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Review

Papillomaviruses in dogs and cats

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ABSTRACT

Papillomaviruses (PVs) cause disease in both dogs and cats. In dogs, PVs are thought to cause oral papillomatosis, cutaneous papillomas and canine viral pigmented plaques, whereas PVs have been rarely associated with the development of oral and cutaneous squamous cell carcinomas in this species. In cats, PVs are currently thought to cause oral papillomas, feline viral plaques, Bowenoid in situ carcinomas and feline sarcoids. Furthermore, there is increasing evidence that PVs may also be a cause of cutaneous squamous cell carcinomas and basal cell carcinomas in cats. These diseases are discussed in this review. Additionally, there is a brief overview of PV biology, including how these viruses cause disease. Diagnostic techniques and possible methods to prevent PV infection are also discussed.

Introduction

Warts have been recorded in folk-lore for centuries in human beings. A viral cause of warts was confirmed in 1907 and the first human papillomavirus (PV) was fully sequenced in 1982 (Danos et al., 1982). The first evidence that PVs can cause cancer was reported from studies in rabbits in 1935 (Rous and Beard, 1935). This was followed in 1981 by the breakthrough demonstration that PVs cause the majority of human cervical cancers (zur Hausen et al., 1981). Subsequent research has expanded the range of human cancers that can be caused by PV infection and it is currently estimated that around 5% of all human cancers are due to PV infection (Parkin, 2006).

In dogs, transmissible warts were first noted in 1898, with a viral aetiology confirmed in 1959 (Nicholls and Stanley, 1999). By using light and electron microscopy, evidence of a PV aetiology was suggested in 1969 and the first canine PV was fully sequenced in 1994 (Delius et al., 1994). In contrast, since PVs only rarely cause papillomas in cats, the first evidence of PV-induced disease in this species was not reported until 1990 (Carney et al., 1990), with the first PV from domestic cats being fully sequenced in 2002 (Tachezy et al., 2002; Terai and Burk, 2002).

In the years since these initial studies of PVs, additional PV types have been identified and PVs have been associated with an expanded range of canine and feline diseases. In addition, it is now accepted that host factors play a significant role in determining whether or not a PV will cause clinically relevant disease. This review provides a general overview of the biology of PVs and the mechanisms by which they cause disease, followed by a detailed discussion of the diseases of dogs and cats that are currently associated with PV infection. The different methods that can be used to diagnose PV-induced disease will be outlined and, for each distinct disease, the clinical presentation, histopathology, prognosis and treatment are described. Lastly, will be a brief discussion of the possible ways that could be used to prevent diseases due to PVs in dogs and cats.

Papillomavirus biology

Papillomaviruses are small, non-enveloped, icosahedral viruses that infect the stratified squamous epithelium of many mammalian, as well as some avian and reptilian, species. Their circular double stranded DNA genome is around 8000 base pairs long and includes five or six early (E) and two late (L) open reading frames (ORF) (Munday and Pasavento, 2017). Papillomaviruses are classified using the *L1 ORF* sequence. Papillomaviruses within the same genus have greater than 60% *L1 ORF* similarity and typically demonstrate similar host, location and behavioural characteristics. Different papillomavirus types have less than 90% similarity in their *L1 ORF* (Bernard et al., 2010).

Currently, 18 *Canis familiaris* papillomavirus (CPV) types have been fully sequenced and classified as *Lambapapillomaviruses*, *Taupapillomaviruses* and *Chipapillomaviruses* (Delius et al., 1994; Tobler et al., 2006, 2008; Yuan et al., 2007, 2012; Lange et al., 2009a,

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Table 1
Summary of papillomaviruses that have been detected in dogs and cats, and their predominant associated lesions.

Species	Papillomavirus genus	Papillomavirus types	Predominant associated lesions
Dog	*Lambda*	CPV-1 and 6	Oral papillomas Cutaneous papillomas
	Tau	CPV-2, 7, 13, 17 and 19	Cutaneous papillomas Oral SCC
	Chi	CPV-3, 4, 5, 8, 9, 10, 11, 12, 14, 15 and 16	Viral pigmented plaques Cutaneous SCC
Cats	*Lambda*	FcaPV-1	Oral papillomas
	Dyotheta	FcaPV-2	Viral plaques/BISC Cutaneous SCC
	Unclassified	FcaPV-3 and 4	Viral plaques/BISC Basal cell carcinoma
	Delta	BPV-14	Feline sarcoids

CPV, canine (*Canis familiaris*) papillomavirus FcaPV, feline (*Felis catus*) papillomavirus; BPV, bovine papillomavirus; SCC, squamous cell carcinoma; BISC, Bowenoid in situ carcinoma.
It should be noted that not all papillomavirus types within a genus will cause all the associated lesions listed. For example, CPV-17 is the only canine *Taupapillomavirus* type associated with oral SCCs and only CPV-2 and CPV-7 have been associated with cutaneous papillomas.

