□ CASE REPORT □

An Adult Case of Multiple Squamous Papillomas of the Trachea Associated with Human Papilloma Virus Type 6

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Abstract

A 72-year-old woman with primary biliary cirrhosis complained of dry cough and wheezing. Chest computed tomography showed a tumor arising from the posterior wall of the trachea. Bronchoscopic examination revealed that the tumor was cauliflower-like, with two small polypoid tumors. They were diagnosed as multiple squamous papillomas. The main tumor was recurrent and removed by repeated microwave coagulation therapy (MCT) through bronchoscopy, whereas the two polypoid tumors were likely to disappear spontaneously. Human papilloma virus (HPV) type 6 DNA was detected in the tumor by polymerase chain reaction (PCR) amplification, suggesting that this virus was the cause of her papillomas.

Key words: multiple papilloma, human papilloma virus, recurrent, microwave coagulation therapy, polymerase chain reaction

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Introduction

Multiple papillomas occur most commonly in the larynx and lower respiratory tract of children, although they have also been described in adults (1). They are manifestations of human papilloma virus (HPV) infection (2). Here, we report an elderly woman case of multiple squamous papillomas of the trachea. The main tumor was recurrent and removed by repeated microwave coagulation therapy (MCT) through bronchoscopy, whereas the two small polypoid tumors were thought to disappear spontaneously. The presence of HPV type 6 DNA in her papilloma biopsy sample was confirmed by polymerase chain reaction (PCR) amplification, suggesting that this virus was the cause of her papillomas.

Case Report

A 72-year-old woman, who had been admitted to the department of gastroenterology of our hospital for the treatment of esophageal varices due to primary biliary cirrhosis, complained of dry cough and wheezing in February 2005. Her symptoms gradually worsened, and she was referred to

our department two months later. She had no history of smoking. Pulmonary examination showed that expiratory wheezing was audible on auscultation, and her physical examination was otherwise normal except that slight pitting edema was observed on both crura. Her laboratory data showed thrombocytopenia ($9.3 \times 10^4/\mu\text{L}$), hypoalbuminemia (3.1 g/dL), decreased level of choline esterase (134 IU/L), slight elevation of aminotransferase (aspartate aminotransferase 45 IU/L, alanine aminotransferase 47 IU/L), and slight hyperbilirubinemia (1.2 mg/dL), reflecting the presence of liver cirrhosis. Pulmonary function tests revealed a severe obstructive impairment: a forced vital capacity (FVC) of 2.40 L (108.1% of predicted), a forced expiratory volume in 1 s (FEV_{1.0}) of 0.62 L (38.7% of predicted), a FEV_{1.0} to FVC ratio of 25.8%, and a peak expiratory flow of 1.01 L/s (18.9% of predicted). Results of chest radiograph were unremarkable. Chest computed tomography revealed a tumor, 8 mm in size, arising from the posterior wall of the trachea (Fig. 1). On bronchoscopic examination, the tumor was located at the fourth tracheal ring from the carina, and had a cauliflower-like shape with mucus on its surface (Fig. 2A). In addition, two small polypoid lesions were observed at one ring above the main tumor (Fig. 2A). No tumorous le-

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sions were seen in the larynx or the bronchi. Biopsy was performed for the main tumor and one of the polypoid tumors. Microscopic findings of both the main tumor and the polypoid lesion showed squamous papilloma with mild atypia (Fig. 3), thus she was diagnosed with multiple squamous papillomas of the trachea.

She was referred to Tokyo Medical University Hospital in June 2005, and underwent bronchoscopy. Most of the main tumor was removed by biopsy and brushing, because of its fragility. MCT was performed for the remaining tumor through bronchoscopy (Fig. 2B). Interestingly, both of the two small polypoid tumors, which had been observed at our hospital only one month earlier, had disappeared by this time.

After treatment, she had been followed up regularly at our hospital with no respiratory symptoms, but bronchoscopic test showed the recurrence of the main tumor in March 2006 (Fig. 2C). No other lesions were observed. Biopsy was performed once again and the same pathological result was obtained. The biopsy sample was sent to a laboratory (SRL Company, Tokyo, Japan) and analyzed for the presence of HPV types 6, 11, 16, 18, 31, 33, 42, 52, or 58 by PCR. HPV DNA was amplified and the subsequent restriction mapping pattern showed the presence of HPV type 6 DNA

in the tumor (Fig. 4) (3), suggesting that her papillomas were caused by HPV type 6. She was referred to Tokyo Medical University Hospital once again and underwent MCT for the recurrent tumor.

