

Low Frequency of Human Papillomavirus and Epstein-Barr Virus DNA in Ameloblastoma of Thai Patients

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ABSTRACT

Aim: This preliminary study aimed to evaluate the frequency of human papillomavirus (HPV) and Epstein-Barr virus (EBV) DNA in solid/multicystic ameloblastoma (AM).

Materials and methods: A total of 20 fresh-frozen AM tissue was investigated for HPV and EBV DNA using polymerase chain reaction (PCR) at L1 of HPV and LMP1 of EBV.

Results: It was found that 2 out of 20 cases (10%) were positive for HPV PCR whereas 3 out of 20 cases (15%) were positive for EBV PCR. Importantly, a mix of HPV and EBV DNA was observed in one case.

Conclusion: Our study presented a low frequency of HPV and EBV DNA in AM. Further studies with different cohorts and larger sample sizes are necessary for a better understanding of the frequency of both viruses in AM.

Clinical significance: HPV and EBV may not be involved in ameloblastogenesis.

Keywords: Ameloblastoma, DNA, Epstein-Barr virus, Human papillomavirus, Thai.

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INTRODUCTION

Ameloblastoma (AM) is a benign neoplasm derived from residual epithelial components of tooth development and generally present in the jawbone. The majority of AM occurs in patients between 20 and 40 years of age, although they can occur at any age. Ameloblastoma was observed in 1% of maxillofacial tumors and approximately 35% of odontogenic tumors in Thailand AM-solid/multicystic type.¹⁻³ This tumor is often asymptomatic, slow-growing but shows locally aggressive behavior and has high recurrence potential among odontogenic tumors. The mechanisms involved in the pathogenesis of AM have not been completely elucidated. Factors such as trauma, tooth eruption, and viral infection have been reported with AM etiopathogenesis.³⁻⁵

To date, several studies reported an association between the presences of viral DNA in many cancers. Both human papillomavirus (HPV) and Epstein-Barr virus (EBV) are known as oncogenic viruses.^{6,7} Human papillomavirus infection is the most common sexually transmitted infection and about 9–13% of the world's population is already infected.⁸ High-risk HPV (hrHPV) is an established cause of various human neoplasms including cervical, vulvar, sinonasal, oral, and penile cancers.⁸⁻¹¹ In addition, EBV is the first human tumor virus that is observed in more than 90% of the world's adult population.⁶ Epstein-Barr virus can contact and cause infectious mononucleosis during childhood. In addition, EBV infection could be linked to several other types of human malignancies, particularly nasopharyngeal cancer (NPC), gastric cancer (GC), Burkitt's lymphoma, some Hodgkin's lymphoma, and B-cell lymphoma.^{6,12}

Epstein-Barr virus and HPV implicate to cellular immortalization and oncogenesis. Their genetic materials can produce viral oncoproteins that inhibit tumor suppressor gene and/or integrate viral DNA to the human genome.^{13,14} Considering the ameloblastoma pathogenesis, the relationship with HPV and EBV

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is needed to be substantiated. In this study, we aimed to evaluate the frequency of HPV and EBV DNA in solid/multicystic AM which could contribute to the knowledge concerning viral-associated AM patients in Thailand.

MATERIALS AND METHODS

Ethical Statement and Sample Recruitment

Ethical consideration of this cross-sectional study was reviewed and approved by the Institutional Review Board of Faculty of the Dentistry/Faculty of Pharmacy, Mahidol University, Bangkok, Thailand (Approval number: 2018/005.1101). An informed consent was obtained from all patients before the collection of specimens. Data were analyzed anonymously. A total of 20 fresh-frozen tissue samples were obtained from the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Mahidol University,

Table 1: Clinicopathological features of ameloblastoma patients and results of EBV and HPV PCR

