



Case report

Recurrent respiratory papillomatosis with lung involvement

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ABSTRACT

Recurrent respiratory papillomatosis (RRP) is a rare disease caused by human papillomavirus. Aggressive forms of RRP require repeated cytoreductive surgery to restore airway patency. Tracheal disease is even less common and lung parenchyma is involved in less than 1% of patients. We present reports of three cases of RRP with progressive lung disease in adult patients.

1. Introduction

Recurrent respiratory papillomatosis (RRP) is a quite rare chronic disease in which tumors grow in the air passages. RRP usually manifests in children. RRP is caused by human papillomavirus (HPV). RRP patients most commonly test positive for two strains of the virus: HPV 6 and HPV 11. Less frequent strains, HPV 16 and HPV 18, are usually associated with malignant transformation of papillomas [1]. There exist two distinct types of RRP: adult-onset RRP and juvenile-onset RRP. Adult-onset RRP does not usually involve the lower airways, and its occurrence rate is quite low [2].

In this article, we present detailed descriptions of three well-documented case reports of RRP with tracheal, bronchial and pulmonary involvement.

2. Case report 1

A 38-year-old male patient admitted in our hospital in 2012, had a history of RRP since age 4. He underwent several endoscopic excisions of laryngeal and tracheal papillomas, received photodynamic therapy (PDT), and had a tracheostomy.

Papillomas were seen in the patient's laryngeal vestibule and subglottic region; solitary lesions were also observed in the middle third of the trachea and the right main bronchus. The mucous membrane above the tracheostomy tube was significantly thickened and swollen; tracheal rings were indistinct; an excessive expiratory collapse of the tracheal walls was seen (tracheomalacia). The patient underwent laser ablation of papillomas and received local and systemic antiviral therapy.

The CT scan (Fig. 1A) revealed multiple irregular-shaped soft-tissue

nodules in both lungs with normal lung tissue around them. The largest lesion, located in the right upper lobe (S2), was 26 × 26 mm. A number of lesions showed cavitations. Thoracic and axillary lymph nodes were within normal limits.

The tracheal and pulmonary specimens were taken from the tracheal wall and from a lesion located in right lower lobe under CT control [Fig. 2A]. The polymerase chain reaction (PCR) showed the presence of HPV 6 and HPV 11 DNA in all the specimens.

In 6 months, the CT scan showed that the soft-tissue infiltration previously seen in the right lung transformed into a thick-walled cavity (Fig. 1B). A number of subpleural lesions were still seen in both lungs. In the right lower lobe, there were air-containing cavities with thick walls (diameter range: 0.5 cm–3.0 cm). The number of lesions did not increase relative to the previous CT scan.

Bronchoscopy showed worsening: tracheal disease progressed, one of the papillomas obstructed about 80% of the tracheal lumen. A big papilloma was removed by loop electro-surgical excision procedure followed by argon plasma coagulation.

Disease characteristics: 1) involvement of pulmonary parenchyma, 2) progression of tracheal and pulmonary disease within five months. The latter was probably caused by biopsy; however, the examination of the biopsy specimen confirmed the presence of HPV 6 and HPV 11 in the lung parenchyma.

3. Case report 2

A 24-year-old female patient with recurrent laryngeal papillomatosis underwent more than 40 surgical excisions and a tracheostomy, admitted in November 2011 with papillomatous growth on the laryngeal vestibule and the glottic region. The patient showed small pink

