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Veterinary Dermatology

CASE REPORT

First report of a papillomavirus-induced viral plaque in the mouth of a dog

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Abstract

Canis familiaris papillomavirus type 16 was amplified from a mass in the mouth of a dog. The mass was histologically consistent with a pigmented viral plaque. This is the first report of an oral viral plaque in a dog. Histological investigation is essential to allow differentiation from an oral melanoma.

KEYWORDS
dog, oral, papillomaviruses, pigmented plaque, viral oncogenesis, viral plaque

INTRODUCTION

Viral plaques (also referred to as pigmented plaques) are uncommon skin lesions of dogs that are caused by a number of closely related Canis familiaris papillomavirus (CPV) types.[1] Plaques are thought to develop owing to an underlying inability to prevent viral replication, and the disease in dogs has some similarities to the human condition epidermodysplasia verruciformis.[2] A role of the immune system is supported by rare reports of plaques developing secondary to immunosuppressive treatment.[3,4] Additionally, some dog breeds, especially pugs and Vizslas, are predisposed.[2,5,6]

Cutaneous viral plaques typically appear as multiple, dark brown or black, 1–10 mm diameter, slightly raised lesions. They are most common on the ventrum and medial aspects of the limbs, although they also can develop around the head, with plaques confined to the pinna reported in one dog.[4,6] Most cutaneous plaques remain small and are only of cosmetic concern, yet rarely can progress to become large exophytic lesions that are present over a large proportion of the body and cause significant pain and pruritus.[7] Additionally, progression to squamous cell carcinoma (SCC) has been reported, especially in plaques that contain CPV16.[1] There are numerous reports of cutaneous viral plaques in dogs, yet none have previously been reported within the oral cavity.

CASE REPORT

A 7-year-old spayed female French bulldog was presented owing to oral pain. The dog was anaesthetised, and oral examination revealed abscessation of multiple right maxillary molars and of the right mandibular canine tooth. Additionally, a 2-mm-diameter black mass that was raised approximately 1 mm was observed on the alveolar mucosa close to the left mandibular canine tooth (Figure 1). Although this lesion was not thought to be the cause of oral pain in the dog, an excisional biopsy was obtained. The mass was fixed in formalin and submitted for histological evaluation. The dog had a history of allergic skin disease, which was being treated with 0.5 mg/kg oclacitinib (Apoquel; Zoetis) per os every 12 h. No information was available as to why the dog was being maintained using twice daily treatment rather than the recommended once daily treatment with this medication. The dog did not have any visible skin disease at the time of oral examination and biopsy.

Histological results revealed a 2-mm-diameter mass with features consistent with those described for viral plaques on the skin.[6] These features included a well-demarcated focus of epithelial hyperplasia (Figure 2) with broad trabeculae of cells that extended into the underlying connective tissue. Basilar epithelial cells appeared crowded and were darkly stained. As has been described in cutaneous viral plaques, the oral lesion

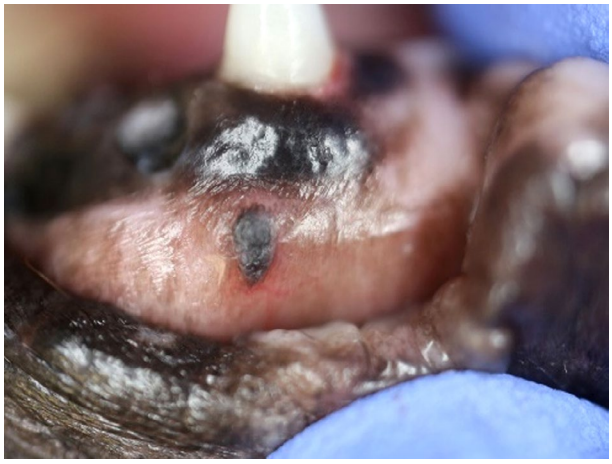

FIGURE 1 Oral viral plaque, intraoral view. The mass is dark brown and only slightly raised above the surrounding oral mucosa.

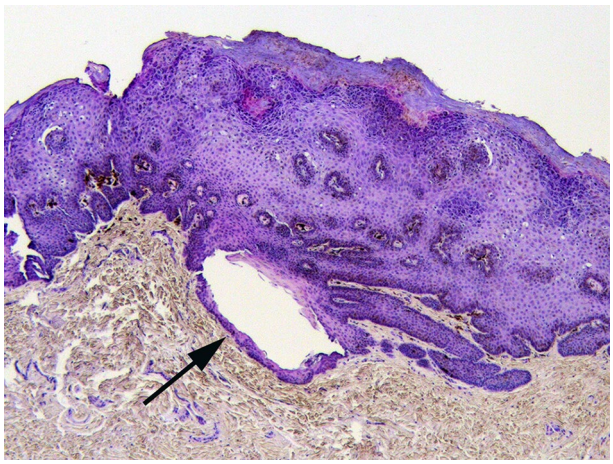

FIGURE 2 Oral viral plaque, photomicrograph (50×). The plaque appears as a focal area of epithelial thickening. The epithelium has become folded resulting in loss of normal organisation and a cyst containing keratin is visible close to the base of the lesion (arrow). Even at low magnification the increased melanin, the darkly basophilic basilar cells and the overlying lightly basophilic keratin are visible. Haematoxylin & eosin.

contained papillomavirus (PV)-associated changes including koilocytosis (Figure 3) and clumped keratohyalin granules. Consistent with the dark brown colour observed clinically, epithelial cells throughout the lesion contained increased quantities of dark brown pigment (interpreted as melanin) and macrophages containing large quantities of melanin were visible within the underlying submucosa.

