Current diagnostic and management trends for recurrent respiratory papillomatosis

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Purpose of review

The purpose of this review is to discuss recent literature regarding diagnostic and management trends for recurrent respiratory papillomatosis (RRP) published within the past year. This includes a discussion of new information regarding the epidemiology and pathogenesis of RRP and an update on adjuvant therapy and new surgical techniques.

Recent findings

Epidemiological studies have confirmed that juvenile-onset RRP is the most common and most aggressive form of the disease. Age at diagnosis is the most important determinant of disease severity, with younger patients requiring significantly more annual surgeries and more likely to have multicentric disease. Distal tracheal or pulmonary RRP is rare, but carries a significant increase in morbidity and mortality. Research into the pathogenesis of RRP has focused on the genetics of HPV infection and host-virus interactions, suggesting a genetic basis for host susceptibility to RRP. At the present time, surgery remains the mainstay of treatment for RRP. However, recurrence after surgery is common and the search for effective adjuvant therapies is ongoing. The antiviral drug cidofovir has demonstrated efficacy against RRP and is considered a promising new adjuvant treatment of this disease. In an attempt to minimize the untoward effects of surgery, the pulsed-dye laser (PDL) has emerged as a safe and efficacious treatment for select patients with RRP.

Summary

While a cure for RRP remains elusive, there has been substantial progress in the diagnosis and management of this disease. Significant advances in clinical and basic science research have dramatically improved our understanding of the epidemiology and pathogenesis of the disease and led to the development of promising new adjuvant therapies and surgical techniques. This has translated to an improved quality of life for many patients with RRP.

Keywords

recurrent respiratory papillomatosis, human papilloma virus, larynx, trachea, cidofovir, pulsed-dye laser

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Introduction

Recurrent respiratory papillomatosis (RRP) is a disease of viral origin characterized by multiple, exophytic lesions of the aerodigestive tract in both children and adults. Although benign, these lesions are a source of significant morbidity due to their location within the upper and lower airway, the frequency with which they recur despite aggressive medical and surgical treatment, and the potential for malignant degeneration over time [1••]. The clinical course of RRP is unpredictable. Spontaneous remission is occasionally seen in some patients, while others have aggressive lesions requiring multiple surgical procedures over a period of many years. Unfortunately, recurrence after surgery is common and morbidity remains high for a large percentage of patients with RRP. As a result, this disease continues to pose a difficult challenge for the treating otolaryngologist. In the present review, we discuss recent advances in the diagnosis and management of RRP. This includes a discussion of new information regarding the epidemiology and pathogenesis of the disease and an update on adjuvant medical therapy and new surgical techniques.

Epidemiology

The onset of RRP may occur during either childhood or adulthood, with a bimodal age-distribution demonstrating the first peak in children younger than 5 years of age and the second peak in patients between 20 and 30 years of age. The juvenile-onset form of RRP is most common, with 25% of cases presenting during infancy [1••]. Juvenile-onset RRP is also considered the most aggressive form of the disease. Children whose RRP is diagnosed at younger ages (< 3 years old) have been found to be 3.6 times more likely to have more than four surgeries per year and almost two times more likely to have multiple anatomic sites affected than children whose RRP is diagnosed at later ages (> 3 years old) [2]. As a result, much of the recent literature describing the epidemiology of RRP has focused on the pediatric population.

An estimated 2000 to 2500 new cases of pediatric papillomatosis occur each year and approximately 6000 children in the United States are treated annually for this disease [3]. Reeves *et al.* [4••] recently reviewed data collected from the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis over the past 5 years and confirmed that young age is the most important determinant of disease severity. In this large series of 603 children with a mean follow-up of 4.9 years, patients diagnosed before 4 years of age required significantly more annual surgeries and were more likely to have multicentric disease than those diagnosed at an older age. Furthermore, children with progressive disease were diagnosed at a significantly younger age than those with stable or remitting disease. No differences in disease severity or progression were observed when analyzed according to gender, ethnicity, or socioeconomic status [4••].

