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CLINICAL STUDY



# Osteoinductive squamous cell carcinoma associated with a putative novel papillomavirus on the digit of a cat

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**ABSTRACT**

**Case history and clinical findings:** An approximately 10-year-old, castrated male domestic short-haired cat developed swelling and ulceration of the second digit of the right front paw. Radiographs revealed a spherical soft tissue swelling with irregular distal margins that contained multiple lacy mineral opacities. The digit was amputated and submitted for histology. No recurrence has been observed 7 months after amputation.

**Pathological and molecular findings:** Histology revealed a moderately well-circumscribed proliferation of well-differentiated squamous cells arranged in trabeculae and nests. Numerous thin spicules of osseous metaplasia were visible throughout the neoplasm. Around 70% of the neoplastic cells contained papillomavirus-induced cell changes including large amphophilic cytoplasmic bodies and cells with shrunken nuclei surrounded by a clear halo. Intense $p16^{CDKN2A}$ protein immunostaining was visible within the neoplastic cells, suggesting papillomavirus-induced changes in cell regulation. A DNA sequence from a putative novel *Taupapillomavirus* type was amplified from the neoplasm.

**Diagnosis:** Osteoinductive squamous cell carcinoma associated with a putative novel papillomavirus type.

**Clinical relevance:** The findings in this case increase the number of papillomavirus types known to infect cats, and the squamous cell carcinoma had histological features that have not been previously reported. The neoplasm was not as invasive as is typical for a squamous cell carcinoma and excision appeared curative. This is the first report of an osteoinductive squamous cell carcinoma of the skin of cats and the neoplasm had a unique radiographic appearance.

**Abbreviations:** FcaPV: *Felis catus* papillomavirus; FIV: Feline immunodeficiency virus; p16: $p16^{CDKN2A}$ protein; PV: Papillomavirus; pRb: Retinoblastoma protein; SCC: Squamous cell carcinoma

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## Introduction

Papillomaviruses (PV) are small circular double-stranded DNA viruses that, with rare exceptions, infect epithelium and are highly host-specific (Bernard *et al.* 2010). As part of the viral replication process, PV produce proteins that increase cell replication. A marked increase in epithelial cell replication can result in a hyperplastic viral papilloma (wart) (Munday *et al.* 2022a). Alternatively, the increased cell replication can predispose to the development of neoplasia. Domestic cats rarely develop viral warts (Munday *et al.* 2022c); however, there is increasing evidence that PV may be an important cause of feline skin cancer (Munday *et al.* 2022b).

Papillomaviruses are classified based on the sequence of the highly conserved *ORF L1* with PV within the same genus sharing > 60% nucleotide similarity and PV of the same type having > 90% similarity (Bernard *et al.* 2010). Seven *Felis catus* papillomavirus (FcaPV) types had been fully sequenced. Of these, FcaPV1 is classified within the *Lambdapapillomavirus* genus (Tachezy *et al.* 2002), FcaPV2 is classified within the *Dyothetapapillomavirus* genus (Lange *et al.* 2009), while FcaPV types 3–7 are all classified within the *Taupapillomavirus* genus (Munday *et al.* 2023). FcaPV types 2, 3, and 4 have all been detected in multiple pre-neoplastic or neoplastic skin lesions in cats, while there are only rare reports describing neoplasms containing FcaPV5, FcaPV6 and FcaPV7 (Munday *et al.* 2022b). Compared to the number of PV types identified from humans and dogs (Munday *et al.* 2022a), relatively few feline PV types have been identified. This suggests it is likely that additional FcaPV types remain to be identified.

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Here, we report a case involving a cat that developed a markedly swollen digit. Histology revealed a squamous cell carcinoma (SCC) with unique histological features including numerous PV-induced cell changes and osseous metaplasia. A DNA sequence from a putative novel PV type was amplified from the SCC.

