Scientific Research Report

The Prevalence of EBV and KSHV in Odontogenic Lesions

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ARTICLE INFO

ABSTRACT

Objectives: Odontogenic lesions evolve as a result of altered dental development. This study aimed to evaluate the prevalence and the coinfection of Epstein-Barr virus (EBV) and Kaposi sarcoma−associated herpesvirus (KSHV) in radicular cysts, dentigerous cysts, odontogenic keratocysts, and ameloblastomas.
Methods: Polymerase chain reaction (PCR) was used to analyse 66 cases of odontogenic lesions for the presence of EBV-DNA and KSHV-DNA. These lesions were 15 radicular cysts, 16 dentigerous cysts, 18 odontogenic keratocysts, and 17 ameloblastomas.
Results: EBV-DNA was detected in 24 (36.4%) of the studied samples as follows: 6 samples (40.0%) of radicular cysts, 4 (25.0%) of dentigerous cysts, 10 (55.6 %) of odontogenic keratocysts, and 4 (23.5%) of ameloblastomas ($P = .168$). KSHV-DNA was found in 16 (24.2%) of the studied samples as follows: 1 sample (6.7%) of radicular cysts, 6 (37.5%) of dentigerous cysts, 8 (44.4 %) of odontogenic keratocysts, and 1 (5.9%) of ameloblastomas ($P = .001$). Additionally, EBV and KSHV were positively correlated in all studied samples ($P = .002$).
Conclusions: Both EBV and KSHV are found in odontogenic cysts and ameloblastomas. KSHV and EBV are more prevalent in odontogenic keratocysts than in other studied odontogenic lesions. Further, there is a high prevalence of EBV and KSHV coinfection in odontogenic cysts and ameloblastomas.

Introduction

Odontogenic cysts and tumours are jaw lesions that could occur in any patient regardless of their sex, age, race, or socioeconomic status. They evolve as a result of altered dental development.[1] These odontogenic epithelial lesions arise from remnants of surviving cells from programmed cell death. However, the stimulus that initiates the odontogenic epithelial growth and further development of these lesions is poorly understood.

Both Epstein-Barr virus (EBV) and Kaposi sarcoma−associated herpesvirus (KSHV) have the potential to stimulate cellular

growth. EBV is a double-stranded DNA gammaherpesvirus that primarily infects B cells and epithelial cells. It causes a variety of diseases and is spread mostly by saliva containing infected epithelial cells. EBV, which causes infectious mononucleosis, infects approximately 95% of adults worldwide.[2,3] KSHV is a double-stranded DNA gammaherpesvirus. It is most closely related to EBV, being a lymphotropic and oncogenic virus that contributes to the oncogenesis of several human tumours. KSHV infects B lymphocytes, T lymphocytes, monocytes, endothelial cells, and epithelial cells. Several human tumours have been associated with KSHV, including Kaposi sarcoma, KSHV-associated inflammatory cytokine syndrome, and multicentric Castleman disease. Whilst EBV was identified in 1964, KSHV was first detected in 1994. Both EBV and KSHV have lytic and latent life cycles, as do all herpesviruses. Once these viruses enter a human cell they may remain latent until reactivation by an external stimulus such as immunosuppressive events

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within the host.[4,5] EBV-positive tumours have been linked to the latent phase of the EBV life cycle. However, there is growing evidence that the lytic phase of EBV has a role in oncogenesis by the creation of infectious particles, in order to infect additional cells, and the control of cellular oncogenic pathways.[6]

Due to its diagnostic value, polymerase chain reaction (PCR) has been incorporated into routine medical practice as a means of early diagnosing EBV-related diseases, assessing treatment efficacy, as well as predicting prognosis.[7] As a relatively newly discovered virus, KSHV currently has more limited diagnostic and therapeutic options than EBV. Accordingly, current research attempts to discover treatment for KSHV infections and their related diseases. Consequently, different nonstandardised diagnostic tests for identifying KSHV are currently in practice.[5]

Several previous studies have reported the presence of EBV in odontogenic cysts and tumours.[8-10] Meanwhile, there is no previous study that has been conducted on the detection of KSHV in these lesions. Studying the prevalence and coexistence of EBV and KSHV in odontogenic lesions will help in better understanding the pathogenesis and management of these lesions. This study aimed to evaluate the prevalence and the coinfection of EBV and KSHV in radicular cysts, dentigerous cysts, odontogenic keratocysts, and ameloblastomas.

