

Mini Review

Recurrent Respiratory Papillomatosis: A Review

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Abstract

Recurrent Respiratory Papillomatosis (RRP) is a benign tumor of the respiratory tract caused by the Human Papillomavirus (HPV). It is considered as a manageable rather than a curable disease because of its high recurrence rates and its unpredictable clinical course. The unique molecular characteristics of the virus, induces cellular proliferation causing airway obstruction. The main symptoms are hoarseness, inspiratory and expiratory stridor and dysphagia. Innumerable, yet not effective, efforts to cure RRP have been attempted. Different treatment modalities, such as surgery and adjuvant therapy, have been published in recent years. Surgery remains the leading practice of treatment; however, because of its tendency to recur, approximately 10% of the patients will require adjuvant therapy. Current medical investigation is focusing on antiviral modalities, photo dynamic therapy, indole-3- carbinol, retinoids, gene therapy, and vaccines. Considering RRP challenging treatment, prevention must be the main focus of physicians. The decision of the optimal therapy must be made on the physician's confidence in the estimated of the treatment effect across the outcomes that matter most to the patients. In addition, the patient's context, goals, values and preferences must be taken into account.

Keywords: Recurrent Respiratory Papillomatosis; Human Papillomavirus

Introduction

Recurrent Respiratory Papillomatosis (RRP) is the most common benign tumor of the larynx and a common cause of pediatric hoarseness. The three peaks of onset observed are: early childhood, third decade and sixth decade of life [1]. Although it is considered to have a benign course, it tends to spread throughout the aerodigestive tract causing airway obstruction [1,2]. In severe cases, death is usually caused by complications of surgical procedures or respiratory failure due to progression of the disease [2]. The incidence in the United States is approximated at 4.3 per 100,000 children and 1.8 per 100,000 adults [3]. It is characterized by a chronic proliferation of squamous papilloma caused by Human Papillomavirus (HPV). RRP is most commonly associated with HPV types 6 and 11 [4]. Persistent infections with HPV types 16 and 18 have been associated with oropharyngeal squamous cell carcinomas [5]. Vertical transmission during delivery through an infected birth canal is presumed to be the mode of transmission to children [6]. Risk factors to acquire RRP are firstborn and vaginally delivered patient immunity, timing and volume of virus exposure, and local trauma [7]. Innumerable, yet not effective, efforts to cure RRP have been attempted. A crescent number of investigations about different treatment modalities have been published in recent years. Nevertheless, no reported uniformity responses of surgical, medical, or adjuvant therapies in the management of the disease.

Pathophysiology

HPV is a DNA virus who is thought to infect stem cells within the basal layer of mucosa. The viral DNA reactivates the host replication genes, inducing cellular proliferation. The viral E-region products bind and inactivate certain cellular tumor-suppressor proteins, and can activate the Epidermal Growth Factor (EGF) associated with proliferation of epithelial cells [8]. The proliferation of the virus

results in finger-like projections with a fibrovascular core covered by stratified squamous epithelium. When papillomas microscopic, they give the mucosa a velvety appearance. Subsequently, when papilloma grows, they appear as "cauliflower" projections [9]. Viral DNA can remain latent with the mucosa appearing clinically and histologically normal. In latency, viral DNA can be detected in mucosa in patients with RRP that has been in remission for years [10].

Signs and symptoms

Vocal fold is the principal site of papilloma growth which leads to hoarseness to be the main symptom. Inspiratory stridor, which progresses to a biphasic stridor, is the second symptom to present. Other symptoms are: dysphagia, dyspnea, chronic cough, failure to thrive, and respiratory tract infections. Aggressive RRP forms can manifest as an acute respiratory distress [11]. The onset of presentation of RRP orients clinicians to the best choice of treatment.

Diagnosis

Many patients are initially assumed to have a more common respiratory problem, such as croup, asthma, or bronchitis [12]. Diagnosis of RRP consists in the visualization of the papilloma with a rigid or flexible laryngoscope. The prime area where papilloma develops is the larynx. Rarely, it can be observed in the nasal cavity, oral cavity, or pharynx. Once papilloma is identified, an excisional biopsy is performed [13].

Treatment

Patients with RRP must know the importance of their disease, its prognosis, and the rate of recurrence. On average, children with RRP require a mean of 4.4 surgical procedures per year and 19.7 procedures over their lifetime [14]. The decision of the optimal therapy must be made on the physician's confidence in the estimated of the treatment effect across the outcomes that matter most to the patients. In

addition, the patient's context, goals, values and preferences must be taken into account [15]. The process by which the optimal decision may be reached for a patient is called shared decision making. The most important attribute of a patient-centered care is the engagement of patients when fateful care decisions must be made [16].

