I  INTRODUCTION

An ever increasing, ever more diverse array of papillomavirus infections are being discovered and described in domestic animals and it is clear that the situation in animals mirrors that of humans. Our domestic species are hosts to a great variety of papillomavirus types that can occur asymptomatically, cause clinically distinct papillomas and/or be associated with neoplastic transformation. This review will address recognized variants of papillomavirus-associated lesions limited to cats, dogs and horses.

II  PAPILLOMAVIRIDAE

The papillomaviridae are non-enveloped viruses that form icosahedral virions and have a circular double-stranded DNA genome, about 8 kb in size. The papillomaviruses are subclassified based upon the degree of shared nucleotide sequence identity into genus (<60%), species (61 to 70%), subtype (71 to 89%) and variants (90 to 99%). These viruses are thought to infect nearly all mammals as well as many birds and reptiles in primarily a species-specific manner. The papillomaviruses have very stable genomes with low mutation rates that appear to have undergone extensive co-evolution with host species. Because papillomaviruses are difficult to culture, our understanding of genomic structure has outpaced our understanding about the biology of these viruses and their host cell interactions.

In humans, over 150 unique papillomaviruses have been identified and still many more are expected based upon subtotal genomic amplicon sequencing. Human papillomaviruses (HPVs) are globally distributed and many are considered to be nearly ubiquitous. HPVs can be detected in newborns in the first days of life and infections persist for extended periods, for years and possibly for the life of individuals for some virus types. Multiple unique HPV viruses can be detected in one individual. Persistent or latent infections without clinical signs are the norm for the majority of papillomaviruses.
Papilloma lesions develop with some variation in morphology and anatomical location and can be promoted by immunosuppression. Importantly, cancer high-risk and low-risk types are recognized, where high-risk types are known to be associated with development of certain cancers, such as cervical cancer.

While the number of discovered papillomavirus types in animals has lagged behind that of humans, it has become clear that the situation in domestic animals is very similar to that of humans. Many domestic animals are now known to be host to multiple unique papillomaviruses, which can be found in a subclinical carrier state, cause different papilloma morphologies and/or affect different anatomic sites. Some papillomaviruses appear strongly associated with neoplastic transformation in animals and the concept of low-risk and high-risk cancer type papillomaviruses is applicable.

Papillomavirus infections are epidermal and/or mucosotropic and occur where micro-injury to predominately stratified squamous epithelium allows the virus access to a basement membrane receptor. After binding, a capsid conformational change allows for secondary receptor binding on basal keratinocytes and basal cell infection, which is the key for development of persistent infection. The virus is maintained in low copy number in basal cells in persistent infection. In certain circumstances, the virus is triggered to go through its life cycle, linked in sequence with keratinocyte differentiation in the epidermis; in which case, viral replication is amplified in suprabasal cells and virus particles are formed in superficial epithelial cells. During papilloma formation, papillomavirus gene expression alters cell differentiation by affecting proliferation, apoptosis, cell polarity, cytoskeleton and cell-cell communication, leading to the more common morphological changes of papilloma formation, including epithelial hyperplasia, dysplasia and koilocytosis. Virions and intranuclear viral inclusions form in the nucleus of superficial keratinocytes and the virus is shed from the body through cellular desquamation.

III  **FELINE PAPILLOMAVIRUS-ASSOCIATED LESIONS**

Evidence of at least three species of papillomaviruses has been described in cats that include Felis domesticus papillomavirus-1 and -2 (FdPV1 and FdPV2) as well as a novel feline sarcoid-associated papillomavirus (FeSarPV). A forth, novel papillomavirus is reported and the list will surely grow. A high percentage of cats are asymptomatic carriers of FdPV2 but not FeSarPV. FeSarPV is currently considered a cross species infection of a papillomavirus from a different host species; current evidence suggests a ruminant host similar to the situation with equine sarcoids caused by bovine papillomavirus-1 and -2. FeSarPV is most similar to bovine papillomavirus-1 and -2 as well as ovine papillomavirus-1.
i. **Feline Oral Papilloma**

*Cause:* Feline Papillomavirus, not further characterized

*Pathology:* Limited descriptions are available for this very rare entity but lesions in one study were described as small (4-8mm), multifocal plaque-like, slightly raised lesions that were light-pink, oval and located on the ventral surfaces of the tongue.

