

Respiratory papillomas

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ABSTRACT

Papillomas are known to occur in the lower respiratory tract. They are however, rare compared to their occurrence in the upper respiratory tract. These are generally exophytic tumors in the more proximal upper airways however cases with more distal location with an inverted growth pattern have also been described in the literature. These can be solitary or multiple and multifocality associated with multiple papillomas in the upper respiratory/aerodigestive tract. The four major types of respiratory papillomas are (1) Recurrent respiratory papillomas, (2) solitary squamous papillomas, (3) solitary glandular papillomas, (4) mixed papillomas. We review the incidence, etiopathology, diagnosis, and possible treatment modalities and algorithms for these respiratory papillomas.

KEY WORDS: Glandular papillomas, mixed papillomas, respiratory papillomas, recurrent respiratory papillomas, squamous papillomas

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INTRODUCTION

Papillomas are known to occur in the lower respiratory tract. They are however rare compared to their occurrence in the upper respiratory tract. These are generally exophytic tumors in the more proximal upper airways however cases with more distal location with an inverted growth pattern have also been described in the literature. These can be solitary or multiple and multifocality associated with multiple papillomas in the upper respiratory/aerodigestive tract.

Tryfon *et al.* described the estimated incidence of solitary respiratory papillomas (SRP) is 3.95 cases/100,000 patients/year. SRPs occur more commonly in men (ratio 3:1). In their study, they described that squamous papillomas occur commonly during the fifth decade of life (65.6% of individuals), glandular papillomas predominated in the sixth decade (8.75%, of individuals), and the distribution of mixed type papillomas is from the third to the sixth decade of life (15.6% of individuals).

al-Saleem *et al.* described a review of 11 cases of lower respiratory papillomas, in which multiple papillomas were rare in isolation of the upper tract involvement.^[1] Tracheobronchial predominance was reported rather than parenchymal disease of the lung. About 2–8% of cases with upper aerodigestive tract involvement had lower airway involvement. In a recent review by Soldatski *et al.* in children,^[2] 9% had lower airway involvement and 2% had pulmonary involvement.

ETIOPATHOGENESIS

The possible etiologies described in the literature include foreign body, smoking, HPV, and passive smoking in females.^[3,4] The relationship between solitary papillomas and human papillomavirus (HPV) has been widely reported and extensively studied in the literature. Recent meta-analyses done about the variability in HPV reported among these tumors found that the differences could not be explained by tests or the geographical distributions.^[5] The

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binding of HPV proteins E6, E7 to the tumor suppressor gene p53 and retinoblastoma protein is thought to play the central role in the induction of cellular proliferation and atypia. The binding of these proteins is different for different subtypes of HPV with certain types of HPV such as HPV 6, and its binding is considered to be the cause of papillomas with no malignant potential.^[6] Given the association and transformation to malignancies, a number of markers have been investigated both for prediction and confirmation of malignant change. High-risk markers include HPV types 16, 18, 31, 33, 35^[7] and one reported a case of 11 was associated with malignant transformation of a papillomatosis to squamous cell carcinoma.^[8] The types of papilloma have been listed in Table 1.

RECURRENT RESPIRATORY PAPILOMATOSIS

Recurrent respiratory papillomatosis (RRP) is caused by infection of the stem cell in the basal layers of the respiratory mucosa by HPV types 6 and 11 are the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness. After changes in voice, stridor is the second most common symptom, first inspiratory, and then biphasic. Less common presenting symptoms include a chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with an upper respiratory tract infection. Reports estimate the incidence of RRP in the United States at 4.3/100,000 children and 1.8/100,000 adults with distal spread associated in at least 5% of individuals. Infection in children has been associated with vertical transmission during vaginal delivery from an infected mother. Younger age at diagnosis is associated with more aggressive disease and the need for more frequent surgical procedures to decrease the airway burden. The activation of epidermal growth factor receptor pathway due to the HPV infection results in abnormal cellular proliferation and defective epithelial differentiation demonstrated by absent or reduced levels of keratin 13 expressions. Proliferation of HPV within these cells causes multiple finger-like projections with a central fibrovascular core covered by squamous epithelial cells with koilocytic atypia - a cauliflower-like exophytic lesion that can cause central airway obstruction.^[9] Although benign, RRP is difficult to control, has a high recurrence rate, causes severe morbidity and can undergo malignant transformation.^[10] The most common complications reported include pneumatoceles, lung abscesses, and tracheal stenosis.^[11] Tracheotomy at a young age has shown to cause tracheobronchial extension in more than 50–95% of cases.^[12,13] While there is no