## Case history

A castrated male domestic short-haired cat presented with swelling and ulceration of the second digit of the right front paw. The cat was a stray that was fed by multiple people in the neighbourhood and was estimated to be around 10 years old. The swelling had first been observed 3 weeks previously with the digit slowly becoming larger and more ulcerated during this time.

## Clinical findings

### *Initial clinical and radiographical findings*

The cat was bright, alert, and responsive on examination and was not pyrexic. The affected digit was 4 cm in diameter and compressing the adjacent third digit. Multiple areas of hair loss and a central area of ulceration were visible, although the claw remained intact (Figure 1). The digit was firm, malodorous, and was judged to be painful when touched. Radiographs showed a spherical soft tissue swelling that had irregular distal margins and was traversed by multiple lacy mineral opacities (Figure 2). Due to superimposition of this mineral, it was not possible to conclusively determine whether osteolysis of the distal phalanx was present. In-house testing of a blood sample revealed a PCV of 17.4% (reference range 29.7–44.5%). Infection by retroviruses was investigated using a Witness feline leukaemia virus antigen-feline immunodeficiency virus (FIV) antibody test (Zoetis NZ, Auckland, NZ). This revealed antibodies against FIV. As the cat was a stray, it was thought unlikely to have been vaccinated against FIV and the antibodies were interpreted as evidence of FIV infection.

A bacterial infection of the digit was considered most likely, although neoplasia or fungal infection were other differentials that were considered. Both to achieve a cure, but also to definitively identify the cause of the swelling, the digit was routinely amputated at the level of the metacarpophalangeal joint and submitted to IDEXX Laboratories (Palmerston North, NZ) for histology. The skin was closed in a cruciate pattern and the wound healed uneventfully over the following 2 weeks. Post-operative pain relief included transmucosal buprenorphine (Buprelieve; Jurox NZ Ltd., Auckland, NZ) at 0.02 mg/kg up to every 8 hours when required in the first 2 days following surgery, and 0.05 mg/kg meloxicam (Metacam; Boehringer Ingelheim NZ Ltd., Manukau City, NZ) orally, once every 24 hours for 8 days.

### *Pathological findings*

The amputated digit was fixed in 10% neutral buffered formalin, processed routinely for histology, and stained

