Canine Papillomatosis

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Introduction

• **Definition:** A benign, exophytic, neoplastic proliferation of the squamous epithelium caused by infection with papillomavirus

• **Synonyms:** *Warts* or *verruca vulgaris*

• **First reported:** 1898 by M’Fadyean and Hobday
Etiology

- A papillomavirus: double stranded DNA virus
- 45-48 nm
Phylogenetic analysis of the L1 sequences of CfPV-2

After EM de Villere et al. (2004); H. Yuan et al. (2007)
Linear representation of ORFs of COPV and CfPV-2 genome

After H. Yuan et al. (2007)
### Characteristics of papillomavirus infections in mammals


<table>
<thead>
<tr>
<th>Virus</th>
<th>Carrier</th>
<th>Location</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human papillomaviruses</td>
<td>Human</td>
<td>Different</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Equine papillomaviruses</td>
<td>Horse</td>
<td>Skin (lip)</td>
<td>Papilloma</td>
</tr>
<tr>
<td><strong>Canine papillomaviruses</strong></td>
<td>Dog</td>
<td>Oral mucosa and skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Rabbit papillomaviruses</td>
<td>Rabbit</td>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Rabbit oral papillomaviruses</td>
<td>Rabbit</td>
<td>Oral mucosa</td>
<td>Papilloma</td>
</tr>
<tr>
<td><strong>Mastomys natalensis</strong> papillomaviruses</td>
<td>Rodents</td>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Chaffinch papillomaviruses</td>
<td>Birds</td>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td><strong>Bovine</strong> papillomaviruses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 1</td>
<td>Cattle</td>
<td>Skin</td>
<td>Fibropapilloma</td>
</tr>
<tr>
<td>type 2</td>
<td>Cattle</td>
<td>Skin</td>
<td>Fibropapilloma</td>
</tr>
<tr>
<td>type 3</td>
<td>Cattle</td>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td>type 4</td>
<td>Cattle</td>
<td>Digestive tract</td>
<td>Papilloma</td>
</tr>
<tr>
<td>type 5</td>
<td>Cattle</td>
<td>Udder</td>
<td>Papilloma</td>
</tr>
<tr>
<td>type 6</td>
<td>Cattle</td>
<td>Skin</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Sheep papillomaviruses</td>
<td>Sheep</td>
<td>Skin</td>
<td>Fibropapilloma</td>
</tr>
<tr>
<td>European elk papillomavirus</td>
<td>Elk</td>
<td>Skin</td>
<td>Fibropapilloma</td>
</tr>
<tr>
<td>Deer fibromavirus</td>
<td>Deer</td>
<td>Skin</td>
<td>Fibroma</td>
</tr>
</tbody>
</table>
Etiology

- two different papillomaviruses in dogs
- species and tissue specific

1. Canine Oral Papilloma Virus (COPV): responsible for the oral papilloma

2. Canine Papilloma Virus (CPV): responsible for the cutaneous and inverted papilloma
Etiology (in Human)

- Warts are caused by a virus called human papilloma virus or HPV.
- There are approximately 130 strains of human papilloma viruses.[2][3]
- Types 1, 2, and 3 cause most of the common warts.[3]
  - **Type 1** is associated with deep plantar (sole of the foot) and palmar (palm of the hand) warts.
  - **Type 2** causes common warts, filiform warts, plantar warts, and mosaic plantar warts.
  - **Type 3** causes plane warts, commonly known as flat warts.

Anogenital warts are caused by types 6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 40 and others.

HPV **types 6 and 11** cause about 90% of genital warts cases.
HPV **types 16 and 18** currently cause about 70% of cervical cancer cases,[4][5] and also cause some vulvar, vaginal,[6] penile and anal cancers.[7]
The 7th rank, found 6.2 % among skin neoplasm of dogs in eastern area of Bangkok (n = 210) *

<table>
<thead>
<tr>
<th>Type of epithelial and skin gland tumors</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Transmissible venereal tumor (TVT)</td>
<td>13.3</td>
</tr>
<tr>
<td>2. Squamous cell carcinoma (SCC)</td>
<td>11.4</td>
</tr>
<tr>
<td>3. Mastocytoma (Mast cell tumor)</td>
<td>11.0</td>
</tr>
<tr>
<td>4. Sebaceous gland adenoma/epithelioma</td>
<td>7.1</td>
</tr>
<tr>
<td>5. Benign mixed mammary tumor</td>
<td>7.1</td>
</tr>
<tr>
<td>6. Mammary carcinoma</td>
<td>7.1</td>
</tr>
<tr>
<td>7. Papilloma (squamous/fibrous)</td>
<td>6.2</td>
</tr>
</tbody>
</table>

* Mamom (2009): on process of publishing data
Epidemiology

- Most common in dogs less than 3 years of age.