therapy to eradicate RRP, the removal of tissues infected with HPV with little disruption to surrounding normal tissue has shown to reduce recurrence. Adjuvant medical therapies include antiviral, cytotoxic agents, interferon, and airway stenting in severe cases with silicone stents. Airway stenting in otherwise unresponsive cases has shown to reduce the tumor burden with regression of tumors and prevent recurrence of tumors. The mechanism is thought to be due to the mechanical pressure exerted on the walls and containment of the cells with a complete resolution of symptoms.^[14]

SOLITARY SQUAMOUS PAPILOMA

Solitary squamous papilloma is the most common pulmonary papilloma in adults. The incidence of such tumors is usually reported to be five in every 15,000 bronchoscopies.^[15] It presents predominantly in men with a median age of 54 years. It is also suspected the HPV virus is acquired in young males by aspiration of secretions, and the disease occurs in older males in the presence of chronic inflammation.^[6] There was a clear predilection of these tumors to occur in smokers than nonsmokers as described by evidence in literature.^[8] Most common presenting symptoms included a cough, hemoptysis, and wheezing. Histologically, the cells are lined by squamous epithelium with keratinization in some cells and viral cytopathic changes in others. HPV *in situ* hybridization can be used as an adjunct in this setting of tumors. They are usually exophytic however atypical inverted endophytic growth has also been described. The presence of such atypical growth makes histological evaluation difficult and hence complete resection is deemed the treatment of choice in such tumors. Carcinoma has not been recognized in such atypical growth patterns, and sleeve resection has been deemed curative for such tumors. The presence of cellular atypia is deemed as malignant potential in these lesions, and hence, resection should be done at the earliest available opportunity.^[16]

SOLITARY GLANDULAR PAPILOMA

Glandular papillomas are the rarest group of papillomas with only 21 cases reported in the English literature since 1954.^[17] They occur predominantly in the central tracheobronchial tree, arise from the mucosal surface, friable, red to tan in color, range in size from 0.7 to 2.5 cm, and cause 40–60% narrowing of the airway lumen.^[18] Diagnostic imaging for these tumors usually reveals findings of atelectasis, air trapping, postobstructive infections, and bronchiectasis. Most common symptom reported is coughing.^[3] The presence of air and solid components within the nodule have also been described in the literature.^[19] As health screening gets advanced, there is a high likelihood that incidental findings of these neoplasms in asymptomatic individuals will increase. Finger clubbing has also known to occur in conjunction with these tumors especially in patients with a history of

Table 1: Types of respiratory papillomas

Recurrent respiratory papillomatosis
Solitary squamous papilloma
Solitary glandular papilloma
Mixed papilloma

pulmonary tuberculosis.^[20] It is essential to distinguish such tumors from active inflammation, granulomatous disease, carcinoid, and lung cancer and hence bronchoscopic biopsy or computed tomography (CT) guided biopsy is needed to confirm the diagnosis. Histologically, these cells are covered by ciliated cells or simple columnar cells or mucous cells with a central fibrovascular core. These tumors seldom show necrosis and presence of ciliated cells are considered important to rule out other malignant tumors. Furthermore, these tumors are limited by the extent of the alveoli and do not breach into the surrounding alveoli. Suzuki *et al.* described an uncommon variant that produced mucous with retention and microinvasion into surrounding alveoli.^[17] There have been no reports to suggest a malignant transformation of such tumors and hence conservative management is deemed appropriate in such tumors, unlike squamous papillomas where surgical resection is deemed necessary. The treatment should be decided on a case by case basis, and surgical resection was done in patients with severe symptoms.^[3]

