



Investigation of Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV) in antrochoanal polyps[☆]

Esra Yılmaz^{a,*}, Necatı Alatas^b, Fahir Ucar^c, Tulin Cora^d, Kurtulus Buruk^e, Yasar Unlu^f

^a Department of Otorhinolaryngology, Dr. Ali Kemal Belviranlı Maternity and Children's Hospital, Turkey

^b Department of Otorhinolaryngology, Medical Sciences University Konya Training and Research Hospital, Turkey

^c Department of Medical Biology & Genetics, Medical Faculty of Akdeniz University, Turkey

^d Department of Medical Biology & Genetics, Medical Faculty of Selçuk University, Turkey

^e Department of Medical Microbiology, Medical Faculty of Karadeniz Technical University, Turkey

^f Department of Medical Pathology, Medical Sciences University Konya Training and Research Hospital, Turkey

ARTICLE INFO

Keywords:

Antrochoanal polyp
HPV
EBV
RT-PCR

ABSTRACT

Objectives/hypotheses: This study aimed to investigate the presence of HPV (HPV types 11 and 16) and EBV in antrochoanal polyps and to contribute to the current literature in this regard.

Study design: A case-control study.

Methods: A total of 100 patients (including 43 patients undergoing surgery for antrochoanal polyp, 27 patients undergoing surgery for nasal polyp, and 30 patients undergoing surgery for hypertrophic inferior turbinate) were included in this study. DNA was isolated from formalin-fixed, paraffin-embedded samples with the aid of the Bioneer's AccuPrep Genomic DNA Extraction Kit. In the obtained genomic DNAs, while the detection of HPV DNA was performed using the nested-PCR method, the detection of HPV types 11/16 and EBV DNA was performed using the RT-PCR method.

Results: The mean age of the patients with antrochoanal polyp was 26.7 ± 15.4 years (range 7–70). There were 20 (46.5%) women and 23 (53.5%) men in the antrochoanal polyp group. HPV DNA was positively detected using the nested-PCR method in 14 (32.6%) of the patients with antrochoanal polyp and in 3 (11.1%) of the patients with nasal polyp. HPV DNA was not detected in the hypertrophic inferior turbinate group (control group). There was a statistically significant difference between all groups in terms of HPV DNA positivity. In the antrochoanal polyp group, 2 patients had HPV 11 positivity and 12 patients had HPV 16 positivity. In the nasal polyp group, 1 patient had HPV 11 positivity and 2 patients had HPV 16 positivity. EBV DNA was positively detected in 16 (37.2%) of the patients with antrochoanal polyp, in 11 (40.7%) of the patients with nasal polyp and in 8 (26.7%) of the patients with hypertrophic inferior turbinate, respectively. There was no statistically significant difference between the groups in terms of EBV DNA positivity.

Conclusions: This study demonstrates that there is a need for further studies investigating the presence of viruses in antrochoanal polyps.

1. Introduction

Antrochoanal polyps are usually large and unilateral benign sinonasal masses that can arise in the maxillary sinus (antrum) and extend into the nasopharynx. It is most commonly seen in adolescents and young adults [1].

Viral infections are considered to be causative agents in some sinonasal masses. Human Papillomavirus (HPV) and Epstein-Barr Virus

(EBV) are the most commonly known agents [2–4]. Human Papillomaviruses (HPVs) are members of the Papillomaviridae family and are isometric, icosahedral, non-enveloped, double-stranded DNA viruses [5]. HPV infections are accused as etiological factors for head and neck neoplasms besides inverted papilloma, laryngeal papillomatosis, oropharyngeal, laryngeal and Waldeyer's ring squamous cell carcinomas, and nasal polyps [2–7]. Epstein-Barr Virus (EBV) (Human Herpes Virus-4) belongs to the Herpesviridae family, subfamily

[☆] This study was supported by the fund of the Educational Planning Committee of Medical Sciences University Konya Training and Research Hospital.

