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# Human cytomegalovirus and Epstein-Barr virus type 1 in periodontal abscesses

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**Objectives:** Recent studies have linked herpesviruses to severe types of periodontal disease, but no information exists on their relationship to periodontal abscesses. The present study determined the presence of human cytomegalovirus (HCMV) and Epstein-Barr virus type 1 (EBV-1) in periodontal abscesses and the effect of treatment on the subgingival occurrence of these viruses.
**Material and methods:** Eighteen adults with periodontal abscesses participated in the study. Subgingival samples were collected from each patient with sterile curettes from an abscess-affected site and a healthy control site. HCMV and EBV-1 were identifed by polymerase chain reaction at the time of the abscess and at 4 months after surgical and systemic doxycycline therapy.
**Results:** HCMV was detected in 66.7% of periodontal abscess sites and in 5.6% of healthy sites ($P = 0.002$). EBV-1 occurred in 72.2% of abscess sites but not in any healthy site ($P < 0.001$). HCMV and EBV-1 co-infection was identified in 55.6% of the abscess sites. Posttreatment, HCMV and EBV-1 were not found in any study site.
**Conclusions:** HCMV and EBV-1 genomes are commonly found in periodontal abscesses. These data favor a model in which a herpesvirus infection of the periodontium impairs the host defense and serves as a platform for the entrance of bacterial pathogens into gingival tissue with subsequent risk of abscess development.

Key words: periodontal abscess; cytomegalovirus; Epstein-Barr virus; pathogenesis

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The periodontal abscess is a localized purulent infection of tissues adjacent to a periodontal pocket (12, 14, 24). Periodontal abscesses occur mostly in conjunction with preexisting periodontitis (32) but can also develop at sites exhibiting little or no prior attachment loss (24). The major symptom of a periodontal abscess is spontaneous or evoked pain. Gingival or mucosal swelling is usually present in the symptomatic area, and affected tissue appears red or reddish blue (1, 13, 19). Suppuration may appear spontaneously or after incision of the abscess (9, 24). Affected teeth typically experience rapid periodontal tissue destruction with deep pocket formation (26), frequently become hypermobile, and may sometimes extrude from the alveolar socket (1). Differential diagnosis between abscesses of periodontal and endodontic origin can be made on the basis of pulp vitality, the presence of deep periodontal pockets versus dental caries, the location of the abscess, radiographic examination, and the response to periodontal therapeutic intervention (9, 12).

Microbiologically, early events in the formation of a periodontal abscess include the multiplication and tissue invasion of one or more subgingival bacterial species (15). Increased bacterial activity may be due to a disturbance in the microbial homeostasis, a destruction of the epithelial barrier, or reduced local host resistance (13). Studies that have investigated the specific microbiota of periodontal abscesses have reported a high occurrence of *Porphyromonas gingivalis, Prevotella intermedia* and *Fusobacterium nucleatum* (3, 23, 24, 38, 50, 53) as well as *Actinobacillus actinomycetemcomitans, Campylobacter rectus* and *Prevotella melaninogenica* (23). *Candida* species can also be recovered from periodontal abscesses (15). In a rabbit wound chamber model, abscesses were produced by *P. intermedia* or *Prevotella nigrescens* strains in combination with *A. actinomycetemcomitans* in 33–100% and with *Streptococcus mitis* in 42–100% of experimental inoculations (22). However, abscess-associated bacteria are also common pathogens in periodontal sites that show no propensity to abscess formation. In fact, abscess formation in the periodontium is a relatively rare occurrence (24). Most likely, in addition to pathogenic bacteria, the development of periodontal abscesses is contingent upon a weakened host defense at the local site.

Recent investigations have identified genomes of human cytomegalovirus (HCMV) and Epstein-Barr type 1 (EBV-1), two herpesviruses, in aggressive types of periodontal disease (28, 32) and periapical pathosis (44). HCMV and EBV infections have the potential to increase the virulence of resident bacterial pathogens. By expressing virally-induced proteins on eukaryotic cell membranes (33, 52), herpesviral infections may enhance bacterial adherence to and bacterial invasiveness into epithelial cells and other mammalian cells (5, 18, 31). Herpesviruses may also lyse infected epithelial cells (27), thereby facilitating the penetration of pathogenic bacteria into connective tissue. Furthermore, HCMV may inhibit the expression of macrophage surface receptors for lipopolysaccharide and the responsiveness to gram-negative bacterial infections (25).

