

## A case report of synchronous bilateral tonsillar carcinoma associated with human papilloma virus

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### Abstract

The case of a 69-year-old man with bilateral synchronous tonsillar carcinoma is reported. The patient complained of nasal closure, strange voice, and discomfort in his pharynx when he was admitted to the Department of Otolaryngology Head and Neck Surgery at Wakayama Medical University, Wakayama, Japan, in March 2017. The palatine tonsils were enlarged and the surface was irregular. Left cervical lymphadenopathy was also evident. Histological examination from both tonsils was performed and bilateral tonsillar squamous cell carcinoma was diagnosed. PCR analysis showed the same HPV-DNA pattern from bilateral tonsils.

Concurrent chemoradiotherapy was performed. Total 70 Gy of irradiation (2Gy/day×35 day) was applied to bilateral tonsillar tumours and upper neck. Follow up was conducted every three months and the patient was free of recurrence for three years. Patient's informed consent was taken to publish the case report.

**Keywords:** bilateral synchronous tonsillar carcinoma, HPV, tonsil.

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### Introduction

Smoking and drinking alcohol have been widely known as prominent risk factors for oropharyngeal carcinoma, but for over 25 years it has become clear that Human Papilloma Virus (HPV) has a role in the carcinogenesis of oropharyngeal carcinoma. Since the prevalence of HPV-related oropharyngeal carcinoma is increasing worldwide, it has recently attracted attention. HPV is detected frequently from palatine tonsils and tonsils at the base of the tongue. As HPV-related oropharyngeal carcinoma is more susceptible to chemotherapy and radiotherapy, it has a better prognosis compared to non-HPV related oropharyngeal carcinoma.<sup>1,2</sup>

A few cases of HPV-related oropharyngeal carcinoma that

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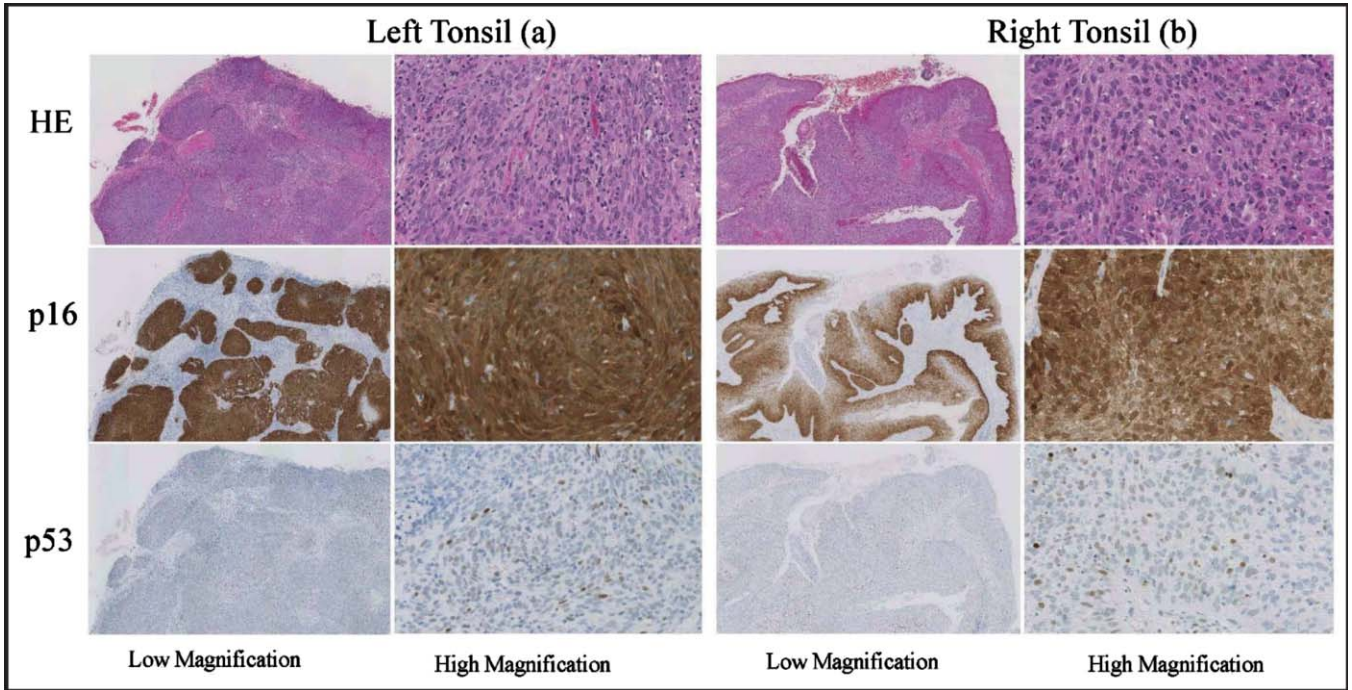
occurred simultaneously on both sides have been reported, and there are many unclear points for the mechanism of carcinogenesis. Herein, we present a rare case of bilateral synchronous HPV-related tonsillar carcinoma.