*Clinical features:* Exophytic, non-planar, papillomas occur very rarely and clinical data is lacking.

*Diagnosis:* This lesion is rare in cats and histopathology is recommended to confirm the diagnosis.

ii. **Feline Viral Plaque and Bowenoid In Situ Carcinoma**

*Cause:* Feline Papillomavirus-2 (FdPV2) (also FdPV1 and a novel PV)

*Pathology:* Feline viral plaques present as solitary or multifocal, very small, slightly elevated, flat epidermal lesions that are hyperpigmented, or non-pigmented, and slightly scalely. Lesions are typically less than 1 cm in diameter but can be larger. Lesions develop on nearly any location of the body. Neoplastic transformation occurs and a portion of cats develop in situ squamous cell carcinoma (Bowenoid in situ carcinoma, multifocal squamous cell carcinoma in situ), which may progress to invasive squamous cell carcinoma. Viral plaques, carcinoma in situ and invasive carcinoma may occur together in the same lesion and/or the same cat. Occasionally basal cell carcinoma develops.

*Clinical features:* Feline viral plaques are considered uncommon and because lesions are often small and in well haired areas, lesions can go unnoticed. Cats less than one year to 15 years of age are affected and older cats and immunosuppressed cats appear predisposed. Viral plaques are considered self-limiting in young cats. Lesion transformation to neoplasia occurs in older cats, usually greater than 10 years of age.

*Diagnosis:* Histopathology confirms the diagnosis and is needed to evaluate for neoplastic transformation.

iii. **Feline Sarcoid (Feline Cutaneous Fibropapilloma)**
**Cause:** A novel feline sarcoid–associated papillomavirus (FeSarPV)

**Pathology:** Cats develop a mesenchymal neoplasm/s most often on the extremities and head, including sites such as philtrum, nares, upper lip, ears, digits and tail. Lesions are rounded dermal to subdermal masses that are broad-based and often are raised due to their anatomic location. Ulceration can occur. Metastasis is not reported.

**Clinical features:** Young male cats from rural environments are more often affected.

**Diagnosis:** Histopathology is diagnostic. The pathologist should be alerted to the potential of this diagnosis because the lesions are uncommon.

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**IV CANINE PAPILLOMAVIRUS-ASSOCIATED LESIONS**

Multiple papillomaviruses have been identified in dogs, many only just recently, and are associated with a diverse array of clinical lesion types. Canine oral papillomavirus (COPV) and canine papillomavirus-2 (CPV2), -3 (CPV3), and -4 (CPV4), -5 (CPV5), -6 (CPV6), -7 (CPV7) are presented here, but still others are being described.

i. **Canine Oral Papilloma**

**Cause:** Canine Oral Papillomavirus/Canine Papillomavirus-1 (COPV/CPV1)

**Pathology:** Well-developed oral papillomas are exophytic, tan-white, papillated small masses with a sessile or narrow base, which are usually less than 1 cm. Oral lesions are typical and may be single or multiple and rarely occur as numerous papillomas in oral papillomatosis. Papillomas may occur concurrently or separately on the nasal planum, eyelids or lips. Immunosuppression has led to concurrent multiple oral and cutaneous papillomas. Transformation to invasive squamous cell carcinoma is considered to be very rare.