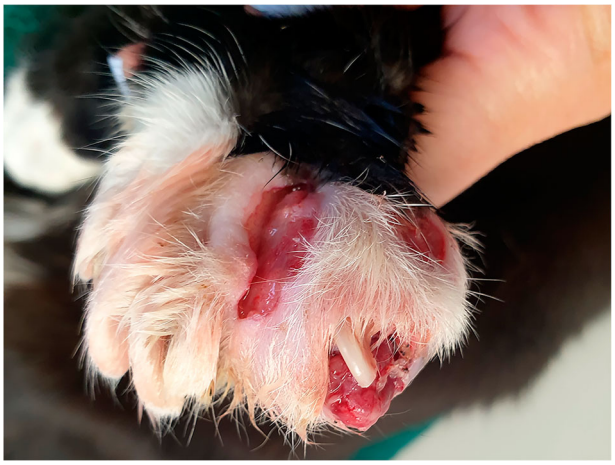

**Figure 1.** Squamous cell carcinoma from the digit of a cat. The digit is markedly swollen and ulcerated.

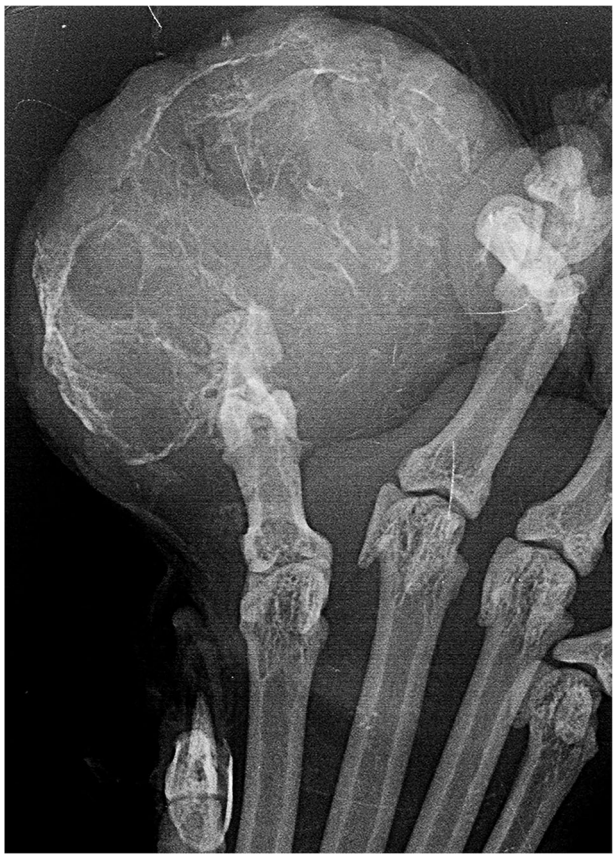

**Figure 2.** Radiograph of the digit of a cat revealing swelling of the digit by a mass that contained numerous lacy opacities and was later shown to be a squamous cell carcinoma. Mineralisation within the neoplasm prevented critical assessment of the distal phalanx for osteolysis.

with H&E. Examination revealed a proliferation of cells arranged within broad trabeculae and nests that were separated by a small amount of fibrous tissue. The cells on the periphery of the trabeculae were small, cuboidal, and dark, while the cells towards the centre were larger, more angular and contained large quantities of eosinophilic cytoplasm. Eosinophilic acellular keratin arranged in concentric layers (keratin pearls) was visible in the centre of some larger trabeculae. The neoplastic cells were a moderately pleomorphic population of polygonal cells with well-defined cell borders. Nuclei were generally central and most contained indistinct nucleoli. Three mitotic figures were visible in 2.37 $mm^2$ (10 contiguous, non-overlapping high-powered fields). Around 70% of the neoplastic cells had features suggestive of infection with PV including the presence of distinct amphophilic cytoplasmic bodies that variably surrounded the nucleus (Figure 3a), cytoplasm distended by granular lightly basophilic material, enlarged nuclei with marginated chromatin, or dark shrunken nuclei surrounded by a clear cytoplasmic halo (koilocytosis). Another prominent feature within the mass was the presence of numerous slender spicules of variably mineralised bone (Figure 3b). Due to the presence of the bone spicules between neoplastic cells, including superficially within the SCC, this was interpreted as osseous metaplasia rather than as osteolysis of the distal phalanx. Examination of the surface of the neoplasm revealed a well-defined transition from normal to neoplastic epidermis. The neoplasm was surrounded by increased fibrous tissue containing numerous lymphocytes and plasma cells and nests of neoplastic cells were only rarely visible infiltrating into surrounding tissue.

To evaluate the mass for potentially PV-induced changes in cell regulation, immunostaining using anti-$p16^{CDKN2A}$ (p16) antibodies was performed as previously described (Munday *et al.* 2011a). A viral plaque that contained FcaPV2 DNA was used as a positive control while the primary antibody was omitted from the negative control. Intense nuclear and cytoplasmic immunostaining was present in around 90% of the neoplastic cells (Figure 3c). Examination of superficial aspects of the SCC revealed a clear demarcation between neoplastic epidermis that showed intense immunostaining and the surrounding normal-appearing epidermis which showed no immunostaining.