Since our understanding of the etiopathogenesis of periodontal abscesses is still incomplete, the present study was designed to investigate the hypothesis that periodontal abscesses are associated with HCMV and EBV-1. A polymerase chain reaction (PCR) assay was used to identify the presence of HCMV and EBV-1 in subgingival plaque samples from 18 periodontal abscess lesions and from 18 normal periodontal sites in the same patients. The study also determined the subgingival presence of HCMV and EBV-1 following the treatment of the periodontal abscesses.

## Material and methods

### Subjects

Eighteen patients (8 women and 10 men; age 19–60 years, mean age 34.7 years) with periodontal abscesses were included in the study. All patients were systemically healthy and had not received periodontal or antibiotic treatment for at least 6 months prior to the study. Each study patient provided written informed consent after all procedures were explained.

The clinical diagnosis of periodontal abscess was based on localized pain, gingival swelling, redness and tenderness, increased periodontal pocket depth, and bleeding and suppuration upon periodontal probing. Pulpal vitality tests and radiologic examination excluded the presence of endodontic abscesses.

### Clinical evaluation

Each study patient was assessed for pain and gingival swelling and redness. Each clinical variable was scored using an analogue scale from 1 to 4:1 (none), 2 (mild), 3 (moderate), 4 (severe). Plaque Index (45), bleeding on probing, suppuration, and tooth mobility were also recorded. Probing pocket depth at the abscess site was determined using a calibrated Williams probe. The same researcher assessed all clinical variables, except pain, which was patient self-reported.

### Treatment

Three abscess-involved teeth were extracted after virologic sampling due to the severity of the infection and the associated tissue destruction. Abscesses in the remaining 15 teeth were resolved after incision and drainage. Patients were prescribed a course of systemic doxycycline, 100 mg every 12 h at the first day followed by 100 mg daily for a total 14 days. During the first 2 weeks posttreatment, patients rinsed for 2 min twice a day with 0.2% chlorhexidine digluconate. Modified Widman flap surgery with maximal preservation of bone and soft tissue was carried out in abscess sites with deep bony defects.

### Virologic sampling

Virologic samples for PCR analysis were obtained when the abscess was present and 4 months post-treatment. Subgingival material was collected by means of a sterile curette. After gently inserting the curette into the bottom of the periodontal site, a single stroke was taken to remove subgingival debris. In each patient, subgingival samples were collected from a periodontal abscess site (5–10 mm probing depth) and from a healthy site of a contralateral tooth (2–3 mm probing depth). Each abscess and healthy site was sampled twice, and all samples were processed separately.

### PCR procedures

The primer set for HCMV consisted of 5'-GAGCGCGTCCACAAAGTCTA-3' and 5'-GTGATCCGACTGGGCGAAAA-3', which generated a 264-bp PCR amplification product (21). Primers for EBV-1 were 5'-AGGGATGCCTGGACACAAGA-3' and 5'-GCCTCGGTTGTGACAGAG-3', which generated a 256-bp PCR product (4). The PCR mixture (50 μl) consisted of 10 pmol of each primer, 1× PCR buffer (Bioron GmbH, Hannover, Germany), 2 units *Taq* polymerase (Bioron GmbH), 2.5 mM $MgCl_2$ (Bioron GmbH), 0.1 mM dNTPs (Sigma-Aldrich Chemie Gmbh, Munich, Germany) and 10 μl sample DNA.

Samples were initially denatured at 94°C for 5 min, followed by 30 cycles, which included denaturation for 30 s at 94°C, annealing for 30 s at 59°C, and extension for 30 s at 72°C, with a final extension at 72°C for 5 min. Controls included HCMV and EBV positive and negative cell lines. Specificity was confirmed by determining the size of the amplicons and retesting of positive samples.

PCR products were detected by electrophoresis in a 1.5% agarose gel containing 0.5 μg/ml ethidium bromide. Gels were analyzed using Quantity One software (BioRad Laboratories, Hercules, CA). Figure 1 shows a representative gel electrophoresis assay of the study viruses.