**Clinical features:** Lesions are common in young dogs less than 2 years of age, where they often spontaneously regress over weeks to months, but can occur at any age. Dogs that develop numerous papillomas concurrently should be evaluated for underlying evidence of immunosuppression. Invasive squamous cell carcinoma was associated with injection of live COPV vaccine in a very limited number of dogs, 9 of 4,500.
**Diagnosis:** Canine oral papillomas are clinically distinctive. Histopathology is diagnostic but often not needed. Regressing lesions are a diagnostic challenge.

ii. **Classical Cutaneous Exophytic Papillomas**

**Cause:** Canine Papillomavirus-1 (CPV1/COPV), Canine papillomavirus-2 (CPV2), Canine papillomavirus-7 (CPV7)

**Pathology:** Gross morphology of lesions is similar to that described for canine oral papillomas, except that lesions can be mildly or markedly hyperkeratotic, even rarely forming a cutaneous horn. Exophytic papillomas occur at nearly any location on the haired skin but are most common of the face, ears and distal limbs. Mucocutaneous junctions maybe involved and then canine oral papilloma is also possible. Footpads are not involved. Transformation to neoplasia is considered rare.

**Clinical features:** Clinical features are similar canine oral papillomas.

**Diagnosis:** Papillary skin lesions are distinctive except during mid to late regression. Histopathology is diagnostic but usually not needed.

iii. **Canine Pigmented Viral Plaque (Verruca Plana, Pigmented Epidermal Nevi)**

**Cause:** Canine papillomavirus-3 (CPV3) and canine papillomavirus-4 (CPV4), Canine papillomavirus-5 (CPV5), Canine papillomavirus-8 (CPV8)

**Pathology:** Pigmented viral plaques typically present as multiple, small (less than 3 cm but often less then 1 cm), slightly raised, mostly flat, darkly pigmented, well-demarcated lesions. Solitary lesions are possible. The surface is slightly scaly and rough surface. Lesions develop most often on the ventral abdomen, ventral thorax and medial proximal legs. Rarely lesions transform to in situ squamous cell carcinoma and subsequently progress to invasive squamous cell carcinoma and form a small to medium sized dermal mass.

**Clinical features:** Pigmented viral plaques are generally considered to be rare and to develop in young adults or older dogs, which may be immunosuppressed. There is a strong breed predisposition for Pugs and Miniature Schnauzers and to some extent Boston Terriers and French Bulldogs. Lesions develop slowly and are persistent and most
are considered to be incidental. Neoplastic transformation to squamous cell carcinoma does rarely occur.

**Diagnosis:** Histopathology is recommended, particularly if mass lesions develop from pre-existing plaque, which can occur in neoplastic transformation.

iv. **Canine Inverted Papilloma**

**Cause:** Canine papillomavirus-2 (CPV2), Canine papillomavirus-6 (COPV6), Canine papillomavirus-1 (CPV1/COPV), Others not classified

**Pathology:** Inverted papillomas typically occur as multiple, raised, smooth, pink-white hairless masses, which are less than 2 cm in diameter, have central umbilication and are broad-based or dome-like. Rarely, lesions are pigmented and small and this may represent different variant of inverted papilloma in the dog. Lesions occur more commonly on the ventral abdomen and distal limbs, including the footpads. Neoplastic transformation to invasive squamous cell carcinoma is a concern in immunocompromised patients.

**Clinical features:** Inverted papillomas are relatively uncommon and generally occur in dogs less than 3 years of age. Breed predispositions have been reported but many breeds are affected. Lesions tend not go undergo spontaneous regression. Immunosuppression in a colony of bone marrow–transplanted severe combined immunodeficiency (SCID) dogs was associated with wide spread inverted papillomas and neoplastic transformation to invasive squamous cell carcinomas, some with metastasis.

**Diagnosis:** Histopathology is recommended because small dermal masses of different causes can develop central umbilication secondarily and can be difficult to differentiate from inverted papillomas.

V **EQUINE PAPILLOMAVIRUS-ASSOCIATED LESIONS**

Three equine papillomaviruses (EcPVs), designated EcPV1, EcPV2 and EcPV3, have been specifically identified in horses to date, which share less than 60% nucleotide sequence homology and are attributed to three different genera. Only a limited number of samples have been sequenced for the different viruses and definitive association of lesion types or lesion distributions to a particular virus is not yet possible. In addition, equine sarcomas are associated with bovine papillomavirus-1 and -2.

i. **Classical Equine Papilloma (“Grass Warts”)**
**Cause:** Equine Papillomavirus-1 (EcPV1)

**Pathology:** Papillomas have a classical papillary surface morphology and are small, tan-white and exophytic masses, which may be sessile or pedunculated. Affected horses often develop multiple papillomas concurrently, which can be very numerous, and qualify as papillomatosis, or can be few, which is more common in older horses. Lesions are usually on the head, especially the muzzle and lips, and occur at other locations on the body, like the distal limbs.