These findings are consistent with a subsequent study by Ruparelia *et al.* [5•], which focused on predictors of remission in juvenile-onset RRP. In this analysis of 165 affected children, younger children were more likely to have persistent disease and required more frequent surgical procedures in the first year after diagnosis. Disease remission, defined as the absence of surgical intervention for at least 1 year, was seen in 21.8% of patients. Older age at diagnosis was positively associated with remission, with the hazards of remission increased by 1.13 for every 1 year in age at the time of diagnosis [5•].

Extralaryngeal spread of RRP to the lower airway is relatively uncommon, but is associated with increased morbidity and potential mortality. Distal tracheal or pulmonary lesions have been reported in approximately 5% and 1% of RRP patients, respectively [6,7]. This is consistent with a recently published series of 90 pediatric RRP patients treated over a 22-year period by Zawadzka-Glos *et al.* [8•], in which they identified lower airway papillomatosis in 4.4% of the study population. However, a recent study by Silver *et al.* [9••] suggests that the incidence may be higher. In their cohort of 106 adult and pediatric RRP patients from three tertiary care centers, the reported incidence of distal tracheal and pulmonary involvement was 12% and 7%, respectively. In both studies, clinical outcome was poor, with patients dying of chronic respiratory insufficiency or malignant transformation to squamous cell carcinoma within 10 years of the diagnosis of pulmonary RRP [8•,9••].

The onset of pulmonary involvement is typically heralded by a history of recurrent pneumonia or bronchiectasis and findings of cysts or nodules on chest radiographs or CT scans [8•]. Once a diagnosis of pulmonary RRP has been confirmed, adjuvant chemotherapy with methotrexate, interferon, and isoretinoin has been advocated in an attempt to slow disease progression. More aggressive chemotherapy regimens, surgical resection of isolated parenchymal lesions, and external beam radiation therapy are generally reserved for rapidly expanding pulmonary lesions with malignant conversion confirmed by transbronchial or transthoracic biopsy. Unfortunately, the development of pulmonary RRP is almost always fatal despite aggressive medical and surgical intervention [9••].

Pathogenesis

Recurrent respiratory papillomatosis is a disease of viral origin caused by the human papilloma virus (HPV). Of the more than 100 HPV subtypes characterized to date, viral subtypes 6 and 11 account for the vast majority of cases. HPV subtypes 16 and 18 have also been demonstrated in respiratory papillomas, but are much less common [10•]. Previous studies have suggested that viral subtype plays an important role in determining the clinical course of RRP, with HPV subtype 11 associated with more aggressive disease and HPV subtypes 16 and 18 demonstrating a higher rate of malignant transformation [1••,2]. However, viral subtype alone is not a reliable predictor of disease severity or response to treatment, and the biologic mechanisms responsible for the variable behavior of RRP remain poorly understood [11•,12].

One approach to improving our understanding of the pathogenesis of RRP has been to search for molecular or genetic markers predictive of aggressive disease. In a recent study by Pou *et al.* [10•], genetic polymorphisms within the upper regulatory region (URR) and E6/E7 coding regions of both HPV-6 and HPV-11 DNA were identified. While the polymorphisms that occurred in the E6/E7 coding regions were silent mutations or favored substitutions that likely do not affect phenotypic expression, the sequence variations in the URR suggest that there may be expressional changes in the E6/E7 regions that could affect the clinical course of the disease [10•]. This is consistent with a recent study by Abramson *et al.* [13•] that implicates E6 and E7 transcriptions products in the activation of latent HPV in patients with laryngeal and tracheal RRP.

