Pediatric Recurrent Respiratory Papillomatosis

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Introduction

Recurrent respiratory papillomatosis (RRP) of the larynx is a direct response to infection by human papilloma virus (HPV) most commonly types 6 and 11. These benign lesions are recurrent in nature and can occur anywhere in the aerodigestive tract, but most commonly at epithelial transition zones such as the pseudostratified columnar and stratified squamous junction at the level of the vocal folds. Presenting symptoms in the pediatric patient can include hoarseness, stridor, recurrent respiratory infections, dysphagia, and respiratory distress. Diagnosis must be made by tissue biopsy. Risk factors include being the first born child, active maternal genital warts during vaginal delivery, and being born to a mother under 20 years of age. The average age at diagnosis in the pediatric population is 3.8 years. An earlier age of presentation is associated with more aggressive disease[1]. Pathogenesis is thought due to infection of mucosal basal layer stem cells and subsequent viral inactivation of host cell tumor-suppressor genes leading to cellular proliferation. Theories of viral activation by immune dysregulation have gained favor, as many HPV carriers remain disease-free their entire lives. There is no cure for this condition; instead patients are symptomatically managed by periodic surgical treatment. Often patients with RRP undergo 50-100 surgeries in their lifetime. More aggressive resection has not been demonstrated to improve long term disease control, duration between recurrences, or functional outcomes. The Derkay staging system quantifies anatomic RRP burden and is positively correlated with Voice Handicap Index-10 (VHI-10) in the adult population [2]. Documenting the Derkay stage is useful for recording extent of disease and may be a useful surrogate for voice-related quality of life.

Surgical management

A key management principle of pediatric RRP is the maintenance of a patent airway without requiring a tracheostomy, because the creation of a new epithelial transition site in the airway and the occurrence of RRP at the tracheostoma results in a significant increase in complexity and care for the patient. Pediatric patients are at higher risk of extralaryngeal spread of RRP than adults [3]. The rate of malignant transformation into squamous cell carcinoma is low, therefore surgery emphasizes preservation of normal anatomy to optimize voice and swallow function and minimization of postoperative complications such as vocal fold scar, glottic web, or airway stenosis.

Historically the carbon dioxide (CO2) laser is favored over cold instruments in RRP for the benefits of precision and hemostasis. It vaporizes tissue by delivering energy into intracellular water in a focused, controlled manner under microlaryngoscopy. Drawbacks include risk of airway fire and safety of operating room

personnel exposed to the laser smoke "plume" that has been found to contain viral DNA. The potassium-titanyl-phosphate (KTP) laser delivers energy at 532nm wavelength, specific for oxyhemoglobin. It induces vascular coagulation while avoiding damage to the superficial lamina propria. Additionally its thinner fiber (0.3mm) can be used through the working channel of the flexible bronchoscope allowing treatment in sedation units. The pulse-dye laser (PDL) works at a 585nm wavelength, specific for blood. It induces microvascular coagulation while preserving overlying tissues, and its advantages are maximized in sessile papillomata and areas with previous scarring.

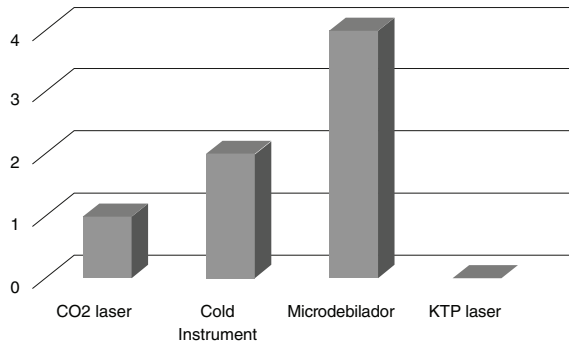

Figure 1. Preferred surgical instruments of Pediatric otolaryngologists (n=59) managing RRP. Each surgical instrument used for papilloma debridement was ranked from "Not used" (0) to "Used the most" (4). Median values are shown. KTP = potassium titanyl phosphate.

From: Derkay CS, Volsky PG, Rosen CA, Pransky SM, McMurray JS, Chadha NK, Froehlich P. Current use of intralesional cidofovir for recurrent respiratory papillomatosis. Laryngoscope. 2013 Mar;123(3):705-12.

A recent survey of ASPO members (**Figure 1**) found that a majority of pediatric otolaryngologists prefer the endoscopic microdebrider as opposed to the KTP laser for children, whereas the KTP laser is more popular for laryngologists treating the adult RRP patient. Pasquale *et al* performed a small randomized study showing improved voice, shorter OR time, less mucosal injury, and cost benefit of the microdebrider versus the CO2 laser [4]. It is recommended to hold the microdebrider blade 1-2mm over the RRP and allow suction from the wand to draw papillomata into the blade to minimize injury to adjacent normal structures. Bilateral lesions of the anterior commissure may be treated in staged fashion to minimize scar formation from apposition of raw surfaces.

