**Complicated tracheo-bronchial papillomatosis**

Walid Abu Arab1, 2; MD, PhD, Dharar Alshehab1; FRCSC, Hassan Jamal Eddine1; MD, Adel Ayed1, 3; FRCSC

*1Thoracic Surgery Unit, Chest Disease Hospital, Kuwait*

*2Cardiothoracic Surgery Department, Faculty of Medicine of Alexandria, Egypt*

*3Department of Surgery, Faculty of Medicine, University of Kuwait, Kuwait*

**Corresponding Author:**

**Prof. Walid Abu Arab**

**Cardiothoracic Surgery Department**

**Faculty of Medicine**

**Middan Al-khartoum**

**Alexandria**

**Egypt**

**Tel. +2 01062335705**

**E-mail:** [**walidabuarab@yahoo.com**](mailto:walidabuarab@yahoo.com)

***Abstract:*** *169*

***Word count:*** *4824*

**Abstract:**

Respiratory papillomas are rare benign lesions. They are characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract. It affects children and young adults. Although the disease affect mainly the upper airways, it may be aggressive and extends distally to the lower respiratory tract and pulmonary parenchyma. The course of the disease unpredictable. It may regress spontaneously, but in other instances it may lead to serious complications ranging from airway obstruction up to malignant transformation. Surgical excision is the main stay of definitive treatment to prevent recurrence and to exclude malignancy. We have reviewed the literature for this rare type of respiratory disease and present a thirty-five years old; male patient who had chronic cough and was referred to our unit with a CT-chest that revealed left main endo-bronchial lesion. Bronchoscopy and biopsy of the lesion was performed and revealed squamous papilloma. Final treatment introduced to the patient was endoscopic thermal ablation. However, the final pathology revealed complicated squamous bronchial papilloma with infection by aspirgellosis and actinomycosis.

***Key words:*** *HPV, Tracheo-bronchial papilmomatosis, endo-broncial lesion, bronchoscopy*

**Background:**

Pulmonary papillomas are rare types of lung neoplasms (1). They can be classified into three groups (1, 2). The first group composed of multiple papillomatoses, which usually affects the larynx, predominantly in children. Juvenile laryngo-tracheal papillomatosis rarely involves the lower respiratory tree. These types of papillomas are usually related to the infection by human papilloma virus (HPV) (1). Although they frequently recur, they have a tendency to regress spontaneously after puberty. The second group includes inflammatory endo-bronchial polyps. These inflammatory polyps usually arise from the mucosa of patients who had chronic respiratory infection. These polyps are covered by respiratory ciliated epithelium. They may show focal squamous metaplasia, and may contain edematous fibrous tissue core with granulation-like tissue and inflammatory cells. The third group of lesions includes the solitary trachea-bronchial papillomas (STBP). It is rare type and represent less than 0.5% of lung tumors (1, 2).

Pulmonary papilloma usually presents as an endo-bronchial lesion in the segmental bronchi. They can be divided histologically into squamous cell, glandular and mixed type papillomas (3-6). Squamous papilloma is characterized by a bimodal age distribution. The young children and young adults most commonly affected (7, 8). The disease is common in age of childhood. The virus is thought to be transmitted vertically through the contact with infected secretions in the birth canal. However, in adults, the HPV infection may occur following oral sex (8-10). The histological presentation is benign squamous epithelial stratification (10). However, respiratory papillomas are considered as tumors of low potential malignancy as they may present with dysplasia, and they have a recurrence rate around 20 % with potential to transform into squamous cell carcinoma (3). Respiratory papilloma is typically restricted to the larynx, but in some occasions, it presents with aggressive behavior, resulting in persistent or recurrent involvement of the naso-pharynx, trachea-bronchial tree and rarely, the pulmonary parenchyma (10-12). Respiratory papillomatosis is a disease of unpredictable course that ranges from spontaneous remission to aggressive behavior, spreading to the lungs and may require multiple surgical procedures to maintain functional airway (13). Diagnosis of respiratory papilloma could be suspected from the clinical presentation and imaging findings, however the decisive final diagnosis is based mainly on histo-pathological examination obtained via biopsy of the lesion (10).

The glandular and mixed types of papillomas are seen in older men, and are less commonly associated with smoking. Squamous cell papilloma can be exophytic, or inverted. Microscopically they resemble viral papillomas that is seen in the genito-perineal region. Glandular papillomas can be lined by ciliated and non-ciliated columnar cells, including occasional goblet cells (6). Mixed papillomas were named before transitional papillomas. Patients can be asymptomatic and discovered incidentally or can present either with obstructive symptoms, or hemoptysis (3).

**Etiology:**

Respiratory papillomatosis has been linked to HPV infection. Studies have revealed that there are more than 180 genotypes of HPV. They have a specific affinity for squamous epithelial cells in different tissue, consequently the infection with HPV can result into different clinical manifestations (7, 9). HPV has been associated with many benign and malignant tumors of epidermal origin. It is associated with cancer of the cervix, tumors of head and neck, and ano-genital tumors (14).