Another approach to elucidating the pathogenesis of RRP has been to determine the genetic basis for host susceptibility to HPV. In a multicenter initiative seeking critical genes in RRP, Buchinsky *et al.* [11•] identified numerous candidate host genes that may confer susceptibility to RRP by modulating the immune response. This includes genes comprising the major histocompatibility complex (MHC), cytokines, interleukins, growth factors, and genes whose products are known to interact with HPV-encoded proteins. Gregoire *et al.* [12] have implicated genes from the HLA system (HLA-D$Q\alpha$ and HLA-D$Q\beta1$) in the pathogenesis of juvenile-onset RRP, with some alleles demonstrating a protective effect and others associated with a high risk for disease. Vambutas

et al. [14•] have shown that a polymorphism in TAP1 (transporter associated with antigen presentation 1) is associated with increased severity of HPV infection in patients with RRP.

These avenues of investigation have improved our understanding of the genetics of HPV infection and the host-virus interactions that underlie the pathogenesis of RRP. Substantial progress has also been made in establishing a reliable animal model for RRP. Whereas the utility of previous animal models was limited by a high rate of spontaneous disease regression, Jahan-Parwar *et al.* [15•] recently reported their success with a canine oral papillomavirus (COPV) model using experimentally induced oral and laryngeal papilloma in which natural regression was delayed using steroid immunosuppression with systemic prednisone. The result is a sustainable animal model that may prove useful in the study of both established and emerging treatments for RRP.

Adjuvant medical therapy

At the present time, surgery is considered the mainstay of treatment for laryngeal and tracheal RRP. Unfortunately, recurrence after surgery is common and morbidity remains high for a large percentage of patients. As a result, the search for effective adjuvant therapies is critical to improving our ability to manage this recalcitrant disease. While numerous adjuvant medical therapies have shown promise in the past, none have demonstrated a lasting or curative effect and many have unfavorable side effects or toxicity profiles. These include interferon-α2a, retinoic acid, indole-3-carbinol, and photodynamic therapy with dihematoporphyrin (DHE) [1••,2,16]. More recently, the antiviral drug cidofovir has demonstrated efficacy against RRP and is considered a promising new adjuvant in the management of this disease.

Cidofovir is an acyclic nucleoside phosphonate that has antiviral activity against a wide range of DNA viruses, including HPV. It exerts its effect through selective inhibition of viral DNA polymerases during viral replication. Cidofovir has been approved by the FDA for treatment of cytomegalovirus (CMV) retinitis in HIV patients at an intravenous dose of 5 mg/kg. When used intravenously at this dose, cidofovir can cause nephrotoxicity and neutropenia. However, recent studies suggest that these side effects are limited to intravenous use, with no evidence of renal, hepatic, or hematologic toxicity when injected into papillomatous lesions of the larynx or trachea [17••,18•,19•]. This is consistent with previous work by Snoeck *et al.* [20], which demonstrated minimal or nondetectable serum concentrations of cidofovir after intralesional injection.

The possibility of local toxicity or tissue changes in response to intralesional cidofovir prompted a study by Chhetri *et al.* [21••], in which various concentrations of cidofovir were injected into canine larynges biweekly for 6 months. Findings of irreversible thyroarytenoid muscle atrophy, necrosis, and fibrosis were limited to concentrations of 40 mg/ml or higher. No distinct changes were noted on H and E stain of the epithelium or superficial lamina propria regardless of concentration [21••]. Initial concerns that cidofovir may have carcinogenic effects when injected locally have also been resolved, with no evidence of tumorigenicity in primate studies and no reports of patients developing laryngeal carcinomas after the use of intralesional cidofovir [22].

Having established the safety of intralesional cidofovir therapy, most recent articles in the literature have focused on the efficacy of cidofovir in the management of RRP. Pransky *et al.* [17••] reported positive results with cidofovir in children with severe RRP and have the longest follow-up period of any series to date (51.6 months). They used a treatment protocol of four initial injections (in conjunction with surgical debulking) at a concentration of 5 mg/ml in 2- to 4-week intervals, followed by subsequent injections as dictated by recurrent disease. Prior to initiation of cidofovir injections, patients required operations every 2 to 6 weeks. After completing treatment with cidofovir, 5 of 11 patients were free of disease and 5 patients had mild disease. One patient had recalcitrant disease and continued to require frequent intervention [17••].