2012a, b, 2013; Luff et al., 2012a, 2015; Zhou et al., 2014, 2015; Munday et al., 2016b; Tisza et al., 2016; Table 1). Four *Felis catus* (FcaPV) types have been fully sequenced, including one that has been classified as a *Lambdapapillomavirus* and one as a *Dyothetapapillomavirus*, while two PV types remain unclassified (Tachezy et al., 2002; Terai and Burk, 2002; Lange et al., 2009b; Munday et al., 2013a; Dunowska et al., 2014). However, short sequences of additional PV types have been amplified from dogs and cats, suggesting that new PV types are likely to be recognised from both species in the future. While bovine *Deltapapillomavirus* is an important exception, PVs are typically highly species specific (Sundberg et al., 2000).

Papillomaviruses are primarily spread by direct contact, although indirect spread is also possible due to their ability to survive in the environment (Roden et al., 1997). Once the PV comes into contact with a mucocutaneous epithelium, the presence of microabrasions allows infection of basal cells, resulting in the production of small numbers of circular PV DNA copies (episomes) within the cell (Schiller et al., 2010). These episomes are maintained in the basal cells as they replicate, providing a reservoir of infection. However, the viral life-cycle is only completed when an infected cell undergoes terminal differentiation (Doorbar, 2005). Keratinocyte differentiation results in the expression of PV E6 and E7 proteins that promote replication of the normally post-mitotic suprabasal cell and allow large-scale amplification of the viral genome (Doorbar et al., 2012). Expression of the PV capsid proteins (L1 and L2) and viral assembly occurs as the infected cell reaches the upper epithelium. Papillomavirus-laden mature keratinocytes are sloughed from the epithelial surface with the subsequent rupture of these cells, releasing infectious virions (Doorbar et al., 2012). Bovine *Deltapapillomavirus* is unique because this group of PVs can also infect mesenchymal cells, although these cells probably do not permit viral replication (Jelinek and Tachezy, 2005).

The clinical presentation of a PV infection is largely determined by the degree of cell proliferation induced by the PV. Most PV types only mildly increase cell proliferation and PV replication occurs slowly in the absence of any visible lesions (Doorbar et al., 2012). Alternatively, a minority of PV types markedly increase cell replication, resulting in rapid production of large numbers of viral particles. Such infections cause marked epithelial hyperplasia that is visible clinically as a papilloma (wart) (Munday, 2014a).

Since the majority of viral replication occurs in the external epithelial layers in the absence of cell lysis, PV infections often only illicit a weak host immune response (Doorbar, 2006). However, when an immune reaction occurs, the response can be subdivided into humoral and cell-mediated immunity. The production of circulating IgG antibodies blocks entry of the PV into the basal cells, preventing further infections by this PV type, although antibodies do not influence resolution of an established PV infection (Nicholls et al., 1999; Ghim et al., 2000). The development of a cell-mediated response results in the resolution of established infections (Egawa and Doorbar, 2017). Since there is significant intra-individual variation in the time taken by the body to mount a cell-mediated response, there is also variation in the time taken to resolve a clinically visible papilloma. As discussed later, resolution may also be delayed in immunosuppressed animals.

In most dogs and cats, infection with PVs is inapparent (Munday and Witham, 2010; Lange et al., 2011; Thomson et al., 2015). These infections usually do not result in clinically visible epithelial hyperplasia because the immune system is able to prevent the PV from markedly changing normal epithelial cell regulation (Egawa and Doorbar, 2017). However, if changes in the host allow greater PV protein expression, the resultant epithelial hyperplasia can produce a lesion. Currently, the host factors that determine whether or not PV infection will cause a visible hyperplastic lesion are poorly understood. However, immunosuppression appears to predispose to the development of some PV-induced lesions (Callan et al., 2005) and the increased frequency of pigmented plaques in certain breeds of dog (Narama et al., 2005; Luff et al., 2016) suggests that genetic factors may also influence whether a PV infection remains asymptomatic or results in clinical disease.

In human beings, the major significance of PVs is the ability of PVs in the high risk *Alphapapillomavirus* group to cause cervical, other anogenital and oral cancer (zur Hausen, 2009). An important process in PV-induced cancer is the accidental integration of the PV E6 and E7 genes into the host DNA, resulting in rapid, uncontrolled cell growth, inhibition of apoptosis, loss of telomerase and disruption of processes that ensure accurate assembly of replicated host DNA (Doorbar et al., 2012). These rapidly dividing, genetically unstable cells quickly accumulate additional mutations, resulting in malignant progression (Pett et al., 2004).

Whilst there is accumulating evidence that PVs may cause cancer in dogs and cats (Munday and Kiupel, 2010; Munday et al., 2011d; Munday, 2014b; Altamura et al., 2016b; Luff et al., 2016; Thomson et al., 2016), the precise functions of the canine and feline PV E6 and E7 proteins have not been fully determined. Furthermore, some neoplasms have been shown to contain productive infections, suggesting that the PV DNA may not be integrated in the host DNA (Munday et al., 2015d; Thomson et al., 2016). Therefore,

additional research is required to define the precise role that PVs have in the development of cancer in dogs and cats.