There are different subtypes of HPV (8, 15). The subtypes 6 and 11 are involved in more than 90 % of recurrent respiratory papillomatosis (9, 16). However, type 11 of HPV is implicated in the development of more aggressive disease (15). The subtypes 16 and 18 of the HPV are considered to have high risk of transformation rate to malignant disease, especially into squamous cell carcinoma (9, 10, 17).

**Prevalence and Epidemiology:**

Respiratory papillomatosis can be presented either during childhood or at early adulthood (8, 13, 18). The respiratory papillomatosis that occur in young patients; less than twenty years; is called juvenile form (10, 19). Usually, this juvenile form include development of multiple papillomatous lesions of aggressive behavior with a high rate of recurrence (10, 16). On the other hand, the form that occur in patients over age of twenty; in the third and fourth decades of life; is called adult form of respiratory papillomatosis (10, 14, 20). It is usually encountered in males. The papillomas occurring in adult form are usually solitary and they do not spread. Moreover, their recurrence rate is lesser than that of juvenile form (16).

The incidence of respiratory papillomas is varying according to its form. The incidence of the juvenile form of respiratory papilloma is about 4 per 100,000, however; the incidence of the adult form is 2 per 100,000 (8, 14, 16, 18, 19). There are some factors that affect the incidence of respiratory papilloma. These include age, socioeconomic status and education level (7, 8). It was found that respiratory papilloma incidence is higher in those with of low socioeconomic status and low educational levels (7, 13).

Infection with HPV in children occurs mostly during birth through passage via the birth canals of infected mothers (8, 9, 10, 11). Transmission of the infection may occurs prior to birth, through the placenta, in approximately 12% of cases (7, 13). One of the primary risk factors for development of juvenile form of respiratory papillomas is the presence of maternal ano-genital warts during pregnancy (7, 9). Approximately, less than 1 % of infants who have been exposed to maternal ano-genital warts developed respiratory papillomatosis (9, 13, 21). In adult patients, the HPV is mostly transmitted sexually, usually through oral sex (8-10). Moreover, the risk of infection in adults increases if the patients has sexual activity with multiple partners (9).

**Pathogenesis:**

HPV infection occurs through contact of minor excoriated mucous or cutaneous surfaces with a source of infection. The virus initially infects the basal epithelial layer (16). Following infection of the basal epithelial layer, the HPV activates the epidermal growth factor receptor pathway and deactivates many of the tumor-suppressing proteins, culminating in cellular proliferation and epithelial differentiation. The final result is production of “cauliflower-like” exophytic lesions of respiratory papilloma (9, 16). Mostly, these lesions located at the transitional areas between the squamous epithelium and the ciliated columnar one (9, 14, 16, 22).

Papillomas can present as solitary or multiple nodules. The nodules can be either exophytic, sessile or pedunculated lesions. Most of lesions; generally appear affecting the larynx (16). However, they may affect any part of the aero-digestive tract and even may extend to the trachea-bronchial tree and pulmonary parenchyma (10, 16, 23). Affection and extension to the distal airway occurs in approximately 2-5 % (10, 12, 23- 25).

Distal spread of the laryngeal papillomatosis has not been explained. Different theories to explain this distal spread have been postulated and they include the extension of papillomas by contiguity, diffuse viral contamination, and iatrogenic factors. The iatrogenic factors include laryngoscopy, bronchoscopy, tracheostomy, and surgical manipulation (10, 12). Furthermore, there are high-risk factors that are implicated in the spread of respiratory papillomatosis toward the lower respiratory tract. These risk factors include infection with HPV-11, age above 3 years, tracheostomy performed to avoid airway obstruction, and previous invasive procedures (9, 21).

Although it is rare, the respiratory papillomatosis can be transformed into bronchogenic squamous cell carcinoma (10, 11, 16). This malignant transformation can occur decades after disease onset, generally in patients with prior spreading to the tracheobronchial tree. Moreover, malignant transformation very infrequently occurs in the laryngeal form of the disease, with no involvement of the distal airway (10). The rates of malignant transformation are less than one percent in children and is between3 and 7 % in adults (16). The risk factors involved in malignant transformation include infection with high-risk HPV subtypes 16 and 18, smoking, previous radiotherapy or the use of cytotoxic drugs, p53 gene mutation, and high severity score or high activity of 20-5’-oligoadenylate synthetase (9, 15). The mechanism by which the malignant transformation develop is not clear. However, some studies attributed the oncological effect of the HPV is related to its interference in the cellular cycle, which consequently alters the control of cellular differentiation (9, 13, 14, 16).

**Clinical presentation:**

The clinical presentation is not typical for all patient as the course of the diseases of respiratory papillomatosis is variable. Spontaneous remission sometimes occur in a minority of patients. However, in majority of cases, it takes an aggressive course that requires multiple interventions (16, 26). In adults, as many of pulmonary illnesses, the respiratory papillomatosis usually presents with non-specific symptoms of airway involvement. These symptoms may include cough of chronic nature that in most of instances not responding to symptomatic treatment. Also, change of voice or hoarseness may be present. Furthermore, wheezing, dyspnea and stridor may occur (9, 10, 16, 26). Meanwhile, in children, characteristically, the clinical presentation of respiratory papillomatosis is composed of a triad of progressive hoarseness, stridor, and dyspnea (7).

