P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com

Case Report

Management of Canine Papillomatosis using Oral Acyclovir – A Case Report

Uwagie-Ero, Edwin Aihanuwa[1*], Abiaezute, Clifford Nwabugwu[2], Odigie Eugene Aimienwanlen[3] and O'kwu Audu James[4]

[1]Department of Surgery, Faculty of Veterinary Medicine, University of Benin, Benin City, Nigeria.
[2]Department of Anatomy, Faculty of Veterinary Medicine, University of Nigeria, Nsukka Enugu State, Nigeria.
[3]Department of Public Health, Faculty of Veterinary Medicine, University of Benin, Benin City, Nigeria.
[4]Department of Pathology, Faculty of Veterinary Medicine, University of Agriculture, Makurdi, Benue State, Nigeria.
***Corresponding author:** edwin.uwagie-ero@uniben.edu

Article History: Received: May 23, 2017 Revised: October 01, 2017 Accepted: October 27, 2017

ABSTRACT

An eight-month-old German shepherd dog was presented for disseminated exophytic papillomatosis affecting the oral mucosa. Grossly, the lesions appeared as white pedunculated cauliflower-like masses in the gingival and oral cavity. Histology of biopsy revealed hyperkeratosis of the stratum corneum, spinous layer hyperplasia, koilocytes, giant keratohyaline granules and basophilic intranuclear inclusion bodies which were consistent with Canine papillomatosis. Treatment with oral acyclovir three times daily for 10 days without any attempt to surgically de-bulk the lesions, allowed for reduction and complete regression of papillomatosis with no adverse effects between days 5 and 10 respectively. This study concludes that acyclovir is an effective and safe option for the treatment and management of canine papillomatosis.

Key words: Canine, Papillomavirus, Oral and Cutaneous papillomatosis, Acyclovir

INTRODUCTION

Canine papillomatosis is caused by *Canine Papillomavirus* (CPV), a double-stranded, non-enveloped DNA virus of the Papovaviridae family which has a strong tropism for cutaneous squamous or mucosal epithelium (Gross *et al.*, 2005). Being non-enveloped, canine oral papillomavirus is fairly stable in the environment and can survive for 63 days at 4-8˚C or for 6 hr at 37˚C. Heating to between 45-80˚C for 60min destroys infectivity. (Greene, 1990) CPV are a cluster of 8 viruses designated CPV1 through to CPV8, affecting dogs worldwide. (Lange *et al.*, 2011) These variant of canine papilloma clades are linked with six recognized lesion types namely oral, cutaneous, inverted cutaneous, multiple pigmented cutaneous, multiple pigmented plaques, and cushions multiple papilloma. (Scott *et al*., 2001) Canine oral papillomas induced by CPV-1(Bernard *et al*., 2010) are common in puppies and are characterized by multiple, invasive, cauliflower-like hyperkeratotic masses typically in the oral mucosa including the lips and mucocutaneous junctions. Occasionally, tongue, pharynx and esophagus can be affected. (Yagci *et al*., 2008) CPV-1 may also be involved in non-regressing lesions and the development of squamous cell carcinomas, endophytic papillomas and cutaneous lesions in haired skin. (Lange and Favrot, 2011) Cutaneous exophytic papillomas may also be induced by CPV-2, CPV-6 and CPV-7. (Yuan *et al*., 2007, Lange and Favrot, 2011).

Canine oral papillomatosis is a contagious disease that mainly affects young dogs and transmission of the virus is through direct contact, formites and possibly insects. The stability of the virus aid rapid spread of the disease under group housing, such as in experimental accommodation or breeding establishments. (Ghim *et al*., 1995) Lesions appear as single or multiple cauliflower-like masses with average size of 1.0 cm in diameter and are located in mucous membranes and the mucocutaneous junction of the oral cavity and conjunctiva. (Goldschmidt *et al*., 2002) Diagnosis of canine papillomatosis is based on histopathology findings of hyperplastic reaction of the epithelium with an increased production of keratin and demonstration of basophilic virus intranuclear inclusion bodies. (Gross *et al*., 2005).

The clinical presentation, extent and duration of lesions of canine papillomas depend on the type of infecting virus, area affected and degree of susceptibility of the host. In young dogs, the common form is the canine

Cite This Article as: Uwagie-Ero, Edwin A., Abiaezute, Clifford N., Odigie, Eugene A., and O'kwu James A., 2017. Management of canine papillomatosis using oral acyclovir – a case report. Inter J Vet Sci, 6(4): 187-190. www.ijvets.com
(©2017 IJVS. All rights reserved)

mucous presentation which is characterized by presence of multiple warts on oral mucous membrane. However, cutaneous papilloma which develops on and around the mucous membranes and occurs as a singular mass is most frequently seen in older dogs. The cutaneous inverted papillomas, affect both young and mature dogs with characteristic raised papulonodules with a keratotic centre on the ventral abdomen. (Gross *et al*., 2005).

