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Case Report

Recurrent respiratory papillomatosis (RRP) of tracheobronchial tree presenting as lung collapse with malignant transformation after a decade

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A B S T R A C T

Recurrent respiratory papillomatosis is a rare disease caused by HPV infection. We hereby report a patient with recurrent respiratory papillomatosis of the tracheobronchial tree with no laryngeal involvement who remained clinically stable for more than 10 years but then developed malignant transformation with metastases.

A 61-year-old lady with good past health presented to our department in 2010 because of chronic cough for years. Chest X-ray showed reduced left lung volume. Bronchoscopy showed multiple nodules over left main bronchus and left upper lobe progressing to involve the posterior trachea and left lower lobe. Biopsy revealed squamous papilloma with mild dysplasia. She refused surgical intervention. She remained relatively stable until November 2022 when she developed left chest pain. CT showed features of malignant transformation with local invasion and metastases. Fine needle aspiration suggested squamous cell carcinoma. She succumbed in December 2022.

Bronchoscopy should be considered in the investigation of unexplained chronic cough so that this rare disease can be detected at an early stage. The disease may not require intervention if uncomplicated. Despite clinical stability for a prolonged period, close monitoring for malignant transformation is warranted indefinitely.

1. Introduction

Recurrent respiratory papillomatosis (RRP) is a rare disease. RRP of the tracheobronchial tree without involving the larynx is even rarer. We hereby report a patient with recurrent respiratory papillomatosis of the tracheobronchial tree with no laryngeal involvement who remained clinically stable for more than 10 years but then developed malignant transformation with metastases.

2. Case presentation

A Chinese lady, a non-smoker and non-drinker with good past health, first presented to our department in 2010 (at the age of 61) because of cough for years. Physical examination was unremarkable. Blood and sputum tests were normal. Chest X-ray in June 2010 showed reduced left lung volume (Fig. 1). Spirometry suggested mild restrictive ventilatory defect. Bronchoscopy in July 2010 showed multiple nodules over left main bronchus and at the entrance of the left upper lobe. Biopsy revealed mild squamous dysplasia. Computed tomography (CT) scan of thorax in October 2010 showed decreased left lung volume, dilated bronchi within left upper and lower lobes, and irregular soft tissue thickenings around left main bronchus, left upper and lower lobes bronchi which appeared to be narrowed. CT in September 2013 showed further reduction of left lung volume with new bronchiectatic changes in the left collapsed lung. Bronchoscopy repeated in October 2013 showed nodules over posterior trachea and multiple nodules involving left main

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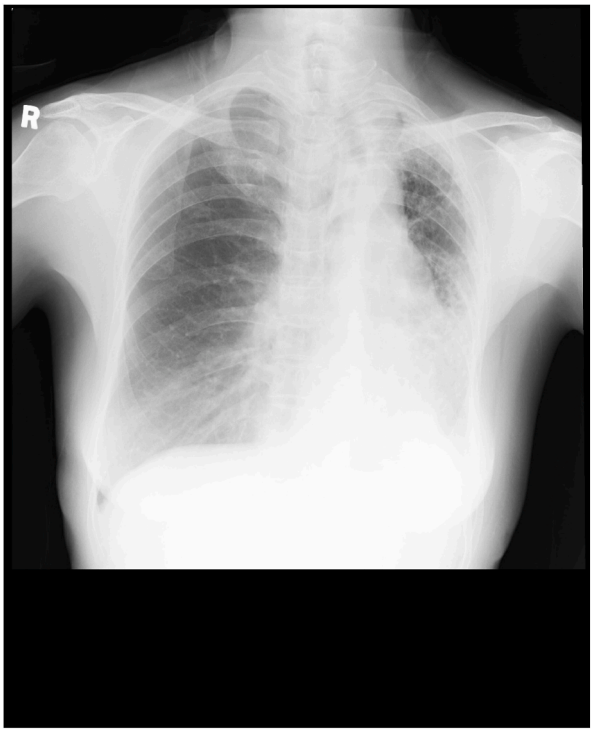

Fig. 1. Chest X-ray in June 2010 showing partial left lung collapse.

bronchus extending to left upper lobe and lower lobe bronchi (Fig. 2). Biopsy revealed squamous papilloma with mild dysplasia. The case was discussed in the multidisciplinary chest conference. It was decided that surgical debridement via rigid bronchoscopy was the preferred treatment option. However, the patient refused repeating bronchoscopy and surgical intervention since then.