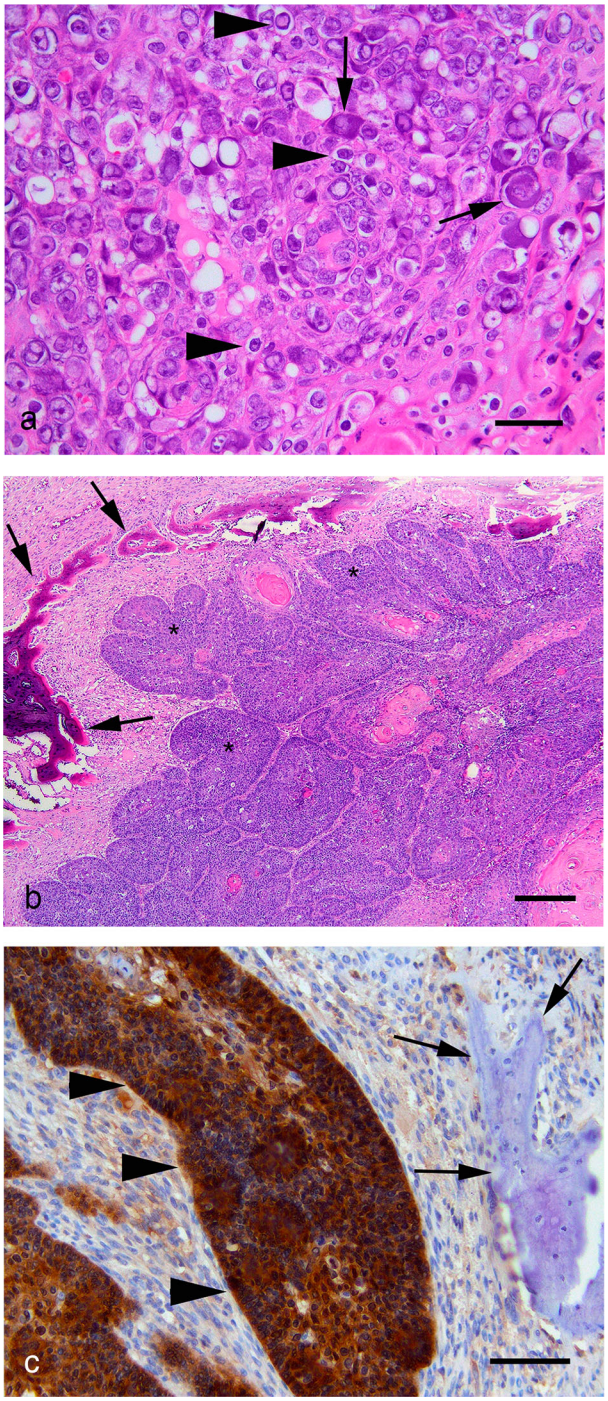


**Figure 3.** Photomicrographs of a section of squamous cell carcinoma from the digit of a cat. (a) Papillomavirus-induced cell changes are prominent including the presence of large amphophilic cytoplasmic bodies that often surround the nucleus (arrows) and cells with shrunken nuclei surrounded by a halo of clear cytoplasm (arrowheads) (H&E; bar = 25 µm). (b) Well-differentiated squamous epithelial cells are arranged within trabeculae and nests (asterisks) and areas of osseous metaplasia are prominent surrounding the neoplastic cell trabeculae (arrows) (H&E; bar = 0.2 mm). (c) Neoplastic cells contain intense nuclear and cytoplasmic $p16^{CDKN2A}$ protein immunostaining (arrowheads) with osseous metaplasia visible adjacent to the neoplastic cells (arrows) (haematoxylin counterstain; bar = 60 µm).

### *Molecular investigation*

A sample of the SCC was excised from the formalin-fixed paraffin-embedded tissue block using a clean scalpel. This allowed DNA to only be taken from the mass and not the surrounding non-neoplastic epidermis. Total DNA was extracted using a NucleoSpin DNA FFPE XS kit (Macherey-Nagel GmbH, Duren, Germany) according to manufacturer's instructions and the MY09/11 consensus primers were used to amplify papillomaviral DNA as previously described (Munday *et al.* 2020). DNA extracted from a viral

plaque that contained FcaPV3 was used as the positive control while no template DNA was added to the negative control.