Methods

This retrospective study included 66 formalin-fixed paraffin-embedded (FFPE) samples as follows: radicular cysts (n = 15), dentigerous cysts (n = 16), odontogenic keratocysts (n = 18), and ameloblastomas (n = 17). The sample size estimation was performed using the statistical software G*Power 3.1.9.7. For the calculation, we used the information about virus DNA presence provided by Li et al.[10] Accordingly, an effect size of 0.35, 80% power, and α error of 5% were used, and 15 cases were required per group. These cases were selected because they represent the most common odontogenic lesions of the jaws. These samples were taken from the Laboratory of Oral Pathology at Tongji Hospital along with their clinical, radiologic, and histopathologic data. Participants were free of acquired immune deficiency syndrome and did not take antivirals or immunosuppressive medications. In accordance with the World Medical Association Declaration of Helsinki, this study was approved by Tongji Medical College's Institutional Review Board.

A special kit for DNA extraction from FFPE samples, based on the silica membrane extraction method, was used in this study (DN32, Aidlab. Co. LTD). A total of 5 pieces of 10-μm thick sections were cut from each FFPE block, deparaffinised in xylene and rehydrated with descending concentrations of ethanol and distilled water. The albumin gene was amplified in each sample using primers specific for that gene. Consequently, all samples were found to be suitable for further molecular analysis.

According to previously validated primers and procedures described in the literature,[11,12] the DNA of EBV and KSHV was identified by conventional PCR method. Primers for the EBV nuclear antigen 1 (EBNA-1) segment of EBV were used with the following sequences: F: 5-AGATGGTGAGCCTGACGTG-3; R: 5-CCAAGTTCCTTCGTCGGTAG-3. In this case, the PCR product derived had 241 base pairs (bp). Meanwhile, primers for the KSHV viral interferon regulatory factor-3 (vIRF-3) segment were as follows: F: 5′ TCC TGG CCC TGT GTT ATT GT 3′; R: 5′ TCG CCA CAG GAA GCT TAG AT 3′. The PCR product was 244 bp long.

The final volume of the PCR was 25 μL, containing 3 μL of the isolated DNA solution, 200 mmol/L each deoxynucleoside triphosphate, 15 pmol of the used primers, and 12.5 μL of 2 $\times$ Taq MasterMix (Aidlab Co. LTD). The PCR conditions were as follows: a 15-minute activation phase at 95 °C followed by 30 seconds of denaturation at 94 °C, 30 seconds of annealing at 55 °C, and 1 minute of extension at 72 °C. Every PCR experiment included a positive and a negative control. A positive control for the EBV experiment was DNA extracted from human B cell lymphoma P3HR1. Nevertheless, DNA from BC1 cells infected with KSHV was used as a positive control for KSHV and distilled water as a negative control for both EBV and KSHV experiments. PCR products were run on a 3% agarose gel and the 241-bp and 244-bp products were stained with ethidium bromide.

The Statistical Package for the Social Sciences (SPSS) 28.0 software (IBM SPSS) was used to analyse the data. Comparing EBV-DNA and KSHV-DNA within and between groups was carried out using McNemar test and chi-square test, respectively. The correlation of the presence of the 2 viruses was analysed by the Spearman rank correlation coefficient. The results were considered statistically significant if $P < .05$.

Results

Table 1 summarises the relevant clinical characteristics of study participants. Sixty-six cases were included in the study.

Table 1 – Clinical features of the studied cases.

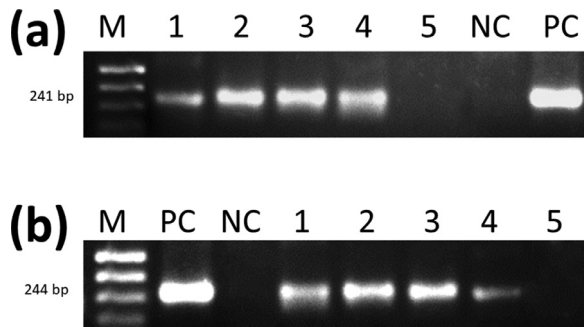| Variables	Total	Radicular cysts	Dentigerous cysts	Odontogenic keratocysts	Ameloblastomas
Patients, n	66	15	16	18	17
Age, y					
Mean	37.26	39.53	39.69	37.39	32.82
Range	12-74	12-73	12-74	15-66	12-70
Sex, n (%)					
Male	44 (66.7%)	11 (73.3%)	13 (81.3%)	11 (61.1%)	9 (52.9%)
Female	22 (33.3%)	4 (26.7%)	3 (18.8%)	7 (38.9%)	8 (47.1%)
Location, n (%)					
Mandible	36 (54.5%)	3 (20.0%)	5 (31.3%)	12 (66.7%)	16 (94.1%)
Maxilla	30 (45.5%)	12 (80.0%)	11 (68.8%)	6 (33.3%)	1 (5.9%)

Fig. 1 – The results of conventional polymerase chain reactions for Epstein-Barr virus DNA (A) and Kaposi sarcoma−associated herpesvirus (B) are shown on ethidium bromide-stained agarose gels. M, molecular marker; PC, positive control; NC, negative control. Results are positive in lanes 1 (radicular cyst), 2 (dentigerous cyst), 3 (odontogenic keratocyst), and 4 (ameloblastoma). Negative results for the studied lesions in lane 5.

