JOURNAL OF VETERINARY AND APPLIED SCIENCES
VOLUME 16, ISSUE 1: 1483 – 1491 (2026)
Published by: Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Nigeria
ISSN: 2315-6856; e-ISSN: 2636-5553; Website: www.jvasonline.com

Case report of papillomas in three exotic dog breeds: Pathology and molecular diagnostic findings

Amos O. Olowookere [1], Olawale O. Ola [2], Comfort O. Aiki-Raji [1], Theophilus A. Jarikre [2], Olugbenga O. Alaka [2], and Olusegun A. Fagbohun [1] *

[1] Department of Veterinary Microbiology, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria.

[2] Department of Veterinary Pathology, Faculty of Veterinary Medicine, University of Ibadan, Ibadan, Nigeria.

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Abstract

Papillomas (warts) are caused by the canine papillomavirus (CPV) in dogs. The papillomas may predispose affected dogs to secondary infections or, in rare cases, transform to malignancies. Despite its clinical significance, diagnostic information on CPV in dogs in Nigeria remains sparse. Three papillomatous skin and oral samples were obtained from exotic dog breeds presented to veterinary clinics in Plateau and Oyo States, Nigeria. Gross examination, histopathology, and molecular characterization, including polymerase chain reaction (PCR) amplification of 350 bp and 261 bp fragments of the CPV E6 and L1 genes, were performed. Sequencing and sequence analysis were employed to characterize the causative virus further. Grossly, the papillomas presented as multiple sessile and pedunculated, fairly circumscribed, exophytic, cauliflower-like lesions of varying sizes, scattered throughout the face, forelimbs and the oral mucosa. Histologically, there was marked acanthosis, hyperkeratosis, hypergranulosis, swollen keratinocytes and eosinophilic intranuclear inclusions, hallmarks of virus-induced lesions. PCR amplified 350 bp and 261 bp amplicons for E6 and L1 genes, respectively. BLAST analysis revealed CPV as the causative agent of the lesions. Sequence analysis showed conserved L1 regions with minor polymorphisms and high variability in E6 sequences. Phylogenetic analysis grouped the CPV under the genus *Lambdapapillomavirus*. This study affirms the presence and genetic features of CPV in exotic dogs in Nigeria. It also reinforces the diagnostic value of histopathology and molecular tools in veterinary dermatology. Understanding the virus's local diversity lays a foundation for better case management, while raising important questions about host susceptibility and the role of ongoing viral evolution in clinical outcomes.

Keywords: Papillomas (warts); Dogs; Canine papillomavirus; *Lambdapapillomavirus*; Pathology; Molecular characterization.

*** Correspondence:** Olusegun A. Fagbohun; Email – oa.fagbohun@ui.edu.ng; Phone: +2348107128206

Article History: Initial manuscript submission received – October 02, 2025; Final revised form received – May 15, 2026; Accepted for publication – May 19, 2026; Published – May 25, 2026.

Introduction

Dogs, taxonomically classified under the order *Carnivora*, family *Canidae*, genus *Canis*, and species *Canis lupus familiaris*, have, since their domestication, occupied a unique position and played multifaceted roles in human society, serving as essential companion animals, working partners in security and livestock management, and vital contributors to human emotional well-being through therapy and service roles (Suluku *et al*., 2012; Sonntag and Overall, 2014). Domesticated over thousands of years, they represent one of the most widely distributed and socially integrated animals on earth, with their utility spanning companionship, law enforcement, search and rescue and assistance for individuals with disabilities. Their welfare and quality of life are significantly influenced by management practices, breeding standards, and environmental conditions, which collectively dictate their overall health status (Sonntag and Overall, 2014). As such, the health of dogs is a primary concern for both dog owners and public health officials, as unmanaged disease can lead to significant morbidity, and negatively impact the human-animal bond (Suluku *et al*., 2012; Seid and Terefe, 2019).

