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Clinical, histological and prognostic features of a novel nail-bed lesion of cats: 41 cases

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Key words

Cat, digit, reparative granuloma, multinucleate giant cells, osseous metaplasia

Abstract

Objectives

There is a distinct subset of lesions arising on the digits of cats, located at or close to the nail-bed epithelium, which are typically composed of proliferative fibroblast-like cells, multinucleate giant cells and areas of osseous metaplasia, but currently there is no published literature detailing the clinical or histological features of these lesions.

Methods

This study identified 41 such cases from two large commercial diagnostic laboratories and assessed various histological and clinical features; 22 cases had additional follow-up data available.

Results

All masses in this study were exophytic, variably inflamed, contained large numbers of spindle cells and had areas of capillary formation. The majority also had areas of ulceration, multinucleate giant cells and osseous metaplasia. The mitotic count was variable, but mitoses were confined to the fibroblast-like cells. Male cats appeared predisposed and the second digit was the most commonly affected.

Conclusions and relevance

These distinctive lesions arising on the digits of cats had potential for local recurrence, but metastasis was not reported. Based on these clinical and histological features, the masses in this study appear most similar to giant cell reparative granulomas, and trauma, injury to the nail or nail-bed and nail-bed infections may potentially contribute to their development.

Introduction

Masses arising on the digits of cats can be either reactive or neoplastic and because these typically have similar clinical presentations but different outcomes, biopsy of the mass or amputation of the affected digit followed by histopathological assessment is often required to reach a diagnosis and prognosis. Depending on the gross features present, potential differential diagnoses might include a primary inflammatory process (including various infectious diseases), a traumatic injury, a primary neoplasm such as soft tissue sarcomas or squamous cell carcinoma, or digital metastasis of a pulmonary adenocarcinoma.

Experience in feline clinical practice and diagnostic pathology laboratories suggests that there is a distinct subset of lesions arising on the digits of cats, typically located at or close to the nail-bed epithelium, which present as exophytic and often ulcerated masses. On histological assessment these lesions typically show proliferative fibroblast-like or spindle cells, multinucleate giant cells (MNGCs) and areas of osseous metaplasia. Despite this unique presentation and histomorphology, there is currently no published literature detailing the clinical or histological features of these lesions. This study identified such cases from two large commercial diagnostic laboratories, one in the UK and the other in New Zealand, obtained additional clinical information and follow-up where available, and reviewed the histological features of each mass. This enabled the behaviour of these distinctive digital lesions and their clinical outcome to be determined and the pathognomonic histological features to be identified.

Materials and Methods

Records from two commercial diagnostic laboratories (Finn Pathologists, Diss, UK and New Zealand Veterinary Pathology Ltd, Palmerston North, New Zealand) were searched for potential cases diagnosed from fixed tissue samples, based on combinations of key words such

as “feline”, “toe”, “digit”, “dewclaw”, “nail”, “nail-bed”, “osteosarcoma”, “sarcoma”, “osseous metaplasia”, “peripheral giant cell granuloma”, “granulation tissue”, “decalcification”, “inconclusive” and “giant cell tumour”.

Clinical details including age, sex and neuter status, breed, and presenting signs were recorded for all 41 cases where available. Further information was then sought and acquired for 22 of these 41 cases using a questionnaire to the submitting veterinary practices, approved by the Royal Veterinary College Clinical Research Ethical Review Board. The requested data comprised further information about the cat (confirmation of signalment, vaccination status, indoor/outdoor access, concurrent conditions and treatments, current age or date and cause of death if no longer alive), about the mass (whether the mass was the reason for presentation to the veterinary surgeon, the foot and digit affected, duration, colour and size of the mass, presence of pain, lameness, inflammation, concurrent nail-bed infection, nail-bed involvement, local recurrence, and details of any previous or concurrent treatments), whether there was any history of trauma and whether the mass was radiographically assessed.

