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A Case of the Intrapulmonary Spread of Recurrent Respiratory Papillomatosis With Malignant Transformation



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Abstract: *Objectives:* To describe an individual with recurrent respiratory papillomatosis that extended into the lung parenchyma and underwent malignant transformation and to discuss the characteristic imaging findings associated with this condition. *Methods:* The clinical presentation of an individual with this unusual malignant transformation was reviewed. A literature search was performed to characterize the epidemiology, imaging findings and management of this condition. *Results:* The patient underwent 30 courses of surgery over 21 years and presented disseminated pulmonary papilloma after childbirth. The interval between dissemination into the lung and malignant transformation was 2.5 years. The tracheal papilloma was positive for type 6 of human papilloma virus (HPV-6). She died because she refused further treatment. *Conclusions:* The clinician should have a high index of suspicion for lung papillomatosis in patients with a tracheotomy. Appropriate diagnostic imaging studies will be helpful in reaching this diagnosis and determining whether a malignancy exists. Treatment options have limited success when lung papillomatosis becomes malignant.

Key Indexing Terms: Recurrent respiratory papillomatosis; Malignant; Pulmonary; Pregnancy; HPV. [*Am J Med Sci* 2015;350(1):55–57.]

Recurrent respiratory papillomatosis (RRP) is a rare disease in which multiple exophytic squamous wart-like lesions occur

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within the larynx and the tracheobronchial tree.¹ RRP is characterized by an unpredictable course, varying from the spontaneous resolution of the papillomas to a rapid progression with life-threatening airway obstruction and rarely leading to malignant transformation of the lesions. Extension into the lung parenchyma occurs in less than 1% of patients and is associated with a low risk of malignant transformation.² The treatment options for intrapulmonary dissemination have limited success. RRP with intrapulmonary dissemination portends a poor prognosis.³ Here, we describe a case of juvenile-onset RRP that progressed to carcinoma in a young adult who died of the disease.

CASE REPORT

The patient was a woman who was born in 1985. She was the first child of her parents and was delivered at full term by natural labor. Her mother denied a history of genital warts during the pregnancy.

She was admitted to a local hospital in 1991 (when she was 6 years old) for the first time because of hoarseness. She was diagnosed as having laryngeal papillomatosis and was given an emergency tracheotomy. She underwent 14 courses of surgery in the local hospital from then until October 2004 at intervals of between 7 days and 5 years.

The patient was subsequently transferred to our hospital in June 2005. She had respiratory distress for 1 month. A surgical resection with a microdebrider was performed under general anesthesia using suspension laryngoscopy. There was an anterior commissural laryngeal web that was 1/3 the length of the vocal cords. Diffuse papillomas were growing subglottic to the tracheal stoma, with the most significant ones being in the subglottic region and near the tracheal stoma. The surgical specimens diagnosed as laryngeal papilloma with type 6 of human papilloma virus (HPV-6) tested by immunohistochemistry.

Subsequently, 8 endoscopic microdebrider ablations of the papillomas were performed (in May 2006, March, July and November of 2007 and February and May of 2008). Routine preoperative chest radiographs showed no obvious abnormalities. Many papillomas were distributed from the subglottic

region to the tracheal stoma. The patient became pregnant in November 2007, and a healthy baby girl was delivered by caesarean section in August 2008.

The patient was admitted to our hospital in June 2009 because her trachea could not be blocked for 1 year. She had no cough, hemoptysis, fever, dyspnea, weight loss, hematuria, joint symptoms or rash. The chest x-ray performed before the laryngeal surgery revealed a cystic lesion in the right midlung zone. The operation showed that there was no significant tumor growth in the supraglottic region, and a bronchoscopy revealed many papillomas growing in the trachea. A pale cauliflower-like neoplasm that was growing in right main tracheal branch indicated pulmonary metastasis of RRP.

A surgical microdebrider was used to remove the tracheal papilloma in April 2010. A computed tomography (CT) scan showed a nodule in the upper lobe of the right lung and multiple cystic lesions in both lungs in June 2011. The images demonstrated bronchiectasis with an infection. During the surgery, after the removal of the tracheal papilloma lesions, large pieces of the papilloma were found to block the right superior bronchial segment. A postobstructive pneumonia was present, and this was partially treated by removal of papillomas.