Papillomaviral DNA was amplified from the digit SCC and positive control, but not from the negative control. The DNA amplified from the SCC was sequenced and compared to other sequences stored in GenBank using the BLAST tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The 334-bp partial *ORF L1* sequence that was amplified from the digit SCC had the greatest similarity to the *Taupapillomavirus* FcaPV types, with 74% similarity to FcaPV6, 72.4% similarity to FcaPV7, and 65% similarity to FcaPV3. When compared to PV types in other genera, the sequence was 56% similar to FcaPV1 and 54.7% similar to FcaPV2. The partial sequence was deposited in GenBank under accession number OR137574. Specific PCR primers were used to determine whether dual infection with FcaPV2, FcaPV3, FcaPV4, or FcaPV7 was present within the mass (Munday *et al.* 2007, 2011b, 2023). While these primers amplified DNA from positive control samples, they did not amplify PV DNA from the presently described digit SCC.

## Diagnosis

The final diagnosis was a SCC with marked PV-induced cell changes and intense p16 immunostaining. The amplification of papillomaviral DNA suggested a possible viral aetiology.

To investigate possible metastatic spread, chest radiographs and aspirates of the prescapular lymph node were performed 2 weeks after the digit had been amputated. Neither revealed evidence of metastases. Additionally, there was no evidence of recurrence when the cat was re-examined 6 months after the mass had been surgically excised. No regional lymphadenopathy was present, and the cat appeared otherwise healthy.

## Discussion

The SCC in the present case contained DNA sequences from a putative novel PV type. While it is not possible to definitively classify a PV without the entire *ORF L1* sequence (Bernard *et al.* 2010), comparison of the partial sequence amplified from the SCC to other FcaPV types suggests the novel PV is most likely to be classified within the *Taupapillomavirus* genus.

As PV often asymptomatically infect skin (Antonsson and Hansson 2002; Thomson *et al.* 2015), detecting papillomaviral DNA within a lesion does not prove causality. In the present case, the marked PV-induced cell changes showed that the PV had infected the neoplastic cells and this infection had altered normal cell replication and differentiation. However, it cannot be determined that this altered cell regulation influenced neoplastic transformation and it remains possible that the PV infection was incidental to the development of the cancer in this case.

While infection by multiple PV types can be detected in some lesions (Munday *et al.* 2009), no other PV types were detected in the SCC by either consensus or specific PCR primers. This suggests that the PV-induced changes were due to the putative novel PV type. However, the possibility that an additional undetected PV type was also present in the SCC cannot be definitively excluded.

Immunostaining to detect p16 protein is used in human pathology to differentiate between oral SCC caused by PV infection and those caused by other factors (El-Naggar and Westra 2012). Increased immunostaining to detect p16 is indicative of a papillomaviral aetiology because the human high risk PV types consistently degrade retinoblastoma protein (pRb) which, in turn, increases cell p16 (Dyson *et al.* 1989; Parry *et al.* 1995). Similarly in cats, loss of pRb and increased p16 has been associated with the presence of papillomaviral DNA and RNA within skin SCC (Munday *et al.* 2011a; Munday and Aberdein 2012). In the present case, the increased p16 immunostaining provides evidence that the PV infection altered cell pathways known to be important in neoplasm development. Therefore, the p16 immunostaining supports a role of the putative novel PV type in the development of the SCC.

Papillomavirus-induced cell changes have been previously described in feline neoplasms associated with PV infection and each FcaPV type results in characteristic changes within the neoplastic cells (Munday and Thomson 2021). An unusual feature in the present SCC was the presence of cell changes in around 70% of the neoplastic cells. This contrasts with most previously described neoplasms in which cell changes were visible in less than 5% of neoplastic cells. Additionally, compared to the cytoplasmic bodies seen in association with infection by the other feline *Taupapillomavirus* types (Munday *et al.* 2017, 2018), the bodies in the SCC in the current case were larger, including some that surrounded the nucleus. While the unusual frequency and appearance of the cell changes visible in the digit SCC may be consistent with them being caused by the novel PV type, additional SCC that contain DNA from the putative novel PV type must be examined.