* Corresponding author at: Dr. Ali Kemal Behviranlı Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Kulak Burun Bogaz Hastalıkları Polikliniği, Fatih Mahallesi, Yeni İstanbul Caddesi No:30, 42285 Selçuklu, Konya, Turkey.

E-mail address: esra_ucar88@hotmail.com (E. Yılmaz).

<https://doi.org/10.1016/j.amjoto.2019.02.008>

Received 4 December 2018

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Gammaherpesvirinae, genus Lymphocryptovirus. It is a DNA virus that is commonly seen in the world and is transmitted through close contact with saliva and throat secretions, blood, and contaminated objects. It is known that EBV is a possible etiological agent in the formation of Undifferentiated Nasopharyngeal Carcinoma, Hodgkin's Disease (HD), Oral Hairy Leukoplakia, and Burkitt's Lymphoma in the head and neck region [7].

This study aimed to investigate the presence of HPV (HPV types 11 and 16) and EBV in antrochoanal polyps and to contribute to the current literature in this regard.

2. Materials and methods

A total of 100 patients (including 43 patients undergoing surgery for antrochoanal polyp, 27 patients undergoing surgery for nasal polyp, and 30 patients undergoing surgery for hypertrophic inferior turbinate between January 2011 and January 2016 in our hospital) were included in this study. Since our study was a retrospective study, we found it appropriate to use nasal polyp tissues in comparison and to investigate hypertrophic mucosa of the inferior turbinate as a control group, similar to the only one virus study in the current literature [2]. Hypertrophic mucosa of the inferior turbinate was preferred as a control group in the majority of studies investigating the presence of HPV in sinonasal polyps [2–4,7]. Genomic DNAs that were isolated from paraffin-embedded tissue samples in the pathology laboratory were examined. The detection of HPV types 11/16 and EBV DNA was performed using the RT-PCR method (real-time polymerase chain reaction). Information on the age, gender, selected surgical method, and anatomical location (left or right side of the nose) of antrochoanal polyp were recorded.

2.1. Genomic DNA isolation

10- μ m sections were taken from formalin-fixed, paraffin-embedded tissue samples. Each sample was resuspended in 1 ml xylene and was mixed for 10 s (with IKA Vortex Genius 3). The suspension was then centrifuged at 14,000 rpm for 2 min. The supernatant was thrown away with the aid of a pipette. 1 ml of 100% ethanol was added. The supernatant was then centrifuged at 14,000 rpm for 2 min. The supernatant was thrown away with the aid of a pipette. It was incubated at 37 °C for 5 min or at room temperature for 10 min. In the next stage, DNA isolation was performed using a commercial kit (the Bioneer's AccuPrep Genomic DNA Extraction Kit). Eventually, DNA isolation was completed.

2.2. Detection of DNA by RT-PCR

The PCR amplification was performed using the human beta-globin gene-specific primers and probes in order to observe the presence of DNA in the samples being of appropriate quality for PCR procedures [8]. For each 25 μ l reaction mixture, primers (0.2 μ M) and probes (0.1 μ M) were added into a Real-Time PCR master mix (AccuPower® Plus DualStar™ qPCR master mix, Bioneer, South Korea), which is a double-concentrated solution. It was then completed to 20 μ l with deionized water. 5 μ l of each sample was added into the mixture. The PCR amplification was performed with an initial denaturation at 95 °C for 10 min followed by 45 cycles of 95 °C for 15 s, 60 °C for 20 s, and 72 °C for 20 s on the LightCycler® 480 Instrument. The fluorescence emission was measured using a device during the amplification process of primers. Accordingly, the amplification curves were generated.