Diagnosis of papillomaviral disease

Oral and cutaneous warts are the most frequent manifestation of PV disease in dogs and the majority of these cases can be diagnosed clinically. Whilst feline oral papillomas likewise have a typical clinical presentation, they may not be recognised due to their rarity. Due to variation in the clinical presentation of the remainder of the PV-induced lesions, histopathology is recommended to allow definitive diagnosis.

Since PVs complete their life cycle by promoting proliferation of epithelial cells, histology of a PV-induced lesion will reveal thickening of the epithelium. If the PV induces marked proliferation of epithelial cells, this can cause folding of the thickened epithelium and a papilloma (Fig. 1). Papillomaviruses that only mildly promote epithelial replication contain more moderate epidermal thickening that typically appears as a raised plaque. The presence of viral replication within a lesion may be visible histologically as PV-induced cell changes that could include enlarged cells with a shrunken nucleus surrounded by a clear cytoplasmic halo (koilocytes), cells with increased quantities of grey or blue fibrillary cytoplasm, cells with intracytoplasmic inclusions or cells with enlarged vesicular nuclei (Fig. 2). Intranuclear inclusions can be visible, although these can be transient and difficult to differentiate from nucleoli. Clumping of keratohyalin granules in the granular cell layer is also often present within PV-induced lesions.

Generally, lesions with more marked epithelial proliferation, such as papillomas, support greater viral replication and are more likely to contain PV-induced cell changes. In contrast, lesions with more modest epithelial proliferation (such as a viral plaque) contain less viral replication and only variably contain PV-induced cell changes. The presence of PV-induced cell changes within a lesion does not necessarily prove that the lesion was caused by PV infection. However, PV-induced changes do confirm that the lesion contains viral replication and therefore suggest that the normal behaviour of cells has been influenced by the PV. The histological features of each PV-induced disease are described in more detail below.

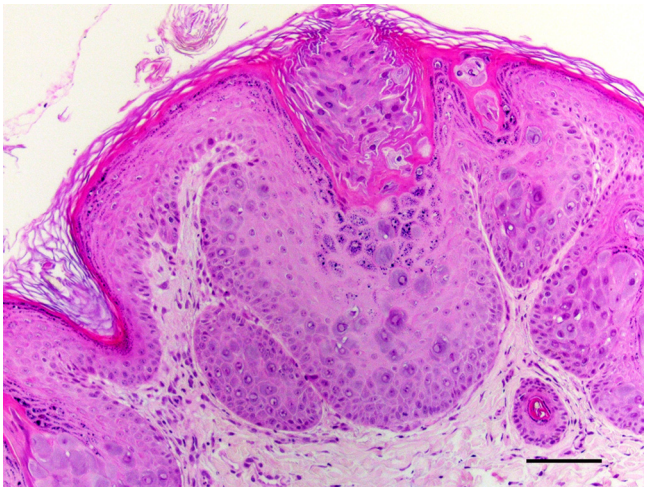

Fig. 1. Inverted papilloma from a dog. Since papillomaviruses promote their replication by increasing proliferation of epithelial cells, some papillomaviral infections can result in marked epithelial hyperplasia. If this hyperplasia causes folding of the epidermis, an exophytic or endophytic papilloma can develop. Scale bar = 100 μm. Haematoxylin and eosin.

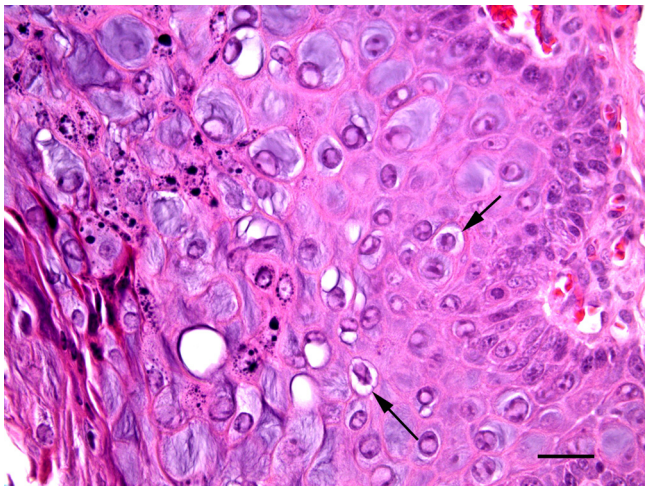

Fig. 2. Inverted papilloma from dog. Papillomaviral replication in a lesion can be detected histologically by the presence of papillomavirus-induced cell changes. Visible in this papilloma are numerous enlarged keratinocytes that contain increased quantities of blue fibrillary material. Additionally, rare cells with shrunken nuclei surrounded by a clear cytoplasmic halo (koilocytes) are visible (arrows). Scale bar = 20 μm. Haematoxylin and eosin.