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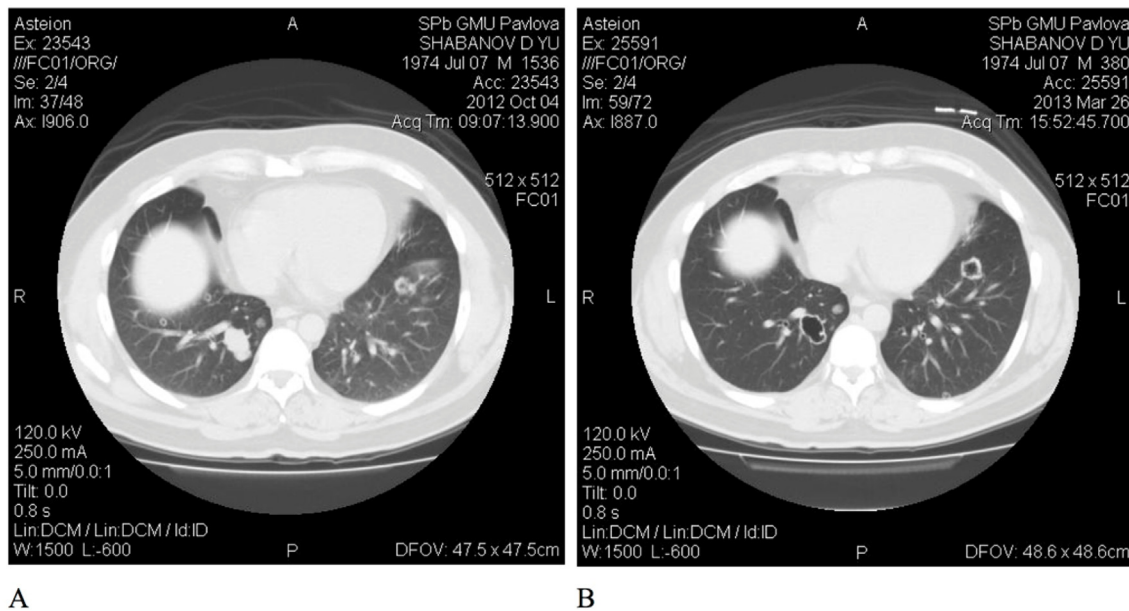


Fig. 1. Chest computed tomography; case report 1. **A.** Multiple irregular-shaped soft-tissue lesions in both lungs. A soft-tissue infiltration is seen in S10 of the right lower lobe. **B.** Six months later: the soft-tissue infiltration previously seen in S10 of the right lung has transformed into a thick-walled cavity.

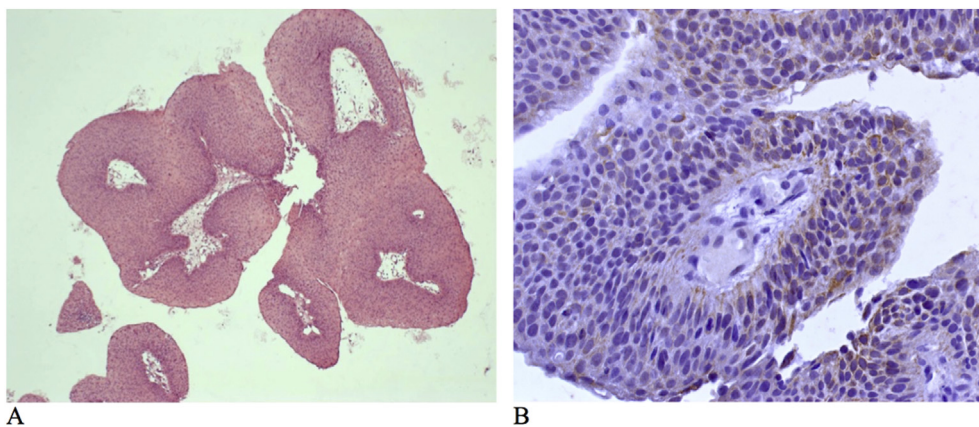


Fig. 2. **A.** Case report 1. Tracheal respiratory papillomatosis showing squamous cover epithelium, many vessels in the stroma (hematoxylin and eosin stain x 50). **B.** Case report 2. Proliferating squamous epithelium, in some places with atypia; the hybridisation staining for HPV subtype 16 (hematoxylin and eosin stain x 180).

papillomatous lesions of about 3 mm in diameter on tracheal walls above, along and under the tracheostomy tube. The CT scan revealed multiple irregular-shaped nodules (diameter range: 5 mm–30 mm) with sharp edges in both lungs, with normal lung tissue around them. The majority of lesions had cavitations. The trachea, main and lobar bronchi showed the normal patency. Thoracic and axillary lymph nodes were within normal limits. The patient underwent laser ablation of laryngeal papillomas. Eighteen days later she received PDT.

Laryngeal brush biopsy specimens tested positive for HPV 6 and HPV 11 (PCR).