### Case Report

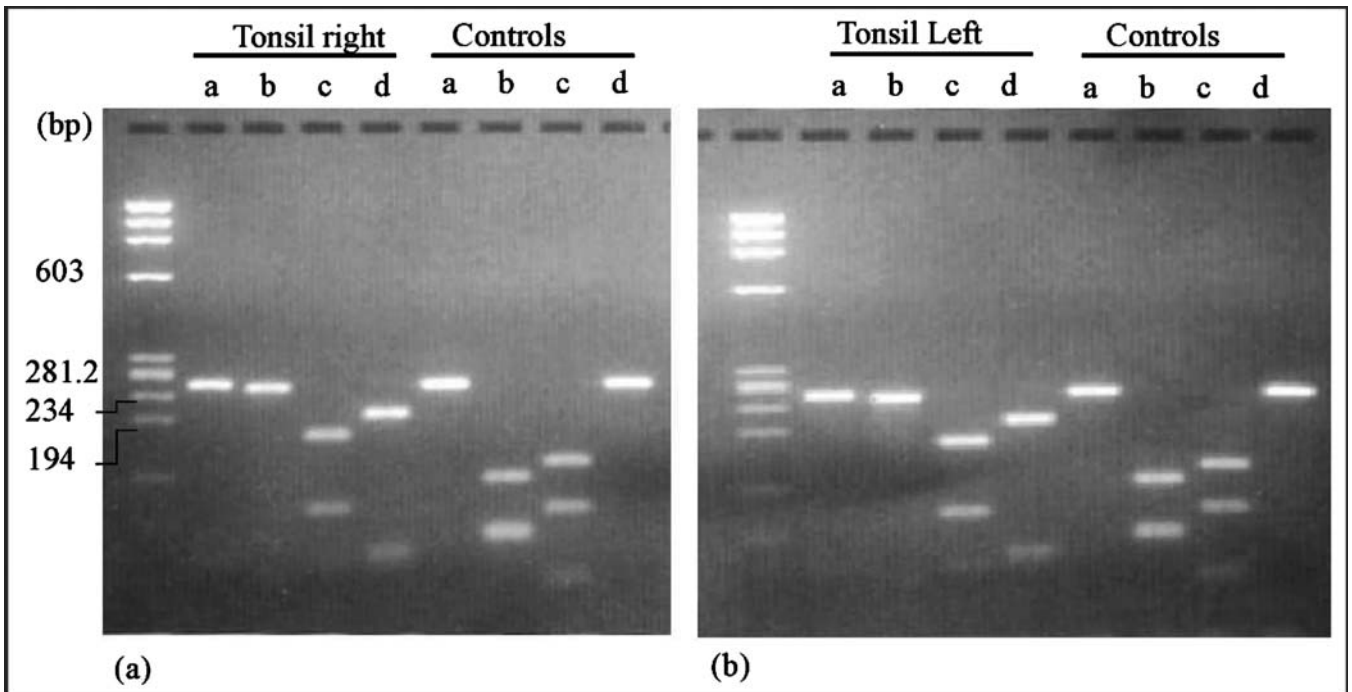
A 69-year-old male was admitted to the Department of Otolaryngology Head and Neck Surgery at Wakayama Medical University, Wakayama, Japan, in March 2017 for oropharyngeal tumour. He complained of nasal closure, strange voice for the past seven months, sore throat, and discomfort in his pharynx for one month. The patient had history of treatments for Bowen Disease of Scrotum, rectal cancer (the patient had had rectal cancer surgery at another hospital at the age of 49, but the details are unknown), hypertension, hyperlipidaemia and hyperuricaemia. His current medications were Benzbromarone (50mg/day), Atorvastatin (10 mg/day), Candesartan (8mg/day), and Amlodipine (5 mg/day). He smoked 25 cigarettes daily for 35 years, and had consumed 700-1,000 ml of beer per week for 50 years.