2.3. Detection of Human Papilloma Virus (HPV) DNA

2.3.1. Detection of HPV DNA by the nested-PCR method

The presence of HPV DNA was investigated by the nested-PCR method as stated in the literature [9,10]. HeLa cells were used as a

positive control. For this purpose, the mixture containing 0.5 μ M primers (MY09 5'-CGTCCMARRGGAWACTGATC-3' and MY11 5'-GCMC-AGGGWCTATAAAYAATGG-3'), 2 mM MgCl₂, 0.2 mM dNTPs, 2.5 U Taq DNA Polymerase (Promega, USA), and 1 $\times$ concentrated buffer was prepared. The isolated DNA samples were added into the mixture. The samples loaded into the thermal cycler (GeneAmp® PCR System 9700, Applied Biosystems, USA) were denatured at 94 °C for 5 min. The first round of amplification was performed with thermal cycling parameters of 40 cycles of 94 °C for 30 s, 42 °C for 80 s, and 72 °C for 1 min. Then, 2.5 μ l of these PCR products was taken. The second-round primers (GP5+ 5'-TTTGTACTGTGGTAGATACAC-3' and GP6+ 5'-GAAAAA TAAACTGTAAATCATATTC-3') instead of MY09 and MY11 primers were added into the mixture. The PCR amplification was performed under the same thermal cycling conditions. The nested-PCR products were run on a 2% agarose gel containing 0.5 μ g/ml ethidium bromide. The bands of 140–142 bp in length under an ultraviolet illuminator were assessed positive.

2.3.2. Detection of HPV types 11 and 16

The presence of HPV types 11 and 16 in HPV positive samples was investigated by the RT-PCR method. The biopsy samples that had been previously positive in the laboratory were used as a positive control. The primers and probes for HPV type 11 that were used by Moreau et al. were used for RT-PCR [11].

The detection of HPV type 16 and the verification of DNA isolation were performed by the primers and probes for HPV type 16 that were used by Schmitz et al. [8]. The amounts of components required for amplification and the thermal cycling conditions were applied as described in the amplification of the human beta-globin gene.

2.4. Detection of Epstein-Barr Virus (EBV) DNA

The oligonucleotides published by Robert et al. were used for detection of EBV in isolated nucleic acid samples [12].

A serum sample that had been previously detected positive in the laboratory was included in the study as a positive control. The amounts of components required for amplification and the thermal cycling conditions were applied as described in the amplification of the human beta-globin gene. The fluorescence emission was measured using a device during the binding process of primers. Accordingly, the amplification curves were generated.

3. Statistical analysis

The ages of the patients with antrochoanal polyp and hypertrophic inferior turbinate (except for the patients with nasal polyp) were not normally distributed according to the Shapiro-Wilk normality test. Therefore, the Mann-Whitney *U* test was used to compare two groups, and the Kruskal-Wallis test was used to compare more than two groups. Information on the age, gender, selected surgical method and location (left or right side of the nose) of antrochoanal polyp were recorded. For the age, gender, anatomical location of antrochoanal polyp, HPV positivity-negativity, and EBV positivity-negativity, the Fisher's exact test was used in 2 $\times$ 2 tables, and the Pearson's chi-squared (χ^2) test was used in 2 $\times$ 3–4 tables. The SPSS 15.0 statistical software package (SPSS Inc., Chicago, USA) was used for statistical analysis. A *p*-value < 0.05 was considered statistically significant.

4. Results

4.1. General findings

A total of 100 patients were enrolled in the study. The patients were divided into three groups. There were 43 patients in Group 1 (antrochoanal polyp), 27 patients in Group 2 (nasal polyp) and 30 patients in Group 3 (hypertrophic inferior turbinate), respectively.

Table 1

The mean age and gender distribution of the groups.

	Antrochoanal polyp (ACP)	Nasal polyp (NP)	Concha hypertrophy (CH)	p1 (ACP-NP)	p2 (ACP-CH)
Age	26.7 ± 15.4 (7–70)	45.63 ± 17.18 (10–79)	27.87 ± 7.99 (18–45)	p = 0.001	p = 0.187
Gender					
Female	20 (46.5%)	11 (40.7%)	8 (26.7%)	p = 0.226	
Male	23 (53.5%)	16 (59.3%)	22 (73.3%)		

The mean age of the patients with antrochoanal polyp was 26.7 ± 15.4 years (range 7–70). The mean age of the patients with nasal polyp was 45.63 ± 17.18 years (range 10–79). The mean age of the patients with hypertrophic inferior turbinate (control group) was 27.87 ± 7.99 years (range 18–45). There was no statistically significant difference between the antrochoanal polyp and control groups in terms of mean age ($p = 0.187$) (Mann-Whitney U test). There was a statistically significant difference between the antrochoanal polyp and nasal polyp groups in terms of mean age ($p = 0.001$) (Mann-Whitney U test) (Table 1).

