

## SHORT COMMUNICATION

# Feline and canine Merkel cell carcinoma: A case series and discussion on cellular origin

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## Abstract

Merkel cell carcinoma (MCC) is in humans and cats a malignant cutaneous neuroendocrine carcinoma, whereas in dogs it possibly has a more benign behaviour. It may be cytologically confused with round cell tumours such as lymphoma because of its striking cytomorphologic similarity. Although MCC is considered to arise from Merkel cells, recent findings indicated that primitive (epi-)dermal stem cells, early B-cells or dermal fibroblasts were the origin of human MCC. The aim of our study was to evaluate a possible lymphoid origin in feline and canine MCCs. Specific analysis of CD3, PAX-5, KIT and PARR assay were performed in 3 feline and 3 canine MCCs. All MCCs (6/6) were negative for CD3 and PAX-5. KIT was expressed in all MCCs (6/6). Assessment of clonality by PARR assay exhibited a polyclonal B- and T-cell receptor rearrangement in all five cases tested. In conclusion, a lymphoid origin of feline and canine MCCs could not be demonstrated. This is in contrast with human MCCs, that often express early B-cell lineage markers.

## KEYWORDS

comparative, Merkel cell carcinoma, origin

## 1 | INTRODUCTION

Merkel cell carcinoma (MCC), also known as Merkel cell tumour or neuroendocrine carcinoma, is a rare cutaneous tumour revealing characteristics of both epithelial and neuroendocrine differentiation.<sup>1-3</sup> Normal Merkel cells are thought to be part of the mechanoreceptor system in the mammalian skin and serve as specialized neural pressure sensitive receptor cells.<sup>2,4</sup>

In humans, MCC is a highly malignant skin cancer, which has a multifactorial aetiology but is associated in about 80% of the cases with the presence of Merkel cell polyomavirus (MCPyV).<sup>5,6</sup> In feline or canine MCC MCPyV genes and antigen were not detected, suggesting a different aetiology from human MCC.<sup>7</sup>

Some case reports in cats and dogs suggest a more benign clinical course.<sup>8-11</sup> However, recurrence and metastases has also been reported

in both species.<sup>3,12-15</sup> In general, canine MCC seems to be more benign and feline MCC seems to be more aggressive.<sup>2,3,8,9</sup> A recent case series of feline MCC reported a poor prognosis with a median overall survival time of 243 days and high recurrence rate (11/20).<sup>3</sup>

Feline MCC often presents as a solitary cutaneous mass.<sup>2,3</sup> It has been reported that MCC show similarities to large lymphocyte-like cells on cytologic examination.<sup>2</sup> Histologic examination of feline MCC reveals nests of round cells separated by a variable amount of a fibrous stroma,<sup>2</sup> or a trabecular pattern consisting of interconnecting strands of neoplastic cells.<sup>11</sup> Other histopathological features of feline MCC include tumour necrosis, vascular invasion and high mitotic counts.<sup>3</sup> Tumour cells often demonstrate immunostaining for cytokeratin (CK) 20, CK18, p63, neuron-specific enolase (NSE) and synaptophysin, consistent with the characteristics of normal Merkel cells.<sup>2,3</sup> In dogs, immunohistochemistry of MCC also often

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demonstrates expression of chromogranin-A, CK, synaptophysin and NSE.<sup>9,15,16</sup> Canine MCC has also been reported to be positive for KIT immunostaining.<sup>16</sup> Current treatment recommendation for feline and canine MCC consist of wide surgical excision.<sup>1</sup> The efficacy of other treatments like chemotherapy or c-KIT-targeted tyrosine kinase inhibition is unknown.<sup>1</sup>

Although MCC is considered to arise from Merkel cells, recent findings indicate that primitive epidermal/dermal stem cells, early B-cells or dermal fibroblasts could be the origin of human MCC.<sup>6,17,18</sup> Human MCC is characterized by immature cells which, because of their striking morphological similarity, may be confused with round cell tumours such as lymphoma.<sup>19</sup> Immunohistochemistry is therefore important for differentiation.