On clinical examination, the palatine tonsils on both sides were enlarged and the surface was irregular. Left cervical lymphadenopathy was also evident. The mass was elastic hard, poorly movable and measured approximately 2 cm in size. There was no remarkable tenderness over the mass.

The mass measured approximately 30 mm x 30 mm x 40 mm in the left palatine tonsil and approximately 20 mm x 15 mm x 30 mm in the right palatine tonsil. Tonsillar appearance before the treatment is shown in Figure-1. Enhanced CT scan revealed homogeneously enhanced tumours in bilateral palatine tonsils. The lymph node in the left upper cervical region was enlarged and in close contact with internal jugular vein. The neck and tonsillar region were free of the tumour after the treatment. Fluoro-2-deoxy-D-glucose (FDG) uptakes were Standard uptake value (SUV) max of 11.37 and 14.88, in the left and right tonsils, respectively and were SUV max of 8.54 in the left upper neck lymph node by PET analysis. PET analysis after the treatment also showed disappearance of the tumour from the primary and neck regions.



**Figure-1:** Histological examination of the left (a) and right (b) tonsil tissues. Heterologous squamous epithelium presenting infiltration and proliferation is recognised. Similar morphological abnormality is observed at the cover mucosal epithelium, and cell division is observed. Although p16 is diffusely positive, p53 positive cells were about 10 to 20%.



**Figure-2:** PCR HPV-DNA hybridisation. Biopsy tissues from bilateral tonsils were submitted for PCR testing from right (a) left (b) tonsils, respectively. DNA and RFLP analysis were performed according to the method in the reference 16. Same PCR pattern was obtained from both the samples, but it was impossible to distinguish the type of the main high-risk HPV.  
 a. DNA amplification only.      b. Digestion with restriction enzyme Rsa I.      c. Digestion with restriction enzyme Dde I.      d. Digestion with restriction enzyme Hae I.

Because tonsillar carcinoma was initially suspected, incisional biopsy was performed under local anaesthesia from bilateral tonsils. Histological examination showed heterologous squamous epithelium presenting infiltration and proliferation diagnosed as squamous cell carcinoma. Immunohistochemical analysis showed diffuse positive staining of p16. However, p53 positive cells were about 10 to 20% (Figure-1). PCR bands not corresponding to HPV types of 11, 16, 18, 31, 33, 42, 52, 58 were detected. In addition, because the same PCR product was obtained from both the specimens of left and right tonsils, it was considered that the same type of HPV was involved in infection and then carcinogenesis (Figure-2). DNA isolation and RFLP analysis were performed.

Blood examination revealed that levels of squamous cell carcinoma antigen (SCC) was high with a level of 28.5ng/ml.