In July 2012 new lesions were seen in the trachea - an 8-mm pedunculated papillomatous lesion grew by the distal end of the tracheostomy tube. Papilloma was removed (electrosurgical excision + argon plasma coagulation). A biopsy specimen tested positive for HPV 18, HPV 6 and HPV 11 (PCR).

Ten months later, though the patient remained clinically stable, CT images showed a significant worsening: the number of cavitory and nodular lesions increased in both lungs (Fig. 3). Bronchoscopy showed multiple papillomas above and under the tracheostomy tube obstructing two-thirds of the tracheal lumen. Aggressive types of HPV (HPV 16, HPV 6, HPV 11) were present in brush biopsy specimens

(Fig. 2B). The specimens tested negative for HPV 18.

Disease characteristics: 1) progression despite active treatment (laser ablation, PDT, electrosurgery): the number of cavitory and nodular lesions in the lungs increased, numerous papillomatous masses appeared in the trachea and obstructed two-thirds of its lumen; 2) presence of more aggressive HPV strains in the specimens: HPV 6 in 2011, HPV 18 in 2012, HPV 16 in 2013.

4. Case report 3

A 17-year-old female patient had a history of RRP since age 2. She developed laryngeal and tracheal lesions. The patient underwent 92 surgical procedures before. A T-shaped stent was placed in the patient's trachea in 2013.

In December 2013, a chest CT scan showed multiple air-filled cavitory lesions in both lungs. The lesions were up to 0.5 mm in diameter and had irregular wall thickness. The right lower lobe showed a nodular lesion up to 3.0 cm in diameter. Six months later, the number of cavitory and nodular lesions increased, multiple nodular lesions were seen in the pulmonary parenchyma. A bronchial lumen bordered on cavitory lesions in the right lateral basal segment (S9) (suspected

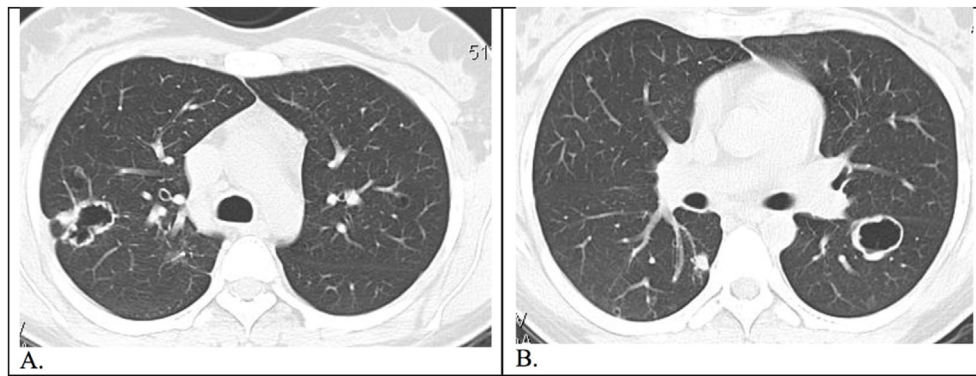


Fig. 3. Chest computed tomography; case report 2. Multiple cavitary lesions in both lungs.

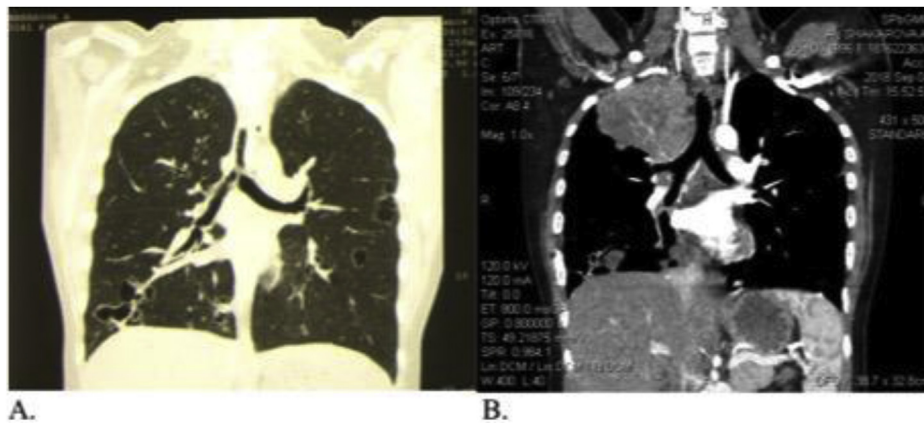


Fig. 4. Case report 3. A. Chest computed tomography, communication between the pulmonary cavity and the right lateral basal bronchus (B9). B. Lung cancer development in right upper lobe.

communication) (Fig. 4A). Aspirate from B9 subsegments tested positive for HPV 6, HPV 11 and HPV 18.