The patient remained asymptomatic except infrequent attacks of infective exacerbation of bronchiectasis throughout the years. Routine follow-up CT scan of thorax in November 2020 showed further reduction of left lung volume, interval enlargement and increase in number of the associated nodular-like wall thickenings. There were new nodular lesions in left upper lung and right lower lobe. CT thorax in November 2022 showed a large (18.8cm) necrotic mass replacing the bronchiectatic left lung with extensive local

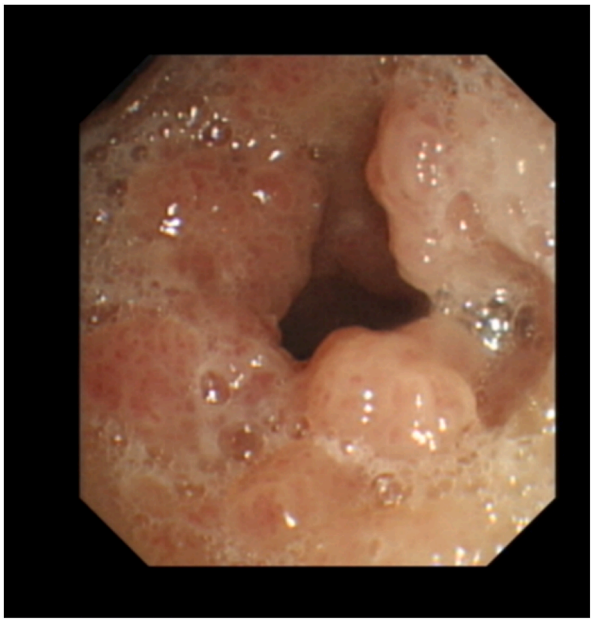

Fig. 2. Bronchoscopic view showing narrowing of left main bronchus with multiple nodules in October 2013.

invasion, enlarged mediastinal lymph nodes, small amount of bilateral pleural effusion and pericardial effusion (Fig. 3). The patient complained of left chest pain, pain and swelling over both ankles. Ultrasound-guided fine needle aspiration of the left lung mass showed necrotic squamous cells. Some of the cells demonstrated degenerated hyperchromatic nuclei and orangeophilic cytoplasm. Her condition deteriorated rapidly and she succumbed in December 2022.

3. Discussion

The appearance of multiple papillomatous lesions in the respiratory tract is referred to as recurrent respiratory papillomatosis (RRP). Most, if not all, of them are caused by human papilloma virus (HPV) infection [1]. HPV is a DNA virus of the Papillomaviridae family with a non-encapsulated, double-chain icosahedric structure [2]. It is a common commensal organism in humans causing widespread latent infection by inhibition of the host immune response. Subtypes 6 and 11 account for more than 90% of the cases of RRP, the latter subtype being associated with more aggressive disease [3]. Exposure of the upper airway to HPV is as common as to rhinovirus such that HBV DNA can be detected in the upper airways of up to 25% of normal subjects. The reason why RRP only develops in some patients is still unclear [4]. Unfortunately, viral typing was not done in the biopsied specimens of our patient.

The disease is characterized by a bimodal distribution with a juvenile form (less than 20 years of age) and an adult form (more than 20 years of age) [5,6]. The estimated incidence is around 4 per 100,000 in children and 2 per 100,000 in adults with a male preponderance in the adult form. In children, the disease is believed to be caused by contact with infected secretions in the birth canal during delivery, especially when the mother has anogenital warts. Transplacental transmission before delivery also occurs (around 12%) [7]. In adults, HPV is transmitted sexually during oral contact with the infected external genitalia. As such, oral sex, multiple sexual partners and gastroesophageal reflux are risk factors [8]. Our case did not have reflux symptoms. Unfortunately, her sexual history was not asked.

The lesions occur primarily in and are generally limited to the larynx. However, they can occur in any part of the aerodigestive tract. Distal spread to the tracheobronchial tree occurs in 2–5% and to the lungs in 1% [5,9]. Tracheobronchial RRP without laryngeal involvement is even rarer [10]. Extension by contiguity, diffuse viral contamination and iatrogenic factors have been postulated as pathogenetic mechanisms for distal spread of the lesions. HPV subtype 11 infection, age less than 3 years, tracheostomy and other invasive procedures are risk factors for distal spread of the disease [8]. In our case, the disease involved the transbronchial tree and the lungs but sparing the larynx.

