have been described in cats with LCH as well and should be included in the differential diagnosis of DHS.[17,18] The Langerhans cells lineage of LCH is confirmed by extensive immunolabeling for E-cadherin, CD18, and ultrastructural cytoplasmic structures called Birbeck's granules, an evidence of the Langerhans cells origin of these dendritic cells. [17,18,26] E-cadherin in our three cases was consistently negative, suggesting that the cells have the immunophenotype of interstitial dendritic cells.

The pathologist is presented with a great challenge in distinguishing between SH and last stages of FPH and LCH. The most distinctive feature that led us to think about SH in our cases series was the higher frequency cytological atypia, such as large round pleomorphic cells, multinucleated cells and bizarre mitotic figures. Besides, the rapid clinical course with multiple masses involving visceral organs was highly suggestive of SH over other conditions.

Ionized calcium-binding adapter molecule 1 (IBA-1) is considered an excellent pan-histiocytic marker in canine and feline histiocytic proliferative, neoplastic and inflammatory disorders;[27] however, since feline SH is rarely described, reports of the application of IBA-1 in feline histiocytic sarcomas are scarce.[14,15,23,28,29] In our case series, IBA-1 was a useful immunomarker for the diagnosis of histiocytic sarcoma, but unfortunately it cannot differentiate langerhans cells from interstitial dendritic cells. Thy-1 (CD90) discriminate between interstitial and Langerhans cell, but this marker is not

assessable in formalin-fixed tissue section. Additionally, it has not been used in feline tissues and may lack specificity for the feline antigen, since it is a canine-specific antibody.[9,24]

In cats, MAC387 has been used to demonstrate monocytes and macrophages in intracranial neoplasms.[30,31] This antibody recognizes MRP14, an intracellular myeloid-related protein that is expressed by recently infiltrated monocytes and macrophages.[32] The absence of immunolabeling in our three cases supports the hypothesis that these are dendritic cells rather than a monocyte-derived cell. Histiocytic sarcoma should also be differentiated from lymphoma, which was ruled out by the lack of immunolabeling for CD3 and CD20.

The low incidence of metastatic FISS found on our database is consistent with their biological behaviour. These are locally invasive neoplasms, but with a low incidence of metastasis.[33] Previously studies on subcutaneous soft tissue sarcomas usually do not verify metastatic disease histologically and information regarding the main metastatic site have not been assessed yet.[2] Very few histologically confirmed cases have been reported in the mediastinum, regional lymph nodes, liver, and lungs.[4,33,34,35] In the current work, lungs were the most common metastatic site, as previously observed in cats submitted to chest radiographies.[36] Nonetheless, metastatic disease may be underestimated could be higher due to lack of necropsies.[36] All cases had multifocal white pinpoints to small nodular areas scattered throughout all pulmonary lobes. Chest radiography may not identify those small metastatic lesions and most sensitive imaging techniques may be necessary.

A recently published study evaluated the prognostic value of the histologic grading of cutaneous and subcutaneous feline soft tissue sarcoma.[2] These authors concluded that the suggested grading system in cats had a significant correlation with

overall survival. Nonetheless, the study did not differentiate between FISS and soft tissue sarcoma not related to injection. There is a tendency for FISS to be high grade due to the high degree of inflammation and necrosis as seen in our four cases in which all were grade III; thus, the prognostic significance of such classification, such as metastatic potential, is not apparent for FISS. Therefore, metastasis to distant skin sites probably reflects disease progression and may biased by the decision of euthanasia and is not necessarily related to tumour histomorphology.[3]

HSA in cats is most often multicentric at the time of diagnosis.[37] In the present study, the primary location of the two HSA was considered to be the colon and the subcutaneous tissue, however, it is difficult to say conclusively whether those sites were the primary sites. On the other hand, intestines are one of the most common described primary sites of visceral HSA in cats, [37, 38] typically metastasizing to the mesenteric lymph nodes[38], as observed in our case (case 12).

Visceral and subcutaneous HSA occur in a very similar frequency, with the former being more likely to metastasize.[38,39] However subcutaneous HSA are also considered to have metastatic potential[40], as seen in case 11. This cat (case 11) was first referred to clinical examination due to a mammary subcutaneous mass two months previously to the necropsy. The thoracic radiographs findings at that time were unremarkable, which suggested a primary subcutaneous HAS at the moment of necropsy. In those cases, as well, chest radiography may lack sensitivity to identify those small metastatic lesions and most sensitive imaging techniques may be necessary. Hence, necropsy was useful to confirm multiple organs involvement such as pulmonary involvement that was not seen at first appointment. Furthermore, cerebral metastases were also detected in this cat, which have been reported for a subcutaneous HSA.[41] This case indicates the cranial metastatic potential of subcutaneous HSA. Both cats in our study developed metastasis

to the liver, suggesting that the liver is commonly affected by hemangiosarcoma also in cats.

This study shows that those diseases named under “nonlymphoid metastatic or multicentric sarcomas” are very rare in domestic cats and comprises different diseases with variable clinical manifestation such as histiocytic sarcomas, feline injection site sarcomas, visceral spindle cell sarcomas and hemangiosarcomas. The main affected sites were lungs followed by kidneys, skin and regional lymph nodes. Grossly, main findings were multifocal pin point to nodular white areas as well as large masses.

Acknowledgements

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) under grant Finance Code 001; and Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS), and Pró-reitoria de Pesquisa da Universidade Federal do Rio Grande do Sul (Propesq/UFRGS).