Code	Sex	Age	Location	Histological subtype	EBV PCR	HPV PCR
AM1	F	30	Mandible	Plexiform	Positive	Positive
AM2	M	63	Mandible	Plexiform	Negative	Negative
AM3	F	47	Mandible	Plexiform	Negative	Negative
AM4	M	11	Mandible	Plexiform	Positive	Negative
AM5	F	60	Mandible	Follicular	Negative	Negative
AM6	M	66	Mandible	Plexiform	Positive	Negative
AM7	M	23	Mandible	Follicular	Negative	Positive
AM8	M	51	Mandible	Follicular	Negative	Negative
AM9	F	30	Mandible	Plexiform	Negative	Negative
AM10	M	37	Mandible	Plexiform	Negative	Negative
AM11	M	59	Mandible	Follicular	Negative	Negative
AM12	M	44	Maxilla	Follicular	Negative	Negative
AM13	F	24	Mandible	Plexiform	Negative	Negative
AM14	F	25	Maxilla	Follicular	Negative	Negative
AM15	M	54	Mandible	Plexiform	Negative	Negative
AM16	F	54	Maxilla	Plexiform	Negative	Negative
AM17	M	73	Mandible	Follicular	Negative	Negative
AM18	F	8	Mandible	Follicular	Negative	Negative
AM19	M	66	Maxilla	Plexiform	Negative	Negative
AM20	M	50	Mandible	Plexiform	Negative	Negative

F, female; M, male

during January 1, 2018, to December 31, 2019. These AM patients were Thai—12 males and 8 females with a median age of 48.5 years (range 8–73 years). Most cases were located in the mandible while only four cases were located in the maxilla. All cases were histologically confirmed as solid multicystic AM 8 follicular and 12 plexiform histological subtypes by two oral pathologists based on current World Health Organization (WHO) guidelines.¹⁵ Clinical and pathological data such as age, sex, anatomic location of the lesions, and histological subtypes are summarized in Table 1.

DNA Isolation

Fresh-frozen tissues were lysed at 50°C overnight with a lysis buffer (0.75 mol/L NaCl, 0.024 mol/L EDTA, pH 8.0) that was mixed with 10% sodium dodecyl sulfate (SDS) and 20 mg/mL proteinase K (Sigma-Aldrich, St. Louis, MO, USA). Next, the DNA purification was done using a standard phenol-chloroform extraction protocol.¹⁶ Thereafter, the purified DNA was air-dried, eluted with distilled water, and stored below –20°C for subsequent use. The DNA concentration was measured using a NanoDrop 2000 spectrophotometer (ND-2000 Spectrophotometer, NanoDrop Technologies, Wilmington, DE, USA). The optical density 260/280 ratio was greater than 1.8, which is acceptable for DNA purity and PCR.

Detection of EBV and HPV DNA by Polymerase Chain Reaction

Polymerase chain reaction (PCR) was performed using the primers, displayed sequences, and conditions as shown in Table 2. Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) served as the internal control to test the quality of DNA. The *L1* HPV primer (GP5+/GP6)¹⁷ that encodes major capsid protein of HPV was tested

Table 2: Oligonucleotide primer sequences and conditions for PCR analyzes

Detection	Primer	Sequence 5'–3'	Amplicon size (bp)	Annealing temperature (°C)
Internal control (<i>GAPDH</i>)	<i>GAPDH</i> forward	CAGCCG-CATCTTCTTTTG	150	60
	<i>GAPDH</i> reverse	CAACAATATC-CACTTTAC		
EBV DNA	<i>LMP1</i> forward	CCAGACAGC-CAACAATTG	129	64
	<i>LMP1</i> reverse	GGTAGAAGAC-CCCCTAC		
HPV DNA	GP5+	TTTGTTACT-GTGGTAGATAC-TAC	150	56
	GP6+	CTTATAC-TAAATGT-CAAATAAAAAG		

to detect HPV DNA. The LMP-1 EBV primer¹⁸ that encodes EBV latent membrane protein was tested to detect EBV DNA.