MIXED PAPILOMA

Mixed papillomas occur predominantly in middle-aged and old people with a male preponderance with a mean age of 58.3 years of age. The disease shows a predilection to smokers hence proving that smoking can be a causative factor for such tumors. Clinical symptoms could vary from asymptomatic individuals with an incidental finding of such tumor to dyspnea, hemoptysis, and recurrent infections. The distribution of such tumors in the lung tends to remain more central arising from the wall of a stem bronchus or its major subdivisions and only a minority four out of 19 cases remain peripheral.^[21] The negative p16 staining in these tumors suggests the absence of HPV as a causative factor. Histologically, such tumors were composed of squamous and glandular epithelium in reports described, a large seated base with a sharp border. Lin *et al.* described transitional urothelium-like morphology present between the two kinds of epithelium in these tumors, which suggests that there could be three different types of epithelium in such tumors describing from a common origin. Some cases showed malignant transformation including focal squamous cell carcinoma *in situ*, adenocarcinoma and spindle and squamous cell carcinoma.^[22] They also described glandular tumor cells extending into adjacent bronchiolar and alveolar spaces with abundant mucus with no cellular atypia in epithelial cells. This result in a diagnostic dilemma for the pathologist as this could often be confused with tumors especially adenocarcinoma. In fact, this morphology had been mentioned in a few cases of mixed papillomas^[23] and glandular papillomas.^[24] Immunological staining reveals positive staining for intracellular mucin MUC5AC, which is expressed in tracheobronchial goblet cells. CAM5.2 and CK19 were diffusely positive, indicating that the tumor originated from the columnar epithelium by squamous metaplasia. CEA and CA19-9 were focally positive. Even

though there were two different epithelia in the same tumor, the immunohistochemical analysis showed these different kinds of epithelia had similar immunophenotype. Staining was also positive for CK7, CK19, CAM5.2, CK5/6 (the staining of the mucous cells were weak), and CK34 β E12, but negative for CK20. All kinds of epithelia were positive for thyroid transcription factor-1, which was strongly immunostained in the basal cells of the squamous component while became weaker as the maturity of squamous epithelium, and finally disappeared in the surface layer of the squamous epithelium. The above histological and immunohistochemical findings underline a common origin for different components of the epithelial cells of the tumor and differentiate into different components, including glandular, squamous, and urothelium-like epitheliums. Recurrence has not been reported in mixed papilloma, and complete resection appears to be a curative treatment for this rare tumor.^[4]

MALIGNANT POTENTIAL

Malignant transformation was observed in a minority of patients (15.7%).^[25] The malignancies consisted of squamous cell carcinoma in two patients, and single cases of small cell lung carcinoma, glandular carcinoma, and low-grade carcinoma. Though loss of Rb immunoreactivity, accumulation of p53 and decrease in p21 have been described as characteristics of malignant cells, these markers have not been reliable to predict malignant transformation before morphologic changes of dysplasia.^[26] Other markers studied include topoisomerase alpha II, however, their role in predicting malignant potential is not well established.

DIAGNOSIS AND MANAGEMENT

Kang *et al.* described the presence of a lobulated contour appearance in CT scan of benign tumors; the lobulated contour is secondary to the papillary growth pattern typical of benign tumors. The presence of such a lobulated contour in CT scan could possibly aid in distinguishing benign from malignant tumors.^[27] Cho *et al.* compared the sensitivity, specificity, and accuracy of CT scan versus fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT and found them to be 95%, 48%, and 84%, respectively compared to 95%, 91%, and 94% for PET/CT.^[28] Benign lesions showed a significantly reduced FDG uptake compared to malignant lesions and cut off at 3.4 showed a sensitivity of 94% and specificity of 91%. The increase in uptake positively correlated with increased probability of malignancy. Hence, careful study of FDG uptake at the site of obstruction irrespective of the increased uptake beyond obstruction due to pneumonitis can be used to distinguish benign from malignant endobronchial lesions.^[28] The usefulness of PET scan also helps to rule out lymphadenopathy that is more often associated with malignant tumors of the lung. The use of multimodality imaging using a combined white light bronchoscopy,

endobronchial ultrasound, optical coherence tomography to identify layered microstructure and penetrance of the underlying cartilage in endobronchial lesions was studied by Colt *et al.*, and reported that the process is technically feasible to distinguish benign and malignant lesions, however, further studies are lacking to confirm this approach.^[9]

