JSM Clinical Cytology and Pathology

Case Report

Diagnosis of Respiratory Papillomatosis in Cytology Preparations: Case Report and Brief Review of the Literature

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Abstract

Recurrent respiratory papillomatosis is a rare and recurring disease characterized by chronic benign papillomas of the epithelial mucosa in the respiratory tract. It is exclusively caused by human papilloma virus. While the majority of human papilloma virus infections are self-limited, some persist, as is the case in recurrent respiratory papillomatosis. Diagnosis is usually achieved by surgical biopsy and the utility of immunohistochemistry studies. Studies showed that cytology specimens in form of fine needle aspiration could provide definite diagnosis of this entity, especially when cytologic sampling is sufficient to produce a cellblock to be utilized for ancillary studies. We report a case of this rare entity diagnosed solely by cytologic sampling. We also discuss the pathophysiology and management modalities.

Keywords: Laryngeal papilloma; Respiratory papilloma; Human papillomavirus; Recurrent papilloma

Abbreviations

RRP: Recurrent respiratory Papillomatosis; HPV: Human Papillomavirus; CSS: Squamous Cell Carcinoma; CISH: Chromogenic In Situ Hybridization; FNA: Fine Needle Aspiration

Introduction

Recurrent respiratory papillomatosis (RRP) is a rare disease characterized by recurrent exophytic papillomas of the epithelial mucosa in the respiratory tract [1]. RRP is caused by human papillomavirus (HPV); most frequently via HPV subtypes 6 and 11 [2]. Of these two subtypes, HPV 11 represents a more aggressive clinical course [3]. While HPV subtypes 6 and 11 are thought to account for over 90% of total RPR cases, other subtypes, such as HPV 16 and 18 have also been implicated in development of RRP [4]. The exophytic papillomas of RRP represent benign growth; however, they have been associated with significant increases in morbidity. For example, RRP is the second most frequent cause of childhood hoarseness and also can present with chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress [2]. The management of these growths, which predominately occur in the limen vestibuli, nasopharyngeal surface of soft palate, midzone of laryngeal surface of epiglottis, upper and lower margins of ventricle, undersurface of vocal folds, carina, and bronchial folds; is surgical intervention [5]. Although primary treatment for RRP is surgical intervention, this method generally yields limited and transient success. For example, one study found the mean number of surgical procedures per child was 4.4 per year, with a range of 0.2-19.3 per year [6]. To illustrate the dubious nature of lasting success, certain cases have occurred in which the arduous course of treatment required 130 excisions [7]. Furthermore, HPV infection maintains a known oncogenic risk. Studies of juvenile cases have reported a transformation rate of <1%, while in adults a rate of 3-7% has been described [8]. The precise transformation mechanism has not been confirmed. Although HPV subtypes 16 and 18 are less common in recurrent respiratory papillomatosis than the low-risk HPV types 6 and 11, subtypes 16 and 18 are more common when the lesions are of malignant potential [9]. Here we present a rare case which represents infection by HPV subtype 16 and illustrates its increased susceptibility of transformation to squamous cell carcinoma. The case was diagnosed utilizing fine needle aspiration (FNA) cytology with cellblock preparation

Submitted: 13 August 2019 | **Accepted:** 20 August 2019 | **Published:** 21 August 2019

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Citation: Noeske M, Truong PM, Coelho M, Balbi A, Aziz M, et al. (2019) Diagnosis of Respiratory Papillomatosis in Cytology Preparations: Case Report and Brief Review of the Literature. JSM Clin Cytol Pathol 4: 4.

Case Presentation

The patient was a 24-year-old man who presented with complaints of hoarseness lasting 6 months. Investigation revealed multiple pulmonary parenchymal nodules, cystic bronchiectasis, and multiple laryngeal nodules. Fine-needle aspiration including cell block preparation of lung nodule was performed, revealing scattered groups and sheets of mildly atypical squamous cells with focal papillary configuration, in a background of acute inflammatory changes (Figure 1, A through C). Immunohistochemical analysis on cytology cellblock preparation revealed that the cells were positive for P16, P53, and HPV 6 and 11. In addition, multiple scattered groups of cells were positive for HPV type 16 [Figure 1, D] leading to the diagnosis of respiratory papillomatosis in cytology preparation. Surgical biopsy of the laryngeal nodules confirmed the diagnosis of respiratory papillomatosis with the same immunohistochemistry pattern as observed in cytology

