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Prevalence of Human Cytomegalovirus in Radicular Cyst in Routine Oral Pathology Service

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ABSTRACT: Background: Radicular cysts are common inflammatory odontogenic lesions associated with chronic periapical infections. Human Cytomegalovirus (HCMV), a widespread herpesvirus, has been implicated in various oral inflammatory conditions, but its role in radicular cysts remains unclear.

Objective: To investigate the presence of HCMV in radicular cyst specimens using immunohistochemical staining.

Materials and Methods: This cross-sectional study analyzed 45 radicular cyst specimens collected from patients undergoing tooth extractions at Taibah University Dental Hospital. Clinical and radiographic examinations confirmed chronic periapical lesions. Specimens were fixed in 10% formalin and processed for histopathological and immunohistochemical evaluation. A mouse monoclonal antibody targeting HCMV (clones 8B1.2, 1G5.2, 2D4.2) was used. CMV expression was categorized as "Focal positive," "Generalized positive," or "None." Data were analyzed using SPSS version 26.0.

Results: Among the 45 specimens, 8 (17.8%) were focal positive, 2 (4.4%) were generalized positive, and 35 (77.8%) showed no CMV expression. Overall, CMV was detected in 10 cases (22.2%) when focal positive and generalized positive categories were combined.

Conclusion: HCMV was identified in a subset of radicular cyst specimens. These findings suggest a potential viral component in the pathogenesis or persistence of some periapical lesions, warranting further investigation.

INTRODUCTION

Periapical lesions are inflammatory disorders affecting the periapical tissues and adjacent alveolar bone, commonly arising from bacterial infections associated with pulpal necrosis and root canal contamination, particularly by Gram-negative anaerobic bacteria [1,2]. Histopathologically, these lesions are characterized by a spectrum of tissue changes, including granulomatous and fibrous tissue proliferation, epithelial proliferation or cyst formation, and infiltration by various inflammatory cells [3–6]. Persistent apical inflammation may result in the formation of periapical granulomas, which consist of granulation tissue infiltrated by lymphocytes, macrophages, plasma cells, and polymorphonuclear leukocytes (PMNs) [7–9].

Radicular cysts (RCs), the most common odontogenic cysts, are classified as inflammatory in origin. They consist of an epithelium-lined cavity surrounded by a fibrous capsule and are thought to originate from epithelial cell rests of Malassez activated by chronic periapical inflammation. Although usually asymptomatic, RCs can become clinically significant when secondarily infected [10].

Human Cytomegalovirus (HCMV), a ubiquitous double-stranded DNA virus from the Herpesviridae family, encodes approximately 165 genes. These viral genes produce proteins that modulate host immune responses and cellular functions, contributing to viral persistence and pathogenicity [11]. HCMV has a broad cell tropism, infecting T lymphocytes, monocytes/macrophages, epithelial cells, fibroblasts, endothelial cells, and PMNs [12]. Viral replication occurs in the host cell nucleus and is histologically identified by large intranuclear and smaller cytoplasmic inclusion bodies [13].

Several studies have explored the presence of HCMV in odontogenic and periapical pathologies, such as apical periodontitis, odontogenic keratocysts (OKCs), and radicular cysts [12,14–19]. HCMV has been implicated in modulating the host immune response and possibly contributing to lesion persistence or severity. However, research specifically investigating the prevalence and pathological role of HCMV in radicular cysts remains limited. Given the immunomodulatory potential of HCMV and its ability to infect key inflammatory and structural cells within periapical tissues, investigating its presence in radicular cysts may reveal a previously underappreciated viral component in their pathogenesis. This study, therefore, aims to examine the occurrence of HCMV in radicular cysts and explore its potential role in lesion development or progression.

MATERIALS AND METHODS

This study included 45 periapical lesion specimens collected from patients attending the Departments of Oral and Maxillofacial Pathology, Oral and Maxillofacial Surgery, Endodontics, and Periodontology at the Dental Hospital, College of Dentistry, Taibah University. All patients were clinically and radiographically diagnosed with chronic periapical lesions and were indicated for tooth extraction.