Malignant transformation, usually to squamous cell carcinoma, occurs in less than 1% of children and 3–7% in adults, especially when there is tracheobronchial involvement [11]. Risk factors include infection with high-risk HPV subtypes (16 and 18), smoking, prior radiotherapy, chemotherapy and high severity score [2,3]. Notably, such malignant transformation can occur decades after disease onset or when there is only laryngeal involvement [5]. However, in this case, there was no risk factor identifiable that could lead to its malignant transformation after 10 years of observation. Symptoms are usually non-specific including dysphonia, chronic cough or shortness of breath. Physical examination may show stridor, wheezing or respiratory distress. Therefore, the disease is often misdiagnosed as laryngitis, bronchitis, asthma or croup [5,8]. Delay in diagnosis is common, even up to a few years [7,11]. The course of RRP is variable, ranging from spontaneous remission in a minority to aggressive progression in most cases. Although the lesions are basically benign, spreading to the distal airways can lead to significant morbidity such as recurrent pneumonia or obstructive atelectasis, and even mortality. Haemoptysis is common when there is distal spread of the lesions. The disease may then be misdiagnosed as

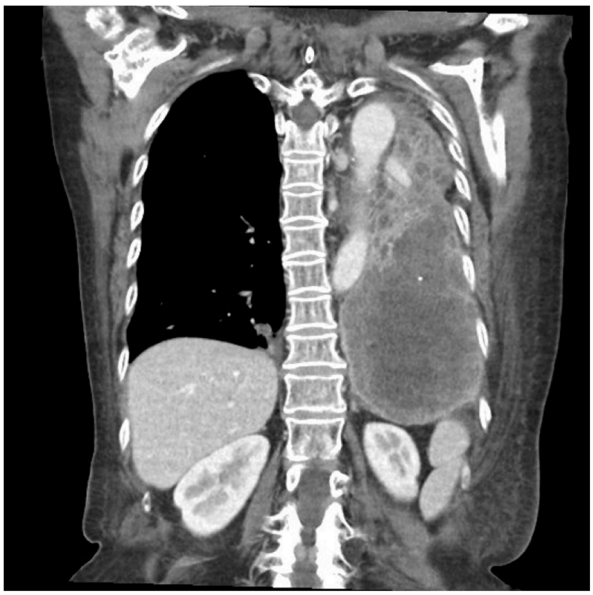

Fig. 3. Coronal view of CT scan showing large necrotic mass occupying the left thoracic cavity with extensive local invasion in November 2022.

active pulmonary tuberculosis [12]. Our case presented wih chronic cough for many years which was only diagnosed when bronchoscopy was performed for reduced left lung volume.

CT scan is more sensitive than chest X-rays in revealing localized or diffuse nodular thickening with vegetant sessile or pedunculated lesions in the trachea and main bronchi. Typical CT findings of pulmonary involvement include multilobulated, well-defined, solid nodular or polypoid lesions of various sizes scattered throughout the lungs (especially in the basal and posterior regions) which may enlarge and form air-filled cysts or cavities with irregular borders. With airway obstruction and secondary infection, CT may demonstrate atelectasis, consolidations, air trapping, and bronchiectasis. Lymphadenopathies and pleural effusion are rare except in cases of malignant transformation [5,9,12]. In our case, multiple nodules over the posterior trachea and left bronchial tree as well as bronchiectatic changes over the left lung were noted before malignant transformation. After malignant transformation, a large necrotic lung mass, mediastinal lymphadenopathies, bilateral pleural effusion as well as pericardial effusion were demonstrated.

Virtual bronchoscopy has the advantage of allowing visualisation of the airways beyond a stenotic area and avoiding the complications of conventional bronchoscopy [13]. However, it does not allow biopsy taking for definitive diagnosis of the disease. Virtual bronchoscopy was not done in our case.

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT scan is not useful in screening for malignant transformation because RRP lesions are FDG-avid due to increased cellular proliferation [14]. The uptake may also be heterogenous due to significant variability in the metabolic behaviour of the lesions [15]. PET-CT was not done in our case.