Immunohistochemistry to detect L1 protein production can be used to investigate a PV aetiology of a lesion. However, since the L1 protein is only produced late in the PV life cycle, immunostaining is restricted to lesions that contain active viral replication (Longworth and Laimins, 2004). In addition, since specific antibodies against canine and feline PVs are not available, some PV types may not be detectable. In human beings, immunohistochemistry to detect $p16^{CDKN2A}$ protein (p16) is used as a marker for a PV aetiology in some lesions (Smeets et al., 2007). This protein is increased because most PVs promote cell replication by degrading retinoblastoma protein (pRb), a change which subsequently increases p16 (Parry et al., 1995). Unlike PV immunostaining, p16 immunostaining therefore detects an effect of PV infection rather than the presence of PV L1 protein in the lesion. Additionally, p16 immunostaining will be increased even if no viral replication is present. Furthermore, human anti-p16 antibodies have been validated for use in dogs and cats. Whilst p16 immunostaining has been associated with PV infection in both dogs and cats, and FcaPV-2 has been shown to degrade pRb (Munday et al., 2011a, 2015d; Munday and Aberdein, 2012; Altamura et al., 2016b), it is currently uncertain whether all canine and feline PVs degrade pRb. Additionally, since other causes of pRb dysfunction have been shown to increase cell p16 in human cancers, it is possible that increased cell p16 can be present in some non-PV-induced lesions in dogs and cats.

Using PCR, it is possible to detect very small quantities of PV DNA within a lesion, even in the absence of PV replication. The use of consensus primers even allows the amplification of DNA from PV types that have not previously been reported. In addition to conventional PCR, reverse transcriptase PCR can be used to detect PV gene expression. Detecting PV RNA suggests that the PVs are producing proteins and therefore are able to influence cell growth and differentiation. In situ hybridisation techniques can also be used to localise either PV DNA or RNA within a lesion. Whilst molecular techniques are useful to detect PV DNA within a sample, PVs are a common commensal of the skin and oral cavity of dogs and cats, so detection of PV DNA within a lesion does not prove causality. Therefore, PCR-based molecular techniques are better suited for research rather than for routine diagnostic testing.

Papillomaviral diseases of dogs

Oral papillomatosis

Oral papillomas caused by CPV-1 (formerly referred to as canine oral PV) are common in young dogs (Lange and Favrot, 2011). The epidemiology of infection by CPV-1 is poorly understood. There are anecdotal reports of outbreaks of canine oral papillomatosis, suggesting that the disease can be acquired through contact with affected dogs. However, since dogs are commonly infected inapparently by CPV-1, avoiding dogs with papillomas may not be sufficient to prevent disease (Lange et al., 2011). The development of oral papillomatosis results in the development of antibodies that prevent new infections by CPV-1. However, it is probable that some dogs remain inapparently infected by CPV-1 following resolution of the initial papillomas (Doorbar et al., 2012). Reports of papillomatosis in older immunosuppressed dogs are consistent with reactivation of inapparent infection (Sundberg et al., 1994; Radowicz and Power, 2005). Oral papillomatosis presents as multiple exophytic vegetative warts involving the lips and oral cavity (Lange and Favrot, 2011; Fig. 3). Most dogs do not show any systemic signs of disease, although there are rare reports of extensive disease that interferes with eating or respiration (Nicholls et al., 1999). Histopathology reveals an exophytic mass comprised of thickened folded epithelium, often with numerous PV-induced cell changes.

The overwhelming majority of canine oral papillomas spontaneously regress and surgical excision is rarely necessary. Regression is due to the development of a cell-mediated immune response. In experimentally induced papillomas, resolution typically occurs within 8 weeks. However, resolution of natural papillomas appears to be more variable, with resolution taking up to 12 months in some dogs (Sancak et al., 2015).

Numerous treatments to hasten the resolution of oral papillomas have been proposed, but most have not been assessed in appropriate studies. However, in a prospective, randomised, double-blinded placebo-controlled study of 17 dogs with papillomas, lesion regression was observed within 50 days in all 10 dogs that were treated with azithromycin, but only 1/7 untreated dogs (Yagci et al., 2008). Stimulating antibody production is not expected to influence lesion regression and papilloma regression was not observed in a dog that received both viral capsid and autologous vaccines, despite the dog developing raised antibody titres (Nicholls et al., 1999).

There are rare reports both of persistent and of repeatedly recurrent oral papillomas; these are thought to develop due to an ineffective cell-mediated immune response against PV-infected cells (Nicholls et al., 1999). Most dogs do not have any other detectable signs of immunosuppression, suggesting an immune deficiency that is specific to PVs. These dogs can develop extensive papillomatosis and may be predisposed to oral squamous cell carcinoma (SCC) (Regalado, 2016). It is suggested that a guarded prognosis should be given to dogs that have papillomas for longer than 18 months.

Cutaneous papillomas

Canine cutaneous papillomas have been associated with CPV-1, 2, 6 and 7 (Sundberg et al., 1994; Yuan et al., 2007; Lange et al., 2009a). Most develop in young dogs, presumably at the time of first infection by the causative PV. Cutaneous papillomas can be single or multiple. They can occur anywhere on the body, but are most common on the face, ears and extremities (Gross et al., 2005; Fig. 4). Both the presence of a skin abrasion and exposure to the relevant PV type currently appear to be important for papilloma development (Debey et al., 2001; Munday et al., 2010a).