Akst *et al.* [23•] reported a similar decrease in disease burden following monthly injections and debulking, although the response was not as dramatic, with 5 of 11 patients requiring an additional four injections at a stepped-up dose of 10 mg/ml with mixed results. The optimal concentration of cidofovir remains unclear. Most authors continue to recommend 5 mg/ml, with higher concentrations of 7.5 to 10 mg/ml reserved for refractory disease [24]. However, these recommendations are based on FDA guidelines for intravenous cidofovir in HIV patients with CMV retinitis, and their application to intralesional injections for RRP is somewhat arbitrary. In contrast, the half-life of cidofovir (17 to 65 hours) has been established and should be considered when determining the optimal interval between injections [25]. Several recent studies have found that if the initial series of injections were more than 4 weeks apart, the therapeutic response was not as favorable [18•,19•,26•].

Cidofovir has been the focus of numerous articles in the contemporary RRP literature, and significant advancements have been made. However, the relatively small number of patients in these studies and the varying inclusion criteria, age groups, and injection regimens (with or without surgery) make it difficult to clearly define the role for cidofovir in the management of RRP. The lack of controlled, randomized clinical trials is also a source of

concern and further studies are necessary before an optimal cidofovir treatment protocol for RRP can be established. There is, however, sufficient evidence to support the efficacy of cidofovir as an adjuvant therapy, with the potential for disease remission when used in conjunction with surgery.

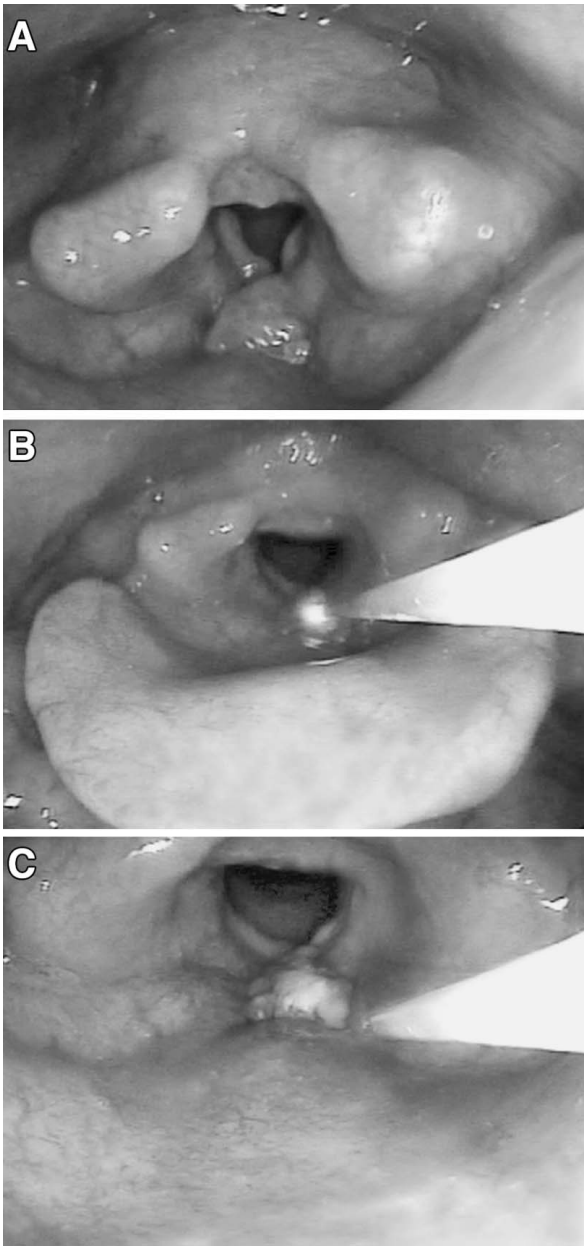
Advances in surgical management

Despite advances in medical therapy, surgery remains the primary treatment modality for RRP. The goal of surgery is removal of as much disease as possible without damaging the adjacent or underlying tissue, which can lead to scarring, stenosis, and loss of function [2]. In an attempt to minimize the untoward effects of surgery, various techniques and instrumentation have been described. These include endoscopic debulking with laryngeal forceps or microdebriders, excision with cold phonomicrosurgical instruments, and a combination of excision and ablation with the CO_2 laser [24]. While there are advocates of each technique, the CO_2 laser and the laryngeal microdebrider are currently the most widely used [1••].