Hoarseness of voice is the most common symptom in adults (10). Other symptoms and signs may present like wheezing, tachypnea, and stridor (9, 10). Furthermore, clinical picture can be more sever in presentation, and patients may be presented with airway obstruction and severe respiratory distress (9, 10, 16). Hence, Respiratory papillomatosis can be misdiagnosed easily or discovered late due to its nonspecific clinical presentations and unpredictable course, that mimic most of the common laryngeal and respiratory diseases (16, 26). Most of the patients are not diagnosed on first presentation and they are treated for the presenting symptoms and signs but do not respond, and moreover the symptoms worsen. Disease then may evolve to severe respiratory distress due to air-way obstruction (7, 12). Respiratory papillomatosis is a benign disease, however, it may lead to significant morbidity and may cause mortality in some instances due to high rate of recurrence and even spread all over the respiratory tract (7). Progressive disease with peripheral dissemination may lead to recurrent small air way obstruction with resultant obstructive atelectasis, and pneumonia. Even more, malignant degeneration may result eventually. Hemoptysis is a common presentation in patients with respiratory papillomatosis and this diseases is usually confused with active pulmonary tuberculosis (27). In juvenile form of the respiratory papillomatosis, the clinical presentation tends to be more severe because of the rapid growth of the lesions and easiness of airway obstruction (7, 8). As the course of the disease is unpredictable and may worsen any time, some children require only follow-up every six months while others more frequent follow-up visits or even admissions due to progressive disease (7, 26).

**Diagnosis:**

Respiratory papillomatosis is usually not diagnosed by clinical presentation nor by findings on the chest X-ray (CXR) (7, 9). In patients who had progressive disease, a solid or cavitated pulmonary nodules may be shown in the CXR. On rare occasions, a sessile or pedunculated nodular lesions can be detected inside the trache-bronchial tree on CXR (7, 10). Computed tomograpgy of the Chest (CT- Chest) is considered the radiological test of choice to assess this entity of pulmonary pathology. It is accurate in the identification and characterization of trachea-bronchial and pulmonary lesions (12). The radiological findings in CT-chest may suggest a diagnosis of papillomatosis at the trachea or bronchi (7, 10). CT- Chest findings may include focal or diffuse airway narrowing caused by the nodular lesions. These lesions may be located on the mucosal surface or even projecting into the air-way lumen. Moreover, pedunculated or sessile nodular lesions may occur. The involvement of pulmonary tissue with respiratory papillomatosis may be manifested in the CT by presence of single or multiple well defined, multilobulated, solid nodular or polypoid lesions of different sizes. These lesions usually have centrilobular distribution, and are scattered throughout the lungs. Some nodules may enlarge in size and transform into air-filled cysts leading to formation of large cavities with irregular internal borders and thick or thin walls (10, 12, 27). The nodular lesions in the lung tissue usually affect more basal and posterior parts. Those lesions that developed cavities are usually get infected. Other findings that may be shown in CT-Chest usually related to the secondary effects or complications of respiratory papillomatosis. These findings may be due to airway obstruction and secondary infections, atelectasis, consolidations, air trapping, or bronchiectasis. Lymph node enlargement and pleural effusion are not encountered frequently, except in patients who developed malignant transformation (10, 12).

On occurrence of malignant transformation, CT-Chest may show enlargement of pulmonary nodular lesions, nodules at the bronchi, or the trachea. This enlargement of the lesions may be associated with numerous enlarged lymph nodes in both mediastinum and neck (7, 28). As lesions mostly affects the tracheobronchial tree, the virtual bronchoscopy is found to be a useful tool in the assessment the disease affecting the air-way. It enables three dimensional visualization of the airways (7). Virtual bronchoscopy has an advantage of avoiding the potential complications of the conventional bronchoscopy. Moreover, it enables visualization and assessment of the distal airways beyond and endo-luminal stricture if present (7, 11). Magnetic resonance imaging (MRI) can show laryngeal, trachea-bronchial, and pulmonary lesions. However, its role in the diagnosis of respiratory papillomatosis has not been definitely established (29). Positron Emission Tomography (PET- Scan) has no major role in the diagnosis of respiratory papillomatosis or early detection of malignancy associated with these lesions. It may show an elevated uptake of the lesion due to elevated cellular proliferation (28, 30).

