Tracheal papillomatosis: what do we know so far?

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Abstract
Tracheal papillomatosis (TP) is a benign condition characterized by papillomatous growth of the bronchial epithelium that involves the trachea. This abnormal growth is a result of infection with human papilloma virus (HPV). Two subtypes of HPV were found in most cases of TP, HPV-6 and HPV-11. TP, presents in two forms, the juvenile onset (JO) or adult onset (AO). The clinical presentation is typically nonspecific and it ranges from mild symptoms like cough to life-threatening conditions like upper airway obstruction. Treatment depends on the location of the papillomas and age of the patient and the plan of therapy is usually made on an individual basis. Treatment can range from observation with symptomatic control to specific medical therapy and multiple surgeries in case of recurrence or progressively worsening disease. The recent invention of HPV vaccine is expected to be the first step in eradicating respiratory papillomatosis.

Keywords
papilloma, tracheal, human papilloma virus, vaccine, recurrent

Introduction
Tracheal papillomatosis (TP) is a benign neoplastic condition that involves the trachea. It is characterized by continuous papillomatous growth of the bronchial epithelium in response to infection with human papilloma virus (HPV). Most cases of TP are due to HPV-6 and HPV-11; but on occasion, HPV-16 and HPV-18 have also been typed in some cases of bronchial and TP. The latter subtypes are usually associated with poorer outcomes.¹ TP, which is the tracheal manifestation of recurrent respiratory papillomatosis (RRP), presents as either juvenile-onset (JO) or adult-onset (AO) papillomatosis. The incidence of RPR varies and is estimated to range from 18 cases per million for AO to 43 cases per million for JO.² The AO TP affects male and female in a 4:1 ratio. TP can present at any age and is reported in all ethnic groups. Most patients are white with bimodal age distribution. The first peak is in early childhood, with a mean age at onset of 3.8 year, whereas the second peak is in the middle age group. Very few cases were reported in the elderly age group. RRP affects the laryngeal area in most cases and is rarely reported as isolated TP.³ Although rare reports of HPV transmission after cesarean delivery exist, the main mechanism of transmission in JO disease is thought to be due to a vertical transmission of the virus after vaginal delivery of an infected mother.⁴ It is unclear whether sexual contacts or latent viral activation is the principal way of HPV transmission in AO respiratory papillomatosis.

Clinical presentation
The clinical presentation of TP is usually nonspecific. Symptoms range from cough, dyspnea at rest or with exertion, to stridor and upper airway obstruction.³ In some instances, TP presents with symptoms of reactive airway disease.¹ It is not uncommon to report a significant delay in making the appropriate diagnosis. Physical exam is not usually helpful in making the diagnosis of this condition. RRP or TP can manifest as an aggressive disease, and so far there is no identifiable risk factors for such presentations. Some authors suggest an association between infection with HPV-11 subtype and aggressive respiratory papillomatosis.
Diagnosis and imaging studies

TP is best diagnosed using flexible bronchoscopy that is in many cases sufficient to confirm the diagnosis. Sometimes tissue diagnosis is necessary to exclude the possibility of squamous metaplasia or early signs of malignant transformation. This occurs in 0.3–5% of RRP patients and is more common in HPV-11 and HPV-16 infections. Other risk factors for malignant transformation include radiation exposure, tobacco use, and bleomycin therapy. Such associations warrant more aggressive diagnostic approach.

In general, the role of imaging studies is limited. Occasionally, chest X-ray reveals signs of tracheal lesions especially on the lateral view, and in some cases, computed tomography (CT) of the chest shows tumorous growth in the trachea and large airways. Pulmonary function test is helpful in showing signs of variable or fixed tracheal obstructions.

Treatment

Treatment of TP is usually difficult and requires multiple endoscopic interventions with or without concurrent medical therapy. Unfortunately, giving the rarity of this condition, there is no available therapeutic guidelines or randomized controlled trials comparing different therapeutic modalities. Treatment is typically tailored based on the type, severity, number, and location of the papillomas. In patients presenting with airway obstruction, treatment is usually expected. In other cases where symptoms are mild or easily controlled by symptomatic medications, observation is an alternative acceptable approach. This is true especially in elderly patients where the risks of treatment outweigh the clinical benefit. In our practice, we had a case of a 73-year-old woman presenting with a 1-year history of cough in association with intermittent wheezing. Physical exam was unremarkable except for mild expiratory wheezing on auscultation. The patient was an ex-smoker and she was subsequently diagnosed with mild obstructive lung disease. The patient continued to have cough even after optimal medical therapy. Both chest X-ray and CT scan of the chest were negative. Because of the history of heavy smoking, flexible bronchoscopy was performed to rule out any endobronchial lesion. The bronchoscopic findings were consistent with isolated TP (Figure 1). The biopsies were negative for squamous metaplasia or malignant transformation. We treated the patient with celecoxib 200 mg once daily. That was effective in relieving her cough. She did not require any further interventions. Ten months later, follow-up bronchoscopy showed stable disease with neither laryngeal nor pulmonary extensions (Figure 2).

Among other therapeutic options, interferon-α, acyclovir, and methotrexate were found effective in some studies. The antiviral cidofovir was recently evaluated in treating RRP. Cidofovir was also successfully used as intralesional injections. Celecoxib was reported in individual cases to be helpful in treating respiratory papillomatosis, and its efficacy is currently being evaluated in a large randomized prospective trial. In some observational and animal studies, consumption of vegetables rich in indole 3-carbinol (13-C) was found to be effective in delaying disease progression and slowing papilloma growths.
Surgical approach is usually more complicated and requires multiple procedures with significant psychological burden on the patients as well as their families. Surgical excision of the papilloma is fundamental in cases of malignant degeneration of RRP. Many endoscopic surgical modalities have been successfully employed. Among those, excision by carbon dioxide laser is the most widely used. Cryotherapy was also successfully used in some cases. In a small series of advanced laryngotracheal papillomata, radiofrequency coblation technique was successfully used with favorable outcome compared to carbon dioxide laser therapy. Another alternative therapy is photodynamic therapy (PDT) with dihematoporphyrinether (DHE). It consists of intravenous injection of DHE 2–3 days prior to laser light delivery at 630 nm to activate the drug. In a study of 81 patients comparing PDT to conventional therapy, patients treated with PDT demonstrated consistent decrease in papilloma growth rate over the 3-year follow-up period. Neodymium-doped yttrium aluminium garnet (Nd:YAG) laser has also been successfully used in RRP, and the results were more encouraging when the light was delivered with the guidance of a fiber optic instrument. Endobronchial stenting is usually reserved for airway compromise secondary to severe refractory cases of papillomatosis and after failure of all medical and endoscopic therapies. Metallic stenting should be avoided because of high complication rate. Silicone stents have been successfully used with acceptable long-term outcomes. For unknown reasons, AO respiratory papillomatosis tend to be more responsive to therapy with less recurrence rate. The outcome of tracheal and respiratory papillomatosis depends mainly on the age of onset, the location and the severity of the presentation as well as the surgical modality used in each case. The recent Food and Drug Administration (FDA) approval of the new HPV vaccine which covers the subtypes 6 and 11 as well as 16 and 18 is expected to decrease future incidence of respiratory papillomatosis with the hope of eradicating this disease.

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**References**

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