Full-length genome sequencing was performed on the tissue specimen. Polymerase chain reaction reactions were performed using Templiphi100 amplification system. Sequencing of the long range polymerase chain reaction products was performed at Huada (Shenzhen, China). The identification of HPV-6 genomic variants was made with BioEdit Sequence Alignment Editor 7.0.9.0, and the sequence of prototype HPV-6 genome (GenBank Acc. No. M14119) was used as a standard for comparison and genomic position numbering. The tracheal papilloma was positive for HPV-6. There were 4 nonsynonymous mutations, at bases 950 (E1, A to G), 1,322 (E1, C to G), 2,553 (E1, T to G) and 5,585 (L2, G to T). The mutant rates of the 4 nonsynonymous mutations are all greater than 99% with little significance. The correlation of these mutations and malignant transformation is unknown.

The CT scans that were performed in September and November of 2011 showed that the nodule in the upper lobe of the right lung had enlarged and that the number of round cystic lesions had gradually increased in both lungs. In addition, many enlarged lymph nodes were observed near the superior vena cava and the right root of the neck. The lung biopsy revealed differentiated squamous-cell carcinoma. For economic reasons, the patient did not obtain further treatment for the lung cancer.

The patient underwent surgeries to remove the endotracheal papilloma to relieve her difficulty in breathing in January, February, March and June of 2012. The chest x-ray in June 2012 revealed atelectasis of the right upper lung lobe and an irregular tracheal wall. Multiple nodular and cystic lesions of different thicknesses were visible in the wall of the right lung (Figure 1). The CT scan performed at the same time showed that the nodule in the upper lobe of the right lung had enlarged, the cystic lesions in both lungs had increased in the sizes of the lesions and many lymph nodes in the mediastinum had grown (Figure 2). Some results of laboratory tests were abnormal, including the white blood cell ($12.5 \times 10^9/L$), hemoglobin (88 g/L), lactic acid dehydrogenase (449 U/L) and highly-sensitive C reactive protein (77.1 mg/L) results. The value of blood clotting function, liver function, renal function and HIV tests was normal. During surgery, after the removal of the papilloma tissues that had almost completely blocked the airway, copious purulent secretions poured from the right upper bronchus. However, the pathological diagnosis of the

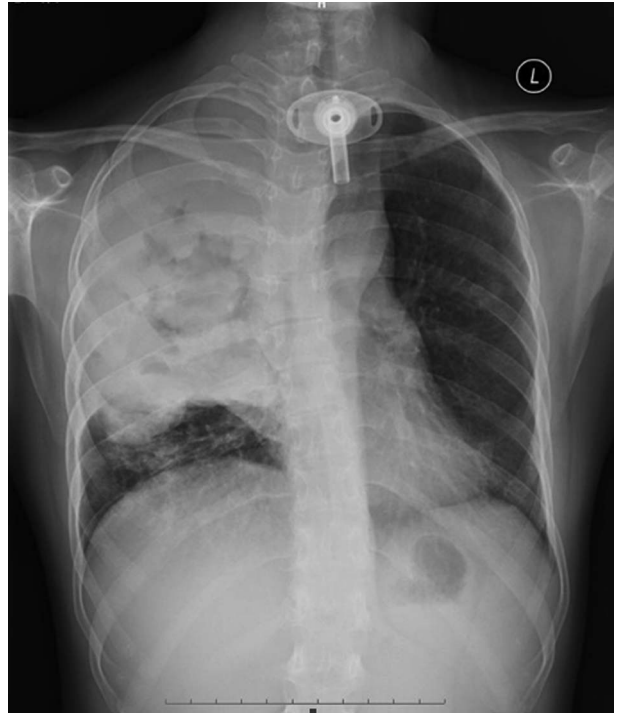


FIGURE 1. Chest x-ray showing atelectasis in the right upper lobe and the irregular appearance of the tracheal wall. Multiple nodular and cystic lesions of different thicknesses are visible in the walls of the right lung.

endotracheal lesions remained papilloma. The patient died in December 2012.