Total DNA was extracted from a sample of the formalin-fixed paraffin-embedded tissue block using a NucleoSpin DNA FFPE XS kit (Macherey-Nagel GmbH) according to the manufacturer's instructions. The CP4/5 consensus PCR primers were used as described previously.[7] Briefly, the PCR mixture contained 0.25 μM of each primer, 1× Hot FirePol Mastermix (SolisBiodyne) and 2 μL of template in a final volume of 20 μL. This was then amplified by 98°C for 10 mins, 45 cycles of 94°C for 1.5 min, 50°C for 1.5 min and 72°C for 1.5 min, with a final extension of 72°C for 5 min. No template DNA was added to the negative control. Amplified PV DNA was purified by incubating the agarose gel in elution

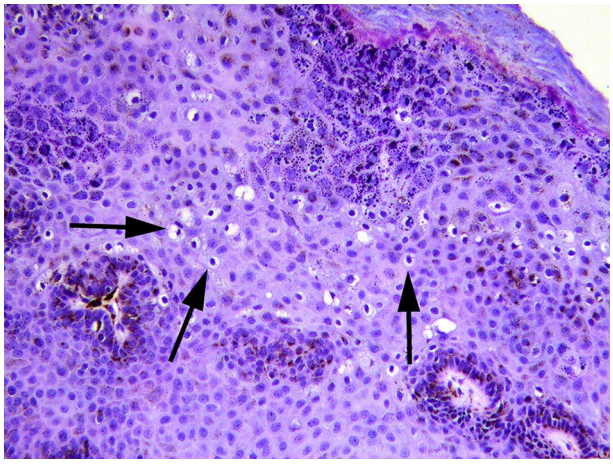

FIGURE 3 Oral viral plaque, photomicrograph (200×). Cells within the more superficial layers of the epithelium have increased quantities of clear cytoplasm and dark shrunken nuclei, suggestive of koilocytosis (arrows). Cells within the plaques also contain prominent darkly basophilic clumped keratohyalin granules and an amphophilic zone underlying the increased surface keratin is prominent. Both of these features also are often visible within viral plaques that develop on haired skin. Haematoxylin & eosin.

buffer overnight at 4°C and directly sequenced using an ABI3730 Genetic Analyser (Applied Biosystems Inc.). The DNA sequences amplified by the consensus primers were compared to other sequences using the BLAST tool in the GenBank database (https://blast.ncbi.nlm.nih.gov/blast.cgi). This revealed that the sequence was identical to a section of *ORF E1* from CPV16 (GenBank NC026640). Although immunohistochemical investigation was considered, this was not done in this case owing to the lack of available anti-PV antibodies that are known to cross-react with CPV16. Additionally, the virally induced cell changes in the lesion provided strong evidence of the presence of PV within the lesions without the use of this additional technique.

At the time of writing, no additional oral or skin lesions had developed in the 9 months since the viral plaque was removed.

DISCUSSION

The oral lesion was considered to be most consistent with a viral plaque. Although an unusual oral papilloma was considered, the lesion was classified as a viral plaque owing to the moderate epithelial hyperplasia resulting in a sessile flattened lesion, rather than the marked epithelial hyperplasia that results in the exophytic wart-like appearance of a papilloma. Additionally, increased quantities of pigment, prominent keratohyalin clumping and basophilic granular orthokeratosis are all features that are described in cutaneous viral plaques and not described in oral papillomas.[6,8] Although cells with PV-induced changes are visible in most oral papillomas,[9] these changes also are present in around 40% of canine cutaneous viral plaques, and thus, their presence cannot be used to differentiate a viral papilloma from a viral plaque.[8]

DNA sequences from CPV16 were amplified from the lesion. As CPV16 is one of several closely related

Chipapillomavirus types that have been detected within cutaneous viral plaques in dogs, this provides further support for a diagnosis of oral viral plaque in this case. However, as PVs are commonly asymptomatically present,[10] detecting PV DNA within a lesion does not prove that the lesion was caused by the PV. Evidence suggesting that the oral lesion was caused by PV infection included the prominent keratohyalin clumping, and cells that have expanded clear cytoplasm and shrunken dark nuclei—features often present in PV-induced lesions.