Removal of the entire tumor is usually the best diagnostic approach as washing is inadequate as most of these tumors are covered by normal respiratory mucosa. Fine needle biopsy is often negative and forceps biopsy is challenging because of the surface and motion involved.^[29] The main concern for the pathologist is distinguishing benign from malignant tumors, particularly intra-operatively as biopsies are difficult due to mobility and approachability of these tumors. The possibility of misdiagnosing an adenocarcinoma should be carefully weighed against the unnecessary surgical intervention in labeling a tumor as to be malignant. Some peripheral papillomas that grow along alveolar walls have a similar appearance to adenocarcinomas of papillary type.^[23] Features which aid in differentiation are the absence of significant cytologic atypia, hyperchromasia, mitoses, and necrosis of papilloma. It has also been reported that extensive inflammation associated with some of these benign tumors can confuse the pathologist with reactive nuclear atypia in such cells.^[30] The presence of inflammation should be always interpreted with caution and should always cause us to refrain from overcalling nuclear enlargement. Distinct nucleoli which may be seen reactive epithelia, lack of hyperchromasia, an intact basal layer of the epithelial lined fronds, no identifiable infiltration into surrounding lung parenchyma and limited lepidic growth at periphery of lesion should point toward a more benign lesion. It is, however, very difficult to exclude the presence of malignancy unless the entire lesion is excised by bronchoscopy. If the presence of any malignant feature is identified, the procedure should be followed through with a lobectomy with staging lymph node dissection. If there are no malignant features, the initial resection is itself curative. Recurrence has been rarely reported in any of these tumors, and the overall survival is good after treatment.

Based on the above extensive review of literature, we suggest four possible management approaches that may be taken for a patient diagnosed with endobronchial papillomas [Figure 1].

- The initial approach would be to simply observe these patients in whom the course could be predicted on clinical circumstances with the absence of associated symptoms of chronic or recurring infection. In this group of patients in whom the injury can be associated to a chronic inflammation resulting in inflammatory polyps, trial of inhaled corticosteroids; systemic steroids and use of long-term antibiotics for more than 3 months especially macrolides for their anti-inflammatory property. If the lesions are deemed

secondary to HPV trial of cytotoxic agents and antiviral agents could also be done. This approach is especially suitable for patients with multiple lesions and not all of them are accessible to biopsy

- The second of these approaches would be simple observation after confirmation with a tissue diagnosis. For this approach, we suggest the FDG PET/CT scan show a benign lesion with low uptake, CT scan diagnostic of the lesion and the biopsy specimen for diagnosis should be judged to be adequate by the pathologist, for the pathologist to unequivocally say that the tumor is benign and not more of an ominous process. Miller *et al.*^[31] described Argon plasma coagulation (APC) as an effective way to shrink these tumors without complete excision and this process works rapidly with no recurrence reported. The advantage of this APC with electrocautery and cryotherapy is that it can be performed with a flexible bronchoscope and it is less expensive compared to laser
- The third approach would require the use of a rigid bronchoscopy with biopsy using a larger cup forceps to remove the tumor endoscopically during the procedure; the removal can be accomplished with the mechanical energy of the bronchoscope and forceps particularly if a rigid bronchoscope is used. This is recommended for tumors where the tissue diagnosis is uncertain, or malignancy cannot be completely ruled out. The removal of the polyp can also be accomplished with the use of a laser by electrocautery for tumors whose removal cannot be accomplished with large cup forceps. The use of flexible fiberoptic bronchoscopy is not recommended in these patients, as small tissue samples are insufficient to confirm diagnosis. Majority of the patients can be reasonably treated with this approach. In patients refractory to the above therapy airway stenting can be accomplished with silicone stents, and this has been shown to decrease the number of tumors and also relieve the obstruction
- The fourth approach is the use of surgery in patients in whom symptoms are chronic and are not controlled by use of steroid and/or antibiotic therapy, surgical resection if the affected lobe would accomplish resolution of symptoms and also result in removal of offending polyp.^[32] In pursuing this particular approach, the use of tissue-sparing techniques must be accomplished with minimally possible parenchymal resection. The excision of the origin – bronchial part (bronchoplasty) should be tried first especially in patients with lesion in main bronchus or lobar bronchus. During such resections, pathologic changes must be noted peri-operatively as additional pulmonary resection might be indicated.^[33] Bronchotomy should be ideally performed during the excision and secretions be removed with expansibility of the underlying lung be checked. Any nodularity in tissue should be sought by palpation and ability of the lung to expand should be checked. The presence of fibrotic changes, bronchiectatic change, and inability to expand should indicate parenchymal resection in these diseases lungs.