Inclusion and Exclusion Criteria

Eligible participants were adult individuals in need of tooth extraction, with no history of severe systemic diseases. Inclusion required confirmed chronic periapical lesions based on clinical findings (e.g., pain on occlusion, tenderness to percussion or palpation, swelling, presence of periapical radiolucency, and probing depth). Patients were excluded if their teeth presented with vertical root fractures, significant periodontal involvement, incomplete root development (open apices), or if they had a history of HIV infection, immunosuppressive conditions, or had received antiviral, immunosuppressive, or antibiotic therapy within three months prior to the study.

Specimen Collection and Processing

Following tooth extraction, periapical lesions were immediately harvested from the root apex and fixed in 10% neutral buffered formalin. Patient demographic data (age and gender) and relevant clinical information were recorded. Each specimen underwent histopathological, immunohistochemical, and histochemical evaluation using high-power field microscopy. The study received ethical approval, and informed consent was obtained. Samples were collected during routine care, with no added risk to patients, and confidentiality was protected throughout.

Immunohistochemical Analysis

To detect the presence of Human Cytomegalovirus (HCMV) in radicular cysts, immunohistochemical staining was performed using a mouse monoclonal antibody specific to CMV (clones 8B1.2, 1G5.2, and 2D4.2; Cell Marque, Sigma-Aldrich Co. LLC; Isotype: IgG2a). The antibody was diluted in Tris buffer (pH 7.3–7.7) containing 1% bovine serum albumin (BSA) and less than 0.1% sodium azide. Working dilutions and incubation conditions were optimized in accordance with the manufacturer's guidelines.

Paraffin-embedded tissue sections were deparaffinized, rehydrated, and subjected to antigen retrieval prior to incubation with the primary antibody. Detection was achieved using a horseradish peroxidase (HRP)-conjugated secondary antibody and 3,3'-diaminobenzidine (DAB) as the chromogen. Slides were counterstained with hematoxylin and examined under light microscopy. The antibody was stored at 2–8°C and was not frozen to ensure stability.

Evaluation of Staining Results

Immunohistochemical staining was independently assessed by two experienced oral pathologists. Positive expression was defined by nuclear staining of cells within the lesions. Any discrepancies in interpretation were resolved through discussion and consensus.

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Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (Chicago, IL, USA). Descriptive statistics were calculated to summarize the frequency and percentage of CMV expression among radicular cyst specimens, categorized as "Focal positive," "Generalized positive," or "None." For inferential analysis, CMV expression was further dichotomized into two groups: CMV detected (including both "Focal positive" and "Generalized positive") and CMV not detected ("None").

RESULTS

A total of 45 radicular cyst specimens were examined for the presence of Cytomegalovirus (CMV) using immunohistochemical staining. CMV expression was classified into three categories: Focal positivity), generalized positivity), and "None" (no staining). Among the specimens, 8 cases (17.8%) were identified as Focal positive, 2 cases (4.4%) were generalized positive, and 35 cases (77.8%) showed no evidence of CMV (Table 1 and Figure 1). When grouped into two broader categories, CMV was detected in 10 cases (22.2%), while 35 cases (77.8%) showed no CMV detection (Table 2). Representative HCMV-positive immunohistochemical staining is shown in Figure 2.

Table 1. Immunohistochemical Detection of CMV in Radicular Cysts (n = 45)

Percentage (%)	Frequency	CMV Expression
17.8%	8	Focal positive
4.4%	2	Generalized positive
77.8%	35	None

Table 2. Grouped CMV Detection Status (n = 45)