High-risk HPV strains (HPV 6, HPV 11) were present in brush biopsy specimens from a tracheal lesion.

Despite local treatment and systemic antiviral therapy, CT scanning and bronchoscopy showed further worsening. Squamous cell carcinoma of the right upper lobe was diagnosed in September 2018 (Fig. 4B).

5. Discussion

The following factors may contribute to the downward spread of papillomatosis: 1) high disease activity with diffuse viral infection of the airways; 2) frequent surgical interventions (endolaryngeal, endotracheal); 3) disease duration. We believe that tracheostomy is the main cause of tracheal, bronchial and pulmonary involvement. The lower airways are involved in 90% of papillomatosis patients with tracheal tubes [3–5]. All three patients in the case reports had tracheal tubes and underwent numerous endoscopic procedures.

CT is the standard imaging modality for patients with papillomatosis. CT is able to visualize pulmonary lesions and disease progression in the lung parenchyma. Therefore, the CT scanning is the best method for the assessment of papillomatosis severity and possible outcomes [6].

Soldatski IL et al. (2005) observed 448 RRP patients over 25 years. Only 1.8% of patients had pulmonary lesions [5]. The characteristic radiologic finding of the lung involvement is nodules scattered throughout the lungs. They may grow in size and may form large cavities with thick or thin walls. As a nodule grows, the blood supply to the center of the lesion is lost, and central necrosis occurs. Communication with an airway results in cavitation. In all described cases, CT showed a fast increase in the number and size of the cystic lesions in the

lungs, which indicates disease progression. Worsening in pulmonary disease followed the progression of laryngeal and tracheal disease.

Malignant transformation of RRP is rarely described [7–9]. The median interval between the diagnosis of RRP and that of cancer was 19 years, with a range of 4–45 years [9]. In our case 3 malignant transformation was diagnosed in patients 22 years old with the duration of RRP about 20 years and in 5 years after the pulmonary parenchyma involvement. Not enough data is available on the association of HPV type and cancer development. Our patient had both HPV types 11 and 6, which are more frequently identified in RRP patients with cancer development [7–9].

The gold standard in the endoscopic diagnostics of laryngeal, tracheal, or bronchial disease is laryngoscopy and bronchoscopy. Chest CT and virtual bronchoscopy can be used to assess the severity of papillomatosis and how far the disease has spread. These methods reduce the risk of spreading the virus downward [1].

However, only invasive methods provide the possibility to visualize the airways for therapeutic interventions and to sample a lesion for histological examination or PCR typing of HPV [10].

A number of treatment options are available for RRP. However, none of them provide radical etiopathogenic treatment for the disease [11]. The clinical practice employs three main approaches to the treatment of RRP or their various combinations: 1) improving existing endoscopic surgical techniques, 2) developing new medications (antiviral, immunologic agents, etc.), or 3) use of HPV vaccines [12]. The most frequently used treatments of patients with lung involvement are antivirals, chemotherapy, immunotherapy, radiation and excision [9]. Unfortunately, the treatment is far from effective in the long term.

Several reports have been made in the recent years about the use of PDT in the treatment of respiratory papillomatosis [13]. In two of the

three described patients, the duration of response to PDT did not exceed 6–12 months. According to K. Harris (2011), patients who received PDT demonstrated decreased papilloma growth during a three-year follow-up [12]. Endobronchial stents are used in patients with severe RRP and patients with no response to medication and endobronchial therapy [14].

Declarations of interest

None.

Conflict of interest

All authors of the article have no conflict of interest. All authors are committed to ethical standards.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2018.10.019>.

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