Discussion

Tracheobronchial papillomas have three distinct clinical presentations: multiple papillomas, inflammatory polyps, or solitary papillomas (4). Multiple papillomas originate primarily in the larynx, with a tracheal incidence of about 2% (5) and lung involvement of <1% (6). They have been divided into juvenile and adult types, because they present distinct clinical courses and different incidence of malignant transformation, according to the age at onset and the presence or absence of laryngeal involvement (7). Thus only a few adult cases of laryngeal papillomas spread into the inferior airways, and in most adult cases, multiple papillomas of tracheobronchial system occur without laryngeal involvement (8), as was observed in the present case. Moreover, it should be noted that almost all of the adult cases of laryn-

Figure 1. Chest computed tomography scan (April 2005) showing a tumor, 8 mm in size, arising from the posterior wall of the trachea (arrow).

Figure 3. Microscopic findings of the main tumor revealing a papillary structure, covered by stratified squamous epithelium with mild atypia (Hematoxylin and Eosin staining, original magnification x200). Similar findings were obtained for one of the polypoid tumors.

Figure 2. A: Bronchoscopic view of the trachea showing a cauliflower-like tumor with mucus on its surface (thick arrow) and two small polypoid tumors (thin arrows) (May 2005). B: After MCT (June 2005). Note that both of the two polypoid tumors had disappeared by this time (compare with Fig. 2A). C: Bronchoscopic test showing the recurrence of the main tumor (March 2006).

Figure 4. Restriction mapping of the amplified HPV DNA from the tumor biopsy sample. The PCR product was cut with the following restriction enzymes, A, uncut; B, *Rsa* I; C, *Dde* I; D, *Hae* III. This mapping pattern showed the presence of HPV type 6 DNA (3). Lane 1, size markers. Positive control, SiHa cells infected by HPV type 16.

geal papillomas which spread into the inferior airways or tracheobronchial papillomas without laryngeal involvement have been men with a high incidence of malignant transformation (8-10).

Multiple papillomas are associated with HPV infection (2) and it was reported that low-risk (i.e., low malignant potential) HPV types 6 and 11 cause about 90% of cases of recurrent respiratory papillomatosis (11). A previous study (2) showed a predominance of HPV type 11 or double infections that included HPV type 6 and type 11, consistent with the results of others (12). Thus, infection with HPV type 6 alone was identified in only 20% of the papillomas and 5.3% of the non-diseased sites by PCR (2). It is unclear why HPV type 11 is more likely to be identified, since HPV types 6 and 11 have greater than 50% homology and thus are similar in genetic makeup. In the present case, only HPV type 6 was detected in the tumor, which is considered to be relatively rare.

Of note, in the present case, the polypoid tumors were likely to disappear spontaneously, whereas the main tumor was recurrent. Indeed, spontaneous regression has been reported in juvenile types of papillomatosis (13). In this context, the importance of an effective immune system in the resolution of HPV infection has been described (14). Although the precise mechanisms of spontaneous regression in the present case are not known, it is quite possible that improved local immune responses at sites of the polypoid tumors might eliminate latent HPV infection or prevent its activation, resulting in spontaneous regression.

Laser technique and other developed coagulation methods (e.g., MCT performed in the present case) make it possible

to remove most papillomas through bronchoscopy, with only little risk to the patient (15). Photodynamic therapy, originally developed for the diagnosis and treatment of cancer, has been applied to the treatment of papillomatosis, with promising results (16). Papillomas that show signs of atypia and peribronchial spreading or that cannot be reached by bronchoscopy sometimes require chest surgery (15). The papillomas in the present case showed mild atypia, but MCT was performed for the following reasons. First, the main tumor was so fragile that most of it could be removed by biopsy and brushing. Second, it was possible that both of the two polypoid tumors would disappear spontaneously. Third, because of her underlying liver disease with esophageal varices, surgical operation may have been too high a risk for her. The recurrence was localized to the main tumor and it could be removed by MCT once again.

It is generally accepted that low-risk HPV type 6 or 11 positivity is associated with a benign clinical course in most cases, whereas high-risk oncogenic HPV-16 or 18 is always accompanied by a poor prognosis (17). However, some reports have demonstrated that squamous cell carcinoma arose from papilloma lesions in which HPV type 6 or 11 was positive (18, 19). These results suggest that HPV types 6 and 11 under certain circumstances might have a carcinogenic or cocarcinogenic effect in the respiratory tract (19). Factors such as cigarette smoking, irradiation, cytotoxic drugs, and perhaps other DNA-damaging viruses must be involved in the malignant transforming process (19). There are also spontaneous genetic changes which cause malignant transformation, such as p53 mutation (20). Indeed, it was reported that p53 genetic mutation was associated with integration of HPV type 11 in histologically malignant lesions in recurrent respiratory papillomatosis (20).

The present case is rare for the following reasons. First, this is an elderly woman case of multiple papillomas localized to the trachea without laryngeal involvement; such findings have been reported predominantly in adult man cases (8-10). Second, only HPV type 6 was detected in the tumor. Third, it is likely that both of the two polypoid tumors regressed spontaneously, whereas the main tumor was recurrent. Careful follow-up studies are required for the early detection of local recurrence, malignant transformation, and recurrence at other sites.

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