Percentage (%)	Frequency	CMV Detection
22.2%	10	Detected
77.8%	35	Not Detected

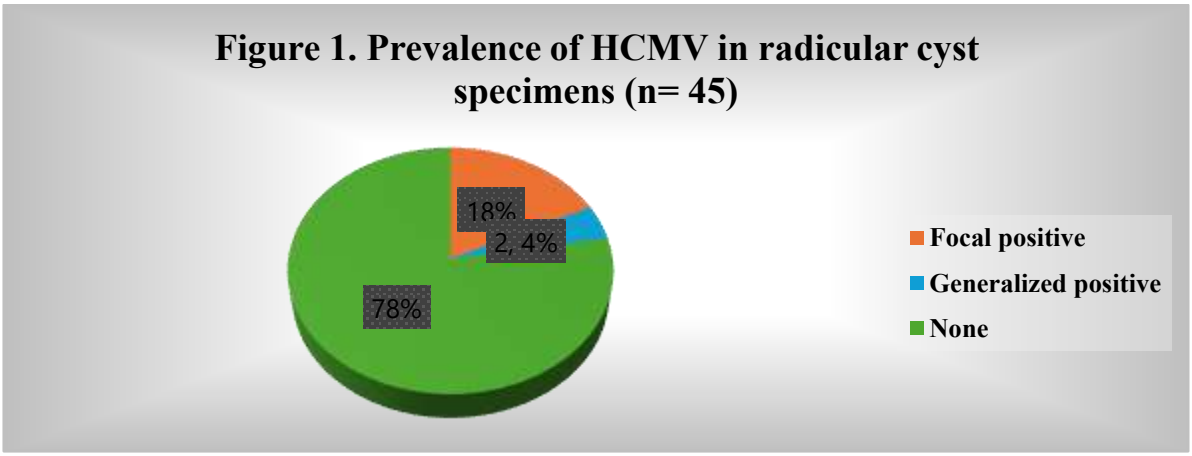


Figure 1. Distribution of immunohistochemical HCMV expression in radicular cyst specimens (n = 45).

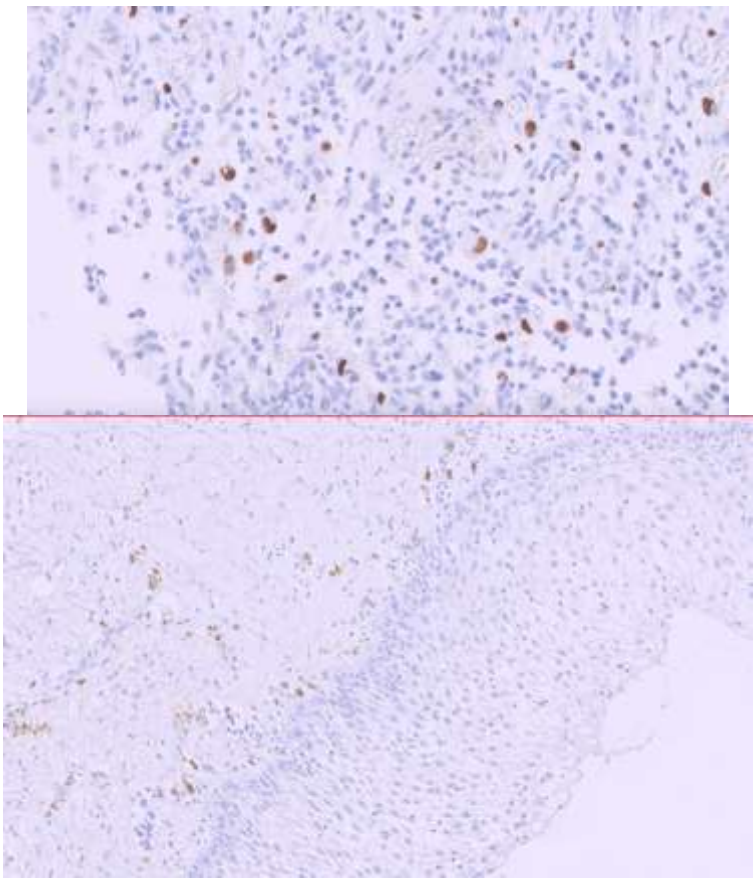


Figure 2. Representative immunohistochemical fields from radicular cyst tissue showing brown nuclear HCMV immunoreactivity against a hematoxylin-counterstained background.

