Pharyngeal Papilloma: a Rare Non-Pulmonary Cause of Hemoptysis

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ABSTRACT
The most common benign neoplasm of the pharynx is papilloma. It is characterized by bulging brittle lesions, which are pedicled or sessile, whitish-grey or pinkish colour. Progressive hoarseness is the main clinical feature. When the papillomata spread throughout the tracheobronchial tree symptoms such as chronic cough, stridor, dyspnea or acute respiratory distress are mostly present. Hemoptysis as a presenting symptom is exceptionally rare in patients with pharyngeal papillomatosis. Herein, we report a case of pharyngeal papillomatosis in which hemoptysis was the primary clinical manifestation. The clinical and therapeutic aspects of the disease are briefly discussed.

KEYWORDS
hemoptysis; pharynx; papilloma

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INTRODUCTION

Papilloma is considered a benign pharyngeal neoplasm (1). It is characterized by warty outgrowths of pharyngeal surface epithelium (2). The lesions are usually multiple occurring on true vocal cords, false cords, epiglottis, subglottic area and rarely tracheobronchial tree. Despite their benign nature, the papillomata are liable to recurrence after surgical resection and extend throughout the entire respiratory tract causing severe airway obstruction; a condition called recurrent respiratory papillomatosis thus bearing considerable morbidity and mortality. Human papilloma virus (HPV) is the causative agent of pharyngo-laryngeal papillomatosis (3).

The most common symptom is hoarseness. In decreasing order, other symptoms include voice change, choking episodes, foreign body sensation in the throat, cough, dyspnea, inspiratory wheeze and stridor, especially when the papillomata extend into the lower respiratory tract. Hemoptysis is extremely rare as major presenting symptom of pharyngo-laryngeal papillomatosis. In this article, we describe a patient with multiple pharyngeal papillomas whose hemoptysis was the principal presenting manifestation.

CASE REPORT

A 41-year-old male, active smoker (40 p/y), was admitted to our department presenting with hemoptysis (about 10 ml of bright red blood daily) for 5 consecutive days prior to hospital admission. He denied any additional symptoms. His past medical history was unremarkable.

A thorough physical examination at the time of the admission was normal. Initial laboratory studies showed a WBC count of 8.500/μL with normal differential count, haemoglobin was 14.4 g/dL, haematocrit was 43.4% and platelet count was 285.000/μL. Erythrocyte sedimentation rate (ESR) was slightly elevated (30 mm/h). C-reactive protein, serum biochemistry tests and urinalysis were within normal range. ECG showed normal sinus rhythm with no acute ST-T wave changes. Tests for antinuclear antibody, rheumatoid factor, complement, antiglomerular basement membrane antibody and antineutrophil cytoplasmic antibody as well as the tuberculin skin test were negative. Arterial blood gas analysis on room air revealed a pO_2: 99 mmHg, pCO_2: 23.3 mmHg, pH: 7.49, HCO_3: 18 mmol/l. Chest radiograph did not reveal abnormal findings but computed tomography of the thorax showed a solitary ground glass appearance in left upper lobe, probably due to aspirated blood (Figure 1). Furthermore, spiral CT pulmonary arterial angiography performed simultaneously was negative for emboli in pulmonary arterial trunk and the following branching system.

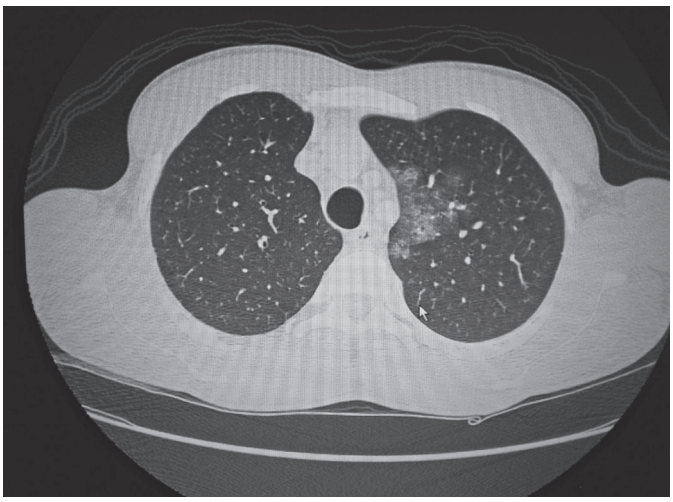

Fig. 1 Chest CT showing a solitary ground glass appearance in left upper lobe.

