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Lymph node metastasis in feline cutaneous low-grade mast cell tumours

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Raphael Arz[1], Lavinia E Chiti[1], Christiane Krudewig[2], Valeria Grieco[3], Valeria Meier[4], Csilla Fejös[4], Damiano Stefanello[3] and Mirja C Nolff[1]

Abstract

Objectives This retrospective study aimed to determine the incidence of nodal metastatic disease in cats affected by low-grade cutaneous mast cell tumours (MCTs) in our study population.

Methods The clinical records of two centres were retrospectively searched for cats with cutaneous MCTs that had undergone lymphadenectomy of enlarged and non-enlarged lymph nodes. All primary tumours were histologically reviewed by two experienced pathologists and graded as high- or low-grade based on the grading system for feline cutaneous MCT. We graded the lymph nodes based on the grading scheme used for canine MCTs and considered HN2 and HN3 nodes to be metastatic. The number of patients with nodal metastasis was calculated.

Results We identified 17 cats with cutaneous MCT resection and concurrent lymphadenectomy. All 21 MCTs were graded as low grade and 30 nodes were removed, with 12 being considered early or overtly metastatic (HN2 or HN3, respectively). Based on nodal status, 10/17 (59%) cats were affected by nodal metastasis in our population.

Conclusions and relevance In contrast to previous reports, high percentage of cats with cutaneous MCTs in which lymphadenectomy was performed were presented with metastatic lymph nodes. The clinical relevance of this finding and a potential benefit of lymphadenectomy must be determined in future studies.

Keywords: Feline cutaneous mastocytosis; nodal grading; nodal metastasis

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Introduction

Cats can develop several forms of mast cell tumour (MCT), including a cutaneous form.[1] This form represents about 20% of all cutaneous tumours in cats.[2] In general, cutaneous MCTs tend to show a rather benign biological behaviour in feline patients, and local recurrence or distant spread after local treatment is rare.[3,4] The recommendation for preoperative oncological staging (including abdominal ultrasonography, thoracic radiography and cytological evaluation of spleen, liver and locoregional lymph nodes) is mostly based on clinical presentation. As in dogs, a full staging might not always be indicated.[5,6]

Recently, Sabattini and Bettini[7] established a two-tier grading scheme for feline MCTs that is similar to the grading system proposed by Kiupel et al[8] in dogs, differentiating between low- and high-grade MCTs. In the study by Sabattini and Bettini, most of the investigated tumours were low grade, and no cat with low-grade tumours showed evidence of lymph node metastasis.[7] Contrarily, it was recently shown in a single case that lymph node metastasis can also occur in feline patients with a low-grade MCT.[9]

[1]Clinic for Small Animal Surgery, Department for Small Animals, Vetsuisse Faculty, University of Zurich, Switzerland
[2]Institute of Veterinary Pathology, Department for Small Animals, Vetsuisse Faculty, University of Zurich, Switzerland
[3]Department of Veterinary Medicine and Animal Science, University of Milan, Lodi, Italy
[4]Division of Radiation Oncology, Department for Small Animals, Vetsuisse Faculty, University of Zurich, Switzerland

Corresponding author:
Raphael Arz DVM, Clinic for Small Animal Surgery, Department for Small Animals, Winterthurerstrasse 260, Zürich 8057, Switzerland
Email: rarz@vetclinics.uzh.ch

Lymphadenectomy is not routinely performed in feline cases as we currently lack studies to show that nodal metastatic disease is a problem in this species. In contrast to cats, in dogs with cutaneous MCTs, lymphadenectomy is now recommended because lymph nodes might be staged as false negative on cytology and because the metastatic grade according to Weishaar et al has been deemed prognostically relevant.[10,11] In addition, several studies have documented that extirpation of lymph nodes with early or overt metastasis in dogs with low- or high-grade cutaneous MCT also improves outcomes.[12–15] For the aforementioned reasons, lymphadenectomy has become routine in the management of canine patients with MCTs, and high rates of histologically detected early (HN2) or overt (HN3) nodal metastases have been reported.[16–19]

To date, comparative investigations or a validated lymph node grading system are missing in cats with cutaneous MCT, and information on the incidence of lymph node metastases detected after histological examination of surgically excised nodes is lacking.

This retrospective study aimed, as a first step, to describe the incidence of lymph node metastasis in feline cutaneous low-grade MCTs. Owing to the absence of a grading scheme for MCT nodal metastasis in cats, the grading system by Weishaar et al was applied.[11] We hypothesised that lymph node metastasis is more common than previously described in feline patients with cutaneous MCTs.

