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Periarticular histiocytic sarcoma with heart metastasis in a cat

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1 **Clinical report**

2 **Periarticular histiocytic sarcoma with heart metastasis in a cat**

3

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12

13 **Case Description**

14 A 4-year-old intact female domestic short-haired cat was referred for
15 recommendations on adjuvant medical treatment one month after left forelimb
16 amputation due to periarticular histiocytic sarcoma (HS).

17 **Clinical Findings**

18 At presentation, physical abnormalities were limited to enlarged ipsilateral superficial
19 cervical and axillary lymph nodes. Routine blood analysis, abdominal ultrasound and
20 thoracic radiology were unremarkable.

21 **Treatment and Outcome**

22 The cat initially received lomustine, without any occurrence of adverse events. Four
23 weeks later, the cat developed severe acute respiratory distress. Results of thoracic
24 radiographs and transthoracic echocardiographic were suggestive of pulmonary and
25 heart metastasis. Due to the cat's poor clinical condition and prognosis, the owner
26 elected euthanasia and a necropsy was performed. Based on gross pathology,
27 histopathology and immunohistochemistry, a HS with nodal, renal, pulmonary and
28 heart (right auricular and right ventricular) metastasis was diagnosed.

29 **Clinical Relevance**

30 This case represents the first description of HS with heart metastasis in a cat,
31 providing further insight into the clinical course and metastatic behavior of this rare
32 malignant neoplasia. Clinicians should be aware of this site of metastasis and
33 consider HS in the list of differential diagnoses of secondary heart tumors in cats.

34 **Abbreviations list**

35 HS histiocytic sarcoma

36 LN lymph node

37

38 A 4-year old 4.7-kg (10.4-lb) intact female domestic short-haired cat with a
39 history of left forelimb amputation due to periarticular histiocytic sarcoma (HS) was
40 referred to the Oncology Unit of the University of Bologna. Seven months prior to
41 referral, the cat had been evaluated by the referring veterinarian for a 1-month history
42 of grade 3 left forelimb lameness. Initially the cat had been treated with oral
43 meloxicam^a (0.05 mg/kg [0.02 mg/lb], q 24 h, for 1 weeks) and exercise restriction.
44 Despite an initial clinical improvement, lameness recurred and a mild soft tissue
45 swelling of the left distal radioulnar joint developed within a few weeks. Regrettably,
46 the travel restrictions due to the Coronavirus pandemic delayed the consultation with
47 an oncologist. The cat was reevaluated by the referring veterinarian only 5 months
48 after the first presentation. At that time, initial diagnostic tests included a left forelimb
49 radiograph (latero-medial view), 3-view thoracic radiographs, an abdominal
50 ultrasound, and routine blood analysis (complete blood count, serum biochemistry,
51 and clotting profile). Forelimb radiography revealed severe permeative lysis of the
52 carpal bones extending across the joint space to the distal radial and ulnar epiphysis
53 and diaphysis, as well as to the first metacarpal bone. Destruction of both medullary
54 and cortical bone was evidenced at these sites with an ill-defined transition zone,
55 along with moderate adjacent soft tissue swelling. The rest of the diagnostic
56 procedures were unremarkable. Due to suspected neoplastic disease, a core biopsy
57 of the bone lesion was submitted for histopathological evaluation. Microscopic
58 examination revealed a small aggregate of highly pleomorphic neoplastic cells

59 infiltrating trabecular bone, without any evidence of osteoid matrix. Given the above,
60 a diagnosis of undifferentiated sarcoma was made, leading to the amputation of the
61 left forelimb and ipsilateral prescapular lymphadenectomy. Subsequent histologic
62 examination of the resected forelimb revealed complete bone effacement and
63 infiltration of the surrounding soft tissues by a highly cellular and infiltrative neoplasm
64 composed of solid areas and bundles of round to spindle cells (diameter 40 μm) with
65 indistinct cell borders, oval nuclei and a moderate amount of eosinophilic cytoplasm.
66 Multinucleated giant cells occurred frequently. Mitoses averaged 3 per hpf. A
67 moderate amount of slightly eosinophilic amorphous matrix was admixed to
68 neoplastic cells, and severe osteolysis and bone remodeling was present. The
69 prescapular lymph node (LN) was severely infiltrated by the same cell population.
70 Immunohistochemistry with Iba-1 antibody revealed a diffuse positivity of neoplastic
71 cells. Based on these findings, a diagnosis of histiocytic sarcoma (HS) with regional
72 LN metastasis was made. The cat recovered uneventfully, and was referred to our
73 institution for further recommendations on adjuvant medical treatment 1 month after
74 surgery.

75 At presentation, abnormal physical exam findings were limited to enlarged left
76 superficial cervical and axillary LNs. A fine-needle aspiration of both LNs was
77 obtained. The smears were highly cellular, with numerous single or aggregated round
78 cells, having a diameter up to 30 μm , admixed with resident lymphocytes. Cells had
79 large indented nuclei and abundant blueish cytoplasm containing numerous small
80 vacuoles. Many nucleated giant cells and mitotic figures were observed (Figure 1).
81 Additionally, complete blood cell count, serum biochemistry, serological tests for FIV
82 and FeLV viruses were unremarkable. To rule out distant metastasis, 3-view thoracic
83 radiographs and abdominal ultrasound were repeated, revealing no abnormalities.