The PCR mixtures of all reactions contained 1× PCR buffer, 200 mM dNTPs, 0.2 mM primers, 0.5 U Taq DNA polymerase (Qiagen, San Diego, CA, USA), and 50 ng of template DNA. DNA from the B958 and HeLa cell lines was used as the positive controls of EBV PCR and HPV PCR, respectively. Distilled water was used as the negative control in every PCR reaction. Following amplification, the PCR products were separated by gel electrophoresis using a 2% agarose gel in



TBE buffer and then stained with SYBR Green nucleic acid gel stain (Gelstar, Lonza, Allendale, NJ, USA). Furthermore, the PCR product being positive for HPV DNA was investigated for HPV typing by Sanger sequencing. The sequencing data were then identified for the HPV genotype by nucleotide blast using <https://blast.ncbi.nlm.nih.gov/Blast.cgi>. Due to the limited positive cases, descriptive statistics were used for characterization of the sample.

RESULTS

As shown in Table 1, the frequency of EBV and HPV was 3/20 (15%) and 2/20 (10%), respectively. From the histopathological feature, koilocytic changes due to viral infection were not observed in all samples. Among EBV-positive cases (AM1, AM4, and AM6), there were two males and one female. All were located in the mandible with histological plexiform subtype. Two HPV positive cases (AM1 and AM7) consisted of one male and one female. Both of them were located in the mandible, with individual histological plexiform and follicular subtypes. After sequencing and blasting, both DNA matched to the HPV 18 (KU298886.1) completely. Our results found a noteworthy case (AM1) showing mixed EBV and HPV DNA (Fig. 1).

DISCUSSION

The EBV and HPV are common cancer-associated viruses. Both viruses have permissive cells and induce tumorigenicity in specific cell types.¹⁴ Race is one of the dependent factors that affect frequencies of EBV and HPV DNA in each individual population.¹² We have summarized the varied frequencies of EBV and HPV DNA in AM from acquired previous studies in Tables 3 and 4. Since, there is no data

about the frequency of HPV and EBV DNA of AM in Thai population (PubMed Database, Scopus, and Web of Science), this preliminary study was carried out to evaluate both viruses' frequencies in Thai patients. Here, we found low frequencies of both viruses, which might suggest their minor involvement in a group of AM patients.

We observed 15% of EBV DNA in AM that was similar to the previous study by Fujita et al.¹⁹ and in range with other studies (0, 26.6, and 48% by Khalele et al.,²¹ Badrawy et al.,¹¹ and Jang et al.,²⁰ respectively) (Table 3). The differences of frequency may be affected by the EBV detection technique and racial involvement. In general, the gold standard technique for EBV detection is by *in situ* hybridization (ISH) of EBER; however, the cost of this technique is very expensive. The PCR is more convenient and highly sensitive, but it might cause false-positive results that require confirmation by immunohistochemistry (IHC) using EBV antibodies or ISH EBV-EBER.²⁰ To ensure the results of this study, future investigations by the other techniques may be needed.

The EBV-associated Burkitt's lymphoma has a high prevalence in sub-Saharan area of Africa, whereas EBV-associated nasopharyngeal cancer has a high prevalence in South China area,²⁰ suggesting that the incidence of EBV-associated cancer may be attributed to racial and/or geographic distribution. The current study in Thai AM patients showed the same frequency as that in Japanese AM patients¹⁹ but, however, was lower than that in Korean AM patients²⁰ (Table 3). Due to the small sample size in our study, investigation of EBV and HPV DNA of AM in a larger population may increase the strength of this epidemiology. It is worth noting that two studies in Egypt showed unequal results that may be caused by different detection techniques.^{11,21}

