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Early Identification and Intervention in Malignant Transformation of Respiratory Papillomatosis

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 21-year-old
Final Diagnosis: Human papilloma virus • malignant transformation of recurrent respiratory papillomatosis
Symptoms: Airway obstruction
Medication: —
Clinical Procedure: Bronchoscopy
Specialty: Pulmonology

Objective: Unusual clinical course

Background: Human papilloma virus is a ubiquitous and preventable disease with the potential to cause recurrent respiratory papillomatosis. These papillomas affect the mucosal surface of the airways and may lead to airway obstruction. The papillomas require excision when breathing is compromised, and may be fatal if untreated. Rarely, these papillomas progress to cancer.

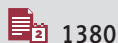
Case Report: We report the case of a 21-year-old woman with a history of HPV 11- and 16-positive recurrent laryngeal and respiratory papillomatosis (RRP) since the age of 7 months, requiring multiple local resections in her respiratory tract. Chest CT demonstrated multiple cavitary lesions throughout both lungs with a rapidly growing mass that occupied most of her right lung. Imaging supported a diagnosis of malignant transformation to squamous cell carcinoma of the lung.

Bilateral involvement of the lungs indicated stage IVa squamous cell lung cancer, which is not curable.

Conclusions: Clinicians should suspect malignant transformation in patients with HPV type 11, especially if they have required multiple excisions. Earlier age at onset and number of excisions may be predictors for severity of the disease course. These patients need continued surveillance imaging to allow early interventions if malignant transformation occurs. We present the case of a 21-year-old being diagnosed with an incurable disease that may have been avoided with adequate preventive care.

Keywords: Carcinoma • Papilloma • Papillomaviridae • Squamous Cell Carcinoma of Head and Neck

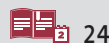
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Background

Recurrent respiratory papillomatosis (RRP) is a chronic viral disease of both children and adults [1]. The true incidence and prevalence of RRP are uncertain. The incidence in the United States is estimated at 4.3 per 100 000 children and 1.8 per 100 000 adults [2,3]. RRP is characterized by the proliferation of benign squamous papillomas within the aerodigestive tract and is caused by human papillomavirus (HPV) types 6 and 11 [4-6].

Both HPV types 6 and 11 are considered to be low-risk oncogenic HPVs, but malignant transformation has been reported. The more aggressive form of disease is most likely to develop in patients with HPV-11 and patients younger than 3 years of age at RRP diagnosis. This can be recognized by higher scores at endoscopic and/or operative debridement procedures per year, a greater desideratum for adjuvant therapy, and a greater incidence of tracheal disease with a tracheotomy [7]. RRP is the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness [8].

HPV infects the stem cells within the basal layer of the mucosa [9,10]. After infecting stem cells, the viral DNA can be actively expressed or it can remain latent, with the mucosa appearing clinically and histologically normal. Inactivation of certain cellular tumor-suppressor proteins and activation of the epidermal growth factor receptor pathway, causing secondary host genomic imbalances, are considered key events in the progression of HPV-promoted lesions [11-14]. The clinical course of the disease is variable. Genetically, the presence of *DRB1*0301* and HPV 6/11 E6/E7 is associated with more severe disease [15]. However, compared with HPV type, age at first onset is a more important factor related to the aggressiveness of juvenile RRP [15]. The risk for malignant transformation is less than 1% [16].

While some fortunate patients may experience complete regression, most patients undergo repeated surgical excisions. These repeated procedures significantly contribute to the health care costs and economic burden for patients and families [17-19]. Here, we report a case of HPV 11- and 16-positive RRP that underwent a spontaneous malignant transformation to squamous cell carcinoma (SCC) after more than 35 operations.

Case Report

The patient was a 21-year-old woman with a history of HPV 11- and 16-positive recurrent laryngeal and respiratory papillomatosis (RRP) since the age of 7 months that has required more than 35 local resections in her respiratory tract. She had also been treated for RRP using chemoimmunotherapy with



Figure 1. Demonstration of mass (red arrow) containing enhancing thick septation, debris, and fluid in the right medial lung, suggestive of progression of respiratory papillomatosis acute infection.

interferon-alpha and received 14 doses, the last of which was on 12/30/2015. Treatment was reportedly stopped due to significant fatigue. In addition, the patient never received HPV vaccinations.