Histologically, papillomas can be subdivided into exophytic papillomas, in which the folded epidermis protrudes above the surface of the skin, and inverted papillomas, in which the folded epithelium is contained within a depressed cup-shaped structure (Campbell et al., 1988; Munday and Pasavento, 2017). Papillomavirus-induced cell changes are typically frequent in both subtypes. Spontaneous resolution is expected, although persistent papillomas have been observed rarely and progression of CPV-2-induced inverted papillomas to SCCs was reported in multiple dogs in a research colony of immunocompromised dogs (Goldschmidt et al., 2006).

Cutaneous viral pigmented plaques

Canine pigmented plaques are associated with a number of closely related *Chipapillomavirus* types (Tobler et al., 2006, 2008; Lange et al., 2009a, 2012b; Luff et al., 2012a, b, 2015; Yuan et al., 2012; Zhou et al., 2014). It is likely that dogs are often asymptomatically infected by these PV types, but only develop

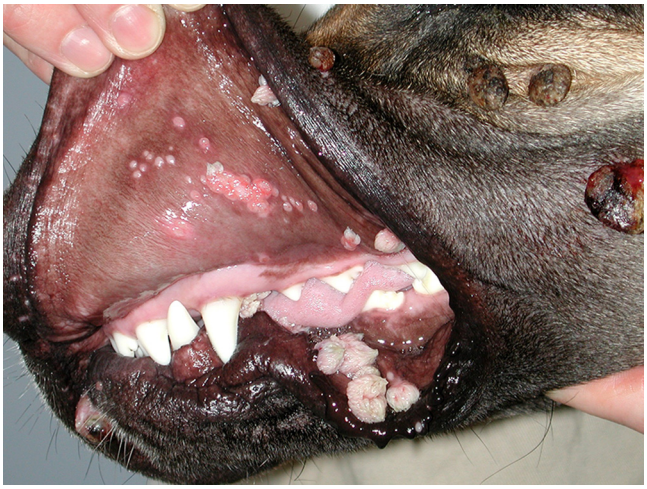

Fig. 3. Oral papillomatosis in a dog. This disease is characterised by the presence of numerous exophytic vegetative growths involving the lips and mouth. This dog also has cutaneous papillomas involving the skin surrounding the mouth (photograph courtesy of Dr Stephen White, University of California Davis, California, USA).

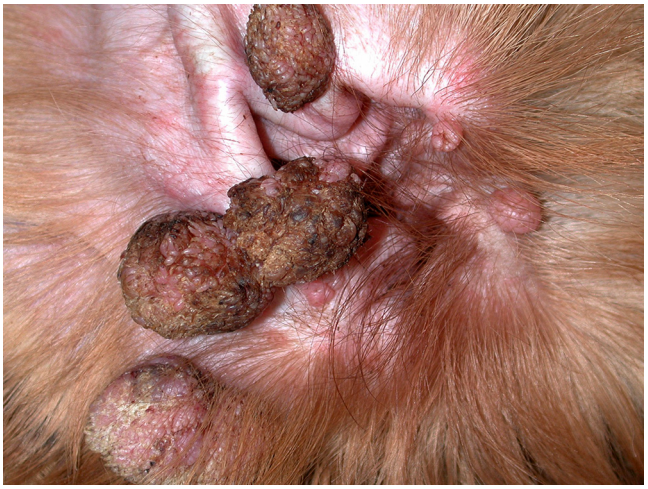

Fig. 4. Cutaneous papillomas on a dog. Papillomas frequently develop around the ears, possibly secondary to self-trauma caused by scratching in this area (photograph courtesy of Dr Stephen White, University of California Davis, California, USA).

plaques when host factors allow increased PV replication. The role of the host in disease development is illustrated by the predisposition to plaques observed in dogs receiving immunosuppressive therapy and in pug dogs (Narama et al., 2005). However, since pigmented plaques also occur in dogs of other breeds without any identifiable immunosuppressive disease, the precise host factors that allow plaque formation are unknown.

Plaques are typically dark, multiple, and 1–10 mm in diameter. They are most common on the ventrum and medial aspects of the limbs (Gross et al., 2005; Munday et al., 2011d; Fig. 5). Histopathology reveals moderate epidermal acanthosis, hyperkeratosis, a typical scalloped appearance of the skin surface, and prominent epidermal and dermal melanin pigmentation. Pigmented plaques can contain viral replication (Lange et al., 2013) and PV-induced cell changes and PV immunostaining are variably present.

Pigmented plaques can spontaneously regress, persist or progress to involve extensive areas of the skin. Generally, pigmented plaques are considered to be cosmetically undesirable, but do not have a negative impact on health. However, pigmented plaques rarely have been reported to undergo malignant transformation to an invasive SCC (Munday et al., 2011d; Luff et al., 2015, 2016). Although malignant transformation has only been reported in plaques that were associated with CPV-9, 12 and 16, the small number of published cases suggests that malignant potential cannot be excluded for plaques caused by other PV types.

Dogs with pigmented plaques should be assessed to exclude any underlying immunosuppressive disease. Whilst treatment is often not required, surgical excision of small numbers of plaques is possible. A dog with numerous viral plaques was reported to be successfully treated using laser therapy (Knight et al., 2016). Plaques should be observed carefully for any evidence of malignant transformation.

