Clinical report

Periarticular histiocytic sarcoma with heart metastasis in a cat

Carmit Chalfon, DVM[1]; Giovanni Romito, DVM, MS, PhD[1]; Silvia Sabattini, DVM, PhD[1]; Antonella Rigillo, DVM, PhD[1]; Manuela Quinci, DVM, PhD; Armando Foglia, DVM, PhD[1] and Laura Marconato, DVM, Prof[1]

[1]Department of Veterinary Medical Sciences, Alma Mater Studiorum - University of Bologna, 40064 Ozzano Emilia, Italy

Address correspondence to Dr. Chalfon (carmit.chalfon@unibo.it)

Case Description

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

Clinical Findings

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

Treatment and Outcome

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

Clinical Relevance

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

Abbreviations list

HS histiocytic sarcoma

LN lymph node

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

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

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

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

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

Discussion

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

disease acquires the definition of disseminated HS.[1-2] Reported metastatic sites of feline HS include lungs, liver, skin, bone marrow, LNs (peripheral, intra-abdominal and thoracic), brain, and kidney.[7-9,11,13,15] Heart metastasis have not been previously reported. Even in other species, secondary cardiac involvement from HS represents an exceptionally unusual condition, with only a few case reports published in dogs[16-19] and humans.[20-22] Accordingly, this report appears to be unique since it documents for the first time a HS affecting the heart of a cat. Another intriguing finding was the specific location within the heart tissue, namely the right auricle and right ventricular free wall. Indeed, in cats, primary and secondary cardiac tumors (i.e., carcinoma, lymphoma, hemangiosarcoma, osteosarcoma) have been predominantly identified in the interventricular septum, left ventricular free wall and pericardium.[23-25] In contrast, no previous reports describe a concomitant right auricular and right ventricular neoplasia in the feline species.

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

Chemotherapy was considered to be the best adjuvant treatment in the present case. Lomustine has shown efficacy against HS in dogs, with a response rate ranging from 29% to 46%.[27] In light of this, lomustine was administered to the cat at a dose of 45 mg/m^2 orally one month after amputation. Chemotherapy was well tolerated. Unfortunately, progressive disease was observed 4 weeks following lomustine administration, and the cat died 7 weeks after surgery. While dogs with localized HS receiving a multimodal treatment consisting of surgery and chemotherapy may live longer than one year,[28-30] adjuvant lomustine did not provide any survival benefit in this cat. Currently feline HS has a poor prognosis and diagnosis often leads to euthanasia.[4-14] Further studies are required to determine effective treatments for feline HS.

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

Acknowledgments

No third-party funding or support was received in connection with this case or the writing or publication of the manuscript. The authors declare that there were no conflicts of interest.

Footnotes

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

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

186

References

1. Clifford CA, Skorupski A, Moore PF. Histiocytic diseases. In: Vail D, Thamm D, Liptak J, eds. *Withrow & MacEwen's Small animal clinical oncology*. 6th ed. St. Louis: Saunders, 2019;797-798.
2. Moore PF. A review of histiocytic disease of dogs and cats. Vet Path 2014;5:167-184.
3. Kraje AC, Patton CS, Edwards DF: Malignant histiocytosis in 3 cats. *J Vet Intern Med* 2001;15:252-256.
4. Austin BR, Henderson RA. What is your diagnosis? Multiple area of lysis of the metaphyses and diaphysis of the left femur. *J Am Vet Med Assoc* 2003;223:1569-1570.
5. Pinard J, Wagg CR, Girard C, et al. Histiocytic sarcoma in the tarsus of a cat. *Vet Pathol* 2006;43:1014-1017.
6. Teshima T, Hata T, Nezu Y, et al. Amputation for histiocytic sarcoma in a cat. *J Feline Med Surg* 2011;14:147-150.
7. Smoliga J, Schatzberg S, Peters J, et al. Myelopathy caused by a histiocytic sarcoma in a cat. *J Small Anim Pract* 2005;46:34-38.
8. Reed N, Begara-McGorum IM, Else RW, et al. Unusual histiocytic disease in a Somali cat. *J Feline Med Surg* 2006;8:129-134.
9. Bisson L, Van den Steen N, Hawkins I, et al. Mediastinal histiocytic sarcoma with abdominal metastasis in a Somali cat. *Vet Rec Case Rep* 2017;5:e000405.
10. Santifort KM, Jurgens B, Grinwis GCm, et al. Invasive nasal histiocytic sarcoma as a cause of temporal lobe epilepsy in a cat. *JFMS Open Rep* 2018;4:2055116918811179.