Direct laryngoscopy or fiberoptic bronchoscopy are the gold standard ways to confirm the diagnosis of respiratory papillomatosis. Bronchoscopy is the most reliable method for the diagnosis of trachea-bronchial papillomatous lesions because it allows direct visualization of the lesions with direct assessment of the coloration of the trachea-bronchial mucosa. Furthermore, biopsy of the lesions can be performed. This is important for histo-pathological diagnosis and viral typing. In addition, bronchoscopy is an important step in planning the treatment. Papilloma lesions can be seen as whitish polypoidal masses with clean and smooth surfaces during bronchoscopy. They may be localized in the larynx, trachea, or bronchi (10, 13, 23). Histopathological examination of these lesions is the best way for definitive diagnosis of respiratory papillomatosis (10, 26).

**Pathology:**

Respiratory papillomas usually presented as exophytic soft and friable nodules or masses. They may be sessile or pedunculated, soft, and friable. Microscopic papilloma appear with velvety mucosa over, while the mucosa appear pinkish-whitish “cauliflower-like” with the exophytic papilloma (13).

On histo-pathological examination, papillomas appear as projections or multiple fronds that have central fibro-vascular cores and covered by stratified squamous epithelium (13). Hyperplasia of the basal cell layer and the large vacuolated epithelial cells are typical findings (10, 12, 13, 18). Basal layer thickening with an increased number of nucleated cells in the supra-basal layer of the stratified epithelium may be detected as the HPV can cause a delay in maturation of the epithelial cells (7, 18). Moreover, histo-pathological examination may reveal abnormal cellular differentiation with abnormal keratin production and expression (18). The papillomatous lesions that extend to the trachea-bronchial tree manifest a squamous or ciliated and cylindrical epithelium (7, 10).

Pulmonary papillomatous lesions are presented in a different histo-pathological way. They have a have a different morphology. They may appear as foci of squamous epithelium that grow circumferentially within the alveoli and have blood supply via alveolar vascularization. The center of the pulmonary papilloma usually shows areas of necrosis and degeneration, while the squamous cells on the periphery invade the adjacent alveoli. These pulmonary lesions grow, coalesce together, and finally destroy the pulmonary parenchyma and forming cavities (10, 12). Papillomas are histologically benign lesions, however; dysplasia and malignant changes may occur (7, 10). If malignant transformation occurs, pathological examination revealed sheets of polygonal tumoral cells with abundant eosinophilic cytoplasm and vesicular nuclei. This is associated with findings of foci of keratinization, atypia, focal necrosis, and a variable mitotic rate, with micro-invasive growth. Immuno-histochemical examination may reveal expression of cytokeratin 5 and 6, which indicate epithelial origin (29).

**Differential Diagnosis:**

The differential diagnosis of respiratory papilloma include wide range of variable respiratory illnesses. It includes many of focal and diffuse central airway diseases (7, 23). Focal lesions may resemble tracheal neoplasms, post-intubation stenosis, traumatic lesions, some infectious diseases, and the systemic diseases that may involve the airways and result in focal trachea-bronchial stenosis (7, 23, 27). Diffuse pulmonary papillomatous lesions should be differentiated from Wegener's granulomatosis, amyloidosis, tracheobronchopathia osteochondroplastica, relapsing poly-chondritis, trachea-bronchomegaly, tuberculosis, neurofibromatosis, and sarcoidosis (23, 27).

Diagnosis is established well via bronchoscopy and biopsy of the lesion. However, CT is an important step in evaluation as the lesion location, presence and pattern of calcification, presence of other parenchymal pulmonary lesions may help in preliminary diagnosis and can help in planning of bronchoscopy or therapeutic intervention (10, 12, 27). In summary, the clinical symptoms and signs of central airway involvement, beside the presence of bronchoscopic or CT findings of tracheal or bronchial wall thickening and irregular narrowing of their lumen, as well as nodular or polypoid non-calcified lesions, are highly suggestive of respiratory papillomatosis. Furthermore, presence of cavitary pulmonary nodules as a distal spread makes a diagnosis of respiratory papillomatosis more likely. Howerver, the final diagnosis is reaches by biopsy and histopathological examination (7, 8, 23, 27).

**Treatment:**

Actually, there is no definitive standard curative treatment of the respiratory papilloma. However, surgical excision of the papillomas are considered the mainstay of treatment. The treatment aims at maintaining a functioning clear airway and to keep the quality of phonation (8, 14, 16, 31). The main aim of the surgical intervention is to debulk the papillomatous lesion as much as possible while keeping normal trachea-bronchial airway and pulmonary tissue structures (7, 32). Conversion into the use of micro-laryngeal surgery and micro-debrider instead of the laser use in debridement was taken place due to the frequent complications associated with laser debridement. These complications include airway burns, laryngeal scarring and stenosis, and trachea-esophageal fistulae (8, 30). Precise debridement can be performed using micro-debrider with less damage to the underlying tissues and greater preservation of the normal epithelium. However, this modality of treatment needs several sessions and should be repeated (7, 8). Serious surgical complications are still occurred in spite of the introduction of techniques in treatment and recent advancement in the surgical equipment. These serious complications include laryngeal synechia and glottic or sub-glottic stenosis. Complications usually encountered in patients who underwent multiple interventions and several recurrences (8). Recurrence following surgical ablation is not uncommon. This could be explained by the persistence of the HPV genome in the remaining (7, 16).