Squamous cell carcinomas

Whilst PV DNA has been detected in canine cutaneous SCCs (Zaugg et al., 2005), currently there is no evidence that PVs are a frequent cause of these cancers (Waropastrakul et al., 2012; Munday et al., 2013c; Sabattini et al., 2016). CPV-17 was detected in multiple oral papillomas that progressed to SCCs in a dog (Munday et al., 2016b). However, most canine oral SCCs do not contain detectable PV DNA suggesting that the majority are not caused by PV infection (Porcellato et al., 2014; Munday et al., 2015b).

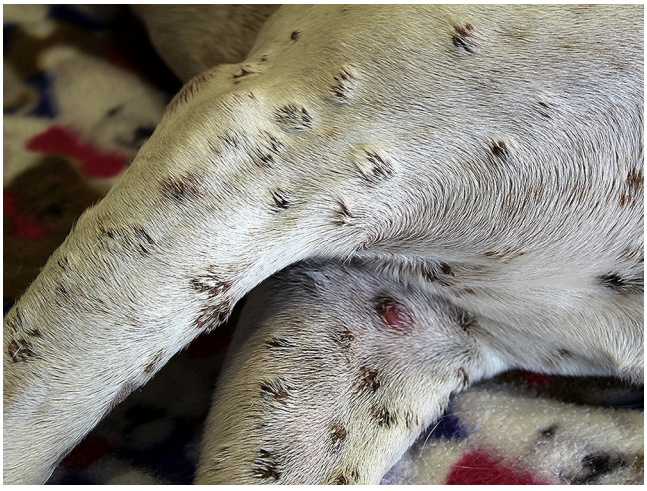

Fig. 5. Pigmented plaques on a dog. Numerous plaques are visible on the ventrum and legs of this dog. The plaques are dark and are covered by keratin scale (photograph courtesy of Dr Mark Turnwald, Belmont Veterinary Clinic, North Shore City, New Zealand).

Papillomaviral diseases of cats

Oral papillomas

Feline oral papillomas are caused by FcaPV-1 (Munday et al., 2015a). Whilst oral papillomas have been reported rarely in cats, the true incidence is unknown, since the majority of these lesions probably spontaneously resolve without causing clinical signs of disease. Papillomas present as a cluster of small exophytic masses on the ventral surface of the tongue (Sundberg et al., 2000). Histologically, they are typical exophytic papillomas that contain prominent PV-induced cell changes, including characteristic eosinophilic intracytoplasmic inclusions. Although feline oral SCCs can also develop on the ventral surface of the tongue, there is no evidence that oral papillomas progress to SCCs in cats (Munday and French, 2015).

Viral plaques and bowenoid in situ carcinomas

Viral plaques and Bowenoid in situ carcinomas (BISCs) are most often caused by FcaPV-2 (Munday et al., 2007; Lange et al., 2009b Munday and Peters-Kennedy, 2010). Most cats are infected with this PV and infection is thought to occur shortly after birth due to shedding of the virus from the queen (Thomson et al., 2015). Since infection is common, but clinical disease is rare, it appears that host factors are important in disease development due to FcaPV-2. Whether immunosuppressed cats are predisposed is uncertain, since viral plaques and BISCs often develop in cats without any immunosuppressive disease. Currently, the changes in the host that allow disease development are poorly understood.

Feline viral plaques and BISCs traditionally have been classified as separate disease entities. However, since both are typically caused by FcaPV-2 and since transitional lesions between viral plaques and BISCs have reported (Wilhelm et al., 2006), they probably represent different severities of the same disease process. Lesions are often multiple and most frequently develop on the head and neck of cats. Viral plaques are typically mildly raised, hairless and less than 1 cm in diameter, whilst BISCs tend to be larger and can be ulcerated or covered by thick scaling (Wilhelm et al., 2006; Munday et al., 2016a; Figs. 6 and 7**)**. Both lesions are often pigmented.

Histological examination of a feline viral plaque reveals a well-demarcated focus of mild epidermal hyperplasia that often contains prominent PV-induced cell changes. Viral plaques rarely may contain foci of sebaceous gland hyperplasia (Munday et al., 2017c). In comparison, BISCs exhibit more marked epidermal hyperplasia, which often extends into follicular infundibula and can result in a nodular mass that bulges into the underlying dermis (Gross et al., 2005). Cellular atypia and crowding is present with groups of basal cells having nuclei that are dorsoventrally elongated, resulting in a 'windblown' appearance. Papillomavirus-induced cell changes may be visible; however, the changes become less common as dysplasia increases (Wilhelm et al., 2006).