No Chipapillomavirus type has been detected previously within the mouth of dogs. In humans, PVs tend to be strictly cutaneous or strictly mucosal. However, CPV1 causes both oral and cutaneous papillomas,[9] and the tissue tropism of other CPV types is unknown. In the present case, the detection of CPV16 DNA within the oral cavity confirms that this PV type, like CPV1, can infect epidermis as well as mucosal epithelium. Whether other Chipapillomavirus PV types can likewise infect the oral mucosa is unknown.

Most canine viral plaques remain small and only of cosmetic concern. Progression of a canine cutaneous viral plaque to SCC is generally considered a rare event, although such progression was reported in almost 10% of cases in a study of viral plaques that had been submitted for histological diagnosis.[6] Many of the initial reports of progression to SCC described plaques associated with CPV16, and it appears that plaques that contain this PV type may be more likely to progress to invasive neoplasia.[11,12] Although the present oral viral plaque contained amplifiable CPV16 DNA, there was no evidence of progression to SCC within the sample, and surgical excision appeared curative in this case. Previous studies have not detected evidence of a PV aetiology in canine oral SCCs,[1] and it appears unlikely that these common neoplasms frequently develop as a result of progression from an undetected oral viral plaque.

The oral viral plaque was darkly pigmented. Dogs frequently develop oral melanomas, and differentiation between an early oral melanoma and a viral plaque could be difficult on clinical examination. Conclusive differentiation using cytological evaluation also may be difficult considering the superficial nature of the viral plaque. Therefore, considering the aggressive behaviour of canine oral melanomas, excisional biopsy may be an appropriate treatment for pigmented oral masses in dogs.

Breed and immunosuppression are considered potential risk factors for canine viral plaques. Although two French bulldogs were included in a study of 55 dogs with viral plaques, this breed is not recognised to be one that is predisposed to plaque development.[6] The presently described dog was not known to have any immunosuppressive disease, yet she was being treated with oclacitinib at a higher than recommended dose. One of the authors (JSM) has seen a small number of cases of unusually extensive oral or cutaneous viral papillomas (warts) in dogs treated with oclacitinib, raising the possibility that oclacitinib could impair the immune response against PV infection. Considering the high number of dogs receiving this medication, any association could be coincidental and additional research is required. Why the present dog developed a plaque within the mouth and not on the skin remains unknown, yet potentially the concurrent dental disease could have altered the local mucosal immune defences allowing increased PV replication and the development of the visible plaque.

In conclusion, this is the first detection of a Chipapillomavirus type in the oral cavity of a dog. Furthermore, this is the first report that a viral plaque has been detected in the mouth of a dog. Excision appeared curative in this case, yet canine cutaneous viral plaques have been reported to progress to SCC in dogs, with transformation potentially more likely in lesions associated with CPV16. Histological evaluation is most likely necessary to differentiate between an oral viral plaque and an oral melanoma.

AUTHOR CONTRIBUTIONS

John S. Munday: Conceptualization; investigation; writing – original draft; methodology. **Paul Hobson:** Investigation; writing – review and editing. **Cynthia M. Bell:** Investigation; writing – review and editing; methodology.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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摘要
犬乳头瘤病毒16型从犬口腔肿块中扩增。肿块组织学上与色素性病毒斑块相符。这是首例犬口腔病毒斑块的报道。组织学检查对于与口腔黑素瘤鉴别至关重要。

Résumé
Le papillomavirus de type 16 de *Canis familiaris* a été amplifié à partir d'une masse dans la bouche d'un chien. La masse correspondait histologiquement à une plaque virale pigmentée. Il s'agit du premier rapport d'une plaque virale buccale chez un chien. L'examen histologique est essentiel pour permettre la différenciation d'un mélanome buccal.

Zusammenfassung
Es wurde ein Canis familiaris Papillomavirus Typ 16 aus der Masse im Maul eines Hundes amplifiziert. Die Masse war histologisch mit einer pigmentierten viralen Plaques vereinbar. Es handelt sich hierbei um den ersten Bericht einer viralen Plaques bei einem Hund. Eine histologische Untersuchung ist essenziell, um die Differenzierung von einem oralen Melanom zu ermöglichen.

要約
イヌの口腔内腫瘤からCanis familiaris papillomavirus type 16が**増**幅された。腫瘤は組織学的にウイルス性色素性プラークと一致した。これはイヌの口腔内ウイルス性プラークに**関**する最初の報告である。口腔**黒**色腫との鑑別には組織学的**検査**が不可欠であった。

Resumo
O papilomavírus tipo 16 de *Canis familiaris* foi amplificado a partir de uma massa na boca de um cão. A massa era histologicamente consistente com uma placa viral pigmentada. Este é o primeiro relato de uma placa viral oral em um cão. A investigação histológica é essencial para permitir a diferenciação de um melanoma oral.

RESUMEN
El virus del papiloma canino tipo 16 se amplificó a partir de una masa en la boca de un perro. La masa fue histológicamente compatible con una placa viral pigmentada. Este es el primer informe de una placa viral oral en un perro. El estudio histológico es esencial para permitir la diferenciación de un melanoma oral.