The simultaneous expression in human MCC of PAX5,<sup>6,19-21</sup> a member of the paired box gene family which plays a role in B-cell ontogeny, and terminal deoxynucleotidyl transferase (TdT),<sup>6,19</sup> a specialized DNA polymerase expressed in immature pre-B/pre-T lymphoid cells, has led to the proposal that the cell of origin of MCCs is a pro/pre-B cell.<sup>6,19</sup>

To the authors' knowledge, there are no comparable published studies evaluating the cellular ancestry of feline and canine MCC. The primary goal was to evaluate a possible lymphoid origin of feline and canine MCCs. For this purpose the present report describes the pathological findings of 6 cases (3 cats and 3 dogs) diagnosed with MCC that were evaluated by an immunohistochemistry panel for characterization of marker expression and for clonality of B and T-cell receptors using a PCR for antigen receptor rearrangements (PARR) assay.

## 2 | MATERIALS AND METHODS

A search for potential cases between 2010 and 2019 was performed in the archive of the Veterinary Pathology Diagnostic Centre (VPDC) of Utrecht University Faculty of Veterinary Medicine. Six cases (3 feline and 3 canine) were retrieved. Relevant data from retrieved cases were reviewed from the submission forms and pathology reports. Cytologic slides of fine needle aspirates (FNA) were available in three cases and re-evaluated.

Haematoxylin and eosin (HE) slides were reviewed to confirm the presence of neoplastic tissue and the diagnosis. The diagnosis of MCC was based on previously described histopathological and immunohistochemical observations.<sup>2,3,16,22</sup>

For immunohistochemistry 4 µm tissue sections on coated glass were stained with antibodies against chromogranin A (CGA; *rabbit anti-CGA, non-commercial*), synaptophysin (SYP; *mouse anti-SYP, Agilent Dako*), pan cytokeratin (PCK; *rabbit anti-AE1/AE3 pan cytokeratin, Agilent Dako*), neuron-specific enolase (NSE; *mouse anti-NSE, Neomarkers Invitrogen*), CD3 (*rabbit anti-CD3, Cell Marque*), PAX-5 (*mouse anti-PAX-5, BD Biosciences*), KIT (*rabbit anti CD117, Agilent Dako*). For visualization of KIT 3,3' diaminobenzidine (DAB) was used, for the other antibodies 3-amino-9-ethylcarbazole (AEC) was used. All immunohistochemistry was performed at the VPDC except staining for KIT which was performed by Institut für Pathologie, Stiftung Tierärztliche Hochschule Hannover, Germany.

Appropriate positive and negative controls were used, including pancreas, skin, lymph node and mast cell tumour. The percentage of positive neoplastic cells was scored as follows: 0 (0%), 1 (<25%), 2 (26%-50%), 3 (51%-75%) and 4 (76%-100%).

The presence of a clonally expanded lymphocyte population was investigated by PARR on the paraffin-embedded tumour tissues of all cases. Ten µm thick paraffin sections of neoplastic tissue were submitted for PARR. Feline MCC were tested by the Central Laboratory of University of Veterinary Medicine Vienna (Austria) and canine MCC were tested by the laboratory of GD Animal Health (Deventer, the Netherlands). PCR was performed for B-cell receptor immunoglobulin heavy chain (IgH) gene and for T-cell receptor gamma (TCRg).<sup>23</sup> Polymerase chain reaction (PCR)-based clonality assays for feline B- and T-cell receptor chain gene rearrangement were performed as described previously.<sup>24,25</sup>

## 3 | RESULTS AND DISCUSSION

Six cases (3 feline and 3 canine) were retrieved for the study. All 3 feline cases were Maine Coon cats. Their age varied from 8.5 to 13.6 years. The dogs were a Boxer, an Airedale terrier and a Stabyhoun. The age of the affected three dogs varied from 8.3 to 9.9 years. Signalment, clinical signs and location of the tumours are shown in Table 1. Although this is only a small case series it is interesting that all three cats were Maine Coon cats and no other breeds were found. No family relationship between these cats could be established. So far, a breed predisposition for Maine Coon cats has not been reported. Of the 46 reported feline cases,<sup>2,3,7,11,13,14</sup> three cases were Maine Coon cats.<sup>3,13</sup> Also, in the dog no breed predisposition has been reported. Further research is necessary to see if there is a true breed predisposition in the cat. In humans, MCC is more likely to occur in Caucasians than other ethnicities and UV exposure is believed to be a major risk factor.<sup>26-29</sup> So far, risk factors for feline and canine MCC have not been identified.<sup>3,7</sup>