Haematoxylin and eosin (HE)-stained 5-micron sections of each mass were blindly reviewed by pathologists (MJD, AF, AMP). Each individual mass was assessed for the presence of MNGCs (defined as three or more nuclei per cell), osseous metaplasia, and spindle cells. The mitotic count per 10 high power fields (HPFs, 400x) was also recorded, together with which cell types included mitotic figures. Other features recorded were exophytic or invasive growth, presence of ulceration, capillary formation, reactive bone changes, vascular invasion, haemorrhage, fibrin, oedema, necrosis and involvement of the nail-bed epithelium. The presence of any inflammation was scored on a subjective basis and allocated a numerical value

(none – 0; mild – 1; mild to moderate – 2; moderate – 3; moderate to severe – 4; severe - 5) and the cell types involved were recorded.

Statistical analysis of the data was conducted using Graphpad Prism 6 (GraphPad Software, Inc., USA). Two categorical variables were analysed using χ^2 (sex, limb or digit prevalence) or Fisher's exact test if there were two binary variables (pedigree verses non-pedigree). A P value of <0.05 was considered significant. The breed of cats in the study population was compared with the breed prevalence of the control population (n = 3771); the control population was based on cats from which fixed tissue samples were received by the Finn Pathologists laboratory throughout the study period and with any diagnosis.

Results

Signalment, clinical presentation and outcome

Signalment data was obtained for all 41 cats in this study (table 1). The age of 36 of the affected cats was known, with a range from one to 18 years and a median of 11 years . Gender was recorded for all 41 cats in the study, with 29 males (70.7%) and 12 females (29.3%); this difference was statistically significant (P = 0.008). All but two cats (one male, one female) were recorded as neutered. Thirty cats were recorded as Domestic Shorthair (DSH, 73.2%), two cats as Siamese (4.9%) and one each (2.4%) as Domestic Longhair (DLH), 'Domestic cat', Maine Coon DSH cross, European Shorthair, Persian, British Blue, and British Shorthair. The breeds of two cats were not recorded. There was no statistical difference (P = 0.205) between the prevalence of non-pedigree cats (DSH, DLH and 'domestic cat'; 32 cats out of 39 with the breed recorded) versus pedigree cats in the study population when compared to the control population.

Of 22 cats with further clinical information available, 19 had indoor / outdoor access and two were indoor-only (one was not recorded), while 16 were fully vaccinated, five were not and the vaccination status of one cat was not recorded.

The affected limb was recorded for 34 cases (table 1), with eight lesions (24.2%) affecting the left hind limb, nine (27.3%) the left forelimb, six (18.2%) the right hind limb, and 10 (30.3%) the right forelimb; there was no statistically significant difference (P = 0.787). One case was described as affecting a forelimb (left or right not specified) and in seven cases the limb was not noted. Overall, 20 (58.8%) cases were affecting a forelimb and 14 a hind limb (41.2%); again this difference was not statistically significant (P = 0.304). The affected digit was recorded for 28 cases (table 1), with two lesions (7.1%) affecting digit 1, 14 involving digit 2 (50%), seven arising from digit 3 (25%), three involving digit 4 (10.7%) and two affecting digit 5 (7.1%); this difference was statistically significant (P = 0.0009, figure 1).

Asked if the mass appeared painful on palpation, eight of the 22 responding primary clinicians replied ‘yes’, 10 responded ‘no’ and four did not answer the question. Five cats were described as lame on the affected limb, while 13 cats were not and there was no response to this question from four cases. The clinicians indicated there was evidence of local inflammation in 18 of the cases, but only one described evidence of more widespread inflammation, in this case a palpably enlarged regional lymph node. The most common terms used to describe the mass were ‘pink’, ‘red’, ‘fleshy’ or ‘flesh-coloured’ and ‘small’. Others terms less frequently used included ‘inflamed’, ‘dark’, ‘raw’, ‘irregular’, ‘raised’, ‘polyp-like’ and ‘shiny’ (figures 2a and 2b).

There was a history of associated trauma to the affected limb in six of the 22 cases, and a suspicion of trauma in a further two. One cat presented with the lesion and forelimb lameness after repeatedly jumping out of a top floor window. Many cases were described as having a concurrent nail-bed infection and/or an injury to the nail itself. In two cases, radiographic assessment of the digit was performed, with no changes evident in one case (figure 2c) and only soft tissue swelling visible in the second.