There were 22 female patients (33%) and 44 male patients (66.7%). Patients' mean age was 37.26 years. The mandible was involved in 36 cases (54.5%), whereas the maxilla was involved in 30 cases (45.5%). Figure 1 illustrates the PCR electrophoresis of the studied viruses, whilst Table 2 shows the prevalence of EBV-DNA and KSHV-DNA in the studied groups.

EBV-DNA was detected in 24 (36.4%) of the studied samples as follows: 6 samples (40.0%) of radicular cysts, 4 (25.0%) of dentigerous cysts, 10 (55.6 %) of odontogenic keratocysts, and 4 (23.5%) of ameloblastomas (Figure 2). Chi-square test revealed a nonsignificant difference in the prevalence of EBV-DNA amongst the studied samples (χ^2 test = 5.054, P = .168). KSHV-DNA was found in 16 (24.2%) of the total odontogenic lesions as follows: 1 sample (6.7%) of radicular cysts, 6 (37.5%) of dentigerous cysts, 8 (44.4 %) of odontogenic keratocysts, and 1 (5.9%) of ameloblastomas (Figure 2). A highly significant difference was found in the presence of KSHV-DNA amongst the tested samples (χ^2 test = 11.175, P = .01). Furthermore, a Spearman correlation test revealed a highly positive correlation of the viruses' presence between EBV-DNA and KSHV-DNA in all study samples (ρ = .381, P = .002).

Discussion

The current study investigated for the first time the coinfection of EBV and KSHV in odontogenic cysts and ameloblastomas. Different herpesviruses have different tissue tropisms and are latently present in the majority of people.[13] EBV is transmitted primarily through saliva and rarely through blood or semen.[3] It usually causes infection in children at an early age, and the majority of cases are uncomplicated and may go unnoticed. Nevertheless, puberty brings about a second peak of seroconversion, caused by increased exposure to infected people. Virus load and immune system state, influenced by gene composition, determine EBV infection course.[3] Although EBV latent infection is generally not harmful to people, a number of diseases might develop due to disorders during the latency period or uncontrolled lytic phase. KSHV is mainly transmitted through saliva. However, transmission by blood, solid organ donation, and sexual contact is possible. The prevalence of KSHV infection in children is higher in endemic countries, suggesting a possibility of horizontal transmission through saliva. Conversely, KSHV infection is uncommon in children living in regions with low seroprevalence. Sexual transmission is likely to be the predominant mode of transmission in these regions.[5] In contrast to EBV, KSHV has a lower seroprevalence rate and fluctuates according to geographic location. According to a recent study, there is a certain percentage of KSHV infection amongst the free blood donors in Wuhan City, suggesting the need for KSHV screening of blood donors.[14]

Odontogenic cysts and tumours are a group of lesions that occur primarily within the jawbone. B cells serve as hosts for both EBV and KSHV, transmitting the viruses throughout the body. This could explain the path through which both viruses reach the jaw bones and infect the odontogenic cysts and tumours. Additionally, it has been found that EBV virions released from B cells prefer epithelial cells due to the makeup of the envelope glycoproteins.[3] KSHV was well known for its intraosseous infection of various bones. In one of the few reports describing Kaposi sarcoma in the jaws, Noel et al described an intraosseous case of KSHV-positive Kaposi sarcoma in the mandible. Interestingly, cutaneous or mucosal lesions were not found in that case.[15] B cells and epithelial cells are the main cells infected by EBV. EBV infects epithelial cells in the oropharynx through oral secretions. EBV can be transmitted to B cells from epithelial cells, but other cell types can also become infected with the virus. Therefore, EBV can shuttle between a variety of cell types, primarily between epithelial cells and B cells.[3]

Several previous studies reported the presence of EBV in odontogenic cysts and tumours.[8-10] The prevalence of EBV in our ameloblastoma samples is comparable to that found by Fujita et al.[8] In contrast to our study, Fujita et al did not detect EBV in either dentigerous cysts or odontogenic keratocysts. This inconsistency may be due to the different methods of analysis used in the 2 studies as well as the different genes that each study targeted. Fujita et al used an in situ

Table 2 – The prevalence of Epstein-Barr virus (EBV) DNA and Kaposi sarcoma−associated herpesvirus (KSHV) DNA in the studied groups.