Lesions appear 4 to 8 weeks following exposure and typically regresses after 4 to 8 weeks of evolution, although it may be persistent in some cases. (Nicholls *et al*., 2001) Effect and duration of the lesion depends on the type of virus, area affected and degree of susceptibility of the dog. Experimental findings suggest that circulating IgG antibodies induced by spontaneous regression of canine papillomas can induce protection against subsequent infections. (Ghim *et al*., 1997). In cases of benign lesions, there is rarely clinical problems unless their location leads to respiratory obstruction or dysphagia. Successive crops of non-regressing warts may necessitate euthanasia when lesions spread throughout the buccal mucosa, tongue, and palate and are refractory to treatment by surgery, autogenous vaccination or other therapies. However, in some cases, lesions may progress to squamous cell carcinoma (Ghim *et al*., 1995, Goldschmidt *et al*., 2002) resulting in poor prognoses. Some squamous cell carcinomas, positive for CPV DNA, also express increased amounts of the tumour-suppressor protein p53, (Lange and Favrot, 2011) which is known to play a role in malignant progression of human papillomavirus-related tumours such as cervical cancer. (Crook and Vousden, 1998) These findings identify possible role of CPV in modelling of Human Papillomavirus. Diagnosis of canine papillomatosis is mainly by anatomical distribution, histopathology, immunohistochemistry, electron micro-scopy, immuno-fluorescence, and in situ hybridization. (Scott *et al*., 2001) Where removal is indicated, it is usually carried out by excision, cryosurgery or electro-surgery. (Collier and Collins, 1994, Miller *et al*., 2012).

Case report and management

An eight-month-old male German shepherd dog was presented with disseminated cauliflower like exophytic warts affecting the oral mucosa noticed two (2) weeks before presentation. Physical examination revealed white, smooth, flat, shiny plaques and firm, hyperkeratotic, pedunculated cauliflower-like masses on the lips, gingiva, tongue and oral cavity. (Fig. 1 and 2) Treatment prior to referral included a three (3) day course of 5% oxytetracycline injection. Biopsies were performed and tissue samples were fixed in 10% buffered formalin and sent for histology.

Treatment

Treatment was initiated with Acyclovir (Zovirax®, GSK, India) at a dose of 400mg P.O q8hr for 10 days, Multivitamin (Sofland®, Hebei Huaran Pharma. Co Ltd., China) at a dose of 1ml/10kg body weight S.C. for 5 days and Diclofenac sodium (Shanxi Shuguang Pharma. Co., Ltd., China) at a dose of 2mg/kg body weight I/M. There was no attempt to surgically debulk the lesions.

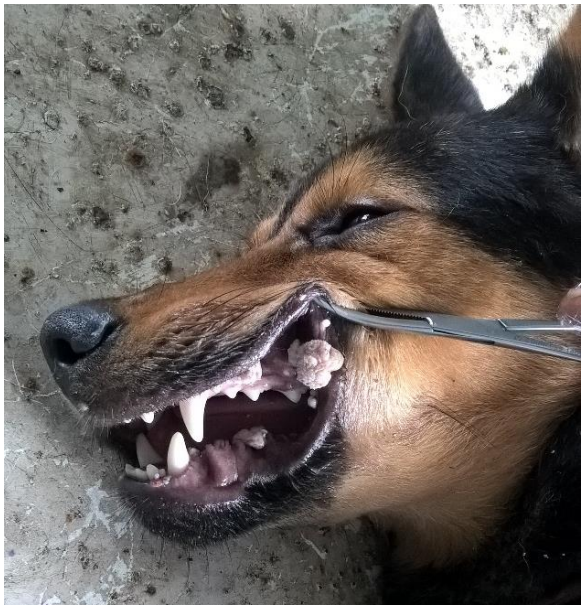

Fig. 1: Numerous white, smooth, rounded shiny plaques and firm, hyperkeratotic, pedunculated cauliflower-like masses were observed on the gingiva of the dog.