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Figure legends

Figure 1: gross findings of histiocytic sarcomas in cats. (A) Case 1, kidneys: multiple multifocal flatted white nodules in the cortical. (B) Case 1, spleen: metastases appear as small white nodules on the capsular surface. (C) Case 2, mediastinum: cut surface of a mediastinal, white mass that involve the esophagus. (D) Case 2, kidney: large white mass of (3 x 2 cm) expand and replace the renal parenchyma. (E) Case 3, lungs: there are multifocal, white small foci up to 0.5 cm on the parietal pleura. (F) Case 3, globe: a white to red mass invades the anterior uvea and infiltrates the anterior chamber.

Figure 2: histological findings of histiocytic sarcomas in cats. (A) Case 1, lungs: anaplastic round cells with abundant eosinophilic cytoplasm obliterate the alveolar spaces. Hematoxylin and eosin (HE), 200×. (B) Case 2, esophagus: highly anaplastic round cells in the submucosa exhibits multinucleation and kariomegaly. Neoplastic cells are occasionally seen inside blood vessels. The remaining esophagus epithelium are seen in top left corner. HE, 200×. (C) Case 3, kidney: neoplastic histiocytes efface renal architecture and entrap the tubules. Haematoxylin and eosin (HE), 200×. (D) Case 3, globe: neoplastic histiocytes diffusely affects and efface the anterior uvea. HE, 200×. (E) Case 2, esophagus: there is moderate membranous and cytoplasmic immunolabeling for Ionized calcium-binding adapter molecule 1 (IBA-1). (F) Case 3, kidney: there is marked membranous and cytoplasmic immunolabeling for Ionized calcium-binding adapter molecule 1 (IBA-1).

Figure 3. Gross and histological findings of metastatic feline injection site sarcomas (FISS) in cats. (A) Case 4, skin: there is a large subcutaneous mass in the interscapular and cervical region. (B) Case 6, lung and kidney involvement: multiple white to red nodules are observed in the lungs and kidneys. (C) Case 6, kidneys: multifocal to coalescing white nodules of various sizes in both kidneys, which efface the cortex and

medulla and eventually have umbilicated centers. (D) Case 6, lungs: multiple randomly distributed white nodules affecting all lung lobes. (E) Case 4, lungs: spindle-shaped neoplastic cells arranged in multiple bundles in a densely collagenized matrix obliterate the alveolar spaces and are intimately associated with blood vessels. Haematoxylin and eosin (HE), 200×. (F) Case 6, cerebellum: metastatic neoplastic spindle cells infiltrate and disrupt the adjacent neuropile. HE, 200×.

Figure 4. Gross and histological findings of visceral spindle cell sarcomas in cats. (A) Case 8, bladder: multifocal to coalescent white masses of varying sizes protruding from the mucosa and into the lumen. (B) Case 8, lung and liver involvement: multifocal white nodules in the liver up to 3 cm in diameter. The same nodules are seen in the lungs that sometimes coalesce. (C) Case 8, kidneys: multifocal white nodules on the capsular surface affecting both kidneys. (D): Case 10, mediastinum: there is a white mass affecting the cranial mediastinum. A single white nodule can be seen in the left caudal lobe of the lung. (E) Case 8, liver: neoplastic spindle cells efface the hepatic cords and dissecting through atrophic hepatocytes. Haemotoxylin and eosin (HE), 200×. (F): Case 10, lung: metastatic myxosarcoma: there is neoplastic stellate to fusiform cells with abundant amorphous basophilic extracellular matrix in the alveolar spaces. HE, 200×.

Figure 5. Multicentric hemangiosarcoma in two cats. (A) Case 11, multiple organ involvement in the thoracic and abdominal cavities. There are multifocal, red, pinpoint to nodular areas in the lungs, liver, kidneys and spleen, measuring up 1.5 cm in diameter. (B) Case 11, brain: there are multifocal red nodules in the cerebellum and telencephalon. (C): Case 12, colon and mesenteric lymph node: metastatic colonic hemangiosarcoma. There is an infiltrative, dark red mass which infiltrates the mesenteric lymph node (asterisk). (D): Case 12, liver: there are multifocal red and white nodules in all hepatic lobes up to 2 cm (E): Case 11, cerebellum: a severe multifocal to coalescent haemorrhage

obscures the neoplastic cell proliferation. The neoplastic cells can be seen in small groups in the adjacent neuropile and form blood-filled vessels (F) Case 12, liver: the neoplastic cells dissect through the adjacent hepatocytes and form blood-filled spaces. HE, 400×.

3. CONSIDERAÇÕES FINAIS

Sarcomas não-linfoides metastáticos ou multicêntricos são neoplasias incomuns em gatos, caracterizadas por doenças distintas entre si, com apresentações clínicas heterogêneas e prognóstico desfavorável.

Os principais sítios envolvidos nessa doença em gatos foram os pulmões seguidos pelos rins, pele e linfonodos regionais. Locais incomuns incluíram a bexiga, esôfago, coração, pâncreas, fígado, adrenal, baço, ureter, medula óssea, musculatura esquelética, cólon, cerebelo, diencéfalo, telencéfalo e medula espinhal.

Macroscopicamente, os principais achados na necropsia referentes às metástases foram áreas brancas variando de puntiformes a nodulares, além da formação de massas grandes, com exceção dos dois casos de hemangiossarcomas, que foram caracterizados por áreas císticas avermelhadas.

A técnica de imuno-histoquímica para IBA-1 em desordens histiocíticas de gatos é pouco explorada e pouco utilizada na literatura. Neste estudo, esse marcador mostrou-se útil na confirmação da linhagem histiocítica das células neoplásicas nos três casos de sarcomas histiocíticos. MAC387, no entanto, mostrou-se ineficaz na confirmação dos casos de sarcomas histiocíticos. Os marcadores utilizados não permitiram confirmar com exatidão a origem intersticial dessas células dendríticas que compõem os SH em gatos.

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