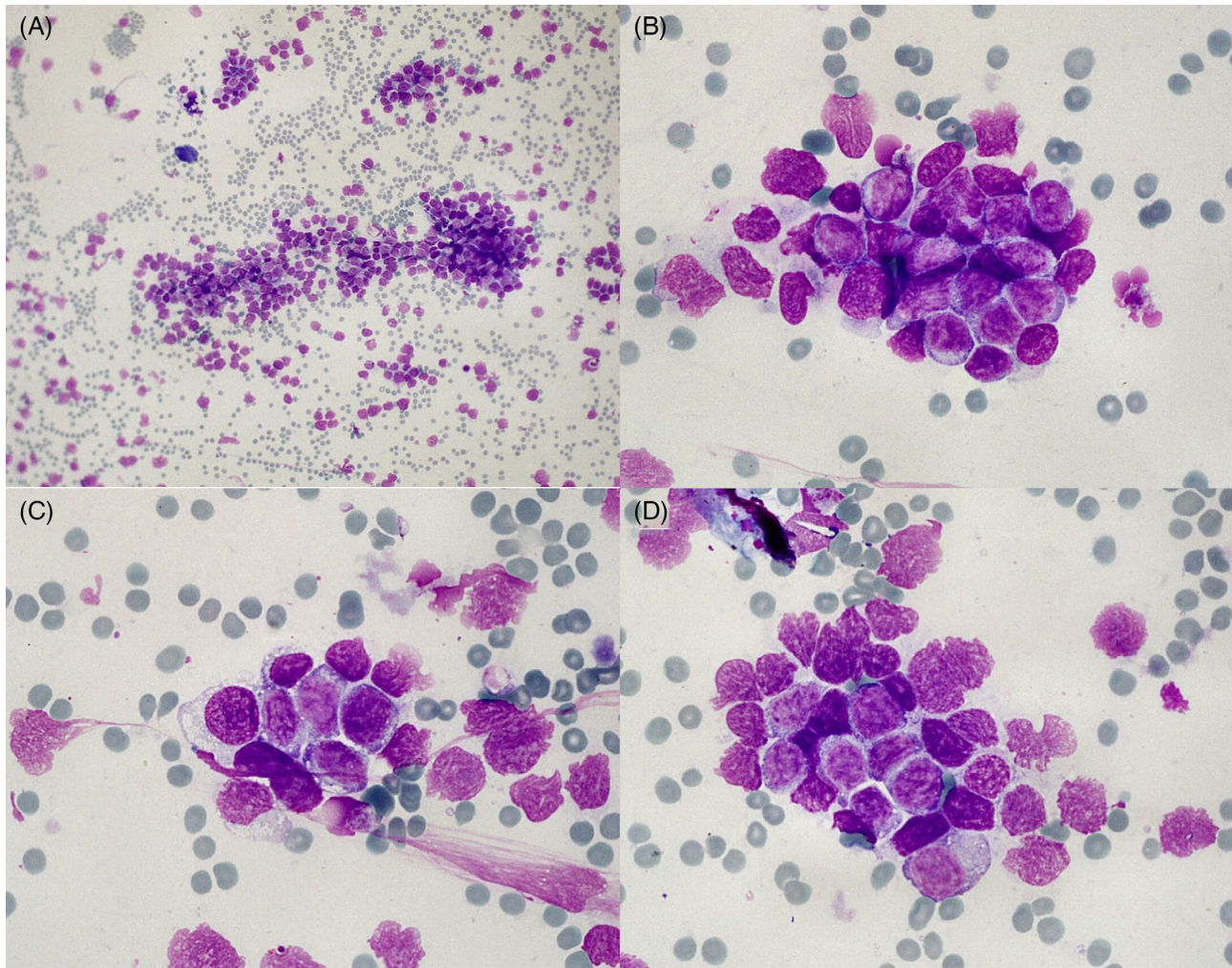
Clinical information is scarce in this study as most of the affected cats and dogs were treated in private clinics and did not undergo a complete clinical examination and diagnostic work-up at the time of evaluation. However, the medical records of two feline cases (case 1 and 2) revealed that initially these cases were incorrectly diagnosed on cytological examination of FNA biopsies as large cell lymphoma. In these two cases, a monomorphic population of abundant round-shaped cells that resembled lymphoma cells were observed on cytology (Figure 1A-D). The similarity of feline MCC with lymphoma on cytology has been reported before,<sup>2</sup> confirming the importance of histology in the diagnosis of MCC in veterinary medicine. The cytologic characteristics of the two feline cases also triggered the interest into the cell of origin of the tumour.