In cases with extensive disease with a risk of laryngeal airway obstruction; following repeated intervention; tracheostomy may be performed (8, 14, 15). Donne *et al.* (15) documented that HPV subtype 11 is more likely to result in tracheostomy. In those patients who had tracheostomy, de-cannulation should be performed once the airway is considered to be stable and the disease is under control. This is to avoid an additional site for rapid viral colonization and progression of the disease distally (8).

Around one fifth of patients with respiratory papillomas require additional adjuvant medical therapy beside the surgical treatment to control the disease (7, 16). The adjuvant therapy is not used from the start. The current criteria for adjuvant therapy in patients with respiratory papillomas include the need for more than four surgical interventions per year, rapid recurrence of the lesions that are associated with a compromise of the airway, and distal spread of the disease. Most of medications use are based on immunomodulation and inhibition of HPV proliferation. These include interferon, antiviral agents, retinoids, and oxigenase-2 cycle inhibitors (16).

Interferon is one of the early drugs that was used as adjuvant treatment for respiratory papilloma. It exhibited positive favorable results in some patients. As it resulted in the reduction of lesion growth (16, 21). However, its intravenous administration may result in systemic toxicity, possible leucopenia and thrombocytopenia (7). Moreover, interferon can lead to some adverse effects that include transient fever, fatigue, nausea, arthralgia, headache, and spastic diplegia in infants (8). Cidofovir is another antiviral medication. It is an analog of cytosine that is currently used commonly as medical adjuvant drug in the treatment of the respiratory papilloma (8, 26). It has the advantage to be administered either intravenously, via nebulization, or by intra-lesional injection. The advantage of intra-lesional injection of the cidofovir is good treatment response where a partial to total regression of lesions occurred. Moreover, this type of treatment is associated with a reduction of the frequency of surgical interventions (7, 8, 26). In addition, the intra-lesional administration of cidofovir maintain the plasma levels below those leading to toxicity in case of systemic treatment. Besides that, it is not associated with local side effect (8, 17,26). Although the long term adverse effects of the intralesional administration of cidofovir are not well known, theories mentioned that a risk of malignant transformation may associate its use. (7, 26).

Vaccination against HPV offers potential for the future eradication of the disease by reduction of the incidence and the transmission of the virus. The quadrivalent vaccine is given for the prevention of cervical, ano-genital cancers, and pre-carcinogenetic lesions that are associated with HPV subtypes 6,11,16, and 18 (32). The vaccine carries a promise for patients affected by respiratory papillomatosis. However, multicenter trials should validate the isolated positive experiences which may determine the true benefits of vaccination as a treatment for respiratory papillomatosis (8).

**Case Presentation:**

We present here a 35 years old male patient who was referred to our unit complaining of as left sided pleuritic chest pain and chronic non-productive cough. The symptoms dated one month prior to presentation and increasing in severity. Patient had no hemoptysis nor loss of weight and there were no other symptoms. Patient had a history of seasonal bronchial asthma and history of pigtail catheter insertion for left sided pleural effusion on 2015 of undetermined nature. Moreover, the patient has a positive family history for breast cancer (three aunts) and questionable family history of lung cancer.

A Chest- X ray (CXR) on admission; revealed a partial atelectasis-consolidation of the left upper lobe While a CT-Chest on April 2017, showed left endo-bronchial lesion located at the left main bronchus measuring (7.5X12.5 mm) that was associated with enlarged left hilar LN causing obstructive consolidation, (Figure 1). PET-CT scan was performed on May 2017. It showed suspicious metabolically active nodule located inside the left main bronchus. V-Q scan Rt 73.9% and Lt 26.1%. Fibre-optic bronchoscopy was performed showed a left main bronchial mass occluding the left upper lobe. Biopsy was taken directly from the mass. Histo-pathological examination revealed a multiple mixed glandular and squamous cell papillomas. Although the pathologist considered the differential diagnosis of inflammatory polyps, he favored the diagnosis of multifocal papillomatosis due to presence of squamous epithelial hyperplasia and glandular epithelium. The surgical resection or ablation was the treatment of choice to restore the patency of the airway and to eradicate the disease. Two options of surgical interventions were proposed. First option was the thermal ablation of the mass lesion via combined rigid and fibre-optic bronchoscopy. The other option was to perform sleeve left upper lobectomy. Following discussion of with the patient, the first option was favored by the patient and the treating medical team. The second surgical option was postponed if the first one was not successful or incomplete.

Patient had general anesthesia and rigid bronchoscopy was performed. Right side was revaluated carefully again with the use of 0.5 mm 30 degree telescope and proved to be healthy and harboring no lesions. Then the left side was evaluated. A sessile large lesion was found located inside the left main bronchus and partially obstructing the left main bronchus and left upper lobar bronchus. It was extending up to the carina and just 1.5 cm away from it. The rigid bronchoscope was unable to pass the lesion. Hence, the fibre-optic bronchoscope was delivered through the lumen of the rigid bronchoscopy and passed the lesion to evaluate the trachea-bronchial tree distally. No other lesions were found beyond this large papilloma.