Materials and methods

The electronic database of two veterinary teaching hospitals (University of Zürich and University of Milan) were searched for cats that underwent surgical excision of cutaneous MCTs and concurrent lymphadenectomy between 2010 and 2022. Cats were included if clinical data were available with information on staging, a full surgical report and a second-look histopathology of tumours and lymph nodes.

Baseline data

Breed, age at time of diagnosis, sex, body weight, size and location of the MCT, presence of a single or multiple cutaneous MCT, if ulcerated or not, freely moveable or fixed, presence of lymphadenomegaly and information on clinical staging (including results of thoracic radiography, abdominal ultrasonography and fine-needle aspiration of lymph nodes, spleen or liver, if performed) were recorded. The location of the MCT was recorded as head, neck, trunk or forelimb/hindlimb.

Gross resection margins were determined based on surgical records, and concurrent splenectomy was recorded if performed. We recorded the number of cats with lymphadenomegaly (determined as nodes considered enlarged based on palpation) and the number of excised nodes per cat.

Descriptive statistics were performed, including mean (range) for continuous data, and number (%) for categorical data. Owing to the relatively low case number and retrospective nature, further statistical tests in addition to descriptive statistics were not performed

Validation of primary MCT and nodal status

All MCTs were histologically re-evaluated by experienced pathologists (CK [board-certified] and VG), and MCTs were graded according to Sabattini and Bettini.[7] Lymph node status was graded based on the grading scheme developed for dogs by Weishaar et al.[11] According to this scheme, lymph nodes were classified as metastatic if they presented multiple aggregates of mast cells (HN2: early metastasis) or when their architecture was disrupted or effaced by node sheets or masses of mast cells (HN3: overt metastasis; Figure 1).

The incidence of nodal metastatic disease was calculated by dividing the number of cats with at least one node defined as HN2 or HN3 by the total number of included cats.

Results

Within the time frame, 38 cats underwent resection of cutaneous MCT at both institutions. Of these, additional lymphadenectomy was performed in 17, which were included in this study.

Mean age at presentation was 10.2 years (range 1.5–17). The majority (n = 14/17; 82%) of cats were European Shorthairs; the other three cats were purebred (one Ragdoll, one Burmese and one Siamese). Nine cats were male, eight cats were female; all were neutered. Two cats presented with a recurrence of a MCT; the other 15 cats had not been treated for a MCT before presentation. Fourteen cats (82%) had a singular MCT and three (18%) had multiple MCTs, with 21 MCTs overall. The mean size of the MCTs was 0.98 cm (range 0.2–2). The locations of the MCTs were as follows: head (n = 12/21); forelimb (n = 2/21); hindlimb (n = 3/21); and trunk (n = 4/21). Four of 21 MCTs were ulcerated; the other 17 were firm masses with no signs of ulceration or inflammation. All MCTs were freely moveable and not fixed in the surrounding tissue. Four cats presented with lymphadenomegaly (two cats with one node each and two cats each with two enlarged nodes). In the other 13 cats the lymph nodes were non-palpable, or the size of the lymph nodes was documented in the file to be normal. Regional lymph nodes were aspirated in 6/17 cats (35%) with cytological evidence of MCT cells in 3/6 cats (50%). All data are summarised in Table 1 in the supplementary material.

Thoracic radiographs were taken in 8/17 (47%) cats and abdominal ultrasonography was performed in 16/17 cats (94%). Ultrasound-guided fine-needle aspiration of the liver and spleen was performed in all but one cat (n = 15/16) that had abdominal ultrasonography, and an