The overall impact of diseases on the health of dogs is profound, affecting not only individual animals but also the broader human communities that depend on them. Infectious, parasitic and chronic conditions frequently result in functional decline, reduced quality of life and systemic physiological stress, emphasizing the need for effective disease surveillance and management (McKenzie *et al*., 2022). Among the range of conditions that affect dogs, viral infections and disease conditions occupy a particularly significant position due to their transmissibility and potential for widespread impact within populations. One such condition is canine papillomatosis, a viral infection caused by species-specific papillomaviruses, which presents notable clinical challenge (Nicholls and Stanley, 1999). Characterized by the development of benign epithelial tumors on oral, cutaneous and/or ocular surfaces, these lesions can cause significant discomfort and functional impairment, such as difficulty in eating or pharyngeal obstruction, particularly in young or immunocompromised individuals (Fernandes et al., 2009).

Canine papillomas (warts) are characterized by the presence of benign tumors on the skin and mucous membranes of affected dogs, which present as multiple cauliflower-like masses seen commonly on the tongue, lips, palate, gingiva, buccal mucosa and pharynx (Teifke *et al*., 2003). They are primarily caused by canine papillomavirus (CPV), which are small, non-enveloped, icosahedral, circular double-stranded DNA viruses that are highly tissue and species-specific and have both affinity and tropism for the skin and mucosal membranes (Nicholls and Stanley, 1999; Campo, 2002; Modis *et al*., 2002; Gross *et al*., 2008). Canine papillomaviruses are inhabitants of healthy skin but are also associated with various neoplastic diseases. Among these canine papilloma viruses, types 1 and 6 (CPV-1 and CPV-6) have been incriminated to be responsible for causing canine oral papillomatosis in young dogs (Lange and Favrot, 2011; Howley, 2013).

Canine oral papillomavirus mainly affects young dogs, up to 18 months old, and there is no reported schism in prevalence between sexes and breeds (Yhee *et al*., 2010; Zayour and Lazova, 2011). Papillomas usually affect the oral mucous membranes of young dogs and the skin of older dogs. Though canine papillomavirus is the cause of oral papillomatosis in dogs, a less consistent association has been made between cutaneous papillomas and papilloma virus lesions in older dogs (Lucroy *et al*., 1998; Zayour and Lazova, 2011).

Papillomatosis is primarily transmitted and spread by direct contact when an uninfected

dog communes with an infected dog and gets inoculated with a specific papilloma virus type (Nicholls and Stanley, 1999). Infection is usually established in immunologically naive dogs. Dogs with immunosuppressive disorders are highly predisposed to canine papillomatosis (Sundberg *et al*., 1994).

Canine oral papillomas can be treated with a variety of therapeutic approaches, including radiation therapy, immunotherapy, homoeopathy, auto-hemotherapy, autogenous vaccination, surgical excision, various antibiotics, and anti-viral medications (Moore *et al*., 2011; Gurgen *et al*., 2020; Raj *et al*., 2020; Sharun *et al*., 2020; Kalita *et al*., 2022). To speed up the healing process, these therapeutic modalities can be blended (Moore *et al*., 2011).

Case presentation

Three female dogs presenting with papillomatous lesions were evaluated across two veterinary facilities in Nigeria. Two cases were recorded at the Veterinary Teaching Hospital, University of Ibadan (VTH, UI), involving a Boerboel and a Caucasian Shepherd, presented in July 2022 and February 2023, respectively. The third case was a Boerboel presented at the Veterinary Teaching Hospital, Jos, in September 2024. All were under three years of age and presented with multiple proliferative lesions affecting the face, oral cavity and forelimbs. The owners reported gradual lesion progression with no associated pain and no systemic signs or behavioral changes.

Grossly, the lesions appeared as multiple sessile to pedunculated, fairly circumscribed, exophytic, cauliflower-like growths of varying sizes. These were distributed across the face, oral mucosa and limbs (Figure 1). Following physical restraint and sedation, representative lesions were aseptically excised from the skin and oral mucosa. The samples were submitted to the Department of Veterinary Pathology, University of Ibadan, for histopathological work up. Samples were routinely processed for histopathology by fixation in 10% neutral buffered formalin for 24 hours, dehydration through graded alcohols, clearing in xylene, and embedding in paraffin wax. Sections of 5 µm thickness were prepared and stained with hematoxylin and eosin (H & E). The stained-glass slides were examined under a light microscope (Olympus CX21), and photomicrographs were captured using a DinoEye eyepiece digital camera.