The patient underwent transnasal fiberoptic bronchoscopy. Neither intraluminal lesion nor bleeding source throughout the tracheobronchial tree was found. Bronchoalveolar lavage (BAL) from left upper lobe was negative for mycobacteria and other common pathogens as well as cytologic examination. BAL fluid analysis was also normal. However, pharyngo-laryngeal examination before the introduction of the bronchoscope into the trachea and distal bronchial tree showed four translucent whitish nodules on the hypopharynx. One of them was more vascular exhibiting incipient bleeding (Figure 2). Biopsies showed the presence of finger-like projections of nonkeratinized stratified squamous epithelium with highly vascularized connective tissue stroma at the core thus confirming the diagnosis of papilloma. Molecular testing

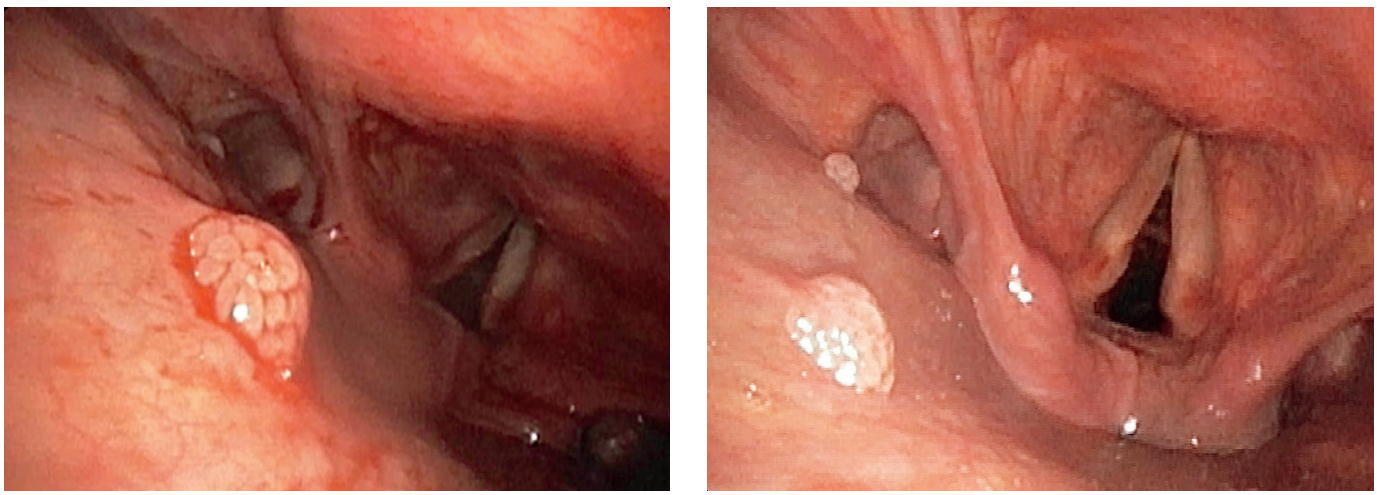

Fig. 2 Pharyngo-laryngeal examination before the introduction of the bronchoscope into the tracheobronchial tree demonstrating translucent whitish nodules on the hypopharynx. One of them was more vascular exhibiting incipient bleeding.

using polymerase chain reaction (PCR) identified HPV type 6 in papilloma tissue. Surgical removal of the papillomata was performed by an otorhinolaryngologist using carbon dioxide (CO_2) laser. The patient was recommended to quit smoking and undergo pharyngo-laryngoscopy and bronchoscopy at regular intervals for detecting papillomata because of their propensity to recur after resection.

DISCUSSION

The most common benign neoplasms of the upper respiratory tract are papillomas (1). They are characterized by bulging brittle exophytic proliferative lesions of connective tissue covered by keratinized squamous epithelium (2). Koilocytes, vacuolated cells with clear cytoplasmic inclusions are present thus indicating viral infection. Dysplastic and malignant transformation can occur. However, malignant degeneration to squamous cell carcininoma is a rare complication since it has been reported in 3–5% of patients. The overall prevalence of respiratory papillomatosis ranges from 2 per 100,000 adults to 4.5 per 100,000 children given that the disease presents in two forms according to the age at onset (4).

It is well-documented that human papilloma virus (HPV) is the exclusive causative agent of respiratory papillomatosis. Nowadays, more than 150 HPV subtypes have been identified. More specifically, viral subtypes 6 and 11 cause the vast majority of cases of respiratory papillomatosis whereas HPV subtypes 16, 18, 31 and 33 have also been detected in papillomas, but are much less common. HPV type 11 produces more aggressive disease (e.g. significant airway obstruction, need for tracheotomy and frequent surgical procedures). Nevertheless, HPV types 6 and 11 are low-risk for malignant degeneration in contrast to HPV types 16, 18, 31 and 33 which are potentially oncogenic. Malignant degeneration is more common with disease caused by HPV-11 and HPV-16. Cigarette smoking, bleomycin therapy, and radiation treatment of involved areas also increase the risk of malignant degeneration. The site of malignancy is usually the bronchial or pulmonary parenchyma in children, whereas the larynx is the usual site in adults (5).