She presented to the emergency department with a chief concern of difficulty breathing and a progressive cough with blood-tinged sputum. In addition, she reported symptoms of dysphagia for solids without liquid, hoarseness, night sweats, and body weight loss of almost 9 kg in 2 months. A thoracic CT was performed and demonstrated multiple cavitary lesions throughout both lungs. The largest lesion was in the right lower lobe and had significantly grown since the previous scan, demonstrated in **Figure 1** below. This mass contained enhancing thick septation, debris, and fluid. These findings suggested progression of respiratory papillomatosis. The interval increase in size was concerning for malignant transformation into squamous cell carcinoma. The perioperative flexible laryngoscope was performed and was negative for upper-airway masses. One week after the initial thoracic CT, a right lower lobe CT-guided biopsy was done due to our concern for malignant transformation and the biopsy showed squamous cell carcinoma, with evidence of partially necrotic tissue replacing alveoli.

The patient's case was discussed at the institute's head and neck multidisciplinary tumor board as well as in the thoracic oncology multidisciplinary tumor board. A consensus was reached that the patient had malignant transformation to squamous cell carcinoma of the lung due to the increasing significant mass occupying most of the right lung, as well as in new parts of the left lung, which was concerning for bilateral involvement in comparison to prior scans. This determined the patient's cancer to be stage IVa squamous cell lung cancer, which is not curable. The patient pursued treatment at an outside facility with Avastin (bevacizumab) and Keytruda (pembrolizumab). Upon her re-presentation to our facility 1 year later, she had repeat CT imaging, which showed stable disease in

her right lung with new cavitory lesions and early papillomatosis in her left lung. She also had increased size of her mid-tracheal papilloma and persistent cervical pain. The patient was taken to the operative suite for a Triamcinolone injection to her vocal cords and bronchoscopy for excision of her tracheal papilloma. The mass was found to be 3 cm in diameter, invading the trachea 6 cm below the level of the glottis and involving approximately 60% of the circumference, with intratracheal and extratracheal components. This mass may have been a papillomatosis lesion, or possibly metastatic lung cancer. There were at least 4 other subcentimeter lesions in her larynx and trachea. Additionally, there was a small amount of air in the prevertebral and paratracheal spaces, raising concern for tracheal and/or esophageal rupture. Despite completing her prescribed chemotherapy, her disease continued to progress.

Discussion

Papillomas appear as exophytic nodules. They infiltrate the pulmonary and digestive systems. Sites of involvement include the larynx, nasopharynx, tracheobronchial tree, and lung parenchyma. These lesions require bronchoscopy to visualize and biopsy lesions. Final diagnosis depends on histopathology. Bronchoscopy offers the additional therapeutic ability to resect lesions and alleviate symptoms [20].

Once the disease has infiltrated the lung parenchyma, helical CT becomes the preferred imaging modality. The disease may present with numerous lesions of different sizes. Often the lesions are cavitated and dispersed throughout the lung. In this case, the patient had the classic findings on CT imaging, with thick septation, debris, and fluid in the mass. She also had multiple lesions scattered throughout both lungs, consistent with the typical disease course.

One finding that must be considered is her co-infection with 2 HPV types. Research suggests that multiple HPV infections can allow DNA integration, and this event may contribute to severe dysplasia of the involved lesions [21].

Primary prevention is the most efficient way to prevent this disease. The quadrivalent HPV vaccine, Gardasil, offers protection against HPV strains 6, 11, 16, and 18. This vaccine is now available to males and females aged 9 to 45. Currently, this vaccine is not required in the United States. The next

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safeguard against disease progression is surveillance with imaging. While there is no consensus on screening guidelines, some authors advocate annual imaging of the thorax to detect pulmonary involvement.

The treatment modalities for aggressive papillomatosis is an area of active research. In our patient's case, she was initially treated with bevacizumab. Recent studies have shown this agent can induce disease response, with the additional benefit of a low complication profile [22].

A study on the long-term follow-up of patients with RRP treated by bevacizumab confirmed these findings, with a proven lower rate of surgical interventions for patients treated with the drug [23]. The second agent used for this patient, pembrolizumab, is a programmed cell death protein (PD-1) pathway inhibitor, and is highly expressed in head and neck cancers, which are related to HPV [24].

Conclusions

There are 2 primary ways to prevent malignant transformation of RRP: primary prevention, and when this fails, frequent monitoring to prevent disease progression. Clinicians should advocate for the HPV vaccination wherever appropriate to prevent this burdensome disease. A population-level approach can reduce the prevalence of HPV and subsequently reduce complications. Once the disease has established itself, timely and appropriate management is key to prevent disease progression. Laryngeal papillomas require prompt excision and frequent monitoring. Bevacizumab has promise in treating this disease. Once a patient has known RRP, they should be screened with chest imaging. Further research needs to be done to establish the appropriate screening intervals for this disease. Physicians must maintain a high degree of suspicion for malignant transformation when lung lesions grow rapidly or spread to the lungs. Vigilant vaccination and surveillance can reduce the healthcare-associated burden of this disease and improve patients' lives.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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