Figure 1: Gross pictures of multiple sessile to pedunculated, fairly circumscribed, exophytic, cauliflower-like growths of varying sizes on the muzzle, lips, and palates of the dogs with papillomas.

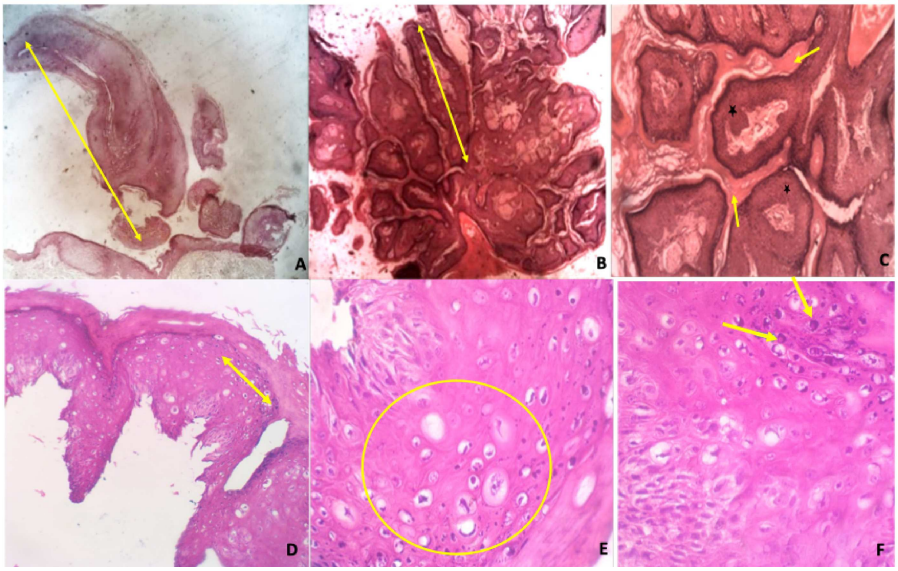

Figure 2: Histopathology of the wart-like growth on the skin and oral mucosa showing the papillary proliferations **(A & B**, yellow double head arrow) of the warts with variable hyperkeratosis (**C**, yellow arrow) and acanthosis (**C**, black star) marked by severe epidermal hyperplasia especially of the stratum granulosum showing hypergranulosis (**D,** yellow double head arrow). Many of the keratinocytes in the granulosum are markedly swollen (degenerates) (**E**, encircled), with very large nuclei and prominent nucleoli and some with eosinophilic intra-nuclear inclusions (**F**. yellow arrows). [H & E, ×40 and ×100].

Microscopically, the lesions presented as prominent epidermal hyperplasia, especially of the stratum granulosum (acanthosis), with papillary projections and moderate cornification (Figure 2). Several keratinocytes appeared swollen, with large nuclei and eosinophilic intranuclear inclusions (Figure 2). Lesions from the mucosa and skin revealed orthokeratotic hyperkeratosis and characteristic papillomatous epidermal projections (Figure 2).

Molecular characterization was performed to confirm its viral etiology. DNA was extracted from paraffin-embedded sections and subjected to PCR targeting 350 bp and 261 bp fragments of the CPV E6 and L1 genes, respectively. Amplicons were resolved using agarose gel electrophoresis, yielding 350 bp and 261 bp bands corresponding to the E6 and L1 genes, respectively (Figures 3a and 3b). Positive samples were sequenced using the Sanger dideoxy method. BLAST analysis confirmed canine papillomavirus identity. Sequence alignment revealed minor single-nucleotide polymorphisms in L1, while E6 showed higher variability. Phylogenetic analysis placed the isolates within the genus *Lambdapapillomavirus*, closely related to other globally reported CPV strains (Figure 4).