Surgical Procedures

The goals of RRP treatment are: reduce the tumor, decrease the spread of the disease, create a safe airway, optimize voice quality, and increase the time interval between the procedures [2]. Although many medical treatments have been attempted to cure RRP, surgery remains the leading practice of treatment. The most common used procedures are the CO₂ laser and removal with cold instruments. Prevention of loss of patient's airway should be considered at induction of general anesthesia [17]. In young patients, where total eradication of the papilloma is impossible, it is recommended to leave minimal amounts of lesions in sites where irreparable scarring may occur (anterior commissure and the posterior glottis) [17]. However, if a papilloma is not removed completely, the chance to spread into the submucosal glands increases. Hence, the submucosal glands should be removed all together to decrease recurrence [18]. Laryngeal scarring develops severely in areas where papilloma had recurred several times. Furthermore, the papilloma had more chances of invading deeper tissue due to breakdown of the base membrane barrier [18]. The CO₂ laser can be used with precision to vaporize RRP lesions with minimal bleeding [19]. The most common complications due to the procedures are bleeding, temporary laryngeal edema, damage of maxillary teeth by the suspension of the laryngoscope, and glottic webs in both therapies. Airway fire may result in patients treated with CO₂ laser. Scar tissue formation, laryngeal stenosis, and soft tissue complications are more frequently observed after surgery with cold instruments [20]. Microdebrider resection has been reported as a safe alternative with quicker improvement of symptoms, shorter procedure time, less postoperative time, and lower overall procedural costs versus patients who underwent removal with CO₂ laser [21]. Pulse dye treatments are preferred among patients as general anesthesia can be avoided. The use of pulse dye therapy is considered relatively effective and safe, yet this method seems less effective for large papilloma [22]. When multiple surgical procedures are made and still unsuccessful to preserve the airway, tracheostomy is the last choice [23].

Adjuvant Therapy

Considering respiratory papilloma's tendency to recur, approximately 10% of the patients will require some form of adjuvant therapy. The decision to begin an adjuvant therapy must recognize benefits and its side effects. The most widely accepted criteria for initiating the adjuvant treatment are: (i) requirement for more than 4 surgical procedures per year, (ii) distal multisite spread of the disease, and (iii) rapid regrowth of papilloma with airway compromise [17]. Current medical investigation is focusing on antiviral modalities, photodynamic therapy, indole-3- carbinol, retinoids, gene therapy, and vaccines. Interferon alfa was the first antiviral adjuvant therapy used and its responsiveness has been proven in several studies [24,25]. Although its exact mechanism is unknown, it plays an important role connecting innate and adaptive immune response, particularly T-cells; it also can activate dendritic cells to promote an

adequate immune response [26]. There are few reports of Ribavirin as adjuvant therapy showing some effectiveness in aggressive disease [27]. Acyclovir appears to be effective when there are concurrent viral infections, and viral co-infections with herpes simplex virus-1, cytomegalovirus, and Epstein-Barr virus. The intralesional injection of cidofovir is used in patients with severe RRP [28]. Studies have shown a reduction of lesions and need for surgery when intralesional cidofovir was injected prior to the procedure [29]. Current gene therapies are based on the current awareness of the differentiation of HPV epithelium. Bevacizumab is a recent recombinant humanized monoclonal antibody against Vascular Endothelial Growth Factor (VEGF). Various studies have demonstrated bevacizumab improvement in resolution of lesions, and decreased interval between treatment times [23,30]. Systemic bevacizumab evidenced significant promise as a treatment modality for severe RRP. All treated patients had significant reduction of surgery procedures intervals and alleviation of airway obstruction, with a low complication profile [31]. Photodynamic Therapy (PDT) has been widely studied as a treatment for RRP. It led to a small decrease in RRP growth, nevertheless the therapy is not well tolerated by patients no matter the used agent [32,33]. Dietary supplement indole-3-carbinol from cruciferous vegetables reduced the formation and cessation of the papilloma growth. Retinoids modulate cellular proliferation and differentiation of diverse histologic cells, they have been found to suppress squamous differentiation. The evidence of its efficacy on RRP is limited [34,35]. Measles, Mumps, and Rubella (MMR) vaccines as adjuvant therapy to lesion debridement in RRP revealed no significant difference in comparison to cidofovir [36]. The HPV-4 vaccine as adjuvant therapy increased the inter-surgical intervals and showed complete and partial remission in the treated patients. Utilizing HPV vaccines as a treatment has a benefit with no downsides. Treating patients with the vaccine can possibly stimulate the host to develop antibodies that will target papilloma cells and clear the disease process [37].