Histologically, all neoplasms showed morphological characteristics consistent with MCC as reported in literature and consisted of solid nests and trabecula of rounded cells that typically show moderate variation in size and shape surrounded by thin fibrovascular septa on which some palisading can be noted (Figure 2A-C).<sup>2,3,10,15,16</sup> The neoplastic cells were polygonal with scant cytoplasm and indistinct cell borders. The nuclei were round-to-ovoid with stippled chromatin and

**TABLE 1** Signalment, tumour localization and deepest anatomical compartment of six cases diagnosed with Merkel cell carcinoma

Case	Species	Age (years)	Gender	Breed	Tumour localization	Deepest anatomical compartment
1	Feline	11.82	FS	Maine Coon	Left inguinal area	Dermis
2	Feline	13.58	MN	Maine Coon	Right flank and back	Subcutaneous
3	Feline	8.45	MN	Maine Coon	Cheek	Dermis
4	Canine	9.90	FS	Boxer	Right medial flank	ND
5	Canine	8.32	F	Airedale Terrier	Thoracic wall	Subcutaneous
6	Canine	8.97	M	Stabyhoun	ND	Subcutaneous

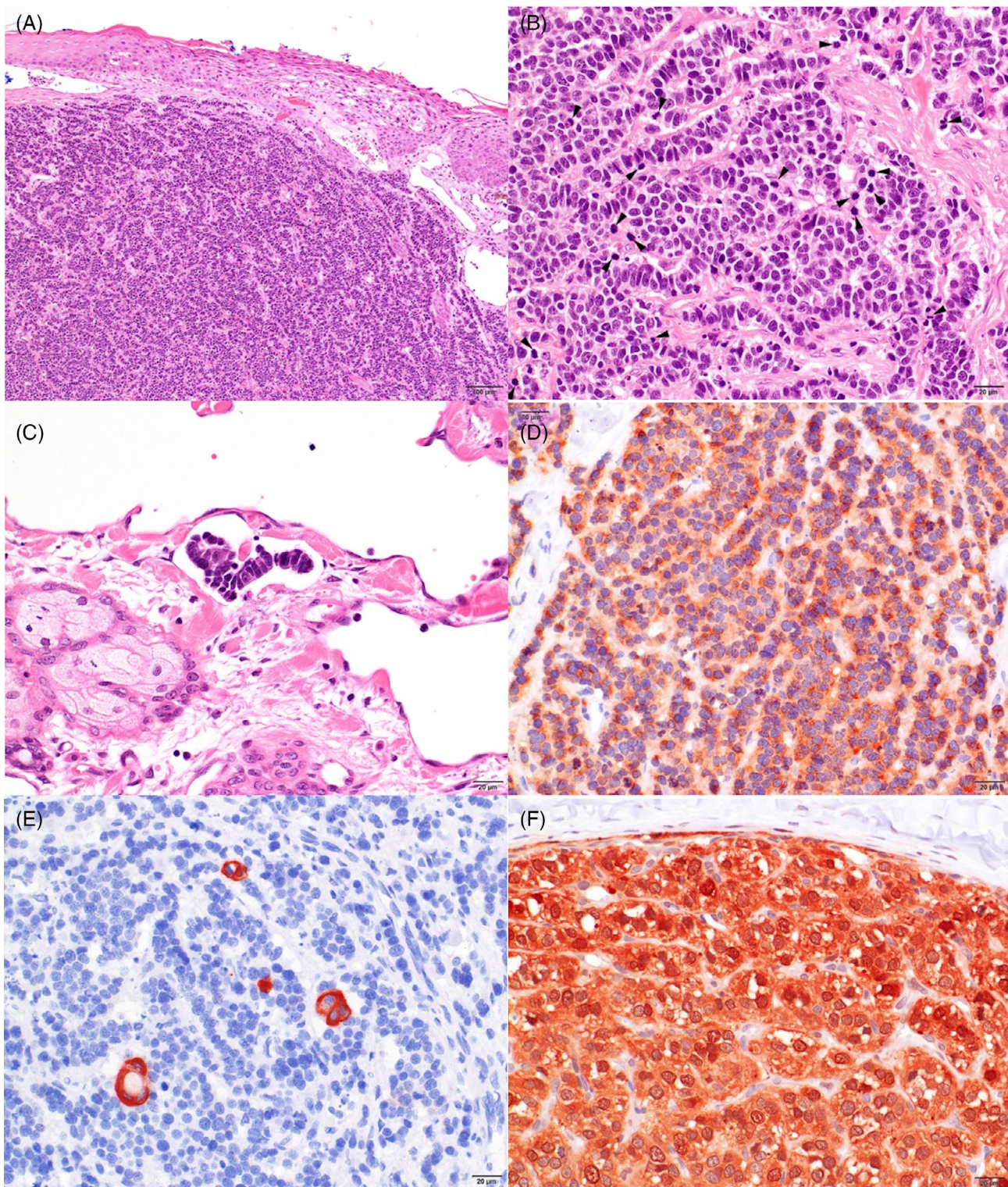
Abbreviations: F, intact female; FS, female spayed; M, intact male; MN, male neutered; ND, no data.