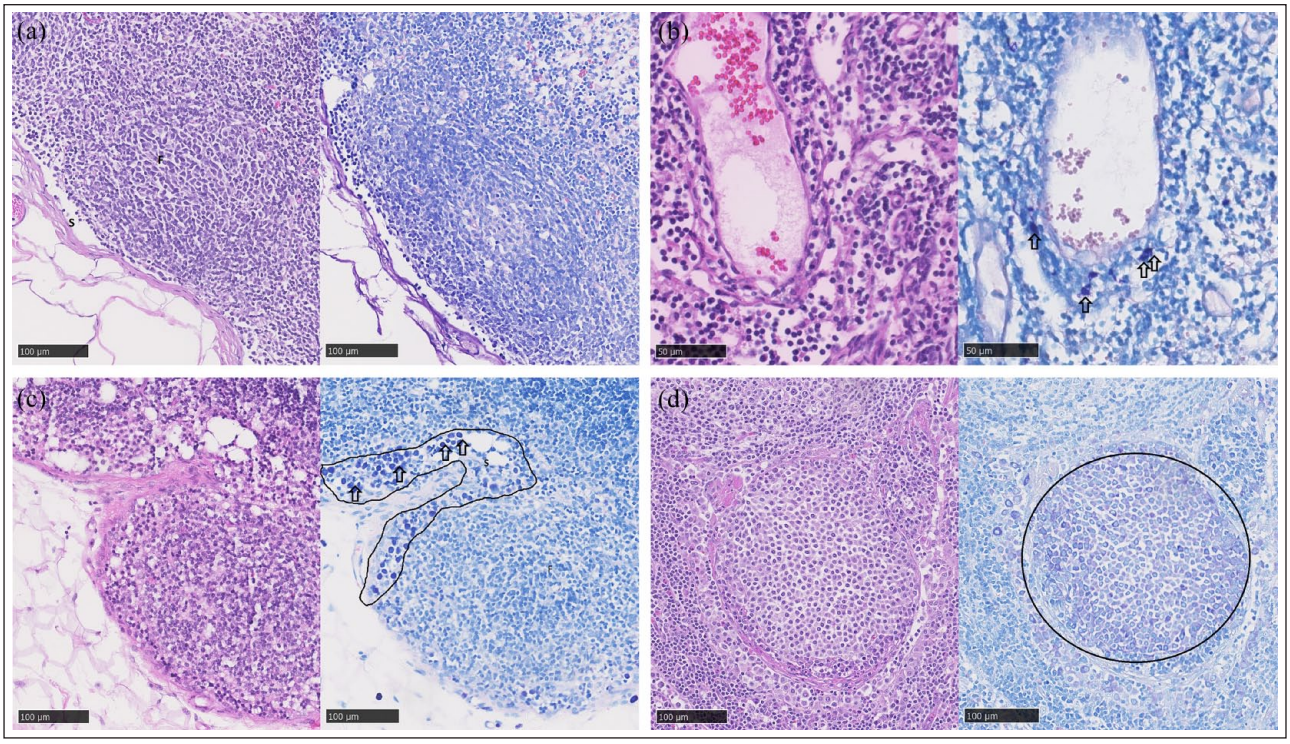

Figure 1 Representative pictures of HN0–HN3 in haematoxylin and eosin (left)- and Giemsa (right)-stained sections of examined lymph nodes in this study. The magnification is indicated on each picture. (a) HN0: no (or <3 individualised) mast cells are present. (b) HN1: mast cells (>3 individualised cells) are present and barely visible on haematoxylin and eosin staining. Metachromatic granules show up in the Giemsa staining (arrows). (c) HN2: mast cells are present in the subcapsular sinus (encircled area) in groups (arrows). There is no disruption of the nodal architecture. (d) HN3: nodule of neoplastic mast cells replacing the normal lymph node architecture (circle encloses mast cells with metachromatic granules). F = follicle; S = sinus

aspirate consistent with a splenic MCT was obtained in one cat.

Overall, 21 MCTs and 30 lymph nodes were excised. Detailed information for the resected nodes is provided in Table 1. A total of five MCTs were resected marginally: two MCTs with 1 cm margins, one MCT with 2 cm margins, 10 with 3 cm margins and for two MCTs, margins were not available. One cat had an additional splenectomy because of cytological evidence of metastatic disease. Mean resection margin was 1.94 cm (range 0–3).

Histological evaluation

All MCTs were graded as low grade. Of the 30 lymph nodes, three were graded as HN0 (non-metastatic, 10%), 15 as HN1 (premetastatic, 50%), nine as HN2 (early metastatic, 30%) and three as HN3 (overtly metastatic, 30%) (Table 2).

HN3-, HN2-, HN1- and HN0-graded lymph nodes were the highest grades found in three cats (18%), seven cats (41%), six cats (35%) and one cat (6%), respectively. Based on this, the incidence of metastatic lymph nodes in our cat population was 10/17 (58.8%). In the three cats in which a cytological suspicion of lymph node metastasis had been established preoperatively, HN3 metastases were histologically diagnosed after node removal. In the three cats without cytological evidence of nodal metastasis, the final lymph node status based on histology was HN2 in one cat, HN1 in one cat and HN0 in one cat. A cat with splenic metastasis also presented with an HN2 regional lymph node.