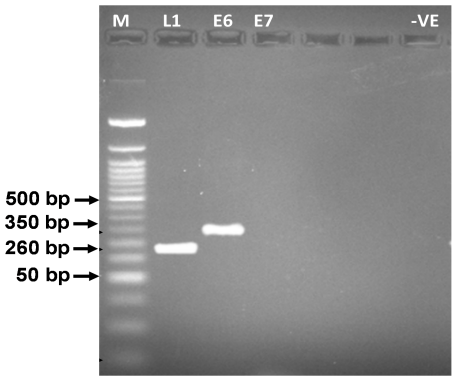

Figure 3a. Agarose gel electrophoresis of 261 bp and 350 bp segment of L1 and E6 protein genes from sample 1. E7 protein gene was not detected or amplified. **Lane 1**: Molecular Weight Marker, **Lane 2**: L1 protein gene, **Lane 3**: E6 protein gene, **Lane 4**: E7 protein gene, **Lane 7**: Negative control.

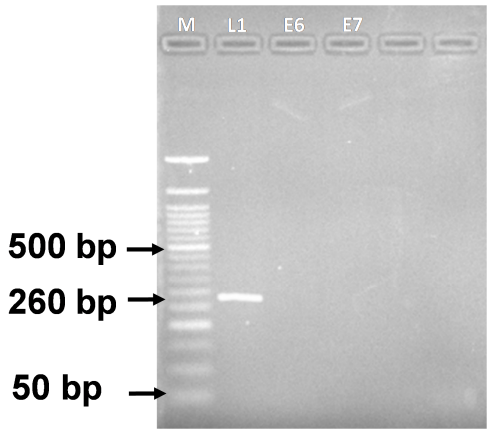

Figure 3b. Agarose gel electrophoresis of 261 bp segment of L1 protein genes from sample 2. E6, E7 protein gene was not detected or amplified. **Lane 1**: Molecular Weight Marker, **Lane 2**: L1 protein gene, **Lane 3**: E6 protein gene, **Lane 4**: E7 protein gene, **Lane 7**: Negative control.

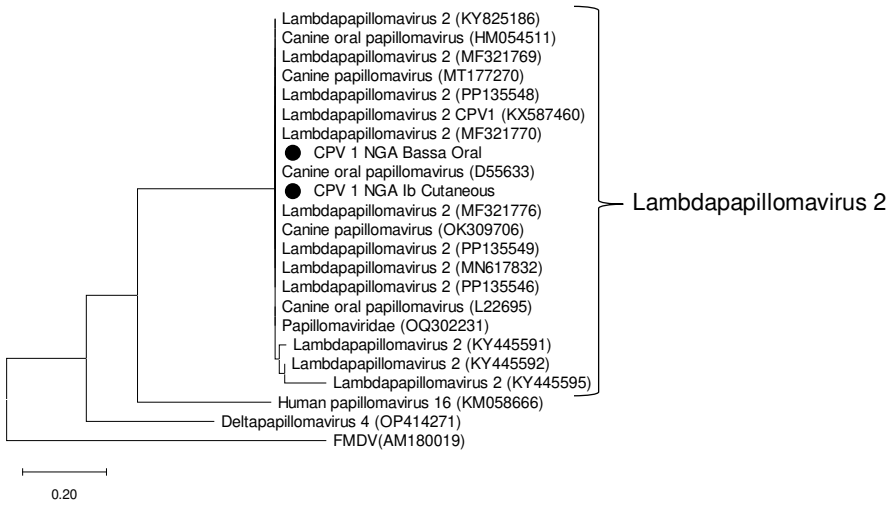

Figure 4. Showing L1 phylogenetic analysis of the sequences generated and selected sequences of canine papilloma virus from the GenBank. The tree was analysed by the maximum likelihood method with bootstrapping (1000). Sequences generated in this study are labelled red.

Discussion

The gross lesions recorded in these cases, such as wart-like nodular lesions, are often suggestive of CPV in dogs and are consistent with previous reports describing the exophytic nature of CPV-induced growths (Lange and Favrot, 2011). The lesions were observed on the skin and oral mucosa, sites previously reported to be the predilection for canine papilloma (Munday, 2014a).