In five of the 22 cases there was evidence of local recurrence (22.7%) at the original site, occurring within one to four months of either excisional biopsy (with histologically incomplete margins) or cauterisation. In three cases the recurring mass was described as similar in appearance to the original lesion. The remaining cases had no evidence of local recurrence, and were either excisional biopsies (often with histologically incomplete margins) or digit amputations, with the length of clinical follow-up available ranging from a week up to six years (table 1). None of the cats developed any evidence of metastasis or multicentric growths.

Histological Features

Forty-one cases were histologically assessed. All of the masses examined were exophytic, variably inflamed, contained large numbers of spindle cells and had areas of capillary formation. All except two cases had obvious areas of ulceration in the sections examined (95.1%; figure 3a). In one case the presence of ulceration was uncertain and in another case ulceration was apparent in one sample but not in a second sample from a recurrent lesion in the same cat.

All except one case had MNGCs present in varying numbers (97.6%, figure 3b); numbers of nuclei per MNGC also varied, with one MNGC containing over 100 nuclei. Osseous metaplasia

was present in 36 cases (87.8%; figure 3c) and extensive in one case. The mitotic count ranged from 0 to 25 per 10 HPFs, with a median of 3; all mitotic figures were present within spindle cells as opposed to MNGCs.

Inflammation ranged from mild to severe. Neutrophils were seen in all cases and were the predominant inflammatory cell type, with other inflammatory cell types (macrophages, plasma cells and lymphocytes) also seen in 12 (29.3%) cases. Thirty-four (82.9%) of the masses contained fibrin and 29 (70.7%) had evidence of oedema, with 29 (70.7%) containing some haemorrhage. Haemosiderin was noted in 6 (14.6%) cases.

Reactive bone changes were present in 13 (31.7%) cases, uncertain in 13 (31.7%) cases and absent in 15 (36.6%) cases.

None of the cases showed any evidence of vascular or lymphatic invasion, nor any evidence of intralesional necrosis.

Involvement of the nail-bed epithelium was histologically apparent in 13 (31.7%) of the cases, but was uncertain or impossible to assess in the remaining cases, often due to the size of the biopsy. Based on the questionnaire results, 19 (90.5%) cases were described as involving or arising from the nail-bed, one case as probably involving the nail-bed and one as arising from the pad (one participant did not respond to the question).

All masses were measured as part of the histological assessment and the size ranged from 1 x 2mm up to 10 x 11mm based on formalin-fixed, paraffin-embedded tissue samples, with a

median size of 6 x 4mm. Based on the questionnaire results, the masses ranged in size from 2-3mm up to 20mm (prior to fixation).

Discussion

The masses described in this study are located on the digit and are generally closely associated with the nail-bed. They are typically described by clinicians as protuberant, pale pink to red, fleshy and small – ranging from 1 to 20mm in size, ulcerated and inflamed. On histology, the masses are exophytic, ulcerated, inflamed, (typically neutrophilic), with multinucleate giant cells, evidence of capillary formation, often with osseous metaplasia, with or without fibrin deposition, oedema and/or haemorrhage, but without necrosis. They may be associated with reactive bone changes but are not destructive. They can have a variable mitotic rate (from none up to 25 per 10 HPFs in the masses in this present study), but mitoses are confined to the spindle cell population and are not seen within the MNGCs.

Any deviation from these gross or histological findings should prompt consideration of other diagnoses. In such circumstances, depending on the features present, the gross differential diagnosis would most likely include granulomatous inflammation, other traumatic injuries, digital metastasis of pulmonary adenocarcinoma, and primary neoplasms such as soft tissue sarcomas or squamous cell carcinoma. Histological differential diagnoses would include reactive granulation tissue and various forms of sarcoma with the potential to contain MNGCs with or without associated osteoid production, including osteosarcoma, giant cell tumour of bone (GCTB), giant cell tumour of tendons/soft tissues, fibrosarcoma or other poorly differentiated sarcomas.