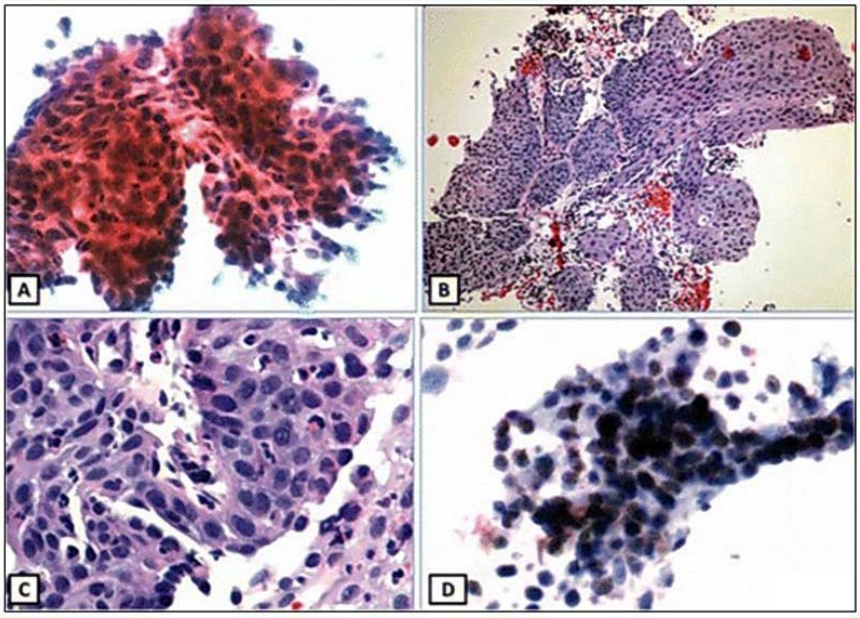

Figure 1 Fine needle aspiration of lung nodule, cytology smears and cellblock
A: Three dimensional sheets and clusters of atypical squamous cells. H&E stain; X20
B: Sheets and clusters of atypical squamous cells in a papillary configuration and chronic inflammatory background; H&E X10
C: Papillary clusters with pleomorphic malignant squamous cells; H&E X40
D: Scattered groups of cells positive for HPV type 16.

preparation. The lung and laryngeal nodules were excised, but the patient suffered multiple episodes of recurrences which required several excisions and laser ablation. The last excised recurrence showed a possible transformation to squamous cell carcinoma as definitive histomorphologic features of either severe dysplasia or squamous cell carcinoma were not clearly defined and the case was diagnosed as suspicious for squamous cell carcinoma. Six months later, a large 5x3.5 cm recurrence in the upper right lung parenchyma showed evidence of well differentiated squamous cell carcinoma in background of benign papillomatosis. Histological examination suggested that the squamous cell carcinoma (SCC) originated from a papillomatous lesion, and chromogenic in situ hybridization (CISH) was performed. Lung lesion showed a positive result in CISH for high-risk HPV type 16 in background of benign papillomatosis positive for low-risk HPV types 6 and 11. After the diagnosis of squamous cell carcinoma, the patient decided to move to his home country and he was lost to follow up.

Discussion

RRP is a rare and recurring disease characterized by chronic benign papillomas of the epithelial mucosa in the respiratory tract [1]. RRP is exclusively caused by human papillomavirus (HPV). Human Papillomaviruses are DNA viruses of oncogenic potential that infect basal epithelial (skin or mucosal) cells. In cases of RRP, the most frequently associated HPV subtypes are the low risk subtypes such as 6 and 11, however, high risk subtypes such as 16 and 18 have also been observed. RRP presents in 2 forms, juvenile and adult, with juvenile being considered more aggressive [10]. The incidence of the disease is estimated to be 4.5 per 100,000 children and 1.8 per 100,000 adults [2]. Evidence suggests that HPV is acquired during passage through the birth canal of an infected mother. It is also hypothesized that the disease can be contracted congenitally in utero. Cesarean section may limit the exposure of children to HPV during childbirth, but its effectiveness is debatable [10]. While the majority of HPV infections are self-limited, some persist, as is the case in recurrent respiratory papillomatosis.

The marriage of cytology and radiology has allowed for minimally invasive, safe, accurate, and cost-effective diagnosis of suspicious masses, previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in specimens procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management and is an integral part of a multimodal approach to various tumor diagnoses. On-site cytology interpretation increases the diagnostic yield of the procedure by allowing for additional needle passes as necessary. The process culminates in a multidisciplinary conference such as tumor board where the results of clinical, radiologic, cytologic, and laboratory evaluations are discussed, and a treatment is planned [11,24]. The definitive diagnosis of RRR was solely established utilizing cytology sampling including cellblock preparations.