Bronchoscopy typically shows exophytic masses or nodules which may be sessile or pedunculated, soft and friable. Histologically, papillomas appear as projections with central fibrovascular cores covered with stratified squamous epithelium [7]. Pulmonary lesions, on the other hand, have a different morphology with foci of squamous epithelium growing circumferentially within the alveoli. Central areas of necrosis and degeneration are typical. These lesions may coalesce and form cavities [5]. The bronchoscopic appearance was typical in our case.

Differential diagnoses include malignancy, tuberculosis, granulomatosis with polyangiitis, amyloidosis, tracheobronchopathia osteochondroplastica, relapsing polychondritis, tracheobronchomegaly, sarcoidosis and neurofibromatosis [16]. Such differential diagnoses were excluded by histopathology in our case.

The gold standard for diagnosis is by biopsy for histopathology with or without viral typing via laryngoscopy or bronchoscopy. In our case, bronchoscopy with biopsy led to a definitive diagnosis of the disease.

There is no definitive curative treatment for the disease. Surgical excision of the papillomas, by debulking the lesions as much as possible without damaging the normal tissues, remains the mainstay of therapy [17]. Lasers have been used for debridement but are associated with surgical complications including respiratory tract burns, scarring, stenosis and fistula formation. Nowadays, a microdebrider is preferred, especially when multiple surgical procedures are required, because it allows more precise debridement with better preservation of the normal structures [1]. Lesion recurrence, however, is common [11]. Tracheostomy may be required for relief of upper airway obstruction but decannulation should be performed as soon as possible because the tracheostomy promotes distal spread of the disease by acting as a conduit [1]. Adjunctive medical therapy may be considered when more than four surgical procedures are required in one year, when there is distal multisite spread of the disease or when the lesions rapidly recur leading to airway compromise. Immune-modulatory drugs or antiviral agents have been used, which include interferon, acyclovir, ribavirin, cidofovir and so on [11]. Amongst them, the antiviral agent cidofovir is the most popular. It can be administered by intravenous or intralesional injection or by nebulization. Intralesional administration of the drug has the advantage of limited systemic or local side effects but the theoretical risk of malignant transformation remains [1,18]. The complete response rate to intralesional cidofovir was 74% in the adult form of RRP [19]. In recent years, bevacizumab, a VEGF monoclonal antibody, has shown promise as a systemic treatment for RRP [20]. In our case, no intervention was performed because of the patient's refusal.

HPV vaccine offers hope for eradication of the disease by preventing viral transmission. The role of HPV vaccine in treatment of the disease needs further validation [17]. Our patient had no history of HPV vaccination.

Our case is remarkable in the following aspects:

Firstly, our patient had tracheobronchial RRP without laryngeal involvement, which was extremely rare. Only a few cases have been reported [10]. Secondly, our patient refused surgical intervention all along but had remained clinically stable up till late 2022. Thirdly, the patient ran a rapid downhill course 12 years after her disease onset due to malignant transformation. In a previous case series of RRP [21], four were adult onset cases. Three had tracheobronchial RRP without laryngeal involvement. Amongst all four cases, two underwent malignant transformation (one had laryngeal involvement and the other did not). However, one case had no follow-up (case 11) and another case (case 10) was only followed up for eleven years. Whether these two cases developed malignancy in the long run was unknown.

4. Conclusion

Recurrent respiratory papillomatosis of the tracheobronchial tree is a rare disease which has the potential of malignant transformation. A few lessons can be learnt from this case.

Firstly, bronchoscopy should be considered when a patient presents with unexplained chronic cough. In our case, she had chronic cough for many years but bronchoscopy was only performed when chest X-ray showed reduced left lung volume. The diagnosis might be established earlier if bronchoscopy was done before her chest X-ray abnormality appeared.

Secondly, our patient remained clinically stable for more than a decade although no surgical intervention was performed as she refused invasive procedures. This means that conservative management can be considered in uncomplicated RRP cases, especially when

the patients are unfit or reluctant for surgery. This was supported by the clinical course of patient 10 of a case series [21]. The patient defaulted follow-up since 1961 when a limited regrowth of the disease was noted but had no chest trouble in 1967.

Thirdly, despite clinical stability for a prolonged period, close monitoring is still warranted in this rare disease so that any malignant transformation can be detected and managed at an early stage.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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