### Statistical analysis

The difference in virologic findings between baseline and 4 months posttreatment was evaluated statistically by means of the Wilcoxon signed rank test.

## Results

Pain and gingival swelling and redness were observed in all abscess sites (Table 1). Suppuration was found in 66.7% and hypermobility in 77.8% of teeth with periodontal abscess (Table 2). Mean probing pocket depth at baseline was 8.4 mm for abscess sites and 2.1 mm for healthy periodontal sites.

At 4 months post-therapy, all clinical variables had improved markedly compared to pre-therapy (Table 2). None of the previous periodontal abscess sites demonstrated pain, swelling or redness. Bleeding on probing and tooth mobility were significantly reduced, and no site showed suppuration. Posttreatment probing pocket depth in previous abscess sites averaged 1.9 mm.

Table 3 shows the distribution of herpesviruses in the study patients. Each set of samples from the same study tooth had the same viral composition. HCMV was detected in 12 (66.7%) and EBV-1 in 13 (72.2%) of the 18 abscess sites studied. Co-infection by HCMV and EBV-1 occurred in 10 (55.6%) of the abscess sites. By contrast, HCMV was found in only one of the 18 (5.6%) healthy periodontal sites and EBV-1 in none (difference between abscess and healthy sites, $P = 0.002$). At 4 months posttherapy, HCMV and EBV-1 were not detected in any study site (decrease compared to pretreatment, $P < 0.001$).

As seen in Table 4, most abscess-associated periodontal sites revealed moderate to severe clinical symptoms and signs. The 15 periodontal abscesses that yielded study herpesviruses tended to demonstrate more

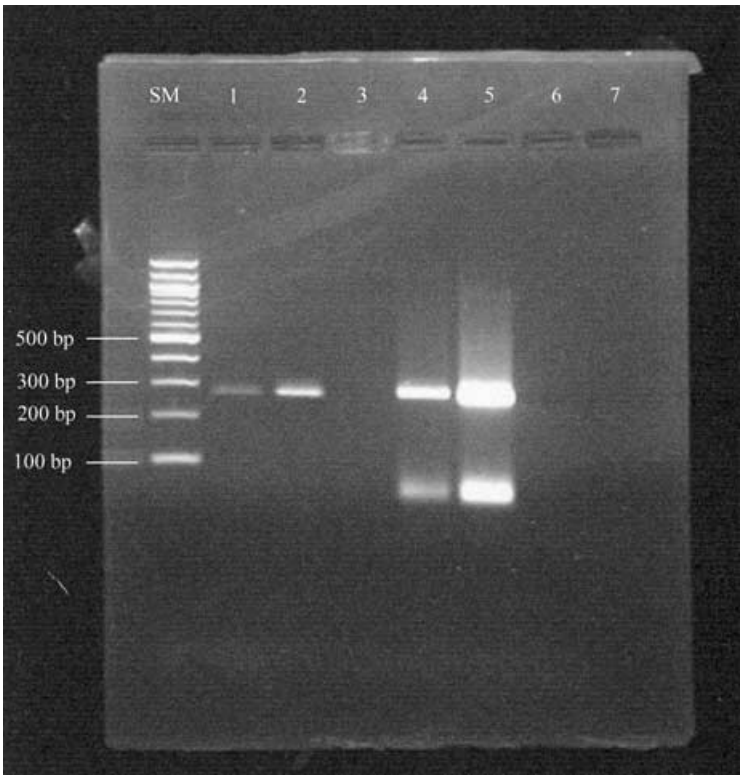


*Fig. 1.* SM: Size Marker (100 bp DNA Ladder; New England Biolabs, Inc, Beverly, MA). Lane 1: Patient sample with EBV. Lane 2: positive control of EBV. Lane 3: negative control of EBV. Lane 4: patient sample with HCMV. Lane 5: positive control of HCMV. Lane 6: negative control of HCMV.