DISCUSSION

RRP is one of the most common benign tumors of the larynx in childhood. The distal trachea and bronchi are involved in only 2% to 17% of patients, and 1% to 5% of patients show pulmonary spread.^{4,5} The precise pathogenesis of the lung involvement is unknown, although it is believed to result from the aerial dissemination of fragments during endoscopic surgery, with seeding of the lung tissue.² Our patient had



FIGURE 2. Axial CT image showing poststenotic atelectasis in the right upper lobe with a central necrotic region. The main tumor is in the center (arrow).

disseminated pulmonary papilloma after childbirth. Whether the changes in her hormone levels and immune status due to pregnancy were related to the metastasis and malignant transformation of the lung papillomas is unknown for the case is so rare.

Very few patients show malignant transformation of pulmonary lesions.⁵ Malignant transformation into squamous-cell carcinoma arises more often in older children or in young adults than in younger children. The youngest child with RRP to die of lung cancer was 6 years old, and 31% of such patients were diagnosed before reaching adulthood (age: 18 years).⁶ Our case involved juvenile-onset RRP that progressed to carcinoma in young adulthood and became malignant. Our department conducts approximately 300 surgeries on juvenile-onset RRP patients through microlaryngoscopy every year. We conducted 316 surgeries on 176 patients with RRP in 2013, including 32 surgeries of 29 adult patients and 284 surgeries of 147 juvenile patients. Our patient had the only case involving the confirmed malignant transformation of pulmonary lesions into squamous-cell carcinoma. In Gerein's report, 7 malignant transformation occurred in 66.7% of the patients with pulmonary spread during the observation period (the interval between the pulmonary spread of RRP and malignant transformation was 14.6 ± 6.3 years). However, the interval time in our case was only 2.5 years.

RRP may affect people of any age, but the age at disease onset is considered to be the most important factor for the prognosis of disease progression. In our case, the patient was not very young, receiving her first operation at the age of 6 years. She underwent 30 courses of surgery over 21 years, which was not very frequent.

The course of the disease may be mild, with only a few recurrences, or aggressive, with frequent recurrences and the need for repeated excisions. There are no definitive explanations for the variation in RRP outcomes, although the risk factors for malignant transformation in RRP include smoking, previous irradiation and the type of HPV present.⁷

In almost every patient with RRP, HPV DNA has been identified, with the most common being HPV-6 and HPV-11. The frequencies of individual HPV serotypes in juvenile-onset papillomas have been reported to be 50% to 84% for HPV-6 and 25% to 37% for HPV-11.^{8,9} Several case reports have described an association between HPV subtype 11 and malignant transformation.^{4,10,11} Patients with subtype 11 are more likely to be diagnosed at an earlier age, have more active disease and undergo more surgical procedures.¹¹ HPV-11 is not commonly associated with the development of invasive carcinoma at other sites but has been correlated with malignant transformation in the setting of juvenile onset recurrent respiratory papillomatosis.⁴ The data from clinical cases indicated that HPV-11 is associated with a greater risk of causing lung cancer than HPV-6, although rarely HPV-6 can cause bronchial carcinomas.¹² Unfortunately, we did not take specimens of the lung and tracheal papillomas to determine the differences in their gene expression patterns.

The most evident CT features of pulmonary papillomatosis are the following: (1) multiple solid and cystic nodules, (2) atelectasis of the lobe secondary to airway obstruction, (3) tracheal wall irregularities due to scarring and papillomas, (4) bronchiectasis secondary to obstruction and chronic infection and (5) superimposed secondary infectious changes with parenchymal consolidation.¹³ If malignant transformation has

occurred, numerous enlarged lymph nodes will be observed in the mediastinum and neck.

The treatment options have had limited success. Two case reports of the use of cidofovir described some regression of the pulmonary lesions.^{3,14} However, there is presently no cidofovir in China. Patients with RRP bear huge physical and mental burdens and experience enormous economic pressures for years. The malignant transformation of lung papilloma may cause the patient to lose hope of a cure and to eventually forgo treatment.

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