84 Lymphadenectomy of both ~~affected metastatic~~ LNs and adjuvant chemotherapy with
85 lomustine were recommended. However, the owner declined further surgery due to
86 financial restrictions. At that time, lomustine^b was administered orally (45 mg/m²)
87 without any occurrence of adverse events. At the following recheck, occurring 4
88 weeks after the first dosing, the cat appeared dyspneic and tachypneic (60
89 breaths/minute). Moreover, the left superficial cervical and left axillary LNS were
90 markedly increased in size compared to the prior evaluation. Given the clinical
91 worsening, thoracic radiography was repeated revealing a complex lung pattern,
92 consisting of mixed bronchial and interstitial unstructured with thick peribronchial
93 cuffing, causing a diffuse severe increase of the lung opacity. Mild bilateral pleural
94 effusion was also present. The cardiac silhouette was interpreted as subjectively
95 enlarged (Figure 2). Differential diagnoses included disseminated pulmonary
96 metastases or, less likely, an atypical presentation of congestive heart failure.
97 Accordingly, a cardiac consultation was requested. On 2-D echocardiography, mild
98 pericardial and pleural effusion were evident. Moreover, a large (12 x 6 mm)
99 homogenous, hyperechoic structure protruding from the right auricle into the right
100 atrium was visualized (Figure 3). Additionally, the right ventricle was mildly dilated
101 and hypokinetic (end-diastolic and end-systolic diameters 11.5 mm and 9.5 mm,
102 respectively; tricuspid annular plane systolic excursion 4 mm), and its free wall
103 appeared heterogeneously hyperechoic. The rest of the echocardiographic
104 examination was considered normal. Based on the patient's medical history, the
105 echocardiographic abnormalities were primarily interpreted as metastatic lesions.
106 Due to the cat's poor clinical conditions and prognosis, the owners elected
107 euthanasia and gave consent to a post-mortem examination (Figure 4). On gross
108 examination, ipsilateral superficial cervical and axillary LNs were markedly increased

109 in size, and a moderate amount of serous exudate filled the thoracic cavity. Lungs
110 showed bilateral multifocal to coalescing, flattened white areas. On cardiac
111 inspection, the right auricle was enlarged and its wall was thickened. On right
112 auricular section, the parenchyma was completely infiltrated by multifocal-to-
113 coalescing greyish tissue and a focal white protruding lesion of 1 mm was present in
114 the right ventricular free wall. Both kidneys showed multifocal 1 mm white foci. All the
115 lesions observed macroscopically corresponded microscopically to tissue infiltration
116 by the same tumor cells previously described. The same tumor cells were identified
117 within the pleural effusion sediment [\(Figure 5\)](#). Immunohistochemistry revealed
118 diffuse positivity of neoplastic cells for anti-CD18 and Iba-1 antibodies, whereas there
119 was no Cad-E immunostaining. Based on these results, a diagnosis of HS with LNs,
120 renal, pulmonary and heart metastasis was made.

121

122 **Discussion**

123 Histiocytic proliferative disorders are uncommon in cats and include HS
124 (i.e., localized and disseminated), hemophagocytic HS, feline progressive
125 histiocytosis and feline pulmonary Langerhans' cell histiocytosis.^{1,2} Histiocytic
126 sarcomas are rare, malignant and aggressive neoplasms which carry a poor
127 prognosis in cats.¹⁻¹⁵ Histiocytic sarcomas originating at a single tissue site or in a
128 single organ (with solitary or multiple foci) are referred to localized HS.¹⁻² In cats,
129 reported primary sites include the nasal cavity, eye, spleen, brain, trachea,
130 mediastinum, femur, tarsus, skin, periarticular tissues and vertebral canal.⁴⁻¹⁴
131 Interestingly, in the present case HS appeared to arise originally from the left forelimb
132 involving metacarpal, carpal, radial and ulnar bones. In cats, localized HS typically
133 progresses rapidly. Once the lesions spread beyond the local draining LN, the

134 disease acquires the definition of disseminated HS.¹⁻² Reported metastatic sites of
135 feline HS include lungs, liver, skin, bone marrow, LNs (peripheral, intra-abdominal
136 and thoracic), brain, and kidney.^{7-9,11,13,15} Heart metastasis have not been previously
137 reported. Even in other species, secondary cardiac involvement from HS represents
138 an exceptionally unusual condition, with only a few case reports published in dogs¹⁶⁻
139 ¹⁹ and humans.²⁰⁻²² Accordingly, this report appears to be unique since it documents
140 for the first time a HS affecting the heart of a cat. Another intriguing finding was the
141 specific location within the heart tissue, namely the right auricle and right ventricular
142 free wall. Indeed, in cats, primary and secondary cardiac tumors (i.e., carcinoma,
143 lymphoma, hemangiosarcoma, osteosarcoma) have been predominantly identified in
144 the interventricular septum, left ventricular free wall and pericardium.²³⁻²⁵ In contrast,
145 no previous reports describe a concomitant right auricular and right ventricular
146 neoplasia in the feline species.