**Clinical Features:** Classical equine papillomas are common and occur most often in young horses, less than 3 years of age, but old horses and immunocompromised horses develop lesions. Multiple young horses may be affected at one time on a farm and from year to year with new foal crops. In normal young horses, lesions are considered self-limiting and usually resolve in 2 to 3 months. Lesions can persist in older horses and may require intervention in some cases.

**Diagnosis:** Lesions are clinically distinct. Large and/or atypical lesions must be differentiated from equine sarcoid. Histopathology confirms the diagnosis but is generally not required.

ii. **Equine genital papillomas and penile squamous cell carcinoma**

**Cause:** Equine Papillomavirus-2 (EcPV2)

**Pathology:** Genital papillomas usually present as multifocal, small, raised, pink-white papules that form variably on the glans and shaft of the penis and on the prepuce. Some lesions are hyperkeratotic. Lesions may coalesce severely and create regional thickening of the penile skin with a lightly bosselated surface. Single or multifocal lesions are reported on vulva. In male horses, lesions occur concurrently or appear to transition to squamous cell carcinoma in situ and/or invasive squamous cell carcinoma on the penis and then lesions are those of a variably sized, invasive, often ulcerated, plaque-like to nodular mass. Squamous cell carcinomas will eventually metastasize to local lymphatic vessels, regional lymph nodes and sometimes to distant organs.

**Clinical features:** The clinical features are not well described in texts nor separated from the features of other papilloma types due to different viruses in the horse. Lesions develop slowly and are persistent.

iii. **Aural Plaques (Equine Ear Papillomas, Pinnal Acanthosis)**
**Cause:** Equine Papillomavirus-3 (EcPV3)

**Pathology:** Individual aural plaques are pink-white, circular, flat-topped and raised. Lesions start out as 1-5 mm small papules and expand to around 5 to 10 mm, but individual mature lesions rarely reach more than one centimeter in diameter and thus are often not true plaques. Lesions can be smooth but others have mild to marked hyperkeratosis that accumulates on the surface of lesions as layered, loosely attached, white scale material, which, when prominent, can nearly appear to fill the ear. Aural plaques usually present with multiple lesions on the inner ear surface, often coalesce to appear larger, and usually involve both ears simultaneously. Similar lesions are described less commonly on the ventral abdomen, peri-sheath area and inner thighs, but the specific viral cause has not been determined. Histologically, lesions develop almost exclusively from hyperplasia and or hyperkeratosis of the epidermis and dermal elements contribute minimally to the mass effect seen clinically.

**Clinical features:** Aural plaques are very common and usually develop in horses of any age but are typically in horses over 1 year of age. Most cases are considered cosmetic complications and have a benign course; neoplastic transformation is not described. However, aural plaques can develop slowly and persist. Aural pain has been attributed to lesions in some horses, but other causes must be excluded. The onset of lesions in summer months in some locations and the overlap in lesion distribution on the inner pinnal, groin and inner thigh surfaces with black fly (*Simulium spp.*) feeding sites supports black flies as a possible vector. Viral sequencing is needed to determine if the same virus causes similar plaque-like lesions at different body sites or if additional viruses are involved.

