Recurrent Respiratory Papillomatosis: An Update

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ABSTRACT

The aim of this article is to describe the pathogenesis, etiology, clinical course, prevention, and management of recurrent respiratory papillomatosis (RRP). RRP is a challenging chronic disease of the respiratory tract that occurs in both children and adults. It is caused by human papillomavirus (HPV), with more than 90% caused by HPV 6 and HPV 11 types. While there is no definitive treatment for RRP, the goal of treatment focuses on improving voice quality and maintaining airway patency. The clinical presentation is nonspecific with the majority of patients presenting with hoarseness, stridor, or dyspnea. Surgical management is the mainstay of treatment of RRP, and about 20% of the patients benefit from adjuvant therapies including cidofovir, bevacizumab, interferon, and others. Prevention of the disease with the HPV vaccine and practicing safe sex may play a major role in decreasing the incidence of HPV infection and RRP.

Keywords: Bevacizumab, Cidofovir, HPV, HPV vaccine, Respiratory papillomatosis.

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INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a disease of recurrent warty lesions of the upper aerodigestive tract. Papillomas are the most common benign laryngeal neoplasm in children. Due to its unpredictable nature and tendency to recur, this benign disease can be quite frustrating. Current management strategies are primarily focused on improving voice quality and maintaining airway patency.

Epidemiology

The incidence of RRP is estimated to be 4.3 per 100,000 children and 1.8 per 100,000 adults.1 There is a bimodal age of distribution, with the juvenile form most commonly occurring in children less than 5 years of age and the adult-onset form occurring between 20 and 40 years of age.2 The juvenile form, which is patients presenting under the age of 12, is generally considered highly aggressive with a high recurrence rate in comparison to the adult form.3 In the adult-onset form, males are affected twice as often as females while there is no gender difference in the juvenile form.4 The triad of first-born, vaginally delivered, and child of a young mother is found in 75% of children who present with RRP.

Etiology

Recurrent respiratory papillomatosis is caused by the human papillomavirus (HPV). This DNA virus is well known and can cause papillomas as well as condylomas and cancer of the cervix, anus, mouth, or throat. It has a nonencapsulated, double chain icosahedral structure, and is composed of 72 capsomeres approximately 55 nm in diameter.5 There are hundreds of strains of HPV. The most common strains found in RRP are HPV 6 and 11 but recent studies have looked at alternate subtypes as well. A study by C. Hoessli et al., found that, in a cohort of 184 patients, 68.1% had HPV 6 and 12.5% had HPV 11. A smaller group of 9.2% had alternative HPV types including 16, 18, 31, 44, 45, 55, and 70, and 3.8% of patients were HPV negative.6 Type of HPV is important due to prognostic and treatment implications. HPV 11 has been found to be more aggressive, requiring more frequent surgical debridements, and more likely to be treated with adjuvant therapy. It also more likely to have extralaryngeal involvement with a higher risk of needing a tracheostomy.7 In the past century, there have been research efforts to study the role of Epstein-Barr virus (EBV) in recurrent respiratory papillomatosis (RRP) pathogenesis. Recently, Costa et al., observed a low EBV prevalence among RRP cases but they concluded that EBV does not seem to play any role in the progression or severity of RRP.8

Mode of Transmission

HPV is the most common sexually transmitted infection in women and infects mucosal areas of the cervix, vagina, vulva, and anus. Prevalence among women ranges from 2–44% and 3.5–45% in men. In women, prevalence is highest in young women and decreases in the middle age groups.9 Adults are at increased risk of HPV infection with a greater number of sexual partners and oral contact with infected external genitalia.10 In most children, infection by HPV occurs during birth as the mother’s genital tract acts as a reservoir for HPV.11 A study showed that 67% of the mothers of children with RRP had a history of active warts during pregnancy.12 Quick et al. recommended that cesarean section (C-section) delivery can prevent transmission of HPV in mothers with active condylomas,12 however there are still 12% of RRP cases transmitted through the placenta.10

Histopathology Feature

Clinically, gross papilloma present as exophytic masses (Fig. 1), which are typically pinkish-whitish “cauliflower-like” compared to microscopic papilloma, which appears as velvety