Source: http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1
Canine Papillomatosis

Epidemiology

• No sex predilection

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>101</td>
<td>21% (21%)</td>
</tr>
<tr>
<td>Female Spayed</td>
<td>150</td>
<td>32% (33%)</td>
</tr>
<tr>
<td>Male</td>
<td>108</td>
<td>23% (25%)</td>
</tr>
<tr>
<td>Male Castrated</td>
<td>111</td>
<td>24% (21%)</td>
</tr>
</tbody>
</table>

(Normal Population %)

Source: http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1
### Epidemiology

- Some breeds *increased* risk

<table>
<thead>
<tr>
<th>Breeds at Increased Risk</th>
<th>N</th>
<th>Probability</th>
<th>OR</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whippet</td>
<td>5</td>
<td>&lt;0.0001</td>
<td>12.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Rhodesian Ridgeback</td>
<td>8</td>
<td>&lt;0.0001</td>
<td>6.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Weimaraner</td>
<td>10</td>
<td>0.0001</td>
<td>4.5</td>
<td>2.40</td>
</tr>
<tr>
<td>Mastiff</td>
<td>5</td>
<td>0.0062</td>
<td>4.4</td>
<td>1.83</td>
</tr>
<tr>
<td>Greyhound</td>
<td>8</td>
<td>0.0008</td>
<td>4.2</td>
<td>2.09</td>
</tr>
<tr>
<td>American Pit Bull Terrier</td>
<td>11</td>
<td>0.0001</td>
<td>4.2</td>
<td>2.30</td>
</tr>
<tr>
<td>Great Dane</td>
<td>13</td>
<td>&lt;0.0001</td>
<td>4.1</td>
<td>2.33</td>
</tr>
<tr>
<td>Jack Russel Terrier</td>
<td>9</td>
<td>0.0006</td>
<td>4.0</td>
<td>2.09</td>
</tr>
<tr>
<td>Beagle</td>
<td>16</td>
<td>0.0507</td>
<td>1.7</td>
<td>1.01</td>
</tr>
<tr>
<td>Labrador Retriever</td>
<td>51</td>
<td>0.0331</td>
<td>1.4</td>
<td>1.04</td>
</tr>
</tbody>
</table>

*Source: [http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1]*
Epidemiology

• Some breeds decreased risk

<table>
<thead>
<tr>
<th>Breeds at Decreased Risk</th>
<th>N</th>
<th>Probability</th>
<th>OR</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed Breed</td>
<td>75</td>
<td>&lt;0.0001</td>
<td>0.6</td>
<td>0.47 0.78</td>
</tr>
<tr>
<td>Cocker Spaniel</td>
<td>8</td>
<td>0.0022</td>
<td>0.4</td>
<td>0.19 0.75</td>
</tr>
<tr>
<td>Miniature Poodle</td>
<td>3</td>
<td>0.0046</td>
<td>0.2</td>
<td>0.08 0.78</td>
</tr>
<tr>
<td>Shetland Sheepdog</td>
<td>1</td>
<td>0.0021</td>
<td>0.1</td>
<td>0.02 0.78</td>
</tr>
</tbody>
</table>

Source: http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1
### Epidemiology

- Common location in dogs.

<table>
<thead>
<tr>
<th>Site</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>52.1%</td>
</tr>
<tr>
<td>Forelimb</td>
<td>12.5%</td>
</tr>
<tr>
<td>Hindlimb</td>
<td>11.2%</td>
</tr>
<tr>
<td>Multiple Sites</td>
<td>10.6%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2.9%</td>
</tr>
<tr>
<td>Thorax</td>
<td>1.6%</td>
</tr>
<tr>
<td>Neck</td>
<td>1.3%</td>
</tr>
<tr>
<td>Perianal Region</td>
<td>0.8%</td>
</tr>
<tr>
<td>Tail</td>
<td>0.5%</td>
</tr>
<tr>
<td>Back</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Source: [http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1](http://www.oncolink.org/types/article.cfm?c=22&s=69&ss=807&id=9513&p=1)
There are 3 different presentations of canine papillomatosis.