Prevention

The best treatment for RRP is prevention of the disease. The most important risk factor for juvenile RRP is maternal infection with HPV. As the mechanism of transmission is unclear, the management remains uncertain. The prevention of genital maternal infection with the virus is the main objective in children. Cesarean section is not recommended as it is associated with a higher morbidity and mortality for the mother. The adult form typically occurs with the reactivation of a latent infection or as a newly acquired sexually transmitted disease. Prevention can be constructed with the application of the prophylactic vaccines for population ages 11 to 12 years. Vaccine may eradicate RRP caused by HPV types 6, and 11 [38]. Additionally, a meticulous examination to determine whether the papilloma has spread to the anterior commissure, laryngeal ventricle, false vocal folds, subglottis, or epiglottis is necessary to prevent recurrence [18].

Conclusions

Recurrent respiratory papillomatosis is the most common tumor of the larynx and a frequent cause of pediatric hoarseness. The main issue of RRP is its tendency to recur. RRP recurs due to the histological characteristics of the papilloma and its clinical course according to the virus subtypes. Furthermore, the high recurrence rate may be caused by the difficulty of entirely removing of the papilloma. For

this reason, RRP is considered a manageable pathology rather than a curable one. Papilloma can grow so extensively that respiratory airway can be obstructed and, if not treated, can lead to death. Yet not effective, innumerable attempts to cure RRP have been attempted. Surgery remains the fundamental practice of treatment. Despite the efforts, the struggle with surgical complications remains a substantial concern in RRP therapy. Scarring and invasive procedures increase the chances of papilloma invading deeper tissue and therefore, it difficult papilloma removal. The focus of recent studies on therapy treatments for RRP is on developing adjuvant treatment methods to reduce recurrence rate and prolong intervals between surgical procedures. Many treatments may be required as the papilloma recur. Considering RRP challenging treatment, prevention must be the main focus of physicians. Treatment must be individualized and based on shared decision making.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Drejet S, Halum S, Brigger M, Skopelja E, Parker N. A systematic review: Outcomes in adult recurrent respiratory papillomatosis treated with intralesional Cidofovir or Bevacizumab. *Otolaryngol Head Neck Surg.* 2017; 156: 435-441.
- Derkay C, Wiatrak B. Recurrent respiratory papillomatosis: A review. *Laryngoscope.* 2008; 118: 1236-1247.
- Reeves W, Ruparella S, Swanson K, Derkay C, Marcus A, Unger E, et al. National registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg.* 2003; 129: 976-982.
- Combrinck CE, Seedat RY, Burt FJ. FRET-based detection and genotyping of HPV-6 and HPV-11 causing recurrent respiratory papillomatosis. *J Virol Methods.* 2013; 189: 271-276.
- Boscolo-Rizzo P, Del Mistro A, Bussu F, Lupato V, Baboci L, Almadori G, et al. New insights into human papillomavirus-associated head and neck squamous cell carcinoma. *Acta Otorhinolaryngol Ital.* 2013; 33: 77-87.
- Silverberg M, Thorsen P, Lindeberg H, Grant L, Shah K. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obs Gynecol.* 2003; 101: 645-652.
- Kashima H, Shah F, Lyles A, Glackin R, Muhammad N, Turner L, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. *Laryngoscope.* 1992; 102: 9-13.
- Vambutas A, Di Lorenzo T, Steinberg B. Laryngeal papilloma cells have high levels of epidermal growth factor receptor and respond to epidermal growth factor by a decrease in epithelial differentiation. *Cancer Res.* 1993; 53: 910-914.
- Swan D, Vernon S, Icenogle J. Cellular proteins involved in papillomavirus-induced transformation. *Arch Virol.* 1994; 138: 105-115.
- Low GM, Thylur DS, N Yamamoto V, Sinha UK. The effect of human papillomavirus on DNA repairs in head and neck squamous cell carcinoma. *Oral Oncol.* 2016; 61: 27-230.
- Benedict PA, Ruiz R, Yoo M, Verma A, Ahmed OH, Wang B, et al. Laryngeal distribution of recurrent respiratory papillomatosis in a previously untreated cohort. *Laryngoscope.* 2018; 128: 138-143.
- Venkatesan N, Pine H, Underbrink M. Recurrent respiratory papillomatosis. *Otolaryngol Clin North Am.* 2012; 45: 671-679.
- Green G, Bauman N, Smith R. Pathogenesis and treatment of juvenile onset recurrent respiratory papillomatosis. *Otolaryngol Clin North Am.* 2000; 33: 187-207.