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Histologically, respiratory papilloma has characteristic features including multiple papillary fronds with a central fibrovascular core covered by stratified squamous epithelium. Other typical findings are abnormal keratinization, hyperkeratosis, and basal cell hyperplasia. Papilloma also has koilocytosis, the presence of a clear perinuclear zone in intermediate and superficial squamous cells; which is highly suggestive of viral infection. While there is no widely accepted staging system, the one most commonly referred to was proposed by Derkay et al. This system assesses severity of disease, response to therapy and allows for patient disease tracking. It can aid in improving communication between laryngeal surgeons who treat RRP. The staging system has six questions regarding the patient’s clinical course including interval of surgery, total number of surgeries, the urgency of surgery, quality of voice, degree of stridor at time of surgery, and degree of respiratory distress. A score of 0–3 (0 = absent, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion) is assigned to each site of the aerodigestive tract (Table 1) with a final numeric score relating to the extent of disease.

### Anatomical Site Predilection

Papilloma usually arises in the transitional areas between the squamous epithelium and the ciliated columnar epithelium. Typical anatomical sites include:

- Larynx:
  - Lingual surface of epiglottis
  - Laryngeal surface of epiglottis
  - Aryepiglottic fold (right/left)
  - False vocal fold (right/left)
  - True vocal fold (right/left)
  - Arytenoids (right/left)
  - Anterior commissure
  - Posterior commissure
  - Subglottis

- Trachea:
  - Upper one-third
  - Middle one-third
  - Lower one-third
  - Bronchi (Right/Left)

- Other:
  - Nose
  - Palate
  - Lungs
  - Esophagus
  - Other
  - Pharynx

### Table 1: Derkay et al. staging system for RRP

<table>
<thead>
<tr>
<th>Larynx</th>
<th>Trachea</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual surface of epiglottis</td>
<td>Upper one-third</td>
<td>Nose</td>
</tr>
<tr>
<td>Laryngeal surface of epiglottis</td>
<td>Middle one-third</td>
<td>Palate</td>
</tr>
<tr>
<td>Aryepiglottic fold (right/left)</td>
<td>Lower one-third</td>
<td>Lungs</td>
</tr>
<tr>
<td>False vocal fold (right/left)</td>
<td>Bronchi (Right/Left)</td>
<td>Esophagus</td>
</tr>
<tr>
<td>True vocal fold (right/left)</td>
<td></td>
<td>Lungs</td>
</tr>
<tr>
<td>Arytenoids (right/left)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recurrent Respiratory Papillomatosis

HPV types of 6 and 11. However, within the low-risk types, HPV 16 and 18 considered high risk in comparison to the low-risk risk factors for malignant transformation includes HPV typing with developing dysplasia or invasive carcinoma in that cohort. Other or use of cidofovir were not noted to be significant risk factors in risk of carcinoma. Gender, smoking history, number of operations, in life, whereas children presenting earlier in life were at higher bronchoscopy with biopsy used to confirm the diagnosis. Helical tract. This can make it difficult to manage and it may delay the tendency toward confluence.

Malignant Transformation

Although RRP is clinically a benign disease, transformation to dysplasia and invasive carcinoma can occur. The rate of dysplasia in RRP patients is approximately 10%, although in some studies it can reach as high as 55%. The risk of malignant transformation is estimated to be 3–7% in adults and <1% in children. A study by Karatayli-Ozgursoy et al., found that age of disease onset is a significant risk factor for dysplasia or carcinoma-ex-papillomatosis. In adult onset RRP, patients with dysplasia or malignant transformation presented a decade later in life, whereas children presenting earlier in life were at higher risk of carcinoma. Gender, smoking history, number of operations, or use of cidofovir were not noted to be significant risk factors in developing dysplasia or invasive carcinoma in that cohort. Other risk factors for malignant transformation includes HPV typing with HPV 16 and 18 considered high risk in comparison to the low-risk HPV types of 6 and 11. However, within the low-risk types, HPV 11 has more malignant potential.

Clinical Course

The clinical course of RRP is variable. RRP patients usually present with nonspecific laryngeal and airway symptoms including progressive hoarseness, chronic cough, shortness of breath, stridor, or wheezing. Children with RRP present with a triad of progressive hoarseness, stridor, and breathing difficulty. Because of nonspecific symptoms, RRP can mimic any disease involving the aerodigestive tract. This can make it difficult to manage and it may delay the diagnosis. The diagnosis of RRP is made by laryngoscopy or flexible bronchoscopy with biopsy used to confirm the diagnosis. CT can help to show some characteristic features in pulmonary RRP lesions, which reveal single or multiple multilobulated, well-defined, solid nodular or polypoid lesions of various sizes, with a centrilobular distribution, scattered throughout the lungs with a tendency toward confluence.