Viral plaques and BISCs can spontaneously resolve, be present persistently without progressing or slowly increase in size and number. In addition, BISCs are pre-neoplastic and all BISCs should be carefully monitored for progression to a SCC. Bowenoid in situ carcinomas in Devon Rex and Sphinx cats appear to be predisposed to rapid progression and the resultant invasive SCCs also demonstrate high metastatic potential. High FcaPV-2 copy numbers and p16 protein immunostaining are detectable within the metastatic lesions, suggesting that the PV infection could have

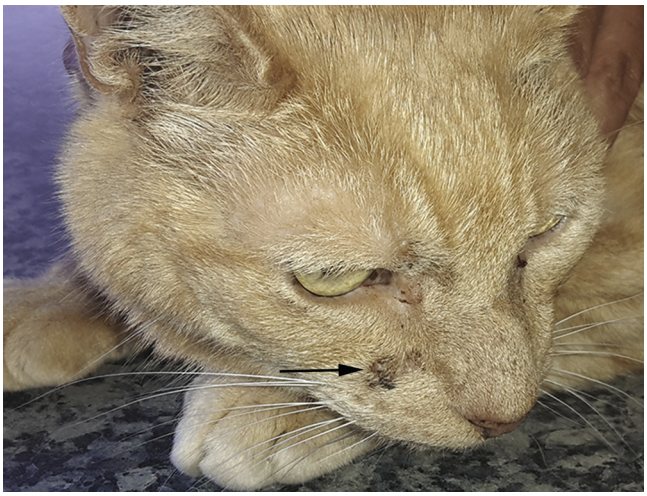

Fig. 6. Feline viral plaque. Plaques most frequently appear as single, focal, slightly raised lesions that often develop around the face of cats. Feline viral plaques and Bowenoid in situ carcinomas appear to be different severities of the same disease process, with viral plaques representing the more mild manifestation of the disease (photograph courtesy of Dr Sharon Marshall, Veterinary Associates, Hastings, New Zealand).

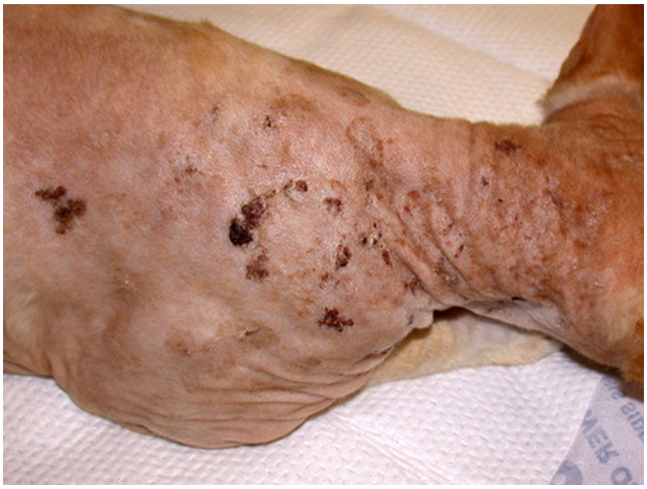

Fig. 7. Bowenoid in situ carcinoma on a cat. This Devon Rex cat developed multiple pigmented, raised, ulcerated lesions that were covered by a layer of keratin. Feline Bowenoid in situ carcinomas can develop anywhere on the cat, but are often are more frequent dorsally on the head and neck (photograph courtesy of Dr Linda Vogelnest, Small Animal Specialist Hospital, New South Wales, Australia).

contributed to malignant progression (Ravens et al., 2013; Munday et al., 2016a).

Surgical excision of a viral plaque or BISC is expected to be curative, although additional lesions may subsequently develop at different locations. In cases in which the large size and number of lesions make surgical excision impractical, imiquimod cream has been suggested as a topical therapy. Topical imiquimod may promote cell-mediated immunity by locally increasing α-interferon and tumour necrosis factor-α (Miller et al., 1999), and has been used to treat genital papillomas in humans. In an uncontrolled study of 12 cats with BISCs, imiquimod resulted in partial resolution of a lesion in all cats and complete remission of at least one BISC was observed in five cats (Gill et al., 2008). However, significant side effects were reported, including local erythema in five cats and systemic toxicity in two cats. Additional controlled studies are required to determine the efficacy and safety of this treatment for BISCs in cats.

Squamous cell carcinomas

Papillomaviruses were first associated with feline cutaneous SCCs in 2008, when FcaPV-2 DNA was amplified significantly more frequently from SCCs than from non-neoplastic skin samples (Munday et al., 2008). Subsequent evidence that FcaPV-2 may be causally associated with SCCs includes the presence of increased p16 and decreased pRb in SCCs that contain FcaPV-2 DNA, and evidence that SCCs that contain PV DNA have a different biological behaviour to those that do not contain PV DNA (Munday et al., 2011b, 2013b). Furthermore, FcaPV-2 RNA can be detected within a proportion of SCCs, and the transforming properties of the corresponding proteins have been demonstrated in cell culture, confirming that the virus has the potential to influence cell behaviour and to contribute to oncogenesis (Altamura et al., 2016a, b; Thomson et al., 2016).

An association with PV infection is observed most frequently in SCCs that develop in areas of the body protected from UV light, such as haired or pigmented skin (Munday et al., 2011b). However, PV DNA and p16 immunostaining are also detectable in a proportion of SCCs from sun-exposed skin, suggesting that PVs could also act as a co-factor with UV light (Munday and Kiupel, 2010; Altamura et al., 2016b). A PV aetiology may also be more likely for SCCs that have an exophytic component (Munday et al., 2017b). Whilst the precise role of the PV is currently uncertain, FcaPV-2 may influence the development of 33–45% of feline cutaneous SCCs (Munday et al., 2011b; Thomson et al., 2016).