Then the fibre-optic bronchoscopy was pulled up to rest above the proximal end of the lesion. A diathermy ablation probe was introduced and thermal ablation of the lesion was taken place starting from the distal end of the lesion at the base. Then, part of the lesion was thermally snared. The lesion was then completely removed by biopsy forceps. The base was thermally ablated completely. Then tracheo-bronchial lavage was performed. Then both, the fibre-optic and rigid bronchoscopes, were removed. Endo-tracheal tube was introduced. Patient was extubated at the operating room. No intraoperative complications were encountered. The excised lesion was sent for histo-pathological examination.

The histo-pathological examination of the specimens sent revealed a bronchial papilloma with mixed fungal infection (actinomycosis and aspergillosis). Patient was discharged on medical treatment for actinomycosis and aspergillosis. Follow-up visits was planned following one month and then every three months. Patient is doing well on follow-up with no complaints.

**Discussion:**

Squamous papillomas are rare tumors. They are usually account for not more than 8 % of all benign pulmonary tumors (2, 33). The majority of the publications found in the literature are case reports. They included one or two patients (33-39). Other publications are small series of patients and included between six and nine patients like those published by Lang *et al.* (40) and Ablanedo-Terrazas *et al.* (41). It is unfrequently to be asymptomatic and discovered incidentally on radiological examination. However, the majority of patients are symptomatic. Symptoms are variable. These include wheezes, cough, hemoptysis, or recurrent pneumonia. In our patient, the main complaint was chronic cough which did not respond to treatment. Usually, symptoms are secondary to the mass obstructive effects inside the airways (7, 33). As respiratory papilloma usually present as endo-bronchial lesion, it usually leads to bronchial stenosis and subsequent atelectasis that predisposes to recurrent infection and pneumonia that finally ends with bronchiectasis (33, 42). Our patient was male at middle age and squamous papillomas are more common to occur in men (33, 34, 35, 39, 40, 43). Squamous papillomas have a potential of malignant transformation in up to 40 % of cases. Furthermore, the incidence of occurrence of malignancy elsewhere in the lung is around 13 % (33, 44, 45). Hence, careful endoscopic examination of the tracheo-bronchial tree with good biopsy specimens are essential for those patients. Pathologist should be meticulous during examinations of these tissues both during first diagnosis and after complete excision. The methods of treatment; either endoscopic removal or surgical resection; are still controversial. Endoscopic ablation by laser or diathermy may prevent a full pathological examination of the whole papilloma, which may harbor a carcinoma (33, 46). Therefore, it is recommended to completely excise the solitary squamous papilloma in order to exclude an invasive malignancy and prevent recurrence (47). In our patient, we passed the bronchoscope first beyond the lesion to evaluate the extent the lesion and then thermal ablation was applied at the periphery of the lesion and the base to completely excise the mass with preservation of tissues for histo-pathological examination to exclude malignancy or malignant transformation. Surgical resection should be deferred as last option and when considered one surgeon should perform lung-sparing surgical techniques as sleeve lobectomy or bronchoplasty instead of extensive resection as these are benign lesions. Extensive pulmonary resection is considered only in case of extension of the disease to the pulmonary parenchyma or in patients who had complicated disease with bronchiectasis (33, 34, 39). Majority of authors recommended endo-bronchial surgical excision using laser, cryo-surgery or thermal ablation or intra-lisional injection of anti-viral drugs instead of resection (35, 38, 39, 41, 43). We preferred thermal ablation for the lesion in our patient. No complications were encountered intra-operatively.

The final histo-pathology revealed a complicated squamous respiratory papilloma with superadded infection by aspirgellosis and actinomycosis. Few cases are reported like this case in the literature especially in immune-competent patients (48, 49). However, those patients reported in the literature had recurrent respiratory papillomas not like our patient who had it for first time. Patient had treatment for the infection associated and instructed for close follow-up.

As this disease is rare and treatment is not standardized, our group of research have proposed an algorithm for its management based on the revision of the literature (Figure 2). This algorithm firstly classifies the lesion either multiple or solitary and then goes forward according to the absence or presence of complications, involvement of pulmonary parenchyma. Furthermore, it takes into consideration the recurrence of the disease and progression of the disease during the course of management of it.

**Conclusion:**

In conclusion, respiratory papillomas are rare benign lesions. They are characterized by the appearance of papillomatous lesions anywhere in the aero-digestive tract. It affects children and young adults. Although the disease affect mainly the upper airways, it may be aggressive and extends distally to the lower respiratory tract and pulmonary parenchyma. The course of the disease is unpredictable. It may regress spontaneously, but in other instances it may lead to serious complications ranging from airway obstruction up to malignant transformation. Endo-bronchial interventions and surgical excision are the main stay of definitive treatment to prevent recurrence and to exclude malignancy.