147 The histopathologic appearance of the neoplastic cells was consistent with the
148 histiocytic lineage. Additional immunohistochemistry with ionized calcium-binding
149 adapter molecule 1 (Iba-1; a marker for cells of histiocytic lineage)²⁶, CD18 (a
150 leukocyte marker, including histiocytes)², and E-cadherin (a marker of Langerhans
151 cells)² was performed to further characterize this tumor, to confirm the histiocytic
152 origin of the neoplastic cells and to rule out feline pulmonary Langerhans' cell
153 histiocytosis. Neoplastic cells expressed Iba-1 and CD18, whereas they did not stain
154 with E-cadherin. Thus, feline pulmonary Langerhans' cell histiocytosis was excluded.
155 Based on the clinical presentation (i.e., absence of solitary or multiple skin nodules),
156 feline progressive histiocytosis was considered unlikely. Based on the clinical,
157 histopathologic, and immunohistochemical findings in this case, a diagnosis of HS
158 with distant metastasis was made.

159 Chemotherapy was considered to be the best adjuvant treatment in the
160 present case. Lomustine has shown efficacy against HS in dogs, with a response
161 rate ranging from 29% to 46%.²⁷ In light of this, lomustine was administered to the cat
162 at a dose of 45 mg/m² orally one month after amputation. Chemotherapy was well
163 tolerated. Unfortunately, progressive disease was observed 4 weeks following
164 lomustine administration, and the cat died 7 weeks after surgery. While dogs with
165 localized HS receiving a multimodal treatment consisting of surgery and
166 chemotherapy may live longer than one year,²⁸⁻³⁰ adjuvant lomustine did not provide
167 any survival benefit in this cat. Currently feline HS has a poor prognosis and
168 diagnosis often leads to euthanasia.⁴⁻¹⁴ Further studies are required to determine
169 effective treatments for feline HS.

170 In conclusion, the present case represents the first description of HS with
171 heart metastasis in a cat, providing further insight into the clinical course and
172 metastatic behavior of this rare malignant neoplasia. Clinicians should be aware of
173 this site of metastasis and add HS to the list of differential diagnoses of secondary
174 heart tumors in cats. Furthermore, this report further highlights that the site of cardiac
175 metastasis of feline tumors is not limited to the ventricular myocardium and
176 pericardium, but also to the right auricle and the right ventricle.

177

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181 conflicts of interest.

182

183 **Footnotes**

184 a. Metacam, Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany

185 b. CeeNU, Bristol-Myers Squibb, Baar, Switzerland

186

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261 localized splenic histiocytic sarcoma treated with splenectomy with or without
262 adjuvant chemotherapy. *J Vet Intern Med* 2020 DOI: 10.1111/jvim.15910.

263

264 **Figure legends**

265

266 Figure 1— Fine-needle aspirate from affected metastatic axillary lymph node. Cells
267 with indented and multiple nuclei are admixed with the resident lymphoid population.
268 May Grunwald-Giemsa, x40 objective.

269

270 Figure 2— Right lateral radiographic projection of the thorax showing a severe
271 diffuse peribronchial interstitial pattern. There is also soft tissue opacity within the
272 pleural space associated with pleural retraction, consistent with pleural effusion.

273

274 Figure 3— Two-dimensional transthoracic echocardiographic images. Right
275 parasternal long axis four-chamber (A) and five-chamber (B) views, left parasternal
276 oblique view optimized for right auricle visualization (C). All views show mild
277 pericardial (asterisks) and pleural (section indicators) effusion, and a hyperechoic
278 structure within the right auricle (white stars). The mass invades the right auricular
279 lumen and protrudes into the right atrium (white dotted lines highlight the mass size
280 and location). Ao = Aorta. LA = left atrium. LV = Left ventricle. RA = Right atrium. RV
281 = Right ventricle.

282

283 Figure 4— Lungs with a mottled appearance due to multifocal to coalescing greyish
284 metastatic lesions (A). The wall of the right auricle is markedly expanded by a
285 neoplastic proliferation (black arrow) and a focal white protruding lesion of 1 mm was
286 present in the right ventricular free wall (white arrow) (B). Histologic evaluation of the
287 right auricle. Myocardocytes are separated and massively infiltrated by round to
288 spindle neoplastic cells; many mitotic figures are observed (H&E stain; bar = 50 μ m)

289 (C). Immunohistochemistry (Iba-1) of the right auricle. Variable cytoplasmic positivity
290 of the neoplastic cells (DAB stain and hematoxylin counterstain; bar = 50 μ m) (D).

291

292 [Figure 5— Pleural effusion, smear from sediment. Aggregates of round cells with](#)
293 [marked anisocytosis and anisokaryosis, multiple nuclei and mitoses are admixed with](#)
294 [rare mesothelial cells. May Grunwald-Giemsa, x40 objective.](#)

295