Cold knife techniques may be advisable for lesions on the true vocal folds where risk of inadvertent heat transfer with a laser or overzealous tissue removal with a microdebrider would be unacceptable. If performing a microflap, the incision should be adjacent to interface of RRP and normal mucosa. Lesions of the true vocal folds may be grasped with microforceps and avulsed cephalad or caudad to minimize stripping of normal cord mucosa. Angled telescopes can help to visualize RRP intraoperatively.

Adjuvant modalities

Although surgery is the standard of care for RRP, 20% of patients with disease will require adjuvant therapy. The widely accepted criteria for "severe RRP" necessitating adjuvant treatment are:

1. four or more procedures per year
2. Spread of disease to distal sites
3. Rapid regrowth with airway compromise

Interferon is a historic initial adjuvant therapy for RRP. These proteins modulate the host immune response encoding endonucleases that cleave viral DNA and inhibit viral replication. Interferons are associated with significant side effects including febrile seizures, nausea, vomiting, thrombocytopenia, hepatotoxicity, spastic diplegia, rash, alopecia, and pruritis. A multicenter randomized trial from 1988 enrolled 169 patients (85 children) in a 2 year single arm trial found that 73% concluded without lesions but 77% with relapse [5]. Over the past 10 years, the usage of interferon has declined from 10% of RRP children to less than 4% in light of newer therapies with much better toxicity profiles [6].

Cidofovir is a nucleoside analogue that incorporates into viral DNA and inhibits Herpes viridae replication. It currently has FDA approval for treatment of HIV patients with CMV infection. Over the past 10 years, numerous reports of cidofovir intralesional injection in RRP have stimulated interest in its off-label use as an effective adjuvant therapy. It is now the most commonly used adjuvant drug for RRP. A systematic review of 158 patients receiving intralesional cidofovir across 17 case series in 2007 showed 57% complete resolution, 35% partial response, 8% no improvement [7]. Multiple other studies show similarly promising results, however there is tremendous variability in the literature with respect to treatment dose, frequency, and interval. In our experience injection of cidofovir at 5mg/ml in 1-3mL aliquots with a fine-gauge needle into the subepithelial plane at the base of the lesions at the same time as staged surgical excision achieves best RRP control. Serial injections can be done up to 5 times biweekly. Successful treatment of severe RRP with pulmonary spread in pediatric patients has also been reported with inhaled and systemic cidofovir [8]. Cidofovir has been associated with dysplasia and malignant transformation. Gilead issued an FDA-mandated warning in their 2003 PDR after rodents receiving intravenous cidofovir developed solid tumors after 19 weeks of once weekly injections, although these were at levels 0.04 times the human systemic exposure at the recommended intralesional dose [9]. A recent meta-analysis showed dysplasia in 2.7% of patients receiving intralesional injection compared to the 2.3% spontaneous transformation rate in the natural progression of RRP [10]. These results are corroborated in a retrospective review of pediatric biopsy specimens [11]. A survey of 82 ORL surgeons who collectively manage 3043 RRP patients resulted in approval of 18 consensus statements by the ASPO-sponsored RRP Task Force recommending: (1) intralesional cidofovir as a viable treatment option for patients with moderate-severe disease not improving with frequent (every 2-3 months) surgery in conjunction with less morbid adjuvant therapy. (2) recommendation against cidofovir for patients with mild disease, until a better understanding of the long term side effect profile is achieved. (3) informed consent and patient counseling regarding unknown status of long term adverse effects of therapy to include carcinogenic and nephrotoxic potential of this drug. (4) close monitoring of adverse events and any evidence of malignant transformation for patients receiving cidofovir therapy for RRP must be reported to the FDA and the RRP task force.

Indole-3-Carbinol (I3C) is a nutritional supplement available over the counter that is found naturally in broccoli, cabbage, and cauliflower. I3C is thought to inhibit HPV proliferation by inhibiting estrogen, which has been shown to increase HPV gene expression [12]. Studies have shown reduced formation of HPV-induced tumors in immunocompromised mice treated with I3C by 75%. A prospective study in 2003 of adult and pediatric patients with RRP showed partial or better response in 70% of the patients treated with I3C, although the children did not respond as well as the adult [13]. Although I3C is well tolerated with minimal side effects, there are no well controlled large scale studies to show benefit.

Acid exposure related to reflux is known to cause inflammatory changes of the aerodigestive mucosa. It is unclear what role this local inflammation has on HPV virulence. A small case series demonstrated improved control of RRP with H2 antihistamines such as cimetidine [14]. In our experience, optimal control of reflux is a useful adjunct with excellent benefit/risk ratio for the pediatric RRP patient.