**Diagnosis:** Clinical lesions are distinctive but occasionally hyperkeratotic variants of aural plaques must be differentiated from hyperkeratotic/verrucose variants of equine sarcoid that can occur in the inner pinnal surface and present with bilateral ear involvement. Histopathology confirms the diagnosis.

iv. **Equine Sarcoid**

**Cause:** Bovine papillomavirus-1 (BPV1), Bovine papillomavirus-2 (BPV2)

**Pathology:** Equine sarcoid morphology varies greatly and includes distinct clinical variants: verrucous, fibroblastic, nodular and occult. Horses can develop more than one sarcoid mass and/or more than one clinical variant simultaneously (mixed sarcoid). Mass lesions are rounded, with or without peripheral invasive projections, and may have papillary exophytic projections from the surface. Fibroblastic
variants are often extensively ulcerated and mimic excessive granulation tissue. Masses can be more superficial and raised or deep in the tissue (subcutaneous). Occult variants are typically subtle plaque lesions that are hyperpigmented, mostly alopecia and less than 3 cm in diameter. Lesions occur on the trunk, neck, head and limbs. Masses can develop on the eyelid and on the inner surface of the pinna, sometimes bilaterally. Metastasis is not a feature.

**Clinical features:** Equine sarcoids are one of the most common neoplasms of horses (a detailed review is out of the scope of this presentation) and all breeds can be affected. Young horses, less than 4 years of age, more frequently develop sarcoids and the head, legs, and ventral trunk, are most commonly affected, possibly because these areas are predisposed to trauma.

**Diagnosis:** Routine diagnosis is by histopathology.

**VI REFERENCES**


Lange CE, Tobler K, Markau T et al. Sequence and classification of FdPV2, a papillomavirus isolated from feline Bowenoid in situ carcinomas. Veterinary


JS Munday, CG Knight and L Howe. The same papillomavirus is present in feline sarcoids from North America and New Zealand but not in any non-sarcoid feline samples. Journal of Veterinary Diagnostic Investigation 2010; 22:97-100.


Diverse presentations of Papillomavirus Infections In Animals

Keith E. Linder DVM, PhD, ACVP
USCAP 2012
Family: Papillomaviridae

- Non-enveloped, icosahedral virus
- Circular, double-stranded DNA genome ≈ 8 kb
- Stabile genomes, extended co-evolution
- Nearly all mammals, including birds, reptiles
- Genus (< 60%), species (61-70%), subtype (71-89%), variant (90-99%) are based on shared nucleotide sequence identity
- Difficult to culture
Papillomaviruses

Humans

- Over 150 HPVs
- Globally distributed and ubiquitous
- Detected in first days of life
- Persistent/latent infection without signs
- Multiple HPVs per individual
- Cancer low and high risk types
- Immune suppression promotes lesions
### Papillomaviruses

<table>
<thead>
<tr>
<th>Animal</th>
<th>PV Type</th>
<th>Year</th>
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<td>Cow</td>
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<td>Horse</td>
<td>EcPV1</td>
<td>2004</td>
<td>3+ EcPVs</td>
<td></td>
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</tbody>
</table>

“...it is extremely likely that only a tiny fraction of all animal PV types have been identified or isolated”

Ethel-Michele de Villiers, Virology 2004
**Papillomavirus**

**Genome Structure**

- **Circular Genome**

**Early genes**
- E5, E6, E7 – maintenance, replication, oncoproteins
- E1, E2 – maintenance, transcription and replication, conserved

**Late genes**
- L1, L2 – structural proteins, viral capsid, conserved

Trends in Microbiology 2011
Papillomavirus Life-cycle
Infection of Stratified Epithelium

1 - Entry at micro-trauma
2 - Bind basement membrane (BM)
3 - Capsid conformational change
4 - Bind basal keratinocyte
5 - Basal keratinocyte entry
Papillomavirus Life-cycle
Persistent Infection

Mitosis

BM

PV Episome

Basal Keratinocytes
Papillomavirus Life-cycle
Differentiation Dependent

- Early gene expression
- Viral maintenance
- Late gene expression
- Genome amplification
- Capsid assembly
- Viral shedding
- Early gene expression
- Viral maintenance

Epidermal surface

BM
Dermis
Papillomavirus Life-cycle
Differentiation Dependent

CPV1 (Nicholls, Virology 1999)
Papillomavirus Life-cycle

Cellular Changes

Papilloma epidermis (40x)