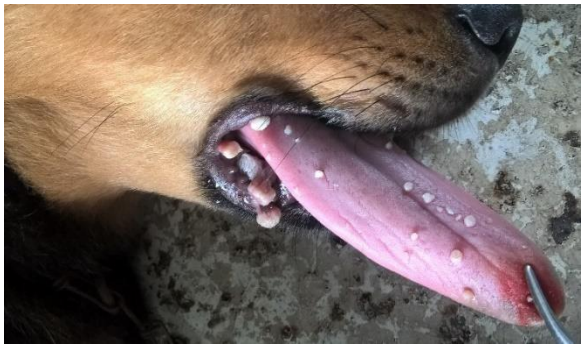

Fig. 2: Numerous white, smooth, rounded shiny plaques and firm, hyperkeratotic, pedunculated cauliflower-like masses were observed on the dorsal and ventral surface of the tongues and lips.

Mechanism of action and pharmacokinetics of acyclovir

Acyclovir, an imidazopyrimidine, when administered orally, intravenously or topically is converted by viral thymidine kinase to Acyclovir monophosphate. The host cell kinases coverts Acyclovir monophosphate to Acyclovir triphosphate which competitively inhibits and inactivates viral DNA polymerases by inhibiting DNA chain elongation. Thus, further viral DNA synthesis is inhibited without disruption of cellular processes. Acyclovir has an oral bioavailability of 15-30% and 2.55-3.3 hours half-life. Its primary route of elimination from the body is the kidney where it is excreted unchanged via tubular secretion.

Results and histopathology

Histological examination of haematoxylin and eosin stained sections revealed hyperkeratosis, papillary epidermal hyperplasia with marked expansion of the stratum corneum. Keratinocytes of the stratum granulosum contained giant keratohyalin granules and increased amount of wispy grey-blue cytoplasm, consistent with viral cytopathic change (Fig. 3). Some koilocytes (keratino-cytes with swollen, clear cytoplasm and a pyknotic nucleus) were

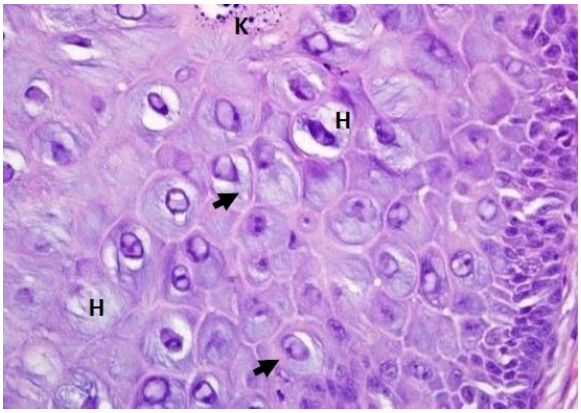

Fig. 3: Histopathological section of cutaneous biopsies (H&E stain, X400), showing koilocytes with perinuclear halo (H), and relatively uniform papillary epidermal hyperplasia with marked expansion of the stratum corneum. Keratinocytes of the stratum granulosum contained giant keratohyalin granules (K) and increased amount of wispy grey-blue cytoplasm (arrow), consistent with viral cytopathic change.

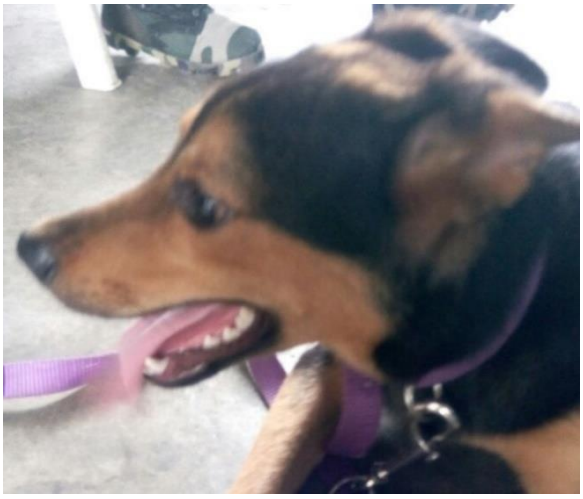

Fig. 4: Complete regression of papillomas observed by day 10 of treatment with Acyclovir.

observed. (Fig. 3) Histopathology revealed multiple finger-like projections of thickened squamous epithelium. The presence of koilocytes, in the spinous layer and their "ghost" cells in the stratum corneum which caused a ballooning degeneration, with nucleus which is both eccentric and pyknotic was consistent with diagnosis of viral papillomatosis. Following commencement of treatment, the oral papilloma was examined daily for size. On day 5, there was a significant reduction in extension and number of papillomas, the masses were shrunken and partial regression was evident. Complete regression of papillomas in the oral cavity was observed by day 10. (Fig. 4) There was no recurrence of papillomatosis in the treated dog during a follow-up period of 6 months and no adverse effects were recorded.