Intralesional bevacizumab (Avastin) is a monoclonal murine antibody against VEGF that impairs angiogenesis. It is FDA approved for metastatic colorectal cancer and is also widely used with success for advanced non-squamous non-small cell lung cancer, metastatic renal cell carcinoma, and glioblastoma multiforme. Recent investigational usage of this medication has shown efficacy as an intralesional adjuvant therapy in severe pediatric RRP. A prospective study to assess safety of high dose bevacizumab in 43 patients showed relative safety and tolerability in adults [15]. A case series of 3 children with severe RRP who underwent surgical debridement, KTP laser, and 1.25mg intralesional bevacizumab showed significant improvement in Derkay score and increased time between operative interventions [16]. Another series of 10 children with severe RRP undergoing 3 consecutive injections of bevacizumab at 2.5mg/mL at 2-3 week intervals showed increased median duration of time between surgeries by 5.9 weeks, number of procedures per year decreased by 4, Derkay staging decreased by 6, and significant improvement of Pediatric Voice-Related Quality of Life (PVRQOL) score in the year after bevacizumab treatment compared to the year prior [17]. Intralesional bevacizumab is an exciting new adjuvant therapy for severe RRP that is well tolerated and shows promise. Further studies are needed to assess for non-superiority over more widely utilized intralesional injections such as cidofovir. Recent case series have demonstrated efficacy and suggest a potential role for systemic bevacizumab for severe disseminated RRP or endoscopically inaccessible lesions. A case series of 5 consecutive patients with severe disease with extralaryngeal papillomas (lung and paranasal sinuses) who received IV bevacizumab showed immediate and sustained regression of papilloma in all five patients [18]. Notably, the number of interventions dropped from 18 to 1 in the year after treatment compared to the year prior. Although 3 patients showed disease progression after discontinuation of treatment, none of the patients showed progression of disease while therapy was ongoing. Further investigation for the role of intralesional and IV bevacizumab is needed in clinical trials.

The Gardasil quadrivalent HPV vaccine (Merck Co.) is United States FDA approved and indicated for prevention of HPV 6, 11, 16, and 18 associated vaginal and cervical dysplasia/carcinoma in girls 9-26 years of age. The Phase 3 FUTURE

I and FUTURE II trial data suggests the vaccine may be most effective if given to individuals prior to becoming sexual active5. The United States CDC has recommended that all males and females age 11 to 12 be vaccinated. A case series of eleven patients aged 13-46 with aggressive RRP who received 3 doses of quadrivalent HPV vaccine were followed for 12-52 months. The average number of surgeries decreased from 2.16 to 0.93 from the year prior to the year after vaccination. One patient showed complete remission of disease. Seven patients had partial response and three had no response [19]. Although there is currently no therapeutic role for Gardasil in patients with RRP, widespread use of the quadrivalent vaccine in the developed world may theoretically reduce RRP vertical transmission and incidence of HPV-associated cancers of the head and neck. Larger studies with longer follow-up are needed to determine the role of HPV vaccination in the prevention and treatment of RRP.

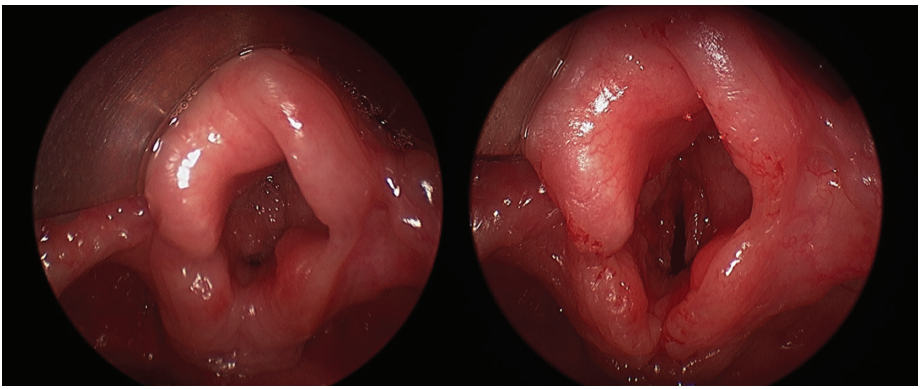

Figure 2. 4 month old child pre and post microdebridement of papillomata

Conclusion

Pediatric recurrent respiratory papillomatosis is a rare and aggressive disease. There is no cure, but surgery continues to play a crucial role in treatment and maintenance of a patent, functional airway (**Figure 2**). Emerging adjuvant therapies have expanded the armamentarium and show potential to improve disease burden and frequency of surgery in severe cases of RRP. Until larger clinical trials are available, we recommend careful patient selection and critical review of the investigational data to support the usage of these modalities.

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