Normal epidermis (60x)
Papillomavirus Infections
Lesion Types

**Papillomas**
- Cutaneous / mucosal tropism
- Site predilections
- Focal or multifocal
- Raised, hyperplastic
- In-apparent to large masses
- Morphological variants

**Neoplasia**
- Carcinoma in-situ (intra-epithelial neoplasia)
- Invasive carcinoma
- Sarcoids

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**Epithelial papillomas**
- Exophytic
- Inverted
- Plaques

**Fibropapillomas**
- Horn
1) Feline oral papilloma (rare)

2) Feline viral plaque (FdPV1, FdPV2)
   Bowenoid in-situ carcinoma (FdPV2)

3) Feline sarcoid (FdSarPV)
Papillomavirus Lesions
Cats

Feline viral plaque
(FdPV1, FdPV2, Others)

Papillomavirus Lesions

Cats

Bowenoid in-situ carcinoma (FdPV2)
Older cats / immune suppression
Papillomavirus Lesions

Cats

Bowenoid in-situ carcinoma (FdPV2)
Bowenoid in-situ carcinoma (FdPV2)
Squamous cell carcinoma
Papillomavirus Lesions
Cats

Feline Viral Plaque
Feline Viral Plaque - Late

In-situ Carcinoma

Invasive Carcinoma

Carcinogenesis

Feline Viral Plaque / Bowenoid in-situ carcinoma / SCC
Papillomavirus Lesions
Cats

Feline sarcoid / Feline fibropapilloma
Felis domesticus sarcoid-associated papillomavirus
(FdSarPV)

Papillomavirus Lesions
Fibropapillomas / Sarcoids

Virus

Epidermal surface

BM

Fibroblast

Dermis

1) Canine oral papilloma (CPV1)

2) Classical cutaneous exophytic papilloma (CPV1, CPV2, CPV7)

3) Pigmented viral plaque (CPV3, CPV4, CPV5, CPV8)

4) Inverted papilloma (CPV1, CPV2, CPV6)
Papillomavirus Lesions
Dogs

Classical cutaneous exophytic papilloma (CPV1, CPV2, CPV7)
Canine oral papilloma (CPV1/COPV)
Papillomavirus Lesions

Dogs
Papillomavirus Lesions
Dogs
Papillomavirus Lesions

Dogs

Classical cutaneous exophytic papilloma (CPV1, CPV2, CPV7)
Canine oral papilloma (CPV1/COPV)
Papillomavirus Lesions

Dogs

Canine oral papilloma / papillomatosis (CPV1)

Papillomavirus Lesions

Dogs

Inverted papilloma (CPV1, CPV2, CPV6)

Dr. Favrot

Papillomavirus Lesions

Dogs

Inverted papilloma

Dr. Favrot

Inverted papilloma
Papillomavirus Lesions
Dogs

Pigmented Viral Plaque (CPV3, CPV4, CPV5, CPV8)
Pugs, Miniature Schnauzer, Boston Terrier and French Bull Dog

Papillomavirus Lesions

Dogs

Squamous Cell Carcinoma (CPV3)

Papilloma and squamous cell carcinoma
1) Classical cutaneous exophytic papilloma (EcPV1)
2) Genital papilloma (EcPV2)
3) Aural plaques (EcPV3)
4) Equine sarcoid (BPV1, BPV2)
5) Equine hoof canker? (BPV1, BPV2?)
Papillomavirus Lesions

Horses

Classical cutaneous exophytic papilloma (EcPV1)
Papillomavirus Lesions
Horses

Equine genital papillomas (EcPV2)
Papillomavirus Lesions

Horses

Equine genital papillomas (EcPV2)
Equine genital papillomas
Squamous cell carcinoma
(EcPV2)
Equine genital papillomas
Squamous cell carcinoma
(EcPV2)
Papillomavirus Lesions
Horses

Equine aural plaque (EcPV3)
Papillomavirus Lesions

Horses

Equine Sarcoid (BPV1, BPV2)
Equine Sarcoid (BPV1, BPV2)