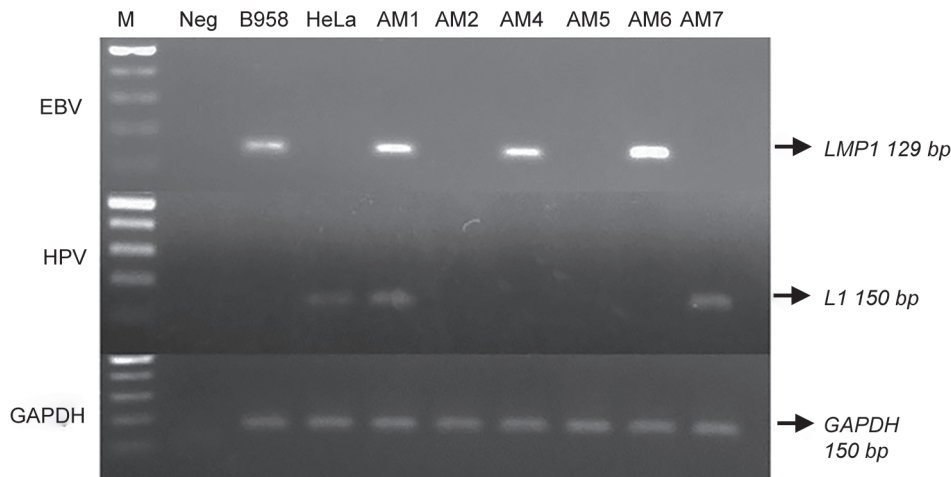


Fig. 1: Gel electrophoresis of EBV (*LMP1*) and HPV (*L1*) and *GAPDH* PCR in AM. Neg; distilled water used as negative control. B958 and HeLa cell lines DNA were used as positive controls. AM1, AM4, and AM6 showed positive for EBV PCR while AM1 and AM7 showed positive for HPV PCR. M: The ladder (left lane) is 100 bp marker

Table 3: Review of EBV DNA frequency in ameloblastoma

Study	Number of samples	EBV DNA (% , n)	Technique	Targeted gene	Country
Fujita et al. ¹⁹	53	15% (8/53)	<i>In situ</i> hybridization	<i>EBER</i>	Japan
Jang et al. ²⁰	17	48% (8/17)	PCR	<i>BamC, BMRF1, IR3</i>	Korea
Badrawy et al. ¹¹	15	26.6% (4/15)	Real-time PCR	EBV genome	Egypt
Khalele ²¹	40	0% (0/40)	Immunohistochemistry	<i>LMP1</i>	Egypt
This study	20	15% (3/20)	PCR	<i>LMP1</i>	Thailand

PCR; polymerase chain reaction

Table 4: Review of HPV DNA frequency in ameloblastoma

Study	Number of samples	HPV DNA (% , n)	HPV typing	Technique	Country
Kahn ⁴	10	30% (3/10)	None reported	IHC	USA
Kahn ²²	1	100% (1/1)	16/18	ISH	USA
van Heerden et al. ²³	1	100% (1/1)	18	ISH	South Africa
Sand et al. ²⁴	18	27.8% (5/18)*	1 case; type 18, 3 cases; mix 18,6/11, 1 case; nonspecific	PCR	Sweden
Namin et al. ²⁵	50	40% (20/50)	8/20; type 6, No types 8, 11, 16, 18, 31, or 33	PCR	Iran
Migaldi et al. ²⁶	18	11% (2/18)	Unknown, absence of type 6, 11, 16, 18, 31, 33, 35, 52, 58	IHC, ISH, nested-PCR	Italy
Mokhtari-Azad et al. ²⁷	100	32% (32/100)	6,11,16,31	PCR	Iran
Correnti et al. ⁵	18	33.3% (6/18)	4 cases; type 6, 1 case; mix 13,33 and 1 case; mix 4,42	IHC, ISH, nested-PCR, IN-NOLiPAHPV Genotyping 2*	Venezuela
Badrawy et al. ¹¹	15	26.6% (4/15)	None reported	RT-PCR	Egypt
Verduin et al. ²⁸	29	3.45% (1/29)	Low risk (6 or 11)	ISH	USA
Singh et al. ²⁹	41	0% (0/41)	Not done	IHC, PCR	Australia
Khalele ²¹	40	0% (0/40)	Not done	IHC	Egypt
Zare Mahmoud Abadi et al. ³⁰	77	6.5% (5/77)	Not done	Real-time PCR	Iran
This study	20	10% (2/20)	18 in both cases	PCR	Thailand