**Conflict of interest:** None-declared

**References:**

1- Lang TU, Khalbuss WE, Monaco SE, et al. Solitary Tracheobronchial Papilloma: Cytomorphology and ancillary studies with histologic correlation. Cytojournal. 2011; 8.

2- Drennan JM, Douglas AC. Solitary papilloma of a bronchus. Journal of clinical pathology. 1965; 18(4):401-2.

3- Flieder DB, Thivolet-Bejui F, Popper H. Squamous cell papilloma. In: Travis WD, Brambilla E, Muller- Hermelink HK, Harris CC, editors. World health classification of tumours. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004. pp. 78–9.

4- Wick MR, Mills SE. Benign and borderline tumors of the lungs and pleura. In: Leslie KO, Wick MR, editors. Practical pulmonary pathology. Philadelphia: Churchill Livingstone; 2005. pp. 673–732.

5- Flieder DB, Thivolet-Bejui F, Popper H. Mixed squamous cell and glandular papilloma. In: Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. World health classification of tumours. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004. p. 81.

6- Flieder DB, Thivolet-Bejui F, Popper H. Glandular papilloma. In: Travis WD, Brambilla E, Muller- Hermelink HK, Harris CC, editors. World health classification of tumours. Tumours of the lung, pleura, thymus and heart. Lyon: IARC Press; 2004. p. 80.

7- Fortes HR, von Ranke FM, Escuissato DL, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respiratory Medicine. 2017 Apr 1.

8- Carifi M, Napolitano D, Morandi M, et al. Recurrent respiratory papillomatosis: current and future perspectives. Therapeutics and clinical risk management. 2015; 11:731-8.

9- Fusconi M, Grasso M, Greco A, et al. Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir. Acta Otorhinolaryngologica Italica. 2014; 34(6):375-381.

10- Marchiori E, Araujo Neto CD, et al. Laryngotracheobronchial papillomatosis: findings on computed tomography scans of the chest. Jornal Brasileiro de Pneumologia. 2008 ; 34(12):1084-9.

11- Chang CH, Wang HC, Wu MT, et al. Virtual bronchoscopy for diagnosis of recurrent respiratory papillomatosis. Journal of the Formosan Medical Association. 2006; 105(6):508-11.

12- Ağgünlü L, Erbaş G. Recurrent respiratory papillomatosis with lung involvement. Diagn Interv Radiol.; 15(2):93-5.

13- Venkatesan NN, Pine HS, Underbrink MP. Recurrent respiratory papillomatosis. Otolaryngologic clinics of North America. 2012; 45(3):671-94.

14- Goon P, Sonnex C, Jani P, et al. Recurrent respiratory papillomatosis: an overview of current thinking and treatment. European Archives of Oto-Rhino-Laryngology. 2008; 265(2):147-51.

15- Donne AJ, Hampson L, Homer JJ, et al. The role of HPV type in Recurrent Respiratory Papillomatosis. International journal of pediatric otorhinolaryngology. 2010; 74(1):7-14.

16- Katsenos S, Becker HD. Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat, with potential to lung cancer transformation: apropos of two cases and a brief literature review. Case reports in oncology. 2011; 4(1):162-71.

17- Gélinas JF, Manoukian J, Côté A. Lung involvement in juvenile onset recurrent respiratory papillomatosis: a systematic review of the literature. International journal of pediatric otorhinolaryngology. 2008; 72(4):433-52.

18- Wiatrak BJ. Overview of recurrent respiratory papillomatosis. Current opinion in otolaryngology & head and neck surgery. 2003; 11(6):433-41.

19- Reeves WC, Ruparelia SS, Swanson KI, et al. National registry for juvenile-onset recurrent respiratory papillomatosis. Archives of Otolaryngology–Head & Neck Surgery. 2003; 129(9):976-82.

20- Martina D, Kurniawan A, Pitoyo CW. Pulmonary papillomatosis: a rare case of recurrent respiratory papillomatosis presenting with multiple nodular and cavitary lesions. Acta Medica Indonesiana. 2016; 46(3).

21- Lee JH, Smith RJ. Recurrent respiratory papillomatosis: pathogenesis to treatment. Current opinion in otolaryngology & head and neck surgery. 2005; 13(6):354-9.

22- Prince JS, Duhamel DR, Levin DL, et al. Nonneoplastic lesions of the tracheobronchial wall: radiologic findings with bronchoscopic correlation. Radiographics. 2002; 22(suppl\_1):S215-30.

23- Taliercio S, Cespedes M, Born H, et al. Adult-onset recurrent respiratory papillomatosis: a review of disease pathogenesis and implications for patient counseling. JAMA Otolaryngology–Head & Neck Surgery. 2015; 141(1):78-83.

24- Kramer SS, Wehunt WD, Stocker JT, et al. Pulmonary manifestations of juvenile laryngotracheal papillomatosis. American Journal of Roentgenology. 1985; 144(4):687-94.

25- Shiau EL, Li MF, Hsu JH, et al. Recurrent respiratory papillomatosis with lung involvement and malignant transformation. Thorax. 2014; 69(3):302-3.