There were 20 (46.5%) women and 23 (53.5%) men in the antrochoanal polyp group, 11 (40.7%) women and 16 (59.3%) men in the nasal polyp group and 8 (26.7%) women and 22 (73.3%) men in the control group, respectively. There was no statistically significant difference between the groups in terms of female/male ratio ($p = 0.226$) (Pearson's chi-square test) (Table 1).

Of the patients with antrochoanal polyp, 23 had right-sided nasal polyp and 20 had left-sided nasal polyp. All patients with nasal polyp had panpolyposis.

4.2. Detection of Human Papilloma Virus (HPV) DNA

HPV DNA was positively detected in 14 (32.6%) of the patients with antrochoanal polyp and in 3 (11.1%) of the patients with nasal polyp. HPV DNA was not detected in the control group. There was a statistically significant difference between the antrochoanal polyp and nasal polyp groups in terms of HPV DNA positivity ($p = 0.049$) (Fisher's Exact test). There was a statistically highly significant difference between the antrochoanal polyp and control groups in terms of HPV DNA positivity ($p = 0.001$) (Fisher's Exact test) (Table 2).

4.3. Detection of HPV types 11 and 16

HPV types 11 and 16 were examined in HPV positive samples. In the antrochoanal polyp group, 2 (14.28%) patients had HPV 11 positivity and 12 (85.72%) patients had HPV 16 positivity. In the nasal polyp group, 1 patient had HPV 11 positivity and 2 patients had HPV 16 positivity.

There was no statistically significant difference between the antrochoanal polyp and nasal polyp groups in terms of HPV type 11 ($p = 1.000$) (Fisher's Exact test). There was no statistically significant difference between the antrochoanal polyp and control groups in terms of HPV type 11 ($p = 0.509$) (Fisher's Exact test).

There was a statistically significant difference between the antrochoanal polyp and nasal polyp groups in terms of HPV type 16 ($p = 0.063$, according to $p < 0.07$) (Fisher's Exact test). There was a statistically highly significant difference between the antrochoanal

polyp and control groups in terms of HPV type 16 ($p = 0.001$) (Fisher's Exact test) (Table 3).

4.4. Detection of Epstein-Barr Virus (EBV) DNA

EBV DNA was positively detected in 16 (37.2%) of the patients with antrochoanal polyp, in 11 (40.7%) of the patients with nasal polyp and in 8 (26.7%) of the patients with hypertrophic inferior turbinate, respectively. There was no statistically significant difference between the antrochoanal polyp and nasal polyp groups in terms of EBV DNA positivity ($p = 0.805$) (Fisher's Exact test). There was no statistically significant difference between the antrochoanal polyp and control groups in terms of EBV DNA positivity ($p = 0.449$) (Fisher's Exact test) (Table 4).

5. Discussion

The aim of this study is to investigate the presence of HPV (HPV types 11 and 16) and EBV in antrochoanal polyps, on which there is only one virus study in the current literature, and to contribute to further studies with the obtained results [2].

The etiopathogenesis of antrochoanal polyps has not been clearly explained. Chronic rhinosinusitis, allergy, arachidonic acid metabolites, matrix metalloproteinases, fibroblast growth factor, transforming growth factor β , mucin genes, inducible nitric oxide synthase expression, staphylococcal exotoxins, galectin-3 expression, and HPV have been investigated in its etiopathogenesis [2,13–22].

Viral infections are considered to be causative agents in some sinonasal masses. Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV) are the most frequently investigated agents. HPV and EBV are DNA viruses, they can settle into the upper respiratory mucosa and cause life-long latent infections [2–7,23].