The patients may have symptoms for months or longer before the disease is recognized. The average time from onset of the symptoms to diagnosis ranges from 1 to 8 years although in a recently published study was found to be 52.3 months (6). Hoarseness is the most common presenting symptom. Additional symptoms that can develop include voice change, chronic cough, difficulty swallowing (dysphagia), shortness of breath or difficulty breathing (dyspnea), stridor, the sensation of a foreign body in the throat, and choking episodes. In particular, juveniles commonly present with a weak cry, episodes of choking, hoarseness, or failure to thrive. In adults, the symptoms of respiratory papillomatosis are hoarseness, strained or breathy voice, choking spells, or a foreign body sensation in the throat. Left untreated, papillomas can eventually cause severe airway obstruction resulting in a serious and life-threatening complication (acute respiratory distress). Hemoptysis as a primary presenting feature is exceedingly rare and has only been described in patients with recurrent respiratory papillomatosis (RRP) (7). In the present case, hemoptysis was the sole clinical manifestation of pharyngeal papillomatosis.

With regard to disease management, surgery remains the mainstay of treatment. Its aim is to maintain an acceptable quality of voice and preserve airway patency. Complete eradication may be detrimental, in that injury of the mucosal surface has been associated with increased expression of HPV in nearby HPV-infected cells. In addition, a judicious surgical approach through sub-total removal of papilloma in the setting of disease involving the anterior or posterior commissure is usually preferred thus preserving proper vocal cord and airway functioning. Surgery has been traditionally performed via microscopic or endoscopic rigid laryngoscopy using a variety of lasers to debulk the papillomatous lesions (8).

For several years now, excision by carbon dioxide laser has been the most commonly employed removal method. It provides good hemostasis, minimizes potential thermal injury of surrounding healthy tissues as well as allows for longer disease-free periods (9). Respiratory tract burns, severe laryngeal scarring and stenosis, distal injuries with tracheoesophageal fistulae as well as high cost have been reported as major drawbacks of the procedure. Therefore, microdebridement of laryngeal lesions is often preferred to laser therapy. Nevertheless, CO_2 laser remains an effective treatment option in the hands of dexterous surgeon, as it occurred in the present case.

The use of microdebridement using angled oscillating blades that incorporate suction and irrigation offers the advantage of shorter time of surgery, lower cost, lower risk of complications, and better patient voice quality when compared to CO_2 laser. It allows the surgeon to quickly remove tissue as it provides good visualization of the area because of the suctioning of secretions during cutting (10, 11). A tracheotomy is generally included among the surgical methods; however, it is indicated for the most aggressive cases with impending airway compromise, where multiple debulking surgical procedures have been proved unsuccessful. Because of its high propensity for distal disease spread to the tracheobronchial tree, tracheotomy is a treatment of last resort. Recurrence is common, irrespective of whether CO_2 laser or microdebridement is used. Persistence of HPV genome within the tissue adjacent to lesions has been proposed as the main cause. Managing recurrence often requires extensive manipulation of the upper respiratory tract thus leading to permanent damage in the form of glottic stenosis and anterior/posterior commissure synechiae. Adjunctive medical treatment is an attempt to minimize disease recurrence, its complications, and reduce or eliminate the necessity for frequent surgical interventions. The current criteria for adjuvant therapy are the requirement for more than 4 surgical procedures annually, rapid regrowth of papillomata with airway compromise and/or remote multisite spread of the disease. Interferon-alpha and cidofovir are the most extensively investigated and effective drugs in the pharmacological armamentarium of RRP (12, 13). Another promising adjuvant pharmacological agent is bevacizumab – a recombinant monoclonal humanized antibody – that blocks angiogenesis by inhibiting the human vascular endothelial growth factor A (VEGF-A), which has been shown to play an important role in the pathogenesis of RRP (14). Several recent studies have demonstrated its satisfactory results by decreasing the growth of papillomatous lesions and prolonging intervals between the surgical procedures (15, 16).

Moreover, the development of HPV vaccines represents a great medical breakthrough in preventing RRP. In particular, the quadrivalent HPV vaccine, Gardasil, has activity against HPV types 6, 11, 16, 18 and its implementation as an adjunctive therapy has a positive effect on the course of RRP, since the recurrence rate seems to be significantly lowered, according to two recently published studies (17, 18). The induction of sufficiently high antibody titers after HPV vaccination and subsequent immunoglobulin secretion on the mucous membranes of the aerodigestive tract could be a plausible explanation for its favourable therapeutic effect (19). Furthermore, the newly-developed nonavalent vaccine, Gardasil-9, achieved encouraging results in a descriptive study, as it abated the course of the disease, lengthened the inter-surgical interval, and decreased morbidity (20). However, large, multicentre randomized controlled trials are needed to adequately assess the efficacy of the HPV vaccination as a therapeutic vaccine in the RRP population.

CONCLUSIONS

In conclusion, the present case is unusual in that the patient manifested hemoptysis and bronchoscopic examination revealed isolated pharyngeal papillomatosis. Hemoptysis has only rarely been reported in patients with disease spread to the tracheobronchial tree. Bronchoscopy is strongly recommended as the primary method for diagnosing and localizing hemoptysis, especially if massive. Clinicians should be aware of the disease to make an early diagnosis. Because of its tendency for recurrences and malignant transformation, meticulous follow-up of patients including HPV typing is crucial for early detection and treatment.

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