DISCUSSION

In the present study, Human Cytomegalovirus (HCMV) was detected in 22.2% of radicular cyst specimens using immunohistochemical staining, with 17.8% showing focal positivity and 4.4% showing generalized positivity. These findings indicate that while the majority of radicular cysts did not exhibit CMV expression, a notable subset demonstrated evidence of viral presence within the lesion tissues.

The detection of HCMV in periapical lesions aligns with previous studies that reported the presence of herpesviruses, particularly HCMV and Epstein–Barr Virus (EBV), in endodontic pathoses such as apical periodontitis and radicular cysts [12, 14–17]. Slots et al. [16] suggested that herpesviruses may contribute to periapical tissue destruction by infecting and impairing immune cells, leading to impaired host defense and prolonged inflammation. Much more recently, a meta-analysis reported an overall HPV prevalence of 18.21% (95% CI: 6.36–33.73) in ameloblastomas and 1.51% (95% CI: 0.00–9.46) in odontogenic cysts [20]. Furthermore, HCMV has been shown to infect a range of cell types present in periapical tissues, including macrophages, lymphocytes, and fibroblasts, potentially contributing to lesion progression [12].

Several studies have identified Human Cytomegalovirus (HCMV) in various jaw lesions. Notably, HCMV has been significantly detected in periapical cysts and odontogenic keratocysts (OKC) [14], and its presence in apical periodontitis has been confirmed using both PCR [6,7] and immunohistochemistry (IHC) [12,18]. Higher prevalence rates have been reported in symptomatic and/or larger chronic periapical lesions compared to asymptomatic or smaller ones [16,17]. Moreover, detection of HCMV in periapical lesions of teeth with intact crowns suggests a hematogenous route of infection via immune cells, rather than oral contamination [15]. In contrast, some studies have reported low prevalence of HCMV in apical lesions [21] and its absence in periapical abscesses [22].

The relatively high proportion of negative cases in this study (77.8%) suggests that HCMV is not universally associated with radicular cysts, supporting the hypothesis that viral involvement may occur selectively in certain inflammatory microenvironments or host immune conditions. This selective presence has been previously attributed to local reactivation of latent virus in immune cells infiltrating the lesion [11, 16].

The observed prevalence closely resembles the 23% HCMV positivity reported by Saboia-Dantas et al. using immunohistochemistry in apical periodontitis lesions [12]. Nevertheless, prevalence estimates from different studies should not be interpreted as directly interchangeable. Published studies have differed in lesion categories, clinical phenotypes, immune-status profiles, tissue compartments, and detection targets. Immunohistochemistry identifies viral antigen within morphologically recognizable cells, whereas polymerase chain reaction can detect low levels of viral DNA without determining whether the virus is transcriptionally active or present within the cells responsible for tissue injury. Consequently, systematic reviews have identified substantial methodological heterogeneity and concluded that evidence supporting a direct etiologic role of HCMV in apical disease remains incomplete [23,24].

A biologically plausible explanation is that HCMV functions as a disease modifier within a polymicrobial inflammatory environment rather than as an independent initiating agent. Bacterial infection within the necrotic root-canal system remains the primary trigger of apical inflammation [1,2]. In some lesions, however, recruitment of latently infected monocytes or macrophages together with local inflammatory signaling may facilitate viral reactivation. HCMV-mediated effects on leukocyte function and cytokine signaling could subsequently impair local antimicrobial defense, sustain inflammatory-cell recruitment, or enhance osteolytic pathways. This model is consistent with the predominantly focal staining observed in the present series and with the broader concept of herpesviral-bacterial synergy proposed in periapical disease [16,23]. This model may also explain why viral antigen is detectable only in a subset of otherwise histologically similar cysts.

The predominance of focal rather than generalized positivity warrants particular attention. Focal immunoreactivity may indicate a low tissue viral burden, localized viral reactivation, or involvement of scattered inflammatory or stromal cells rather than diffuse infection of the cyst lining. Conversely, negative immunohistochemistry cannot entirely exclude latent infection, low-copy viral DNA, sampling outside a focal positive area, or antigen levels below the detection threshold. Accordingly, future studies should integrate standardized immunohistochemical scoring with quantitative PCR and, when feasible, RNA-based assays or markers of productive viral replication. Concordance across complementary detection methods would help differentiate latent viral carriage, active local replication, and nonspecific or technically limited staining [23,24].