Management

The goal of RRP management is to eradicate symptomatic lesions, maintain airway patency, improve vocal quality, prevent disease spread, all while preventing secondary complications. RRP is primarily managed with a variety of surgical techniques. There is no known cure for this condition. Surgery can remove the visible warty lesions but it is important to remember that HPV genome remains in normal-appearing tissue and leads to a high rate of recurrence. The current standard of care for RRP is surgical excision for symptomatic lesions.

Surgical Management of RRP

There are multiple modalities used for the surgical excision of papilloma. The objective of surgery is to debulk and remove the papilloma with preservation of surrounding normal structure. Care must be taken to avoid inadvertently damaging surrounding tissue. Aggressive excision of normal tissue can cause scarring, and if it occurs in the anterior commissure, can lead to anterior glottic web formation. There can be permanent dysphonia associated with this. Surgical modalities include use of microdebrider, a variety of lasers, and cold-instrument excision. Choice of modality is surgeon-dependent.

Laser: Laser surgery is one of the newer modalities for treating papilloma. The laser effect depends on the type of laser and tissue to treat. It is a minimally invasive procedure to remove or debulk papilloma. Effects depend on the interaction of a laser light of a specific wavelength with a light-activated photosensitizer. There are different categories of laser used to treat RRP including CO₂, potassium titanylphosphate (KTP) or pulsed dye (PDL) lasers (Table 2). Advantages in using the laser include its hemostatic properties and superior visualization compared to cold instruments or the use of the microdebrider. One of the disadvantages of lasers in RRP is delayed tissue injury which can lead to vocal cord stiffness, dysphonia, formation of anterior or posterior glottic webs, and interarytenoid scarring and/or fixation. The pulsed KTP laser is the most common laser used by laryngologists due to its absorption by oxyhemoglobin. Since it is a fiber-based laser, it can be used both in the operating room via direct laryngoscopy and in office via a nasolaryngoscope. Advantages of in-office procedures (Fig. 2) include avoidance of general anesthesia, less time required to complete the procedure, and less cost. Rees et al. also found that 87% of patients preferred in-office laser procedures to surgery in the operating room when possible. In a study by J Miller et al., four of the 17 patients (23.5%) reported significant anxiety or discomfort during the (in-office) laser procedure.

Microdebrider: The microdebrider is commonly used to remove bulky lesions and can be used in combination with lasers or on its own (Fig. 3). It can help decrease operating time, decrease cost, and also creates less thermal injury in comparison to laser surgery.

Cold instruments: Cold laryngeal microsurgery has largely been supplanted by use of the microdebrider but is used per surgeon preference and can be used in conjunction with the laser, microdebrider, and other adjuvant therapies. When compared to laser surgery, cold instrument surgery has been shown to have an increased complication rate and decrease in postoperative voice quality but this is highly dependent on the surgeon’s skill.

Tracheostomy: Tracheostomy is avoided in RRP patients, if possible, as it creates an iatrogenic squamocolumnar junction which can be a source for the development of papilloma. If a tracheostomy is required for patient safety, early decannulation is recommended.

Table 2: The difference between the laser types used to treated RRP

<table>
<thead>
<tr>
<th>Type of laser</th>
<th>Wavelength</th>
<th>Vaporize</th>
<th>Cut</th>
<th>Coagulate</th>
<th>Absorption characteristics of the Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>10,600 nm</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Watery rich tissue</td>
</tr>
<tr>
<td>KTP</td>
<td>532 nm</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Pigmented tissue (hemoglobin or melanin)</td>
</tr>
<tr>
<td>PDL</td>
<td>577–630 nm</td>
<td>+</td>
<td>-+</td>
<td>+</td>
<td>Pigmented tissue (hemoglobin or melanin)</td>
</tr>
</tbody>
</table>

PDL, pulsed dye laser; KTP, potassium titanyl phosphate; CO₂, carbon dioxide.
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Adjuvant Therapy

Although surgical intervention is the mainstay management for RRP, about 20% of RRP patients require adjuvant therapy. Criteria for initiation of adjuvant therapy include disease requiring more than four surgical procedures per year, rapid regrowth of the lesions with airway compromise, and distal airway spread of the disease. Multiple adjuvant therapies have been used including cidofovir, interferon, bevacizumab, and PD-1 Inhibitor (Table 3).