ISH, *in situ* hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction

*Primary surgery site

Another key oncogenic virus is HPV. Since 1989, more than 10 studies have reported the frequency of HPV DNA in AM that varied from 0 to 40% as summarized in Table 4. Our exploration is the first study in Southeast Asia and the HPV DNA frequency is 10% that was similar to the report of Migaldi et al.²⁶ Considering for HPV typing in Table 4, several studies encountered high-risk HPV and HPV 18 were mostly observed.²²⁻²⁵ Nevertheless, some studies displayed low-risk and intermediate-risk HPV types whichever may not involve in AM oncogenesis. In the present study, it is to be noted that both positive cases were HPV 18, the hrHPV that may be directly involved in AM oncogenesis.

Both HPV and EBV DNA have been remarkably observed in one case of AM. Regarding to the recent study reviewed the evidence of EBV and HPV co-infection in several cancers including cancer of nasopharynx, cervix, breast and prostate gland.³¹ Apolipoprotein B mRNA editing enzyme catalytic polypeptide3 (APOBEC3) deaminase was proven to involve virus innate immunity response and may promote viral coinfection.³² *APOBEC3B* mRNA levels were higher in oral squamous cell carcinoma compared to normal oral epithelium,³³ but there is no study on *APOBEC3B* in AM. The study of *APOBEC3* in this case may elucidate whether the coinfection of EBV and HPV plays any role in the development of AM.

The EBV and HPV association in AM oncogenesis has been curiously underlined. In this study, we did not observe koilocytic changes in both HPV positive samples, meaning that no morphological appearance of HPV infection like what observed in the study of Migaldi et al.²⁶ We also did not observe syncytial formation in EBV-positive cases. Both viruses may transform normal odontogenic epithelium to ameloblastoma epithelial cells without any feature of viral cytopathologic changes. It was also suggested that HPV in AM may represent a background infection without AM oncogenesis development.²⁸

Sensitivity of PCR technique should also be a concern. Both HPV and EBV DNA might contaminate in normal epithelium or from the surgically acquired contamination during the procedure. In the other aspects, the common permissive cells of EBV are lymphocytes and epithelial cells, while of HPV are epithelial cells.^{8,31,34} Several reports exhibited HPV and EBV positive cases derived from the *in situ* hybridization technique and demonstrated EBV and HPV infected in AM cells.^{5,19,22,23,26,28} (Tables 3 and 4). We hypothesize that AM may possess EBV and HPV receptors, which need to be explored in further studies. To evaluate if EBV and HPV were related to AM oncogenesis, the PCR positive cases must be confirmed by ISH or IHC.

CONCLUSION

The low frequencies of EBV and HPV DNA in a group of Thai AM patients may suggest their minor participation in the biological events related to AM pathogenesis. Nevertheless, it could not be concluded that the virus was involved in the etiology and pathogenesis of the lesions. These studies are preliminary in nature involving limited number of AM patients and hence further work with a larger sample size comprising various techniques is required. Finally, the studies of in-depth mechanisms in the role of viruses in AM oncogenesis were suggested for further prevention and treatment of virus-associated ameloblastoma.

CLINICAL SIGNIFICANCE

HPV and EBV may not be involved in ameloblastogenesis.

AVAILABILITY OF DATA AND MATERIALS

The data analyzed during this present study are available from corresponding author on reasonable request.

AUTHOR'S CONTRIBUTIONS

Dusit Bumalee and Nakarin Kitkumthorn conceived the original idea, designed the experiment, analyzed data, and interpreted results. Dusit Bumalee, Puangwan Lapthanasupkul, Eakapong Tamboon, Anchisa Aittiwaraipoj, Boworn Klongnoi, and Nakarin Kitkumthorn performed the experiment and collected data. Dusit Bumalee wrote the manuscript with support from Nakarin Kitkumthorn. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of Faculty of the Dentistry/Faculty of Pharmacy, Mahidol University, Bangkok, Thailand (approval number: 2018/005.1101).

CONSENT TO PUBLISH

The authors have given the consent for publication.

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