Histopathological evaluation supported CPV involvement. The oral mucosal histopathology lesions revealed classic features such as severe epidermal hyperplasia, hypergranulosis, papillary projections and eosinophilic intranuclear inclusions, which are known hallmarks of viral cytopathic effect. The cutaneous lesions similarly exhibited papillomatous epidermal projections, orthokeratotic hyperkeratosis and acanthosis.

These findings are consistent with established descriptions of mucosal and cutaneous papillomas (Munday, 2014a, 2014b; Munday *et al*., 2017). However, similar presentations have been reported to also occur in non-viral conditions like xanthogranulomas or cutaneous papillary hyperplasia (Barreau *et al*., 2012; Irwin *et al*., 2020). Thus, sole reliance on clinical or histopathological evaluation can be misleading.

Results of the molecular diagnosis reinforced these observations. The L1 gene, which encodes the major capsid protein and serves as a reliable marker for papillomavirus detection (Bernard *et al*., 2010), was successfully amplified in two of the three samples. The E6 oncogene, involved in disrupting tumor suppressor pathways (Doorbar, 2005), was detected in one lesion, while the E7 gene was undetectable in all. This differential detection is believed to reflect variations in viral load, replication stage or possible immune clearance in different tissues. Similar inconsistencies in E7 detection have been previously reported (Munday *et al*., 2017; Munday and Kiupel, 2010). The molecular characterization of CPV in two of the three samples further strengthens their diagnosis. The amplification of the E6 oncogenic and L1 capsid protein genes aligns with the expected molecular profile of canine papillomavirus type 1 (CPV-1) (Tanabe *et al*., 2000; Christensen *et al*., 2017; Reis *et al*., 2019).

Sequence analysis of the L1 gene revealed 100% similarity with known CPV strains within the genus Lambdapapillomavirus, while the E6 sequences showed more variability, with approximately 60% similarity. The observed single-nucleotide polymorphism in the L1 gene did not result in an amino acid substitution, classifying it as a silent mutation, likely due to codon redundancy (Munday, 2014a). This genetic stability of L1 supports its continued use as a robust molecular marker (Bernard *et al*., 2010). In contrast, the heterogeneity of the E6 gene aligns with earlier reports and may have implications for lesion persistence, recurrence, and potential oncogenic transformation (Cruz-Gregorio and Aranda-Rivera, 2023).

Phylogenetic analysis clearly positioned the Nigerian isolates within the genus *Lambdapapillomavirus*, clustering closely with CPV-1 strains from the USA and Turkey. This finding suggests that CPV-1, a globally distributed type, may also be the dominant strain in Nigerian dog populations, with implications for understanding CPV epidemiology and guiding vaccine development.

A key limitation of this study is the small sample size, which limits broader epidemiological conclusions. Additionally, while PCR and sequencing were employed, other confirmatory tools like immunohistochemistry or in situ hybridization were not used. Future studies should also investigate host immune response and clinical outcomes, which could reveal differences in pathogenicity or treatment response across CPV variants.

Conclusion: This case report confirmed the presence and genetic identity of CPV-1 in exotic dog breeds in Nigeria, and emphasizes that histopathology and molecular analysis proved complementary in accurate diagnosis. While histology remains foundational for lesion characterization, PCR and sequencing enabled definitive confirmation and phylogenetic mapping. The genetic stability of the L1 gene reinforces its diagnostic value, while E6 variability may influence lesion behavior. This case report confirms the diagnostic value of combining gross, histopathological and molecular techniques in the confirmatory diagnosis of canine papilloma in dogs.

Conflict of interest

All authors declare no conflict of interest.

Acknowledgements

We appreciate the efforts of the technical staff of the clinical and histopathological laboratories of the Department of Veterinary Pathology, University of Ibadan, Nigeria.

Ethical Statement

All applicable international, national and/or institutional guidelines for the care and use of animal samples were followed.

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