11. Wong VM, Snyman HN, Ackerley C, et al. Primary nasal histiocytic sarcoma of macrophage-myeloid cell type in a cat. *J Comp Pathol* 2012;147:209-213.
12. Friedrichs KR, Young KM. Histiocytic sarcoma of macrophage origin in a cat: case report with a literature review of feline histiocytic malignancies and comparison with canine hemophagocytic histiocytic sarcoma. *Vet Clin Pathol* 2008;37:121-128.
13. Bell R, Philbey AW, Martineau H, et al. Dynamic tracheal collapse associated with disseminated histiocytic sarcoma in a cat. *J Small Anim Pract* 2006;47:461-464.
14. Scurrell E, Trott A, Rozmanec M, et al. Ocular histiocytic sarcoma in a cat. *Vet Ophthalmol* 2013;Suppl 1:173-178.
15. Ide K, Setoguchi-Mukai A, Nakagawa T, et al. Disseminated histiocytic sarcoma with excessive hemophagocytosis in a cat. *J Vet med Sci* 2009;71:817-820.
16. Faccincani F. Primary histiocytic sarcoma of the heart in a dog. *Riv Anat Patol Oncol* 1953;6:1073-1088.
17. Uno Y, Momoi Y, Watari T, et al. Malignant histiocytosis with multiple skin lesions in a dog. *J Vet Med Sci* 1993;55:1059-1061.
18. Jakab C, Szász AM, Kulka J, et al. Secondary tumoural valvulopathy in a dog. *Acta Vet Hung* 2009;57:63-67.
19. Kovacevic A, Rossier C, Gurtner C, et al. Primary histiocytic sarcoma of the aortic valve as a trigger of heart failure in a crossbreed dog. *Schweiz Arch Tierheilkd* 2019;161:165-169.
20. Haynes HR, Melegh Z, Vanjani S, et al. Sudden unexpected death from an undiagnosed histiocytic sarcoma in an adolescent female. *Forensic Sci Med Pathol* 2016;12:486-490.

21. Dong A, Wang Y, Cui Y, et al. Enhanced CT and FDG PET/CT in histiocytic sarcoma of the pericardium. *Clin Nucl Med* 2016;41:326-327.
22. Thattassery E, Sundaram S. Images in geriatric cardiology. Histiocytic sarcoma presenting as left ventricular mass demonstrated by two-dimensional echocardiography. *Am J Geriatr Cardiol* 2007;16:388-389.
23. Aupperle H, März I, Ellenberger, C, et al. J. Primary and secondary heart tumours in dogs and cats. *J Comp Path* 2007;136:18-26.
24. Treggiari E, Pedro B, Dukes-McEwan J, et al. A descriptive review of cardiac tumors in dogs and cats. *Vet Comp Oncol* 2017;15:273-288.
25. Amati M, Venco L, Roccabianca P, et al. Pericardial lymphoma in seven cats. *J Feline Med Surg* 2014;16:507-512.
26. Pierezan F, Mansell J, Ambrus A, et al. Immunohistochemical expression for ionized calcium binding adapter molecule 1 in cutaneous histiocytic proliferative, neoplastic and inflammatory disorders of dogs and cats. *J Comp Pathol* 2014;151:347-351.
27. Rassnick KM, Moore AS, Russell DS, et al. Phase II, open-label trial of single-agent CCNU in dogs with previously untreated histiocytic sarcoma. *J Vet Intern Med* 2010;24:1528-1531.
28. Skorupski KA, Rodriguez CO, Krick EL, et al. Long-term survival in dogs with localized histiocytic sarcoma treated with CCNU as an adjuvant to local therapy. *Vet Comp Oncol* 2009;7:139-144.
29. Marconato L, Sabattini S, Buchholz J, et al. Outcome comparison between radiation therapy and surgery as primary treatment for dogs with periarticular histiocytic sarcoma: An Italian Society of Veterinary Oncology study. *Vet Comp Oncol* 2020;18:778-786.

30. Latifi M, Tuohy JL, Ott-Coutermarsh SH, et al. Clinical outcomes in dogs with localized splenic histiocytic sarcoma treated with splenectomy with or without adjuvant chemotherapy. *J Vet Intern Med* 2020 DOI: 10.1111/jvim.15910.

Figure legends

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

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

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

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

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

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