Male cats were over-represented in the study population; possibly this reflects an increased likelihood of male cats experiencing digital trauma due to roaming, fighting and hunting. Although all digits can potentially be involved, half of the lesions in this study arose on the second digit of the affected limb, implying this is a predisposed site. Trauma, injury to the nail or nail-bed and nail-bed infections may contribute to their development. These masses have some potential for local recurrence if incompletely excised, but metastasis or multicentric growths are not recorded.

In a recently published review of benign bone lesions that may be confused diagnostically with true osseous neoplasms in humans,[1] a proliferative and lytic lesion which contains numerous osteoclast-like giant cells is described, termed a giant cell reparative granuloma – however, this is an intraosseous (i.e. central) lesion. It most typically occurs in the mandible or maxilla, but it has also been described in distal appendicular skeletal sites, most notably the phalanges or metatarsal and metacarpal bones. Microscopically, there is a proliferation of fusiform and ovoid stromal cells with no nuclear atypia, punctuated by an irregular distribution of osteoclast-like giant cells. Other authors argue that the lesions affecting the appendicular sites are different from those affecting the jaws.[2]

A histologically similar lesion to these masses is the giant cell epulis (recently renamed giant cell granuloma), described in both dogs[3] and cats.[4,5] De Bruijn et al.[4] described a series of 52 feline epulides, of which 15 were giant cell epulides. In that study the MNGCs and some of the mononuclear cells stained positive for vimentin and for TRAP (tartrate-resistant acid phosphatase), a marker for osteoclasts. Osteoid and woven bone formation was present in 11 of the 15 cases. The authors speculated the osteoclast-like giant cells in the epulides are most

likely formed from a monocyte/macrophage-like precursor that differentiates into osteoclasts under the influence of the mononuclear osteoblast-like stromal cells.

The renaming of such lesions as giant cell granulomas rather than epulides reflects the fact that these lesions are generally considered reactive and non-neoplastic in nature, although in humans the cause of such lesions is still poorly understood; interestingly an association with trauma, haemorrhage and/or periodontal disease has been suggested in humans. In dogs, these lesions are reported rarely to recur,[3] while in cats they have a higher recurrence rate following marginal excision alone when compared to other feline epulides. De Bruijn et al. speculated this recurrence may be related to the rapid growth and poor demarcation of such lesions, associated with a persistent inflammatory component.[4]

In an article reviewing the diagnoses made from 85 surgically amputated feline digits,[6] neoplastic disease was diagnosed in 63 of the submissions, of which 60 were considered malignant. The remaining 22 were purely inflammatory and not described further. Interestingly, two of the tumours were denoted as GCTB, not previously reported in the digits of cats. The authors of that study[6] believed that the fibroblast-like stromal cells in the tumours were the proliferating component and that the giant cells were non-neoplastic, reactive cells with immunohistochemical staining properties consistent with osteoclasts. In that study, the GCTB were from the toes of young cats (3 and 5 years) while the reported age range in the literature for cats with GCTBs from any site is from 1 to 12 years.[6,7,8]

Conclusions

This study describes the clinical and histological features of these distinctive feline lesions based on 41 cases, identifying the pathognomonic histological features as well as potential

variations which may be noted by clinicians and pathologists. Histological features include an exophytic growth pattern, with ulceration, neutrophilic inflammation, multinucleate giant cells, capillary formation and often foci of osseous metaplasia. Fibrin deposition, oedema and haemorrhage may or may not be evident, but necrosis is absent. Male cats were over-represented in this study and the second digit appears to be a predisposed site. These masses have some potential for local recurrence if incompletely excised, however there is no evidence that they are malignant, i.e. there was no evidence of metastatic potential or multicentric growths identified. Based on these clinical and histological features, the masses in this study appear most similar to giant cell reparative granulomas, which have been described affecting the phalanges in humans, and trauma, injury to the nail or nail-bed and nail-bed infections may potentially contribute to their development in cats.

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Conflict of interest

The Authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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307 **Table 1. Signalment, affected foot and digit and outcome for 41 cats with this novel nail-**
308 **bed lesion**. DSH – Domestic Shorthair; BSH – British Shorthair; BB – British Blue; MC x –
309 Maine Coon cross DSH; DC – Domestic cat; ESH – European Shorthair; DLH – Domestic
310 Longhair; FN – female neutered; F – female; MN – male neutered; M – male; LF – left fore
311 foot; RF – right fore foot; RH – right hind foot; LH – left hind foot; n/r – not recorded; NR
312 causes – non-related causes.