More recently, the pulsed-dye laser (PDL) has emerged as a safe and efficacious treatment for select patients with RRP. Papillomatous lesions are particularly well suited for this technique due to their abundant microvasculature, which is preferentially targeted by the 585-nm PDL. Laser energy at this wavelength passes through the surface epithelium and is absorbed by the chromophore oxyhemoglobin. The result is selective destruction of the subepithelial microvasculature and ischemia of the diseased epithelium with minimal thermal damage to adjacent tissues. The PDL also has the advantage of delivery via a transnasal flexible esophagoscope, which can be performed in the outpatient clinic using topical nasal and laryngopharyngeal anesthesia (Fig. 1) [27•].

There have been several recent studies using the PDL laser for glottal RRP. In 2001, Valdez *et al.* [28] demonstrated complete resolution of vocal fold papillomas 1 month after PDL treatment in 7 of 10 patients. Two patients had partial regression, and 1 patient was lost to follow-up. There was no evidence of soft tissue complications and all patients had subjective improvement in voice after treatment [28]. In 2002, Franco *et al.* [29] performed a study of 41 adult cases of glottal RRP treated with the PDL. Involution of disease without anterior commissure web formation was observed in 26 of 41 cases (including 20 cases with involvement of the anterior commissure) treated for bilateral disease without microflap excision. The PDL was less effective in the management of exophytic lesions due to its limited depth of penetration (2 mm), and these lesions required a combination of PDL therapy and cold instrument microflap resection [29].

Figure 1. Pulsed-dye laser in the treatment of laryngeal recurrent respiratory papillomatosis



(**A**) Endoscopic view of laryngeal RRP involving the anterior glottis with extension to the false vocal folds and petiole of the epiglottis. (**B**) The laser fiber is advanced through the working channel of a transnasal flexible esophagoscope and lasing commences at a distance of 2 mm from the surface of the lesion. (**C**) Selective absorption of laser energy by the underlying microvasculature causes ischemia of the diseased epithelium with visible blanching of the papilloma following pulsed-dye laser treatment. (Photos courtesy of Dr. Gregory N. Postma at the Center for Voice Disorders, Wake Forest University, Winston-Salem, NC). Modified from [27•].

More recently, Zeitels *et al.* [30••] published their results of office-based treatment of glottal dysplasia and papillomatosis with the 585-nm PDL. In this prospective analysis of 30 cases of recurrent glottal papillomatosis and 50 cases of glottal dysplasia, there was at least a 50% disease involution in 88% of cases and a 25 to 50% dis-

ease regression in the remaining 12%. Patient self-assessment of voice after treatment revealed that 44% were improved, 51% were unchanged, 5% were slightly worse, and none were substantially worse [30••]. These results support the conclusion that diseased laryngeal mucosa can be normalized using the PDL without tissue resection or substantial loss of vocal function, the implications of which suggest that the PDL will likely assume an important role in the management of RRP.

Conclusion

While a cure for RRP remains elusive, there has been substantial progress in the diagnosis and management of this disease. Significant advances in clinical and basic science research have dramatically improved our understanding of the epidemiology and pathogenesis of the disease and led to the development of promising new adjuvant therapies and surgical techniques. This has translated to an improved quality of life for many patients with RRP. However, morbidity remains high for a large percentage of patients, and these advances should be viewed with cautious optimism. As a result, RRP will likely remain an area of active investigation in the otolaryngology literature as we continue to be the challenged by this difficult disease.

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