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

2

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18 **Key words**

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

20

21 **Abstract**

22 *Objectives*

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

27 *Methods*

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

31 *Results*

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

37 *Conclusions and relevance*

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

42

43 **Introduction**

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

51

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

63

64 **Materials and Methods**

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

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

71

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

83

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

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

94

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

102

103 **Results**

104 *Signalment, clinical presentation and outcome*

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

116

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

120

121 The affected limb was recorded for 34 cases (table 1), with eight lesions (24.2%) affecting the
122 left hind limb, nine (27.3%) the left forelimb, six (18.2%) the right hind limb, and 10 (30.3%)
123 the right forelimb; there was no statistically significant difference ($P = 0.787$). One case was
124 described as affecting a forelimb (left or right not specified) and in seven cases the limb was
125 not noted. Overall, 20 (58.8%) cases were affecting a forelimb and 14 a hind limb (41.2%);
126 again this difference was not statistically significant ($P = 0.304$). The affected digit was
127 recorded for 28 cases (table 1), with two lesions (7.1%) affecting digit 1, 14 involving digit 2
128 (50%), seven arising from digit 3 (25%), three involving digit 4 (10.7%) and two affecting digit
129 5 (7.1%); this difference was statistically significant ($P = 0.0009$, figure 1).

130

131 Asked if the mass appeared painful on palpation, eight of the 22 responding primary clinicians
132 replied 'yes', 10 responded 'no' and four did not answer the question. Five cats were described
133 as lame on the affected limb, while 13 cats were not and there was no response to this question
134 from four cases. The clinicians indicated there was evidence of local inflammation in 18 of the
135 cases, but only one described evidence of more widespread inflammation, in this case a
136 palpably enlarged regional lymph node. The most common terms used to describe the mass
137 were 'pink', 'red', 'fleshy' or 'flesh-coloured' and 'small'. Others terms less frequently used
138 included 'inflamed', 'dark', 'raw', 'irregular', 'raised', 'polyp-like' and 'shiny' (figures 2a and
139 2b).

140

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

147

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

155

156 *Histological Features*

157 Forty-one cases were histologically assessed. All of the masses examined were exophytic,
158 variably inflamed, contained large numbers of spindle cells and had areas of capillary
159 formation. All except two cases had obvious areas of ulceration in the sections examined
160 (95.1%; figure 3a). In one case the presence of ulceration was uncertain and in another case
161 ulceration was apparent in one sample but not in a second sample from a recurrent lesion in the
162 same cat.

163

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

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

169

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

175

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

178

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

181

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

187

188 All masses were measured as part of the histological assessment and the size ranged from 1 x
189 2mm up to 10 x 11mm based on formalin-fixed, paraffin-embedded tissue samples, with a

190 median size of 6 x 4mm. Based on the questionnaire results, the masses ranged in size from 2-
191 3mm up to 20mm (prior to fixation).

192

193 **Discussion**

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

203

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

213

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

221

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

231

232 A histologically similar lesion to these masses is the giant cell epulis (recently renamed giant
233 cell granuloma), described in both dogs³ and cats.^{4,5} De Bruijn et al.⁴ described a series of 52
234 feline epulides, of which 15 were giant cell epulides. In that study the MNGCs and some of the
235 mononuclear cells stained positive for vimentin and for TRAP (tartrate-resistant acid
236 phosphatase), a marker for osteoclasts. Osteoid and woven bone formation was present in 11
237 of the 15 cases. The authors speculated the osteoclast-like giant cells in the epulides are most

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

240

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

249

250 In an article reviewing the diagnoses made from 85 surgically amputated feline digits,⁶
251 neoplastic disease was diagnosed in 63 of the submissions, of which 60 were considered
252 malignant. The remaining 22 were purely inflammatory and not described further.
253 Interestingly, two of the tumours were denoted as GCTB, not previously reported in the digits
254 of cats. The authors of that study⁶ believed that the fibroblast-like stromal cells in the tumours
255 were the proliferating component and that the giant cells were non-neoplastic, reactive cells
256 with immunohistochemical staining properties consistent with osteoclasts. In that study, the
257 GCTB were from the toes of young cats (3 and 5 years) while the reported age range in the
258 literature for cats with GCTBs from any site is from 1 to 12 years.^{6,7,8}

259

260 **Conclusions**

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

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

274

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282 year research project (RAF) supported by the Royal Veterinary College.

283

284 **Conflict of interest**

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

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306

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	

313

314

315

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