As a chronic disease, the management of RRP often requires frequent surgical intervention. Because of the intractable nature of RRP, the goals of treatment are predominantly improving vocal function, preserving laryngeal tissues, and maintaining airway integrity [11]. As a result of frequent intervention, the financial

impact can be noteworthy. The average lifetime cost to treat one patient with RRP has been estimated at $60,000 to $470,000 in the United States. On a national level, it is estimated that there are 15,000 surgical procedures performed every year in adults and children with RRP, with a total health care cost of nearly $150 million [12].

Due to the prolonged and costly intervention regimen, alternative and adjuvant treatment methods are actively researched including treatment with interferon-alpha (IFN), acyclovir, and cidofovir. We will now briefly discuss each of these treatment methods.

Interferons are signaling proteins produced by human leukocytes. Interferons bind to membrane receptors, resulting in alterations in cellular metabolism, with the purpose of generating antiviral, antiproliferative and immunomodulatory effects [13]. However, interferon can result in systemic toxicity which yields it a less desirable treatment mechanism. Furthermore, the effectiveness of interferon treatment is debatable. Some groups have found success in treatment with interferon alfa-n1 in slowing growth of respiratory papillomas [14]. Conversely, other groups have found that interferon is neither cures nor offers adjunctive support [15].

Acyclovir is a retroviral used for herpes viruses. In an early study, Endres et al. found that the beneficial effect of acyclovir appeared to improve outcomes in quantitative measures of overall disease extent, laryngeal involvement, and degree of glottic obstructions [16]. However, two patients who were using interferon-alpha prior to beginning acyclovir demonstrated worsening disease consistent with rebound phenomenon of stopping interferon [16]. In a more recent study, Chaturvedi et al. found that antiviral drugs at regular intervals in addition to a short course of oral steroids can lead to a more rapid recovery and prevented latent viral activation, effectively maintaining long term improvement and avoidance of repeated surgeries [17].

Cidofovir is used in treatment of RRP as an inhibitor of viral DNA polymerase. Similarly to Acyclovir, the use of Cidofovir has been found to produce mixed results. McMuarry et all studied RRP over a 12 month period produced no net difference in effect when compared to the placebo group [18]. On the other hand, Chadha found that 35% of patients observed a complete resolution following treatment, however noting that insufficient evidence from controlled trials exists for reliable conclusions [19].

Recently, increasing research indicates the promise of treatment utilizing the quadrivalent HPV vaccine, known commercially as Gardasil. The quadrivalent vaccine offers protection against HPV subtypes 6, 11, 16, and 18. A study by Goon et al. found a >7 fold decrease in incidence rates of papillomatosis requiring surgical intervention from the pre-vaccination period to the post vaccination period (47.44 to 6.71 /1000-patient months) [20]. For this reason the quadrivalent vaccine may be the most promising treatment method.

Malignant transformation of PRR is rare, having been described in about 1-4% of cases. Molecular evidence has supported a role for HPV, particularly HPV-16, in the pathogenesis of SCC [21]. Here we present a case of malignant transformation of PRR in an adult patient with history of multiple recurrences. The transformation from benign RRP to squamous cell carcinoma is well documented; however, the underlying exact mechanism of the malignant transformation has not been completely illuminated. Fifteen articles were found in the English literature, totaling 28 cases of malignant transformation of PRR with onset in adult patients [25]. Our case is an addition to the previously reported cases.

Our understanding of the high-risk HPV types 16 and 18 is considerable, with most research focused on oncogenes E6 and E7, targeting tumor suppressors p53 and Rb, respectively [22]. The degradation of tumor suppressors p53 results in deficiencies in cell cycle monitoring, DNA repair, and apoptotic pathways. These cell cycle deficiencies are critically linked to the progression of neoplasia. Furthermore, a correlation has been established between the levels of E6 and E7 expression and the rate of neoplastic progression [23]. Treatment options for malignant neoplasms arising from such mechanism have not been well studied, and this marks a potential area for future research. Current treatment continues to produce mixed results. The management of RRP is consistently evolving, focus tends to shift from treatment to prevention and limiting spread [23,24].

In conclusion, RRP maintains enigmatic characteristics in both its pathogenesis and treatment. Undoubtedly, better understanding of these two aspects would produce a synergistic benefit in improved treatment of the condition. Additional research to improve RRP detection and treatment, particularly before malignant transformation, is, however, needed. The risk of malignant transformation must be considered in all cases of laryngeal papillomatosis. Special attention should be given to cases with multiple recurrences especially those positive for high risk HPV such as HPV 16 and 18. The current study suggests the involvement of the high-risk HPV types in the pathogenesis of squamous cell carcinoma in pulmonary papillomatosis. The case also shows that definitive diagnosis of pulmonary papillomatosis can be accomplished solely based on cytology preparation including cellblock.

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