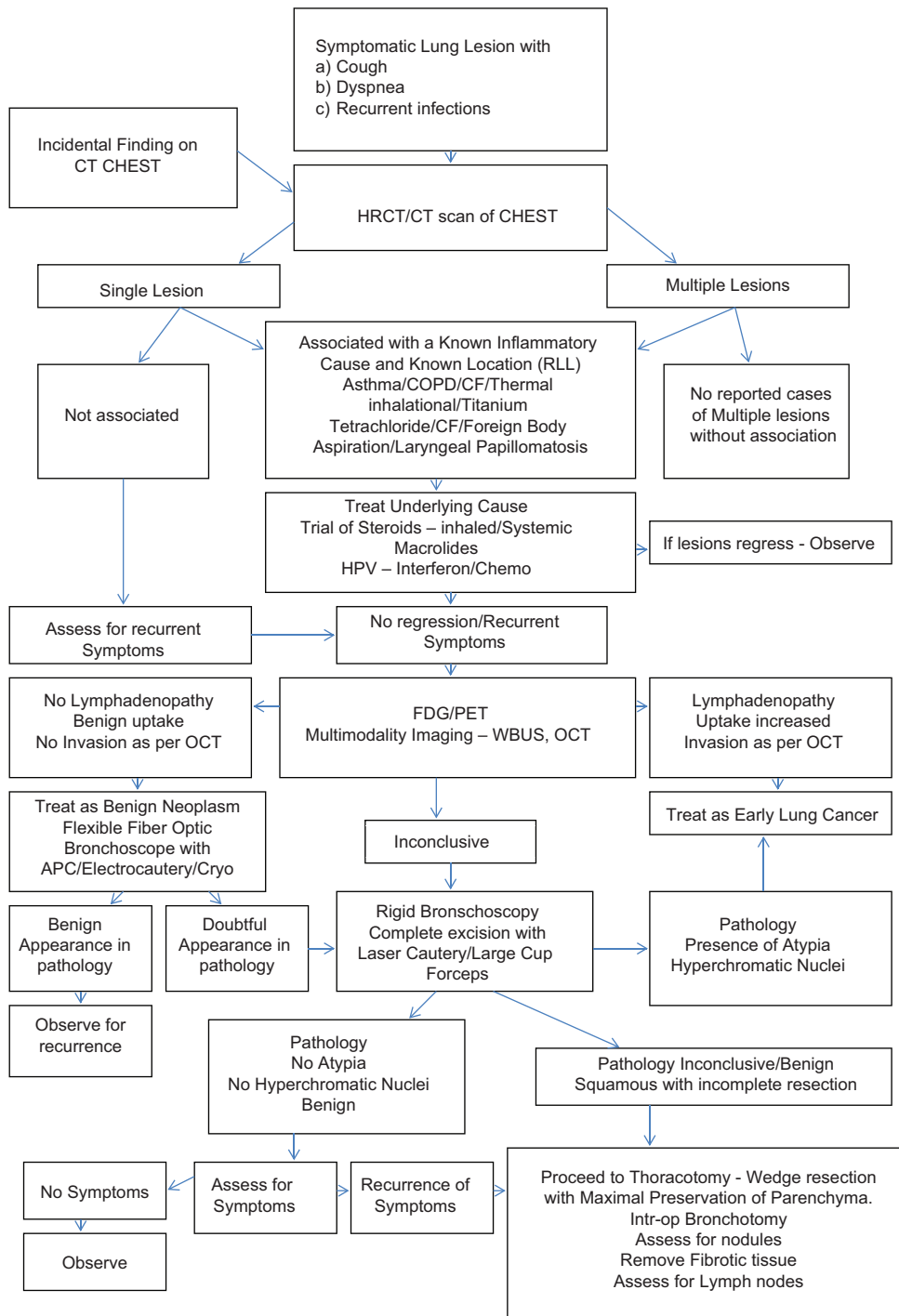


Figure 1: Approach to patients with respiratory papillomas

The obvious need of the following diagnostic algorithms is to avoid unnecessary thoracotomies and wedge resections for otherwise benign tumors. The need for such diagnostic algorithms in this otherwise rare group of tumors is necessary for proper diagnosis and to increase the awareness among surgeons to avoid procedures associated with significant mortality and morbidity.^[34,35] The diagnostic approaches and the appropriate treatment options have been summarized in the flowchart provided.

CONCLUSION

Early diagnosis is the key in these lesions, and early diagnosis helps to rule out malignancy and treatment is essential to prevent further complications and prevent resection in otherwise benign self-limited lesions.

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Conflicts of interest

There are no conflicts of interest.

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