DISCUSSION

Unusually severe or persistent and non-self-limiting forms of papilloma have been associated with immunosuppression, old age and recent chemotherapy or corticosteroid and cyclosporine-A therapy or without any identifiable underlying cause. (Callan *et al*., 2005, Favrot *et al*., 2005, Albanese *et al*., 2006, Goldschmidt *et al*., 2006) The histopathologic findings in this study are similar to what has been reported in 70% of cases. (Nicholls *et al*., 2001, Goldschmidt *et al*., 2002, Gross *et al*., 2005, Biricik *et al*., 2008, Miller *et al*., 2012) However, there was no presence of basophilic intranuclear inclusion body in cells from the spinous layer. Also, histopathological examination showed neither apoptotic keratinocytes nor prominent lymphocytic infiltrate, features compatible with a non-regressing form of papilloma. This differs with some regressing papillomas as described by Nichols *et al.* (2001) Therefore, we opined that this may be due to biopsies been obtained at the later development of the papilloma and may well indicate that there was less likelihood of a spontaneous regression in the dog in this report.

The exact mechanisms resulting in spontaneous regression or spread of papillomas are unknown. Papilloma regression is thought to be associated with the presence of CD4+ and CD8+ lymphocytes. These cells, especially the CD4+ cells, activate macrophages, inhibit viruses via cytokines, kill keratinocytes, or all of these. Favorable prognosis is associated with spontaneous regression of papilloma in dog, in cases of disease regression, marked by lymphocytic infiltrates and other inflammatory cells. When lesions are persistent or poses health challenge, surgical excision, cryosurgery or electrosurgery has been recommended. The use of autogenous vaccines, including subcutaneous live papillomavirus vaccine, as a preventive strategy against canine papillomatosis has been suggested but not proven.

The use of a specific and effective drug for treatment of canine papillomatosis is debatable. However, various drugs have been prescribed for treatment of canine papillomatosis with varied level of effectiveness. Some of these drugs include oral azithromycin, cimetidine, etretinate, human recombinant interferon-α 2a, intramuscular *Propionibacterium acnes*, topical application and/or subcutaneous injection of *Thuja occidentalis* has been used (in human, dog and cattle), intravenous taurolidine and topical applications of 5-fluorouracil or imiquimod. (Stokking *et al*., 2004, Gourreau and Bendali, 2008, Biricik *et al*., 2008, Lira *et al*., 2012, Miller *et al*., 2012, Umadevi and Umakanthan, 2013) In spite of these alternatives, no single treatment has been shown to be superior.

The effectiveness of Acyclovir in this study is similar to a randomized, double-blinded study, placebo-controlled clinical trial to test the efficacy of Azithromycin (Yagci *et al*., 2011, Fantini *et al*., 2015). In the use of both Acyclovir and Azithromycin, lesions disappeared at approximately 10-15 days after treatment commenced and there was no recurrence of papillomas in Azithromycin-treated dogs after 8 months. Likewise, Azithromycin was found to be safe and effective. However, the onset of regression of oral papillomas was found to occur earlier with the use of Acyclovir in this study. The use of Acyclovir in this case study was significantly effective than the use of subcutaneous feline recombinant interferon- ω in which complete regression of the papillomas was observed after day 50. (Fantini *et al.*, 2015) A good indication of complete regression of papilloma is non-recurrence of lesions following months of treatment. In this study, a six-month

period of non-recurrence of lesions following commencement of treatment indicates a favourable prognosis.

Conclusion

Even though further randomized, double-blind, placebo-control studies will be necessary to confirm the therapeutic efficacy of acyclovir in canine papillomatosis, we think that a delayed spontaneous regression is unlikely, due to the histopathological findings, the rapid response to treatment and complete regression of papillomas in 10 days. Therefore, we conclude that acyclovir is an effective and safe option for the treatment of canine papillomatosis.

REFERENCES

Albanese F, FL Salerni and S Giordano, 2006. Extragenital transmissible venereal tumour associated with circulating neoplastic cells in an immunologically compromised dog. Vet Comp Oncol, 4: 57-62.

Bernard HU, RD Burk, Z Chen, VD Koenraad, ZH Harald, DV Ethel-Michele, 2010. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virol, 401: 70-79.