Cidofovir

Cidofovir is a cytosine nucleotide analog that, in its diphosphate form, blocks the replication of DNA viruses by inhibiting viral DNA polymerase. The primary indication for use of cidofovir is in the management of CMV retinitis in HIV patients. Multiple studies have looked at the optimal concentration to use for intralesional injection and generally, results have been positive. Fusconi et al. found that intralesional injections from 2.5–15 mg have shown to be effective in decreasing the overall number of surgeries. A total of 4–5 injections at 2-week to 6-week intervals is a suggested regimen. Currently, cidofovir is used as an off-label medication per the FDA, and patients have to be made aware of the side effects of this medication. Cidofovir can cause serious side effects including nephrotoxicity, neutropenia, and oncogenicity. An international study on the safety of intralesional use of cidofovir on 635 RRP patients reported no clinical evidence of nephrotoxicity, neutropenia, or laryngeal malignancy after intralesional administration of cidofovir. Coulombeau et al. found that 89% of the adult RRP patients in their study have complete remission at 24 months follow-up, while Lee et al., found only 77% of their patients have complete remission. However, most of these studies are smaller studies without control groups. Recently, there have been some questions regarding carcinogenesis of cidofovir in RRP patients and progressive of dysplasia. Rebecca et al. concluded that no statistically significant differences in the rates of development of dysplasia in their patients group. Another article evaluating the use of adjuvant cidofovir in patients with RRP demonstrated a 5% malignant transformation risk in patients not treated with cidofovir compared with 1% malignant transformation in patients treated with cidofovir. Intralesional injection of cidofovir does not appear to be associated with dysplastic changes.

Interferon

Interferon (IFN) therapy was one of the first systemic therapies used for RRP treatment. Interferons are polypeptides that are released as part of human immune response to viral infection. Although the mechanism of action of interferon on the treatment of RRP is not clearly understood, it has some antiproliferative effect which likely affects lesional growth. Use of interferon is limited, however, due to its multiple side effects when used systemically. These common side effects include fever, headache, arthralgia, leukopenia, and thrombocytopenia. The efficacy of interferon is controversial is has not been well defined in the literature. In one study, Nodarse et al., concluded that 73.1% of their patients treated with adjuvant IFN-alpha-2b had complete or partial response measured by extent of recurrence in comparison to other studies which showed no reduction in papilloma growth. Success can also vary depending on subtype. Szeps et al. found that patients with HPV6 responded more readily to IFN-alpha therapy than those with HPV11 or NPV-negative. Interferon is now rarely used due to intralesional adjuvants such as bevacizumab and cidofovir.

Bevacizumab

Bevacizumab (Avastin) is one of the most recent adjuvant therapies to manage RRP. It is a recombinant monoclonal antibody targeting
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Table 3: Summary of adjuvant therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cidofovir</th>
<th>Interferon</th>
<th>Bevacizumab</th>
<th>PD-1 Inhibitor</th>
<th>Acyclovir</th>
<th>Indole-3-carbonil</th>
<th>Retinoids</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Viral DNA polymerase inhibitor. It blocks the replication of DNA viruses.</td>
<td>Inhibit viral protein synthesis by modulating the host immune response</td>
<td>Vascular endothelial growth factor inhibitor (anti-VEGF)</td>
<td>Programmed death 1 (PD-1) pathway inhibitors. Decrease the papilloma growth</td>
<td>Acyclic purine nucleoside analog. It inhibits DNA viral replication</td>
<td>Plays a role in estrogen metabolism, cytochrome P450 inducer</td>
<td>Vitamin A analog</td>
<td>Synthetic nucleoside. Viral RNA synthesis inhibitor.</td>
</tr>
<tr>
<td>Dose</td>
<td>2.5–15 mg, total of 4–5 injections at 2–week to 6-week intervals</td>
<td>2–5 MU/m², 3 times per week for 6 mo to 1 year.</td>
<td>Intralosal: 12.5 to 25 mg/ml Parenteral: 5–10 mg/kg every 2–4 weeks, for 6–12 months</td>
<td>500–600 mg/daily orally for 5–6 months.</td>
<td>adult dose: 200 mg orally, twice daily.</td>
<td>1 mg/kg/day</td>
<td>23 mg/kg/day for 3–6 months</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Nephrotoxicity, neutropenia, and oncogenicity</td>
<td>fever, headache, arthralgia, leukopenia, and thrombocytopenia</td>
<td>Hypertension and increase of bleeding risk</td>
<td>Nausea, vomiting, fever, chills, seizures, headache.</td>
<td>skin rashes, nausea</td>
<td>Peeling, drying, and cracking of mucocutaneous surfaces</td>
<td>Anemia with reticulocytosis, fatigue, and headache.</td>
<td></td>
</tr>
</tbody>
</table>