Case No.	Age (years)	Breed	Sex (Neuter)	Paw, digit	Duration of follow up, outcome
1	9	DSH	MN	LH, 2	No recurrence after 6 months
2	11	DSH	FN	RF, 2	No recurrence after 6 months
3	6	n/r	MN	RF, 1	No recurrence after 3 months
4	18	DSH	FN	LH, 3	Recurrence within months
5	18	MC x	FN	LH, 3	No recurrence after 6 years
6	n/r	DSH	MN	RF, 2	No recurrence after 3 months, died of NR causes
7	14	DSH	FN	RF, 2	No recurrence after 5 years
8	16	DSH	MN	RF, 2	Recurrence within months
9	14	DLH	MN	RF, n/r	No recurrence after 3 years
10	13	ESH	MN	LF, 3	Minimal follow-up (weeks)
11	11	Persian	MN	RH, 2	Minimal follow-up (weeks)
12	11	DSH	MN	RH, 2	No recurrence after 2 years
13	n/r	Siamese	MN	LH, 4	No recurrence after 13 months, died of NR causes
14	10	DSH	MN	RF, 1	Minimal follow-up (weeks)
15	14	DSH	FN	LF, 4	Recurrence within 3 months
16	12	DSH	FN	LF, 2	Incisional biopsy only
17	n/r	DSH	FN	RH, 2	No recurrence after 10 months, died of NR causes
18	n/r	DSH	MN	RF, 3	No recurrence after 14 months, died of NR causes
19	13	DSH	MN	LF, 2	No recurrence after 1 year
20	11	DSH	FN	LF, 4	Recurrence after 4 months
21	n/r	DC	FN	LF, 2	Recurrence reported, but died of NR causes
22	6	DSH	FN	LF, 2	No recurrence after 2 years
23	12	DSH	MN	RF, n/r	
24	15	DSH	MN	n/r, n/r	
25	4	n/r	MN	RH, 5	
26	9	DSH	MN	RH, n/r	
27	5	Siamese	MN	n/r, n/r	
28	17	DSH	M	LH, 3	
29	13	BB	MN	LF, 2	
30	12	DSH	MN	RH, 5	
31	12	DSH	MN	n/r, n/r	
32	1	DSH	MN	n/r, n/r	
33	14	DSH	MN	F, n/r	
34	9	DSH	MN	RF, 2	

35	9	DSH	MN	n/r, n/r	
36	10	DSH	FN	n/r, n/r	
37	14	DSH	F	LF, n/r	
38	4	DSH	MN	n/r, n/r	
39	11	DSH	MN	LH, 3	
40	6	BSH	MN	LH, n/r	
41	9	DSH	MN	LH, 3	

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316 **Figure legends**

317 Figure 1. Distribution of lesions on different feet and digits of affected cats. D1 – digit one; D2
318 – digit two; D3 – digit 3; D4 - digit four; D5 – digit five; LF – left forelimb; RF – right forelimb;
319 LH – left hind limb; RH – right hind limb; ALL – all limbs.

320

321 Figure 2. Two photographs and one radiograph of typical lesions arising from the nail-bed. a):
322 Right forelimb, digit 5: the mass can be seen protruding from the ventral aspect of the nail; b).
323 Right hind limb, digit 2: in this case the mass is associated with trauma and injury to the claw;
324 c). Radiograph of a lesion arising on the right forelimb, digit 5. No radiographic changes can
325 be seen, which correlates with the absence of bone destruction or lysis on histological
326 examination.

327

328 Figure 3. Histological appearance of a typical nail-bed lesion. a). Section through an exophytic
329 and ulcerated (arrows) mass composed of a spindle cell population, areas of osseous metaplasia
330 (asterisk) and multinucleate giant cells (HE-stain, 40x); b). multinucleate giant cells (arrows)
331 surrounded by spindle cells (HE-stain, 400x); c). areas of osseous metaplasia (asterisk),
332 surrounded by spindle cells (HE-stain, 400x).

333