Biricik HS, M Cabalar and MY Gulbahar, 2008. Oral Papillomatosis in a dog and its therapy with Taurolidine. Acta Vet., 77: 373-375.

Callan MB, D Preziosi and E Mauldin, 2005. Multiple papillomavirus-associated epidermal hamartomas and squamous cell carcinomas in situ in a dog following chronic treatment with prednisone and cyclosporine. Vet Dermatol, 16: 338-345.

Crook T and KH Vousden, 1996. HPV oncoprotein functions. In: Papillomavirus Reviews: Current Research on Papillomaviruses. C. Lacey, Ed., Leeds University Press, Leeds, pp: 55-60.

Fantini O, E Videmont E and D Pin, 2015. Successful treatment of florid papillomatosis in a dog using subcutaneous feline recombinant interferon- ω. Revue Med Vet, 166: 25-29.

Favrot C, T Olivry, AH Werner, G Nespecca, A Utiger, P Grest, and M Ackermann, 2005. Evaluation of papillomaviruses associated with cyclosporine-induced hyperplastic verrucous lesions in dogs. Am J Vet Res, 66: 1764–1769.

Ghim SJ, J Newsome, J Bell, JA Suzich, JP Sundberg, R Schlegel and AB Jenson, 1997. Spontaneously regressing oral papillomas induce systemic antibodies that neutralise canine oral papillomavirus. 16th International Papillomavirus Conference, University of Siena (Italy), p: 322.

Goldschmidt MH and MJ Hendrick, 2002. Tumors of the skin and soft tissues, In: Meuten D.J. (Ed.), Tumors in Domestic Animals. 2002, 4th (ed) Blackwell, Iowa, pp: 45-118.

Goldschmidt MH, JS Kennedy and DR Kennedy, 2006. Severe papillomavirus infection progressing to metastatic squamous cell carcinoma in bone marrow-transplanted X-linked SCID dogs. J Virol, 80: 6621-6628.

Gourreau J and F Bendali, 2008. The papillomatosis. In France Agricole (ed): Diseases of cattle, 376- 379.

Greene CE, 1990. Environmental survival of certain microorganisms and some effective bactericidal agents. In: Infectious diseases of the dog and cat, CE Green, Ed., WB Saunders, Philadelphia, Appendix 9.

Gross TL, PJ Ihrke, EJ Walder and VK Affolter, 2005. Skin Diseases of the Dog and Cat: Clinical and histopathologic diagnosis. 2nd ed. Blackwell, Oxford. pp: 932.

Joseph R, S Pulimood, P Abraham and GT John, 2013. Successful treatment of verruca vulgaris with Thuja occidentalis in a renal allograft recipient. Indian J Nephrol, 233: 62–364.

Lange CE and C Favrot, 2011. Canine papillomaviruses. Vet Clin North Am Small Anim Pract 41:1183-1195

Lira R, M Lempek, P Marinho, C Neves and HR Trombini, 2012. Use of Thuja occidentalis in the treatment of canine oral papillomatosis. Pub Vet, 6: 16.

Miller WH, CE Griffin and KL Campbell, 2012. Viral, Rickettsial, and Protozoal Skin Diseases. In Muller and Kirk's Small Animal Dermatology. 7th ed. Philadelphia, pp: 349.

Nicholls PK, PF Moore, DM Anderson, RA Moore, NR Parry, GW Gough and MA Stanley, 2001. Regression of canine oral papillomas is associated with infiltration of CD4+ and CD8+Lymphocytes. Virol, 283: 31–39.

Scott DW, DH Miller and CE Griffin, 2001. Muller and Kirk's Small Animal Dermatology. 6th ed. W.B. Saunders, Philadelphia, 2001, pp: 1528.

Stokking LB, EJ Ehrhart and CA Lichtensteiner, 2004. Pigmented epidermal plaques in three dogs. J Am Anim Hosp Assoc, 40: 411-417.

Umadevi U and T Umakanthan, 2013. Successful combined drug therapy for the treatment of papilloma in cattle. Intl J Biomed Pharma Sci, 4: 657-658.

Yagci BB, K Ural, N Ocal, and AE Haydardedeoglu, 2008. Azithromycin therapy of papillomatosis in dogs: a prospective, randomized, double-blinded, placebo-controlled clinical trial. Vet Dermatol, 19: 194- 198.

Yuan H, S Ghim and J Newsome, 2007. An epidermotropic canine papillomavirus with malignant potential contains an E5 gene and establishes a unique genus. Virol, 359: 28–36.