Cutaneous SCCs do not have histological evidence of PV infection. They are typically highly infiltrative neoplasms that can be difficult to excise surgically and, whilst SCCs are generally slow to metastasise, they can cause significant disease due to the local effects of the neoplasm. While PV DNA is detectable in a small proportion of feline oral SCCs, there is no evidence that PVs are a significant cause of these neoplasms (Munday et al., 2009, 2011c; O'Neill et al., 2011; Munday and French, 2015; Altamura et al., 2016b).

Basal cell carcinomas

An association between cutaneous basal cell carcinomas (BCCs) and PVs was first proposed after BISC-like changes were observed in the epidermis overlying some BCCs (Gross et al., 2005). Subsequently, BCCs containing PV-induced cell changes and PV DNA have been reported, suggesting that some BCCs may be caused by infection by non-FcaPV-2 types (Munday et al., 2017a).

Feline sarcoid

Feline sarcoids are most likely to be caused by "dead end" cross-species infection by bovine papillomavirus (BPV)-14 (Munday et al., 2015c). Evidence of a role for this PV includes the consistent detection of the PV in feline sarcoids, but not any non-sarcoid feline sample (Munday et al., 2010b). BPV-14 is a *Deltapapillomavirus* that is closely related to the BPVs that cause equine sarcoids. Unsurprisingly, feline sarcoids are restricted to cats that have contact with cattle and affected cats are typically younger male cats that live on farms (Schulman et al., 2001).

Feline sarcoids most frequently develop on the nasal philtrum or lips, although they can develop anywhere on the body (Schulman et al., 2001; Teifke et al., 2003). Whilst the mechanism of transmission from cow to cat is currently unknown, the distribution of lesions suggests that biting flies or cat fight wounds may be important for infection with BPV-14. Feline sarcoids are typically non-ulcerated exophytic firm masses. Histopathology reveals proliferation of mesenchymal and epithelial cells, with

well-differentiated dermal fibroblast-like cells underlying a thickened epidermis, which has characteristic broad interlacing rete pegs. Papillomaviral DNA can be detected by in situ hybridisation within the mesenchymal cells (Teifke et al., 2003). However, since infection does not result in viral replication, neither PV-induced cytopathology or anti-PV immunostaining are evident. Sarcoids tend to be infiltrative and local recurrence is common after surgical excision. Treatment of a feline sarcoid with imiquimod did not appear to slow disease progression (Munday et al., 2015c).

Prevention of papillomaviral diseases

Papillomas in dogs are thought to develop when an uninfected dog is first infected by a specific PV type. The development of a papilloma coincides with the shedding of large numbers of infectious virions (Sancak et al., 2015). Therefore, preventing contact between an affected dog and a dog that has never had papillomas is advisable. However, since many dogs are inapparently infected by PVs and these viruses are resistant within the environment, infection may be possible even without contact with an affected dog (Roden et al., 1997; Debey et al., 2001).

Since host factors appear to be important in the development of pigmented plaques in dogs, and viral plaques and BISCs in cats, minimising immunosuppressive drugs and treating immunosuppressive diseases should reduce the likelihood of disease. However, other host factors also appear to influence disease development and PV-induced disease can occur in animals without any identifiable immunosuppressive disease.

In human beings, virus-like particle PV vaccines are used to prevent PV infection and subsequent PV-induced disease. Whilst such vaccines also prevent PV infection in veterinary species (Suzich et al., 1995), there are three important limitations to the use of vaccines to prevent PV-induced disease in dogs and cats. Firstly, each virus-like particle type can only protect against a single PV type. In humans, small numbers of high-risk HPV types cause most PV-induced cancers, so producing a vaccine against these types is feasible (Pitisuttithum et al., 2015). Similarly, in cats the majority of PV-induced diseases appear to be due to FcaPV-2. However, many different PV types cause disease in dogs suggesting that a canine PV vaccine would need numerous components. Secondly, for a PV vaccine to prevent infection, it has to be given prior to first exposure to the PV (Pitisuttithum et al., 2015). This is possible in human beings, since the high-risk HPVs are sexually transmitted. However, since FcaPV-2 appears to be acquired from the queen soon after birth (Thomson et al., 2015), it is possible that novel vaccination strategies may be required to protect cats against FcaPV-2 induced cancer. Thirdly, a vaccine has to be economically viable and it is uncertain whether a vaccine to prevent a common, but typically self-resolving disease, such as oral papillomatosis, or a rare, but life-threatening disease, such as feline BISCs, would be commercially viable.

Conclusions

Papillomaviruses are becoming increasingly recognised as a cause of oral and skin disease in dogs and cats. The vast majority of PV-induced papillomas are self-resolving. However, there is evidence that PVs also cause pre-neoplastic and neoplastic diseases in dogs and cats. Whilst further research is required to determine the epidemiology of infection and the pathogenesis of disease, the role of PVs in some disease may provide novel strategies for prevention or treatment.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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