The meta-analysis of 21 articles with 24 studies investigating the relationship between respiratory viral infection, HPV, and EBV and nasal polyps, odds ratio of HPV and EBV were significantly higher than other respiratory viruses [24]. In the current literature, the prevalence of HPV in nasal polyps ranges from 0 to 50%. HPV genotypes in nasal polyps are classified as low and high risk groups. HPV11 and HPV58 genotypes are reported as the most prevalent low-risk and high risk genotypes in nasal polyps, respectively [2,25].

A single study with antrochoanal polyps conducted by Knör et al., HPV DNA was positively detected in 53.8% of the patients with antrochoanal polyp in 15.1% of the patients with nasal polyp, and in 5.8% of the controls, respectively. In the same study, it was determined that HPV 16 (61.9%) and 11 (14.3%) were the most frequently detected HPV genotypes [2]. This result was quite interesting for the oncogenic HPV genotype 16. Therefore, we wanted investigated HPV genotype 16

Table 2

HPV DNA results.

HPV DNA	ACP n = 43	NP n = 27	CH n = 30	p1 (ACP-NP)	p2 (ACP-CH)
Positive (sample numbers)	14 (32.6%) (5, 6, 11, 16, 17, 19, 20, 21, 22, 28, 29, 40, 41, 43)	3 (11.1%) [8,9,20]	0	p = 0.049	p = 0.001
Negative	29 (67.4%)	24 (88.9%)			

Table 3
HPV types 11 and 16 results.

HPV DNA types 11 and 16	ACP n = 43	NP n = 27	CH n = 30	p1 (ACP–NP)	p2 (ACP–CH)
HPV 11 (number of positive samples)	2 (19, 22)	1 (20)	0	p = 1.000	p = 0.509
HPV 16 (number of positive samples)	12 (5, 6, 11, 16, 17, 20, 21, 28, 29, 40, 41, 43)	2 (8, 9)	0	p = 0.063	p = 0.001

Table 4
EBV RT-PCR results.

EBV DNA	ACP n = 43	NP n = 27	CH n = 30	p1 (ACP–NP)	p2 (ACP–CH)
Positive	16 (37.2%)	11 (40.7%)	8 (26.7%)	p = 0.805	p = 0.449
Negative	27 (62.8%)	16 (59.3%)	22 (73.3%)		

in our study. In our study, HPV DNA was positively detected in 14 (32,6%) of the patients with antrochoanal polyp. This detection rate was significantly higher compared with the other groups. The detection rates of HPV genotypes 16 and 11 in HPV DNA positive-patients were 85.72% and 14.28%, respectively. In both studies, the detection rate of HPV type 16 was significantly higher. When the studies that investigated HPV DNA in patients with nasal polyp were examined, Pei et al. found a prevalence of 40.2% in the Chinese population. They also reported that HPV DNA could not be detected in the control group [25]. Zaravinos et al. found that the prevalence of HPV DNA was 13% in the nasal polyp group and 4% in the control group by the PCR method [4]. In the study of Koçoğlu et al., HPV DNA was positively detected in 13,3% of the patients [23].

Our study was the first study to investigate the presence of EBV in antrochoanal polyp tissues. The presence of EBV in antrochoanal polyp had not been previously investigated. In the study of Zaravinos et al., EBV DNA was positively detected in 35% of the 23 patients with nasal polyp but was not detected in the controls [4]. In the study of Ioannidis et al., EBV DNA was positively detected in 26.4% of the 91 patients with nasal polyp and in 10.5% of the controls [3]. In our study, EBV DNA was positively detected in 16 (37.2%) of the patients with antrochoanal polyp, in 11 (40.7%) of the patients with nasal polyp and in 8 (26.7%) of the patients with hypertrophic inferior turbinate, respectively. We did not find statistically significant difference between the three groups.

The age groups, gender ratios, and anatomic localization of antrochoanal polyps in our study were similar to other studies on antrochoanal polyps in the current literature [1,2,13–16,26,27].

6. Conclusion

This study demonstrates that there is a need for further studies investigating the presence of viruses in antrochoanal polyps. Further studies will allow us to have more information about this disease with unknown etiology.

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