26- Tasca RA, Clarke RW. Recurrent respiratory papillomatosis. Archives of disease in childhood. 2006; 91(8):689-91.

27- Marchiori E, Pozes AS, Souza Junior AS, et al. Diffuse abnormalities of the trachea: computed tomography findings. Jornal Brasileiro de Pneumologia. 2008; 34 (1):47-54.

28- Xiao Y, Wang J, Han D, et al. A case of the intrapulmonary spread of recurrent respiratory papillomatosis with malignant transformation. The American journal of the medical sciences. 2015; 350(1):55-7.

29- Mauz PS, Zago M, Kurth R, et al. A case of recurrent respiratory papillomatosis with malignant transformation, HPV11 DNAemia, high L1 antibody titre and a fatal papillary endocardial lesion. Virology journal. 2014; 11(1):114.

30- John-Paul JY, Barajas Jr RF, Olorunsola D, et al. Heterogeneous 18F-FDG uptake in recurrent respiratory papillomatosis. Clinical nuclear medicine. 2013; 38(5):387-9.

31- Dyrstad SW, Rao KA. Recurrent respiratory papillomatosis (RRP)—juvenile onset. Clinical Medicine. Oncology. 2008; 2:481-6.

32- Wilcox LJ, Hull BP, Baldassari CM, et al. Diagnosis and management of recurrent respiratory papillomatosis. The Pediatric infectious disease journal. 2014; 33(12):1283-4.

33- Lee YO, Kim DH, Kim CH, et al. Rare tumor of the tracheobronchial tree: solitary squamous papilloma. The Thoracic and cardiovascular surgeon. 2009; 57(03):178-9.

34- Inamura K, Kumasaka T, Furuta R, et al. Mixed squamous cell and glandular papilloma of the lung: a case study and literature review. Pathology international. 2011; 61(4):252-8.

35- Limsukon A, Susanto I, Hoo GW, et al. Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy. Chest. 2009; 136(3):924-6.

36- Marchiori E, Zanetti G, Mauro Mano C. Tracheobronchial papillomatosis with diffuse cavitary lung lesions. Pediatric radiology. 2010; 40 (7):1301-2.

37- Grunzke M, Hayes K, Bourland W, et al. Diffuse cavitary lung lesions. Pediatric radiology. 2010; 40(2):215-8.

38- Mohan KT, Greenheck J, Rubio ER. Recurring tracheal papillomatosis treated with cryosurgery. Southern medical journal. 2008; 101(9):967-8.

39- Katsenos S, Becker HD. Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat, with potential to lung cancer transformation: apropos of two cases and a brief literature review. Case reports in oncology. 2011; 4(1):162-71.

40- Lang TU, Khalbuss WE, Monaco SE, et al. Solitary Tracheobronchial Papilloma: Cytomorphology and ancillary studies with histologic correlation. Cytojournal. 2011; 8.

41- Ablanedo-Terrazas Y, Soda-Merhy A, Hernández-Palestina M, et al. Intralesional cidofovir in severe juvenile respiratory papillomatosis. B-ENT. 2012; 8 (3):197-202.

42- Katial RK, Ranlett R, Whitlock WL. Human papilloma virus associated with solitary squamous papilloma complicated by bronchiectasis and bronchial stenosis. Chest 1994; 106: 1887–1889.

43- Bondaryev A, Makris D, Breen DP, et al. Airway stenting for severe endobronchial papillomatosis. Respiration. 2009; 77(4):455-8.

44- Popper HH, el-Shabrawi Y, Wockel W et al. Prognostic importance of human papilloma virus typing in squamous cell papilloma of the bronchus: comparison of in situ hybridization and the polymerase chain reaction. Hum Pathol 1994; 25: 1191–1197

45- Inoue Y, Oka M, Ishii H, et al. A solitary bronchial papilloma with malignant changes. Intern Med 2001; 40: 56–60.

46- Miura H, Tsuchida T, Kawate N, et al. Asymptomatic solitary papilloma of the bronchus: review of occurrence in Japan. Eur Respir J 1993; 6: 1070–1073.

47- Litzky L. Epithelial and soft tissue tumors of the tracheobronchial tree. Chest Surg Clin N Am 2003; 13: 1–40.

48- Robb PK, Weinberger PM, Perakis H, et al. Association of asthma with clinically aggressive recurrent respiratory papillomatosis. Archives of Otolaryngology–Head & Neck Surgery. 2011; 137(4):368-72.

49- Kuruvilla S, Saldanha R, Joseph LD. Recurrent respiratory papillomatosis complicated by aspergillosis: A case report with review of literature. Journal of postgraduate medicine. 2008; 54(1):32.

**Figure legends:**

**Figure 1:**

CT-Chest (mediastinal window) of the patient with respiratory papilloma showing a endo-luminal mass located at the left main bronchus and encroaching on the left upper lobe bronchus

**Figure 2:**

Management of respiratory papillomatosis algorithm