the vascular endothelial growth factor (anti-VEGF) that leads to reduce the angiogenesis. Several studies have shown it is safe to inject the Bevacizumab to the vocal cord with promising positive effects on the treatment of papilloma. Bevacizumab is usually used in conjunction with surgical management of RRP in the operating room by intralosal injection of the bevacizumab after removal of the papilloma. The typical dose of Bevacizumab is 12.5–25 mg/ml. Sidell et al. used intralosal bevacizumab in addition to KTP laser removal of papilloma in their juvenile RRP patients which they reported increase in the time between procedures and in some cases there has been a complete response. Also, the zeitels group reported that 95% of their adult RRP patients had better disease control in the bevacizumab/KTP laser treated vocal fold in comparison to the KTP laser only treated vocal fold. Recent study by Tkacuck et al., on Parenteral Bevacizumab use to treat severe adult RRP patients concluded that Intravenous bevacizumab for the primary treatment of severe RRP in adults appears clinically effective and safe. The two common side effects of Bevacizumab are hypertension and increase in bleeding risk. It is recommended to monitor the blood pressure closely during the treatment to manage any hypertension and it is expected that the blood pressure will return to pretreatment values upon discontinuation of bevacizumab.

PD-1 Inhibitor

One of the new and promising treatments of papilloma are the programmed death 1 (PD-1) pathway inhibitors. Programmed cell death protein 1 (PD-1) and its ligand on the T lymphocyte surface play a role in the papillomatous growth and it was found to be highly expressed in HPV related head and neck cancer. Multiple PD-1 inhibitors such as pembrolizumab and avelumab are involved in clinical trials for treatment of adult RRP.

Acyclovir

Acyclovir is an acyclic purine nucleoside analog that is recognized by herpetic thymidine kinase and converted to the active monophosphorylated form with subsequent phosphorylation by cellular enzymes. It targets herpes simplex virus and Epstein-Barr virus which can be concurrent and coinfection of HPV in RRP. The mechanism of action of acyclovir in RRP is not clear, but it is thought to inhibit DNA viral replication. Acyclovir is used systemically, with dosing in literature ranging from 500–600 mg daily for 5–6 months.

Other Adjuvant Therapy

There are other therapies involved in treatment of RRP such as ribavirin, indole-3-carbonil, and retinoic acid. Indole-3-carbonil plays a role in estrogen metabolism which is a cytochrome P450 inducer. It is found in high concentrations in cruciferous vegetables, such as cabbage, broccoli, and cauliflower. In some studies, indole-3-carbonil has been shown to reduce the development of papilloma in HPV-infected laryngeal tissue. Rosen and his group reported that, of the patients who were treated with oral indole-3-carbonil, 33% had no growth in their papilloma and required no more surgeries, 33% had reduced papilloma growth and 33% had no clinical response. Although multiple adjuvant therapies have been described in the RRP literature, the clinical use is not well defined yet.

HPV Vaccine and Prevention

Recently, multiple studies have been evaluating the efficacy of the HPV vaccine to eradicate the disease and decrease the risk of transmission of RRP. The quadrivalent HPV vaccine, Gardasil, has some activity against HPV types 6, 11, 16, 18, and assists in the prevention of cervical and anogenital cancers. In the RRP literature, Young et al. found an increase in the time between surgical intervention about 3.1 months after HPV vaccination in their RRP patients. Additionally, eight patients experienced complete remission and five patients experienced partial remission. In another study, Yiu et al., showed an increase in time interval between surgeries to 9.3 months and 5/14 vaccinated patients. Overall, patients required 1.89 fewer average procedures annually after completing the HPV vaccination series. A systematic
review by Dion and his group found that treating active RRP with quadrivalent HPV vaccine increases time between surgeries and decreases recurrence of papilloma.57 Gardasil 9 is the newer HPV vaccine and protects against diseases caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. It is recommended for individuals ages 9–45 years old and is given in 2 or 3 doses. Despite the encouraging literature on adjuvant HPV vaccination for secondary prevention in RRP, it has not been accepted widely in treating the RRP population.

References