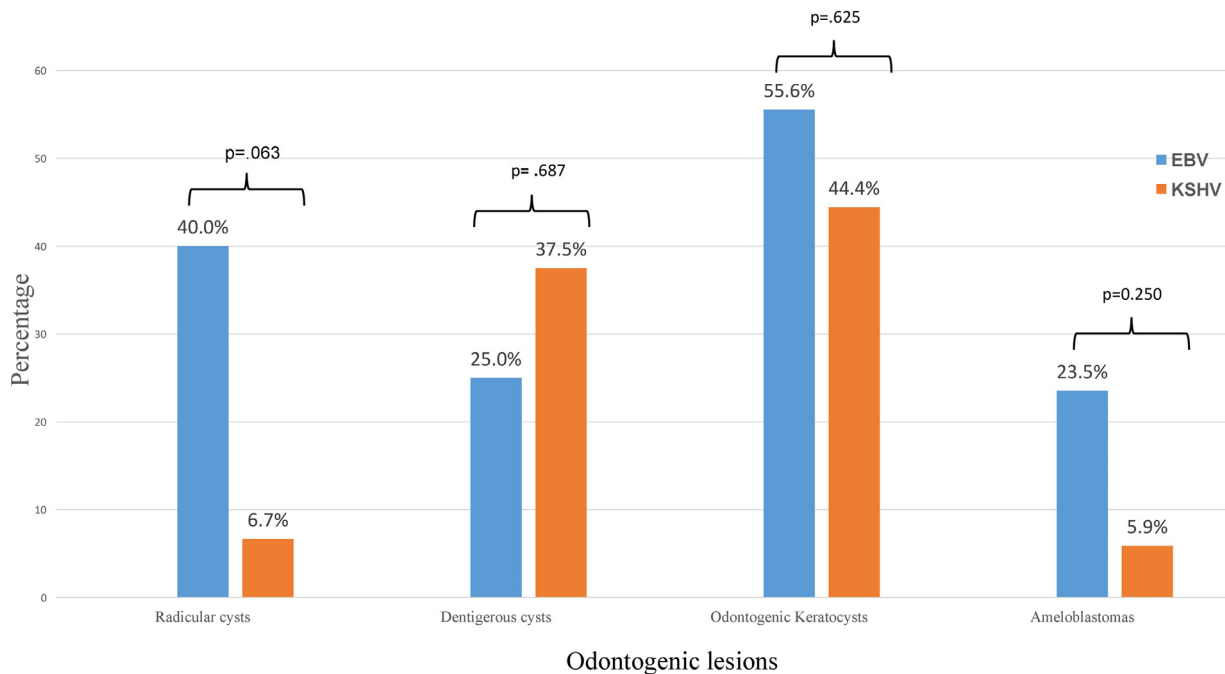|	Radicular cysts, n = 15	Dentigerous cysts, n = 16	Odontogenic keratocysts, n = 18	Ameloblastomas, n = 17	P value
EBV	(n = 6) 40.0%	(n = 4) 25.0%	(n = 10) 55.6%	(n = 4) 23.5%	.168
KSHV	(n = 1) 6.7%	(n = 6) 37.5%	(n = 8) 44.4%	(n = 1) 5.9%	.01*

* Significant.

Fig. 2 – Prevalence of Epstein-Barr virus and Kaposi sarcoma–associated herpesvirus in odontogenic lesions. P values were determined by McNemar test.

hybridisation method detecting EBV-encoded small RNA, whilst we used a conventional PCR method detecting EBNA-1. It has been concluded that each EBV-DNA might function variously in tumours and a specific part of EBV-DNA could be transforming in different tissues.[9] Furthermore, different EBV-DNA genes were found in 48% of ameloblastomas[9] and in 33.3% of radicular cysts.[10] Meanwhile, there is no previous study that has been conducted on the detection of KSHV in odontogenic cysts and tumours.