The clinical implications should therefore be interpreted conservatively. Detection of HCMV antigen does not establish that antiviral treatment would improve outcomes in radicular cysts, and the present findings do not justify altering established management directed at eliminating the endodontic source and surgically treating persistent cystic disease when indicated. Rather, the findings generate testable hypotheses. Larger prospective investigations should incorporate healthy periapical and non-radicular odontogenic cyst controls, document lesion size, symptoms, endodontic status, recurrence, and host immune factors, apply blinded scoring with assessment of interobserver agreement, and determine whether viral positivity independently predicts inflammatory intensity, bone destruction, treatment response, or recurrence. A recent systematic review of viruses in pulpal and apical disease similarly concluded that herpesviruses, particularly EBV and HCMV, are frequently detected, although better-designed studies are needed to determine their pathogenic significance [24].

Molecular studies further demonstrate why prevalence estimates must be interpreted in the context of the detection method used. Ozbek et al. investigated HCMV and EBV DNA in symptomatic and asymptomatic apical periodontitis lesions using real-time PCR [25]. Molecular amplification is especially useful for detecting low-copy viral genomes that may not generate sufficient antigen for immunohistochemical detection. However, PCR positivity may reflect latent viral DNA, infected infiltrating leukocytes, or active viral replication. The present immunohistochemical findings therefore add complementary spatial information, although combined assessment of antigen, DNA, and RNA would provide a more reliable characterization of biologically active infection.

The broader quantitative evidence likewise supports a cautious interpretation. Botero et al., in a systematic review and meta-analysis, reported a strong association between subgingival HCMV detection and marginal periodontitis, whereas the pooled association with apical periodontitis was not statistically significant and was estimated with a wide confidence interval [26]. A subsequent umbrella review likewise concluded that evidence linking herpesviruses to apical periodontitis of endodontic

origin came from low-quality, heterogeneous studies and did not establish direct viral involvement [27]. These syntheses do not invalidate the tissue-level positivity observed in the present series; instead, they suggest that HCMV detection should currently be interpreted as evidence of a potentially relevant local biological process rather than proof that HCMV initiates radicular cyst formation. This distinction reinforces the need for controlled, adequately powered studies that distinguish viral presence from active infection and evaluate whether positivity is independently associated with lesion phenotype or clinical outcome.

The use of immunohistochemistry in this study provides a direct visualization of viral protein expression in tissue sections, which complements previous PCR-based studies and reinforces the relevance of HCMV in oral inflammatory pathology [13, 15]. Accordingly, the use of immunohistochemical staining in this study is a key strength, as it allowed for the direct visualization of Cytomegalovirus (CMV) within radicular cyst tissues, providing localized evidence of viral presence. This method enhances the specificity of detection and adds a valuable histopathological dimension to the investigation. Additionally, the study utilized clinically and radiographically confirmed specimens, ensuring accurate diagnosis and sample selection. Another strength lies in its contribution to the limited literature on viral involvement, specifically HCMV, in odontogenic cysts. However, the relatively small sample size may limit the generalizability of the findings. Furthermore, the reliance solely on immunohistochemistry, without parallel molecular testing such as polymerase chain reaction (PCR), may have reduced the sensitivity of viral detection, particularly in cases with low viral load. The study also did not analyze associations between CMV detection and clinical variables such as symptoms, lesion size, or patient immune status, which could offer deeper insight into the clinical relevance of the findings. Being cross-sectional in nature, the study cannot establish causal relationships between CMV and the pathogenesis of radicular cysts.

In conclusion, CMV was detected in 22.2% of radicular cyst specimens, suggesting that the virus may play a role in the development or persistence of a subset of periapical lesions. These findings support the possibility of a viral component in the pathogenesis of odontogenic inflammatory conditions and highlight the need for further research using larger samples and molecular diagnostic approaches.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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