**FIGURE 1** (A-D) Cytological examination of feline Merkel cell carcinoma of case 1. Many large round-shaped cells (15–30  $\mu\text{m}$  in diameter), discretely or in loose groups, with a quite high N/C ratio and light basophilic cytoplasm were observed. Regularly, cells had multiple small cytoplasmic vacuoles. Most cells had a round nucleus with 1 or 2 small nucleoli. (A) May-Grünwald-Giemsa (MGG), obj. 20 $\times$ . (B-D) MGG, obj. 100 $\times$  [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

indistinct nucleoli. The histopathological features included tumour necrosis in 4 cases (4/6), vascular invasion in 2 cases (Figure 2C, 2/6), and sometimes high mitotic counts (Figure 2B, median: 11 per HPF, range: 1–25). The number of mitotic figures per HPF varied greatly in the three cats (from 1 to 25), whereas the number of mitotic figures in the canine cases were typically below 10 per HPF. Apart from this, no

major differences between the feline and canine MCC were noted in histologic appearance. Although a presumptive diagnosis can be made based on the architectural characteristics of Merkel cell tumours after routine histological evaluation, the use of immunohistochemistry is recommended for diagnostic confirmation of MCC in cats and dogs.<sup>2,3,16</sup> Also in humans, diagnosis can be challenging because MCC



**FIGURE 2** (A-C) Histological findings of feline Merkel cell carcinoma. (A) Case 1. The dermis contains rounded neoplastic cells in nests and trabecula, separated by thin fibrovascular septa. The superficial dermis shows marked vascular dilation (lymph vessels and venules). Haematoxylin and eosin (HE), obj. 10 $\times$ . (B) Case 1. Higher magnification of the same neoplasm revealing a trabecular pattern of fairly uniform neoplastic cells with numerous mitotic figures (arrowheads). HE, obj. 40 $\times$ . (C) Case 3. Presence of an embolus of neoplastic cells in a lymph vessel (vascular invasion). Above and below on the right several other markedly dilated lymph vessels. HE, obj. 40 $\times$ . (D-F) Immunohistochemistry findings. (D) Case 1. Moderate to strong cytoplasmic immunoreactivity for synaptophysin in the majority of neoplastic cells. Obj. 40 $\times$ . (E) Case 1. Note a few variably sized groups of neoplastic cells with strong cytoplasmic immunoreactivity for keratin (AE1/AE3). However, the majority of neoplastic cells is negative. Obj. 40 $\times$ . (F) Case 3. Strong cytoplasmic immunoreactivity for neuron specific enolase. Obj. 40 $\times$  [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 2** Results of immunohistochemistry for Merkel cell carcinoma cases

Case	Chromogranin A	Synaptophysin	Pan Cytokeratin	NSE	CD3	PAX-5	KIT <sup>a</sup>
1	0	3	1	2	0	0	+
2	0	4	1	2	0	0	+
3	0	0	0	4	0	0	+
4	0	0	4	4	0	0	+
5	0	1	0	2	0	0	+
6	0	0	1	2	0	0	+

Note: Percentage of positive neoplastic cells: 0 (0%), 1 (<25%), 2 (26%-50%), 3 (51%-75%) and 4 (76%-100%).

Abbreviations: CD3, cluster of differentiation 3; KIT, cluster of differentiation 117 (CD117); NSE, neuron-specific enolase; PAX-5, paired box protein 5.