Discussion

In this retrospective study, we confirmed our hypothesis that lymph node metastases occur in cats with cutaneous MCTs, even in the case of low-grade tumours. The current body of literature provides scarce information on the incidence of nodal metastases in cats with cutaneous MCTs with palpable and non-palpable/or enlarged lymph nodes. Most available studies either did not include any form of nodal standing or cytological evaluation of the regional nodes in selected cases, with reported rates of metastases being as low as 0–5%.[4,7,20,21]

The incidence of lymph node metastasis in canine patients has been documented to be between 18% and 68%, depending on the node (regional vs sentinel lymph node) that was investigated.[16,17,19,22] The incidence of

Table 1 Case number, location and size of the mast cell tumour (MCT) and the status of the lymph node: palpatory, cytological and histopathological findings

Case number	Anatomical region of MCT	MCT size (cm)	Lymph node size	Cytology lymph node*	Removed lymph node	Grade
1	Head	0.5	Normal	Negative	Mandibular left	HN1
	Hindlimb	0.3	Normal		Mandibular right	HN1
2	Forelimb	1.7	Enlarged	Positive	Cervicalis superficialis right	HN3
3	Head	0.2	Normal	Negative	Mandibular left 1	HN0
			Normal		Mandibular left 2	HN1
			Normal		Axillary right	HN1
	Head	0.2	Normal		Cervicalis superficialis left	HN1
	Forelimb	0.2	Normal		Cervicalis superficialis right	HN2
4	Hindlimb	NA	Enlarged	Negative	Popliteal right	HN2
5	Trunk	4.0	Normal	Positive	Axillary left	HN3
6	Head	1.5	Normal	Not performed	Mandibular left	HN0
7	Head	0.3	Normal	Not performed	Mandibular left	HN1
			Normal		Mandibular right	HN1
8	Head	0.3	Normal	Not performed	Mandibular right	HN2
	Trunk	0.3				
9	Head	1.0	Normal	Not performed	Mandibular right	HN1
10	Trunk	1.0	Normal	Not performed	Cervicalis superficialis	HN2
11	Hindlimb	2.0	Normal	Not performed	Inguinal right	HN2
12	Head	NA	Normal	Not performed	Mandibular right	HN2
13	Trunk	2.0	Normal	Not performed	Meseraic	HN1
14	Head	0.9	Enlarged	Positive	Mandibular right	HN3
			Normal		Mandibular left 1	HN1
			Normal		Mandibular left 2	HN1
			Enlarged		Retropharyngeal right	HN2
15	Head	1.0	Normal	Not performed	Parotid	HN1
			Normal		Cervicalis superficialis right	HN1
16	Head	0.3	Normal	Not performed	Mandibular right	HN1
			Normal		Mandibular left	HN1
17†	Head	0.2	Enlarged	Not performed	Mandibular left	HN2
			Normal		Mandibular right	HN2
	(Spleen)		Enlarged		Meseraic	HN0

*Positive = metastases; negative = clean
†Splenectomy was performed simultaneously
NA = not available

Table 2 Histological grading of all resected lymph nodes

Grading according to Weishaar et al[11]	HN0	HN1	HN2	HN3
Number of lymph nodes	3	15	9	3

HN3-, HN2-, HN1- and HN0-graded lymph nodes were the highest grades found in three cats, seven cats, six cats and one cat, respectively

lymph node metastasis in our study was within this range if only HN2 and HN3 lymph nodes were counted as metastatic.

In both institutions, owing to recently published results on regional and sentinel lymph node metastasis in canine cutaneous MCT, lymphadenectomy became the standard procedure for all patients presented for cutaneous MCTs in the past 4 years.[12,14,23] Simultaneously, we have also increasingly advised lymphadenectomy in cats affected by cutaneous MCTs, especially as we started to detect nodal metastasis in these cases as well. However, owing to the retrospective nature of this study, a certain selection bias cannot be completely excluded. Unfortunately, we could not trace which lymph nodes were excised because of the clinical presentation and which lymph nodes were excised by default, as this information was not recorded in the patient files.

Our results demonstrated that cytology and/or palpation alone is not sufficient to detect the presence of nodal metastasis, as lymph nodes can be normal in size or cytologically unremarkable and still be metastatic. Similar to dogs, lymphadenectomy and histopathological

evaluation of the nodes are needed in cats to determine the metastatic status. A large proportion of cats included in this study (59%) had nodal metastasis (HN2 or HN3), a number that is more comparable to the situation in dogs than to the published reports for cats.[4,7,17]

The high incidence of lymph node metastasis is especially remarkable, as all tumours were deemed low grade according to Sabattini and Bettini.[7] In the original study published by this group, none of the cats with low-grade tumours had any sign of metastatic disease, while 3/15 cats with high-grade tumours had regional nodal metastasis at the time of diagnosis.[7]

In two recent canine studies of MCTs, the presence of regional and sentinel nodal metastases failed to correlate with tumour grade.[18,23] Although in the study presented here correlation between nodal metastases and other relevant prognostic factors, including grade, was not statistically assessed, our result suggests that nodal metastases can also occur in cats, even in the absence of concurrent negative prognostic factors, as previously reported.[21] Further investigations are warranted to better understand the correlation between relevant prognostic indicators of feline MCTs and the presence of nodal metastases, and to establish the prognostic relevance of the latter.