- Armstrong L, Derkay C, Reeves W. Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg.* 1999; 125: 743-748.
- Ting H, Brito J, Montori V. Shared decision making: science and action. *Circ Cardiovasc Qual Outcomes.* 2014; 7: 323-327.
- Barry M, Edgman- Levitan S. Shared decision making- the pinnacle of patient-centered care. *N engl J Med.* 2012; 366: 780-781.
- Stamatakis S, Nikolopoulos T, Korres S, Felekis D, Tzangaroulakis A, Ferekidis E, et al. Juvenile recurrent respiratory papillomatosis: Still a mystery disease with difficult management. *Head Neck.* 2007; 29: 155-162.
- Kim H, Baizhumanova A. Is recurrent respiratory papillomatosis a manageable or curable disease? *Laryngoscope.* 2016; 126: 1359-1364.
- Dedo H, Yu K. CO₂ laser treatment in 244 patients with respiratory papillomatosis. *Laryngoscope.* 2001; 111: 1639-1644.
- Preuss S, Klussmann J, Jungehulsing M, Eckel H, Guntinas-Lichius O, Damm M, et al. Long-term results of surgical treatment for recurrent respiratory papillomatosis. *Acta Otolaryngol.* 2007; 127: 1196-1201.
- Pasquale K, Wiatrak B, Woolley A, Lewis L. Microdebrider versus CO₂ laser removal of recurrent respiratory papillomas: A prospective analysis. *Laryngoscope.* 2003; 113: 139-143.
- Rees C, Halum S, Wijewickrama R, Koufman J, Postma G. Patient tolerance of in-office pulsed dye laser treatments to the upper aerodigestive tract. *Otolaryngol Head Neck Surg.* 2006; 134: 1023-1027.
- Bowen A, Bryson P. OR management of recurrent respiratory papilloma. *Curr Otorhinolaryngol Repo.* 2016; 4: 76-84.
- Healy G, Gelber R, Trwobridge A, Grundfast K, Ruben R, Price K, et al. Treatment of recurrent respiratory papillomatosis with human leukocyte interferon. Results of a multicenter randomized clinical trial. *N Engl J Med.* 1998; 319: 104-107.
- Gerein V, Rastorguev E, Gerein J, Jecker P, Pfister H. Use of interferon-alpha in recurrent respiratory papillomatosis: 20-year follow-up. *Ann Otol Rhinol Laryngol.* 2005; 114: 463-471.
- Suter-Montano T, Montañó E, Martínez C, Plascencia T, Sepulveda MT, Rodríguez M, et al. Adult recurrent respirator papillomatosis: A new therapeutic approach with pegylated interferon alpha 2a (Peg-IFN α -2a) and GM-CSF. *Otolaryngol Head Neck Surg.* 2013; 148: 253-260.
- Chadha NK, James AL. Antiviral agents for the treatment of recurrent respiratory papillomatosis: A systematic review of the English-language literature. *Otolaryngol Head Neck Surg.* 2007; 136: 863-869.
- Fusconi M, Grasso M, Greco A, Gallo A, Campo F, Remacle M, et al. Recurrent respiratory papillomatosis by HPV: Review of the literature and update on the use of cidofovir. *Acta Otorhinolaryngol Ital.* 2014; 34: 375-381.
- Co J, Woo P. Serial office-based intralesional injection of cidofovir in adult-onset recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol.* 2004; 113: 859-862.
- Zeitels S, Barbu A, Landau-Zemer T, Lopez-Guerra G, Burns J, Friedman A, et al. Local injection of bevacizumab (Avastin) and angiolytic KTP laser treatment of recurrent respiratory papillomatosis of the vocal folds: A prospective study. *Ann Otol Rhinol Laryngol.* 2011; 120: 627-634.
- Best S, Mohr M, Zur K. Systemic Bevacizumab for recurrent respiratory papillomatosis: A national survey. *Laryngoscope.* 2017; 127: 2225-2229.
- Shikowitz M, Abramson A, Freeman K, Steinberg B, Nouri M. Efficacy of DHE photodynamic therapy for respiratory papillomatosis: Immediate and long-term results. *Laryngoscope.* 1998; 108: 962-967.
- Shikowitz M, Abramson A, Steinberg B, DeVoti J, Bonagura V, Mullooly V, et al. Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg.* 2005; 131: 99-105.
- Newfield L, Goldsmith A, Bradlow H, Auburn K. Estrogen metabolism and human papillomavirus-induced tumors of the larynx: Chemo-prophylaxis with indole-3-carbinol. *Anticancer Res.* 1993; 13: 337-341.

35. Rosen C, Bryson P. Indole-3-carbinol for recurrent respiratory papillomatosis: Long-term results. *J Voice*. 2004; 18: 248-253.
36. Meacham R, Thompson J. Comparison of cidofovir and the measles, mumps, and rubella vaccine in the treatment of recurrent respiratory papillomatosis. *Ear Nose Throat J*. 2017; 96: 69-74.
37. Santarelli G, Derkay C. HPV vaccines for treatment and prevention of recurrent respiratory papillomatosis. *Curr Otorhinolaryngol Repo*. 2016; 4: 85-89.
38. Mustafa M, Patawari P, Muniandy R, JAWAD M, Hamed S, Rahman M, et al. Transmission and prevention of recurrent respiratory papillomatosis. *IOSR-JDMS*. 2015; 14: 86-91.