Neoplasia of the digits is uncommon in cats, with metastases from pulmonary adenocarcinoma comprising most of the neoplasms at this site (van der Linde-Sipman and van den Ingh 2000). Due to the predominance of digital masses in cats developing as metastases from a primary pulmonary adenocarcinoma, chest radiographs should be taken to exclude metastases prior to excising a digit mass from a cat. In the present case, radiographs were not performed prior

to amputation as the mass was suspected to be due to bacterial infection. Furthermore, a large single mass on the digit of a cat is less likely to represent metastatic disease than the presence of masses on multiple digits. In the present case, an underlying pulmonary carcinoma was later excluded by the absence of significant findings in a thoracic radiograph that was taken after the digit had been excised. Fungal infections can also result in digital masses and retaining unfixed tissue for possible fungal culture is also advised when assessing digital masses in cats. Although SCC of the nail bed epithelium have been reported in cats (van der Linde-Sipman and van den Ingh 2000), the retention of the claw of the affected digit makes this less likely.

The digit SCC contained numerous elongated spicules of bone that resulted in a lacy radiographic appearance. The new bone was arranged surrounding the neoplastic cells, consistent with the neoplastic cells producing an osteoinductive protein. Osseus metaplasia is frequently seen in some adenocarcinomas, for example canine mammary gland adenocarcinoma (Saad *et al.* 2017). It has also been previously reported in a subset of feline oral SCC (Martin *et al.* 2011). However, to the authors' knowledge, osseous metaplasia has not previously been reported in a feline cutaneous SCC. This feature of the SCC is worth noting because the unusual radiographic appearance could be misinterpreted. Whether or not the osseous metaplasia was due to the presence of the PV cannot be determined.

Squamous cell carcinomas are typically highly invasive neoplasms. Therefore, the absence of numerous nests of neoplastic cells infiltrating tissues away from the main neoplasm mass was unexpected. In both humans and cats, SCC caused by PV infection have a less aggressive clinical behaviour than SCC caused by other factors (Munday *et al.* 2013; Karpathiou *et al.* 2016). Therefore, if the SCC were caused by the putative novel PV, this could explain the lack of the expected high degree of invasiveness and the apparent surgical cure that was achieved in this case. Feline cutaneous SCC have been reported to infrequently develop metastases (Lino *et al.* 2019) and no evidence of metastases was detected in the present case.

The papillomaviral DNA sequence amplified from the digit SCC has not been previously reported. This could suggest that cats are only rarely infected by the putative novel PV type. However, previous studies show most FcaPV infections are asymptomatic (Thomson *et al.* 2015). Therefore, it remains possible that infection by the novel PV type is common, but this PV type is a rare cause of disease in cats. Although the pathogenesis of papillomaviral disease in cats is poorly understood, host factors are considered likely to be important in the development of disease (Munday *et al.* 2022b). The cat in the current case was infected by FIV, and it is possible that this infection could have disrupted host defences and therefore allowed the PV to cause clinical disease. However, whether FIV causes clinically relevant immunosuppression in cats in New Zealand is uncertain (Westman *et al.* 2022) and FIV infection was not associated with increased PV infection in a study of New Zealand cats (Munday and Witham 2010). Furthermore, the present cat has not showed any evidence of immunosuppression after excision of the digit. Therefore, the role of FIV, if any, in the PV infection is uncertain.

In conclusion, this is the first report of a novel putative PV type. This PV was amplified from a SCC that showed unusual clinical and histological features including unique PV-induced cell changes and osseus metaplasia. While it cannot be determined that the PV caused the cancer, the cell changes and intense p16 immunostaining is consistent with the PV disrupting normal cell regulation.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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