One cat in the study population with a low-grade cutaneous tumour had a concurrent splenic MCT, suggesting that, as for regional nodal metastases, distant spread could also be possible, regardless of grade. However, this hypothesis should be considered with caution, as it is difficult to determine if this was some form of metastatic disease or if the cat was affected by two different forms of MCT (a splenic and a cutaneous primary tumour).

To determine the metastatic grade of the nodes, we used the system of Weishaar et al for the staging of nodal disease in dogs.[11] In cats, no cut-off values have been validated to classify lymph nodes in patients with MCT. Also, to the best of our knowledge, we currently lack baseline data on the pattern and frequency of mast cells in normal feline lymph nodes and therefore we only classified HN2/HN3 as metastatic, as these findings are clearly abnormal. Nevertheless, we also suspect HN1 to be an abnormal finding in feline lymph nodes, although this statement needs to be validated. If we additionally consider HN1 to be relevant to premetastatic disease, only three cats did not show any lymph node involvement.

In canine patients, the grade of the node has been determined as a prognostic factor.[11] In addition, some studies also suggest a therapeutic benefit if HN2 and HN3 nodes are removed.[12,14,15,24] Corresponding data are not available for cats, and, owing to a relatively low follow-up time and small group size, we did not evaluate survival time in our population and refrained from comparing this group with cats that only had MCT resection without lymphadenectomy. In addition, as lymphadenectomy has only become a standard procedure recently (during the last 2–3 years), many of the surgeries included in the study were also performed recently. We expect cats with low-grade cutaneous to survive for a long time.[7] Nevertheless, this represents a major limitation that will need to be addressed in the future.

Based on the findings of Sabattini and Bettini,[7] the presence of regional nodal metastasis might also be a prognostic factor in cats. They divided their population into two groups, depending on their survival time. Cats in group 1 were still alive 1000 days postoperatively, and none of these cats had regional lymph node metastasis. In group 2, the median survival time of the cats was 349 days. In this group, regional lymph node metastasis was diagnosed in 20% of the patients. However, only one patient had a low-grade MCT (and did not have lymph node metastasis); therefore, a direct comparison is not possible, as all of our cats with nodal metastasis had low-grade tumours. Despite the above-mentioned limitations, this study has documented a high rate of nodal metastasis in cats. Based on a potential impact on management, lymphadenectomy in cats could potentially have a role, as it does for dogs. However, future studies need to investigate the physiological and abnormal composition of mast cells in feline lymph nodes to evaluate if the Weishaar et al[11] scheme is truly valid in cats; if the nodal status has a prognostic value; and if lymphadenectomy of metastatic nodes offers a therapeutic benefit in the treatment of cutaneous MCT in cats.

Finally, it must be determined if regional lymphadenectomy is sufficient, or if sentinel node mapping should also be encouraged in cats. In dogs, current evidence underlines the value of node mapping techniques similar to the current recommendations in human patients.[17,18,25,26] So far, there is only one case report available that documents the feasibility of near-infrared mapping technique in cats.[9] In this case, all nodes that were identified by the mapping technique were considered HN1 or higher grade. By identifying sentinel lymph nodes, more lymph node metastasis might be detected in the future in feline low-grade cutaneous MCTs.

Conclusions

We were able to document a high number of nodal metastases in cats with low-grade cutaneous MCTs (10/17 cats). Our results indicate that regional lymphadenectomy should be considered in cats affected by cutaneous MCT; however, the therapeutic and prognostic impact still has to be further investigated.

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Supplementary material The following file is available online:

Table 1: Summary data of the study population.

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Ethical approval The work described in this manuscript involved the use of non-experimental animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of the animal described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Raphael Arz https://orcid.org/0000-0001-8894-5209
Christiane Krudewig https://orcid.org/0000-0001-5894-6665
Valeria Meier https://orcid.org/0000-0003-0793-9005
Damiano Stefanello https://orcid.org/0000-0003-2726-0366
Mirja Christine Nolff https://orcid.org/0000-0001-9317-7769

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