Surgery was not performed and the patient received concurrent chemoradiotherapy (CCRT) after one course of systemic chemotherapy of TPF (docetaxel, cisplatin and 5FU). Total 70 Gy of irradiation (2Gy/day×35 days 54-104) was applied to bilateral tonsillar tumour and left upper neck. In parallel with irradiation, 100 mg/m<sup>2</sup> of Cisplatin was administered four times (day 29, 54, 75, 96). SCC antigen in the serum decreased prominently as the treatment advanced, and the tumour also shrunk. After CCRT, Enhanced CT and PET-CT showed continued regression of the tumour. Follow-ups were conducted every three months. The patient was free of recurrence for about three years.

## Discussion

Smoking and drinking have been pointed out as risk factors for oropharyngeal cancer for a long time, but in recent years it has become clear that HPV was also involved in carcinogenesis in about 20% of oropharyngeal carcinoma. And the occurrence rate of HPV-related oropharyngeal carcinoma is increasing.<sup>1,2</sup> More than 100 kinds of HPV viruses have been identified so far. Among these, HPV-16 and HPV-18 are considered to be of high risk, HPV-31 and HPV-33 medium risk, HPV-6 and HPV-11 are low risk group for HPV-induced malignancy such as cervical squamous cell carcinoma, cervical adenocarcinoma and squamous cell carcinoma of tonsils. HPV has oncogenes related to virus replication in the viral genome and specifically E6 and E7 genes are related to transformation of cells and strongly related to carcinogenesis in high-risk HPV.<sup>2</sup>

In oropharyngeal carcinoma, the frequency of genetic mutation of p53 was low in HPV DNA-positive cases and conversely, in the case of HPV DNA negative cases, the

frequency of genetic mutation of p53 was high.<sup>3</sup> In the case of HPV DNA negative cases, it showed resistance to apoptosis due to mutation of p53, and as a result, treatment resistance against chemotherapy.<sup>4</sup>

Bilateral simultaneous tonsillar cancer is rare and only 30 cases have been reported so far. Among them, HPV infection was revealed only in seven cases.<sup>5-12</sup>

How HPV is involved in carcinogenesis of bilateral oropharyngeal carcinoma has not yet been clarified. Three mechanisms are suggested. The first is called field effect, which causes transformation by persistent infection of HPV to some tissues and causes duplicated cancer at other sites. The second is the mechanism by which duplicated cancers arise by the migration of HPV-infected tumour cells to other sites. Third, it is reported that multiple infections of HPV infection occurred in independent organisms, resulting in duplicated cancers.<sup>5,6</sup> In the current case, bilateral simultaneous tonsillar cancer was detected and the same HPV-DNA was detected from the palatine tonsils on both sides. Although exact HPV subtyping could not be done, PCR-DNA was able to obtain similar results from both sides. The possibility of either the first or the second mechanism was considered.

HPV positive bilateral simultaneous tonsillar carcinoma is a rare disease. HPV infection has been confirmed in only seven cases in the literature.<sup>5-12</sup> Reports regarding the presence or absence of HPV infection showed more than 75% of tumours were either p16 positive or HPV-ISH positive. However, it should be noted that it is not true that positive staining for p16 by fluorescent antibody is equally positive for HPV-PCR. The mechanism by which p16 is overexpressed by HPV infection is roughly divided into two mechanisms. The first is the mechanism by which the E7 protein causes damage to the cell cycle through repression of the Rb family protein, and the other is the mechanism by which the E6 protein suppresses apoptosis via inhibition of p53. Both mechanisms lead to cell immortalisation, cellular senescence and cause overexpression of p16. Overexpression of p16 is common as HPV positive surrogate marker. However, among p16 positive cases, cases containing HPV negative are included in about 10 to 20%. Golusinski et al reported that the prognosis of HPV negative p16 positive oropharyngeal carcinoma is relatively poor.<sup>13</sup> It was reported that p16 was positive by fluorescent antibody staining in tissues in nine cases.

## Conclusion

Here we report a rare case of bilateral synchronous tonsillar carcinoma. Molecular and histopathological

analysis indicated HPV's role in the etiopathogenesis of this tumour type.

**Disclaimer:** None to declare

**Conflict of Interest:** None to declare

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