*Table 1.* Clinical characteristics of 18 periodontal abscess sites

| Symptoms/ signs | Total no. of abscess lesions | No. (%) of lesions with severe symptoms/ signs | No. (%) of lesions with moderate symptoms/signs | No. (%) of lesions with mild symptoms/signs | No. (%) of lesions with no symptoms/ signs |
|---|---|---|---|---|---|
| Pain | 18 | 10 (55.6) | 6 (33.3) | 2 (11.1) | 0 |
| Swelling | 18 | 8 (44.4) | 7 (38.9) | 3 (16.7) | 0 |
| Redness | 18 | 9 (50) | 7 (38.9) | 2 (11.1) | 0 |

*Table 2.* Clinical characteristics at baseline and at 4 months posttreatment of 18 periodontal abscess sites

| Clinical variables | Baseline | 4 months posttreatment | *P*-value (Wilcoxon signed rank test) |
|---|---|---|---|
| Mean probing pocket depth in mm | $8.4 \pm 1.5$ | $1.9 \pm 0.8$ | 0.001 |
| % sites showing bleeding upon probing | 100% | 16.7% | 0.001 |
| % sites showing suppuration upon probing | 66.7% | 0% | $<0.001$ |
| % abscess teeth showing tooth hypermobility | 77.8% | 13.3% | 0.002 |
| Mean Plaque Index at abscess teeth | $1.5 \pm 0.6$ | $0.4 \pm 0.5$ | 0.001 |

*Table 3.* Occurrence of HCMV and EBV-1 in 18 periodontal abscess and 18 periodontally healthy sites

| Items | No. (%) of sites showing HCMV | No. (%) of sites showing EBV-1 | No. (%) of sites showing HCMV–EBV-1 co-infection | No. (%) of sites showing neither HCMV nor EBV-1 |
|---|---|---|---|---|
| Periodontal abscesses ($n = 18$) | 12 (66.7) | 13 (72.2) | 10 (55.6) | 3 (16.7) |
| Healthy sites ($n = 18$) | 1 (5.6) | 0 | 0 | 17 (94.4) |
| *P*-value (Wilcoxon signed rank test) | 0.002 | $<0.001$ | 0.002 | $<0.001$ |

severe pathosis than the three abscesses with no herpesviruses. The highest proportion of hypermobile teeth was found with abscesses showing HCMV and EBV-1 co-infection. However, the small study size precluded a statistical evaluation of the relationship between periodontal herpesviruses and abscess severity.

## Discussion

The understanding of the condition or set of conditions that are causal antecedents of periodontal abscess formation is still developing. This study found a significantly higher presence of HCMV and EBV-1 in subgingival samples from periodontal abscess lesions than from healthy periodontal sites. HCMV and EBV are also associated with symptomatic periapical pathosis (44) and necrotizing ulcerative gingivitis (10). In HIV-infected patients, HCMV has been implicated in periodontal abscess formation and other acute oral infections (6, 16, 51). HCMV (8, 41, 54) and EBV (47, 48) have been linked to extraoral abscess development as well. The present findings together with the potential of herpesviruses to induce acute inflammation provide supportive evidence for a herpesviral role in the pathogenesis of periodontal abscesses.

We hypothesize that some types of periodontal abscesses develop as a result of a series of interactions among herpesviruses, bacteria and host immune reactions. Specifically, we suggest that acute exacerbation of periapical disease is due to an escalation of pathophysiologic events, in which herpesvirus activation can play an important role. Herpesviruses exert higher pathogenicity during productive replication than in the latent state of infection (2). Reactivation of latent viruses can occur spontaneously or after tissue trauma, emotional stress, fever, exposure to ultraviolet light, drugs and immunosuppression (2). HCMV is intermittently shed and anti-HCMV antibody levels fluctuate over time (17, 36), and EBV-seropositive individuals excrete low levels of the virus for extended periods of time (30, 43), indicating episodic asymptomatic reactivation of latent herpesviruses throughout life. To cope with hostile host environments, herpesviruses have developed strategies to down-regulate antiviral host defenses to suit their replication needs. Herpesviruses aim to destroy components of the major histocompatibility complex pathways within macrophages, markedly impairing their principal role in antigen presentation, silence natural killer cells, inhibit apopto-