<sup>a</sup>Percentage of KIT positive cells not reported.

**TABLE 3** Results of PARR for Merkel cell carcinoma cases

Case	PARR
1	Insufficient DNA
2	Polyclonal for B- and T-cell
3	Polyclonal for B- and T-cell
4	Polyclonal for B- and T-cell
5	Polyclonal for B- and T-cell
6	Polyclonal for B- and T-cell

Abbreviation: PARR, PCR for antigen receptor rearrangements.

shares histologic features similar to a variety of other widely recognized small blue round cell tumours, such as small cell or amelanotic melanoma, pulmonary small cell carcinoma and lymphoma.<sup>19,29</sup> Human MCC on HE-stained sections typically contain small round blue cells with sparse cytoplasm, abundant mitoses, and dense core granules in the cytoplasm.<sup>29</sup> Immunohistochemical stains have proven to be useful for distinguishing MCC from other small round cell tumours, like CK20, synaptophysin and chromogranin A.<sup>6,29</sup>

The immunohistochemistry findings in all six cases are given in Table 2 and shown in Figure 2D-F. Immunohistochemically, the neoplasms were positive for NSE and KIT in all cases. In two cats and two dogs, the neoplastic cells were positive for PCK (Figure 2E), and synaptophysin was positive in two cats and one dog (Figure 2D) (Table 2). Neoplastic cells were negative for chromogranin A, CD3 and PAX-5 antibodies in all cases. A variable amount of scattered lymphocytes and plasma cells were present in the background. The immunohistochemical studies supported the histological diagnosis of MCC.

In humans, the cellular ancestry of MCC is under debate. It has been suggested that MCC originate from early B-cells, based on morphology, the consistent expression of early B-cell lineage markers and the finding of clonal immunoglobulin chain rearrangement in MCC cells.<sup>6,17</sup> PAX-5 expression is frequently encountered in human MCC.<sup>6,19,20,30,31</sup> The transcription factor PAX-5 is essential for commitment of lymphoid progenitors to the B-lymphocyte lineage.<sup>18,32</sup> Although PAX-5 is often expressed in MCC, it is considered to be fairly specific for B-cell lineage.<sup>21,30</sup> Another critical factor in early B-cell development is KIT (CD117).<sup>18,33</sup> Also, KIT expression is

frequently described in human MCCs.<sup>18,34,35</sup> However, the absence of mutations makes KIT an unlikely candidate of MCC oncogenesis.<sup>34,35</sup>

To our knowledge, this is the first study to investigate possible lymphoid origin of feline and canine MCC. Additional immunolabelling with CD3, PAX-5, KIT and PARR analysis were performed. All cases included in the current study were consistently negative for the applied lymphocytic markers (CD3 and PAX-5). This is in contrast with human MCC, which often have immunoexpression of PAX-5.<sup>6,19,20,30,31</sup> Although, PAX-5 is not widely used as a B-cell marker in cats, it has been reported to result in similar staining as in human and canine samples.<sup>36</sup> KIT expression was positive in all cases examined, which is in line with previous findings in canine and human MCC.<sup>16,18,34,35</sup> C-KIT mutations can induce increased cell proliferation, mobility and resistance to apoptosis.<sup>37,38</sup> The positive KIT expression in feline and canine MCCs warrants further investigation for mutation status and possible treatment options like the use of tyrosine kinase inhibitors.

The presence of a clonally expanded lymphocyte population was investigated by PARR assay on the paraffin-embedded tumour tissues (Table 3). Five samples exhibited a polyclonal B- and T-cell receptor rearrangement, consistent with the presence of reactive lymphoid cells, probably as a “background” population or because of a dermatitis. The sample with insufficient DNA concentration (case 1), was excluded from clonal assessment, as a low quantity of DNA may decrease the assay sensitivity.<sup>23</sup> The PARR finding of polyclonal B- and T-cell receptor rearrangement is consistent with the negative immunohistochemical stains of the tumour cells for CD3 and PAX-5 and indicates the presence of a reactive lymphoid population in the tissue.

In conclusion, although feline and canine MCC share histological features with their human counterpart, the current findings are not consistent with the hypothesis that MCCs in dogs and cats derive from early B-cells. The immunohistochemistry panel confirms a neuroendocrine origin.

#### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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