1. **Oral Papillomatosis**
   - with multiple papillomas found in the oral cavity

2. **Cutaneous Papilloma**
   - solitary or multiple lesions found on the skin surface.

3. **Inverted Papilloma**
   - a benign endophytic (growing inward) proliferation of the epidermis.
Clinical Presentation

• A narrow based mass projecting upward and outward from a thickened epidermis.

• Cut section often consist of multiple finger-like projections covered by keratinous material

• Normal adjacent skin

• Secondary bacterial infections may be found.
Clinical Presentation

Vary with form of disease

- Oral Form: halitosis, ptyalism, oral bleeding, and reluctance to eat

Lesions: vary from smooth, white mucosal elevations to cauliflower-like warts on the lip margins, oral mucosa, tongue, palate, pharynx, and epiglottis. Tumors (50-100) may be present at time of first diagnosis.

Clinical Presentation

• Ocular Form: wart lesions on conjunctiva, cornea, and eyelid margins

• Cutaneous Form: papilloma site distribution is variable.

Lesions have been noted on the lower extremities, foot pads, and subungually.

Pathogenesis

- Papillomavirus enter epidermis and induce proliferation of epidermal cells result to cutaneous lesion.

- Naturally developing lesions was divided into three phases:
  1. a growing phase
  2. a developing phase
  3. a regressing phase.
1. The growing phase: characterized by
   o basal cell hyperplasia
   o Acanthosis
   o hyper- and parakeratosis
   o a few intranuclear inclusion bodies.

2. The developing phase: characterized by
   o marked acanthosis with cell swelling
   o marked hyper- and parakeratosis with presence of many intranuclear inclusion bodies in swollen or degenerating cells in stratum spinosum and granulosum.

3. The regressing phase: characterized by
   o mild epidermal hyperplasia around dermal core
   o moderate fibroplasias and collagen deposition
   o lymphocytic cells infiltration at epidermal-dermal interface.
Pathogenesis

Stratum Corneum

Keratogenic Zone

Stratum Spinosum

Stratum Germinitivum
Pathology

Cytology

- intranuclear eosinophilic inclusion bodies may be seen in some cells from the granular cell layer.

- lymphocytes, plasma cells, and neutrophils may be seen, which is indicative of secondary inflammatory changes.
Pathology
Pathology

Papilloma- Papilliferous Subtype

- elongated rete at the periphery of the papilloma which are slanted towards the center
- supported by a thin core of dermal fibrous connective tissue
- epidermal hyperplasia, thickened stratum corneum, may be orthokeratotic or parakeratotic
- granular cell layer absent or very prominent with enlarged keratohyaline granules in the cytoplasm
- in some cells the normal cell eosinophilic (red) cytoplasm of the cells of the spinous layer is replaced by a grey-blue finely granular material (viral cytopathic effect)
- occasional intranuclear pale basophilic inclusions (virus)
- lymphoplasmacytic and neutrophilic infiltration of the dermis.
Pathology
Pathology
Immunostaining for human papillomavirus antigen. Positivity is seen in the koilocytic nuclei and vacuolated cornified layer component.
Verruca plana is often encountered on the face of the young, and HPV, types 3 or 10 is the causative agent.
Diagnosis

DIFFERENTIAL DIAGNOSIS
• Transmissible venereal tumor (TVT)
• Squamous cell carcinoma
• Fibromatous epulis

CBC/BIOCHEMISTRY/URINALYSIS
Usually within normal limits unless dogs have become malnourished as a result of prolonged dysphagia

OTHER LABORATORY TESTS N/A

IMAGING N/A

OTHER DIAGNOSTIC PROCEDURES
• Rarely needed

An epidermotropic canine papillomavirus with malignant potential contains an E5 gene and establishes a unique genus

Hang Yuan\textsuperscript{a}, Shinje Ghim\textsuperscript{b}, Joe Newsome\textsuperscript{c}, Tania Apolinario\textsuperscript{a}, Vanessa Olcense\textsuperscript{a}, Mary Martin\textsuperscript{a}, Hajo Delius\textsuperscript{d}, Peter Felsburg\textsuperscript{e}, Bennett Jenson\textsuperscript{b}, Richard Schlegel\textsuperscript{a,*}

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\textsuperscript{b} Brown Cancer Center, University of Louisville, Louisville, KY, USA
\textsuperscript{c} Division of Laboratory Animal Resources, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
\textsuperscript{d} Division for the Characterization of Tumorviruses, Deutsches Krebsforschungszentrum, Heidelberg, Germany
\textsuperscript{e} Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA

Received 25 April 2006; returned to author for revision 1 June 2006; accepted 11 August 2006
Available online 10 October 2006
Research and Case reports

After H. Yuan et al. (2007)
Research and Case reports

After H. Yuan et al. (2007)
Digital papillomatosis in a confined Beagle

Brad M. DeBey, Mary Bagladi-Swanson, Sanjay Kapil, Frederick W. Oehme

Abstract. Papillomavirus-induced papillomas were diagnosed on multiple digits of all 4 feet of a young Beagle. No other cutaneous or oral involvement was identified. Papillomavirus antigen was confirmed by immunoperoxidase localization within keratinocyte nuclei. In addition to the typical basophilic intranuclear inclusions associated with papillomavirus infections, keratinocytes within the papillomas contained large, eosinophilic cytoplasmic inclusions that previously have been described in a Boxer with cutaneous lesions associated with a papillomavirus infection. The papillomas in this Beagle regressed completely within 2 months of the initial diagnosis.
Canine Papillomatosis

Research and Case reports

After Debay et.al. (2001)
Minireview

Classification of papillomaviruses

Ethel-Michele de Villiers, Claude Fauquet, Thomas R. Broker, Hans-Ulrich Bernard, and Harald zur Hausen

Reference Center for Papillomaviruses, Division for the Characterization of Tumorviruses, Deutsches Krebsforschungszentrum, 69120 Heidelberg, Germany
ILTAB, Danforth Plant Science Center, St. Louis, MO 63132, USA
Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL 35294-0005, USA
Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92697-3900, USA

Received 2 February 2004; returned to author for revision 9 March 2004; accepted 24 March 2004

Available online at www.sciencedirect.com


After EM de Villere et al. (2004)
Canine Papillomatosis

After EM de Villere et al. (2004)
Canine cutaneous papilloma. Study of seven cases

Authors: Kaldrymidou, E.; Papaioannou, N.; Poutahidis, T.h.; van Garderen, E.; Karayanopoulou, M.
Source: Journal of the Hellenic Veterinary Medical Society, Volume 52, Number 2, April - June 2001, pp. 126-134(9)
Publisher: Hellenic Veterinary Medical Society

Abstract:
Seven cases of canine papilloma were studied histopathologically using light and electron microscopy. Papillomavirus was detected immunohistochemically and by the polymerase chain reaction (PCR) method.
- The classical squamous papilloma was found in four dogs (#1,2,3,4)
- the inverted papilloma in one dog (#5)
- the fibropapilloma in two dogs (#6,7).
- Virus particles were detected electromicroscopically in two cases (#1,2)
- Immunohistochemistry, revealed the presence of the papillomavirus antigen in three cases (#1,2,3).
- The PCR method resulted in positive for COPV in two cases (#1,2).

These results support the view that except for the canine oral papillomavirus, there might be other types of papillomavirus that induce papilloma in dogs.
• Papillomas caused by COPV are typically multiple and occur in young dogs.

• Noninfectious papillomas are solitary and occur typically in older patients.

• Dogs only: Papillomaviruses are usually species specific.

• Affected animals are typically younger than 2 years of age with oral papillomas, 6 months to 4 years with ocular papillomas, and the age range for cutaneous papillomas caused by virus is uncertain.

• Owners may report difficulty eating or apparent discomfort.
<table>
<thead>
<tr>
<th>Variants of Canine Papillomavirus:</th>
<th>Associated Syndromes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Canine Oral Papillomavirus (COPV)</td>
<td>• Oral papillomatosis</td>
</tr>
<tr>
<td>• Canine Papillomavirus (variants)</td>
<td>• Canine exophytic cutaneous papillomatosis</td>
</tr>
<tr>
<td></td>
<td>• Cutaneous inverted papilloma</td>
</tr>
<tr>
<td></td>
<td>• Pigmented epidermal plaques</td>
</tr>
<tr>
<td></td>
<td>• Squamous cell carcinoma</td>
</tr>
</tbody>
</table>
Clinical Behavior

• Many papillomas regress spontaneously (weeks to months) due to cell mediated immunity and humoral immunity.

• Failure to regress: may indicate immunodeficiency or an immunocompromised animal (receiving corticosteroid therapy).

• Some papilloma virus infections have been known to progress into carcinomas, primarily squamous cell carcinomas.
References

Acknowledgements

MVDC staff

• Dr. Suvarin Pavasutthipaisit
• Khun Siriwan tapetien
• Khun Patcharee Kongpeng
Thank you for your attention!