*Table 4.* Relationship between herpesviruses and clinical severity of periodontal abscesses

| Periodontal herpesviruses | No. of abscesses | Pain* | Swelling* | Redness* | Mean probing depth in mm | % teeth with hypermobility |
|---|---|---|---|---|---|---|
| HCMV+/EBV– | 2 | 3.5 | 3.5 | 3.5 | 8.0 | 50.0 |
| HCMV–/EBV+ | 3 | 4.0 | 3.0 | 3.3 | 9.0 | 66.7 |
| HCMV+/EBV+ | 10 | 3.5 | 3.2 | 3.6 | 8.9 | 90.0 |
| HCMV–/EBV– | 3 | 2.7 | 3.1 | 3.0 | 6.7 | 66.7 |

*Mean clinical severity score was assessed using an analogue scale from 1 to 4: 1 (none), 2 (mild), 3 (moderate), 4 (severe).

sis, and divert potent antiviral cytokine responses (7, 35, 37). As discussed above, herpesvirus infections can also facilitate bacterial colonization of epithelial and connective tissue cells (5, 18, 25, 27, 31). Dual infection of herpesviruses can result in a particularly severe disruption of the immune system and worsened clinical outcome (46, 49). However, the limited sample size of this study prevented analyses of such relationships. By perturbing a diverse set of host defenses, herpesvirus periodontal infections may help enhance the growth and tissue invasiveness of abscess-producing bacteria.

Considering the frequent occurrence of herpesviruses and pathogenic bacteria in periodontal lesions, it is not clear why periodontal abscesses are relatively rare. Most likely, the periodontal pocket opening can normally support an outflow of pus from subgingival areas, which is adequate to prevent a significant accumulation of pathogenic bacteria, polymorphonuclear leukocytes and cellular debris. However, periodontal abscess formation can result from dental trauma (42) and periodontal treatment (20). Abscesses may preferentially occur in periodontal sites that exhibit herpesvirus reactivation and high bacterial pathogen burden together with low levels of antiviral cytotoxic $CD8^+$ T-lymphocytes and anti-bacterial antibodies. Consistent with this hypothesis, Hafström et al. (23) found low antibody levels against bacterial strains recovered from periodontal abscesses.

The absence of herpesviruses in the periodontium after antimicrobial therapy is of interest. Pacheco et al. (39) reported a similar anti-herpesviral effect of periodontal therapy. It seems that gingival inflammation is a requirement for a sustained presence of periodontal herpesviruses. HCMV infects periodontal monocytes/macrophages and T-lymphocytes and EBV infects B-lymphocytes (11). Since macrophages and other inflammatory cells have a restricted lifespan of a few months (40), herpesviruses may not persist in the periodontium unless they are replenished by infected cells or experience extended survival time due to herpesvirus-mediated inhibition of apoptosis (55). However, present evidence supports the notion that herpesviruses are not merely passive bystanders to gingival inflammation and periodontal breakdown. Kamma et al. (29) found that, even if no difference was observed in degrees of gingival inflammation, herpesviruses occurred more frequently in actively progressing than in stable periodontitis sites. In aggressive periodontitis patients, Kubar et al. (32) showed that periodontal sites with HCMV presence were associated with increased periodontal pocket depth and attachment loss compared with sites with no HCMV presence but the two types of sites did not differ significantly in clinical inflammation. Also, symptomatic periapical lesions exhibit more active herpesvirus infections than asymptomatic lesions of similar radiographic size (44). The ability of efficacious antimicrobial therapy to markedly reduce or eliminate periodontal herpesviruses may in part be responsible for a positive therapeutic outcome.

In summary, the present study found a significantly higher occurrence of HCMV and EBV-1 in periodontal abscess lesions than in healthy periodontal sites. Although herpesviruses may not have the ability to develop or maintain an abscess on their own, they may play an important contributory role in the polymicrobial abscess infection. However, the present evidence for a role of herpesviruses in periodontal abscess formation is circumstantial and a cause-and-effect relationship remains to be established. To distinguish between correlation and causality, information is needed on the extent to which an active herpesvirus infection gives rise to periodontal acute pathosis and the extent to which acute periodontal disease may activate latent herpesviruses. The possible causal involvement of herpesviruses in the development of periodontal abscesses merits further investigation.

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