An interesting finding is the correlated presence of EBV and KSHV in the studied odontogenic cysts and ameloblastomas. It brings attention to the importance of herpesviruses interaction in odontogenic cysts and tumours. In fact, KSHV is closely related to EBV.[16] The cooperation between EBV and KSHV is quite evident in some lesions, such as primary effusion lymphoma, which harbor EBV and KSHV genomes coinfecting lymphoma cells.[13,17] KSHV replication seems to be triggered by viral coinfection, both by direct activation of toll-like receptors and by the production of inflammatory cytokines.[18] Indeed, EBV might facilitate KSHV plasmid persistence by modulating the genome of the KSHV, in particular by promoting the expression of progrowth lytic genes. Additionally, EBNA-1 overexpression increases KSHV loads and KSHV latency-associated nuclear antigen expression in primary effusion lymphomas.[13] In vitro, EBV facilitates the persistence of KSHV infection in B cells. Therefore, any effect of KSHV on human immune compartments should preferably be investigated in association with infection by EBV.[16]

Both EBV and KSHV have the potential to stimulate cellular growth. They develop their oncogenic properties by continuing expression of genetic products that manipulate anti-apoptotic, proliferative, or immune escape functions by

interacting with cells' genetic material.[19] There are 2 mechanisms underlying the oncogenic role of KSHV. The classical mechanism of neoplastic transformation induced by viral proto-oncogenes and KSHV-induced viral proteins and inflammatory cytokines. Moreover, due to the paradox that neither lytic nor latent KSHV can cause cellular transformation, a hypothesis called paracrine oncogenesis has been presumed. KSHV infection can have its oncogenic effects only in conjunction with co-factors such as immunosuppression and genetic susceptibility.[5,20] In addition to EBV having oncogenic properties, Makino et al suggested that its effect is attributed to its presence in plasma and B cells of the jaw lesions. As a result, EBV enhances tissue damage and bone resorption in the affected area.[21] In contrast, it has been recently shown that infection with certain viruses, including EBV, can trigger T cells to respond in a positive manner against abnormally expressed tumour-associated cellular antigens.[22]

The PCR technique cannot determine the spatial distribution of a virus within a lesion. KSHV infects B lymphocytes, T lymphocytes, monocytes, endothelial cells, and keratinocytes. Meanwhile, EBV infects mainly epithelial and B cells.[3] Hence, the presence of these 2 viruses in odontogenic lesions might simply reflect their coincidental presence within inflammatory cells inside the lesions. Radicular cysts are inflammatory odontogenic cysts where inflammatory cells are expected to be present in large numbers. Despite this, the current study showed that KSHV was more prevalent in odontogenic keratocysts and dentigerous cysts than in radicular cysts and ameloblastomas. In addition, odontogenic keratocysts have a higher incidence of EBV than other studied odontogenic lesions. In spite of being classified as developmental lesions, the majority of odontogenic keratocysts and dentigerous cysts are characterised by the presence of

chronic inflammatory infiltrate in the connective tissues.[23] Furthermore, the inflammatory reaction is also observed in ameloblastomas.[1] In this study, we used a primer designed to detect EBV-DNA by targeting EBNA-1 segment. EBNA-1 was selected due to its extensive conservation, nonpolymorphism, and activity during both the lytic and latent phases.[24] For the detection of KSHV-DNA in this study, we used primers targeting vIRF-3. vIRF-3 is expressed during lytic replication and is also a bona fide latency gene.[25]

The prevalence rate of EBV was higher than that of KSHV in the studied odontogenic cysts and ameloblastomas. This result could be due to the widespread presence of EBV over KSHV amongst the population. In the current study, we demonstrated for the first time that KSHV-DNA was present in odontogenic cysts and ameloblastomas. This result could pave the way for further research that targets the role of KSHV in the pathogenesis of odontogenic cysts and tumours. However, just the presence of a virus inside a lesion does not imply that the virus should have a role in the pathogeneses or severity of that lesions. For example, Jang et al demonstrated that EBV-DNA is present in 48% of ameloblastomas but in 92% of normal oral tissues like the tongue, gingiva, and buccal mucosa.[9]

Although several studies have demonstrated the presence of EBV and KSHV in tumours and other pathologic and normal tissues, the exact mechanisms and roles of the viruses are unclear in these lesions. Certainly, identifying the specific RNA and proteins of KSHV and EBV will greatly improve the sensitivity and specificity of DNA detection techniques and uncover the different pathways associated with EBV and KSHV infections. In situ hybridisation and immunohistochemistry are essential for determining the viruses' spatial distribution.

Conclusions

Both EBV and KSHV are found in odontogenic cysts and ameloblastomas. KSHV and EBV are more prevalent in odontogenic keratocysts than in other studied odontogenic lesions. Further, there is a high prevalence of EBV and KSHV coinfections in odontogenic cysts and ameloblastomas.

Funding

Conflict of interest

None disclosed.

Acknowledgements

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