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Contemporary Review

Recurrent Respiratory Papillomatosis: A Review

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Recurrent respiratory papillomatosis (RRP), which is caused by human papillomavirus types 6 and 11, is the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness. After changes in voice, stridor is the second most common symptom, first inspiratory and then biphasic. Less common presenting symptoms include chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with an upper respiratory tract infection. Differential diagnoses include asthma, croup, allergies, vocal nodules, or bronchitis. Reports estimate the incidence of RRP in the United States at 4.3 per 100,000 children and 1.8 per 100,000 adults. Infection in children has been associated with vertical transmission during vaginal delivery from an infected mother. Younger age at diagnosis is associated with more aggressive disease and the need for more frequent surgical procedures to decrease the airway burden. When surgical therapy is needed more frequently than four times in 12 months or there is evidence of RRP outside the larynx, adjuvant medical therapy should be considered. Adjuvant therapies that have been investigated include dietary supplements, control of extra-esophageal reflux disease, potent antiviral and chemotherapeutic agents, and photodynamic therapies; although several have shown promise, none to date has "cured" RRP, and some may have serious side effects. Because RRP, although histologicallybenign, is so difficult to control and can cause severe morbidity and death, better therapies are needed. The potential for a quadrivalent human papilloma vaccine is being explored to reduce the incidence of this disease.

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INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a chronic disease of viral etiology that occurs in both children and adults. Many treatments have been tried, both medical and surgical, but there is no known cure. Although it is benign, RRP tends to take a more aggressive clinical course in children and can be fatal because of its tendency to recur and spread throughout the respiratory tract.

Initiatives to better understand RRP have been launched in the United States through coordination between the Centers for Disease Control and Prevention (CDC) and the American Society of Pediatric Otolaryngology (ASPO) and internationally through the British Association of Pediatric Otolaryngology and Canadian pediatric otolaryngology physicians. This paper reviews current knowledge about RRP and its management, particularly in children.

EPIDEMIOLOGY

RRP is caused by human papillomavirus (HPV) types 6 and 11 and is characterized by the proliferation of benign squamous papillomas within the aerodigestive tract.[1–3] RRP is the most common benign neoplasm of the larynx among children and the second most frequent cause of childhood hoarseness.[4]

Although it is a benign disease that usually involves the larynx, RRP has an unpredictable clinical course, tends to recur and spread throughout the aerodigestive tract, and can undergo malignant conversion.[5] In addition, it puts a heavy emotional burden onto patients and families when repeated surgeries are needed,[6] and its economic cost is high, estimated at $150 million annually.[7]

RRP may have its onset during childhood or adulthood; the youngest patient in one series was 1 day old and the oldest 84 years.[7] Two forms of RRP are generally recognized:

a more aggressive form that typically occurs in children and a less aggressive form that typically occurs in adults.

Although aggressive RRP can occur in adults, younger age at diagnosis is associated with more aggressive disease. Presentation in the neonatal period poses higher risk for tracheotomy and attendant morbidity and mortality,[8,9] and death of a patient with RRP is usually caused by complications of frequent surgical procedures or respiratory failure because of distal disease progression. Diagnosis before versus after 3 years of age is associated with 3.6 times greater likelihood of needing more than four surgical procedures per year and almost 2 times greater likelihood of having two or more anatomic sites affected.[7] Similarly, children with disease progression are generally diagnosed at younger ages than those who remain stable or become disease free.[10] In 75% of children with RRP, the diagnosis was made before the child's fifth birthday.[11]

The true incidence and prevalence of RRP are uncertain. It is estimated that between 80 and 1,500 new cases of childhood-onset RRP occur in the United States each year.[7,12] The incidence in the United States is estimated at 4.3 per 100,000 children and 1.8 per 100,000 adults.[7,13] These figures are comparable with those found in a Danish survey (3.62 per 100,000 children and 3.94 per 100,000 adults).[14] According to the National Registry of Children with RRP, which includes patients of 22 pediatric otolaryngology practices, children with RRP undergo an average of 19.7 procedures or an average of 4.4 procedures per year,[7,13] equivalent to more than 10,000 surgical procedures annually for children with RRP in the United States.

VIROLOGY

HPV belongs to the Papovaviridae family. It is a small, icosahedral (20-sided), capsid virus without an envelope. The double-stranded circular DNA molecule of 7,900 base-pairs is an epitheliotropic virus (infects epithelial cells).

Nearly 110 different HPV types have been identified and grouped on the basis of genetic code homology. The groupings correlate with pathophysiology and preference for tissue.[15] Other species-specific HPV types include bovine, canine, and murine papillomavirus, and these HPV types also exhibit specificity for epithelial tissues of different sites (e.g., oral mucosa, genital mucosa, or skin).

In the 1990s, HPV was confirmed as the causative agent in RRP. With the advent of molecular probes, HPV DNA has been identified in virtually every papilloma lesion studied. The most common types identified in the airway are HPV 6 and HPV 11, the same types responsible for more than 90% of genital condylomata. Specific viral subtypes may be correlated with disease severity and clinical course. Children infected with HPV 11 appear to be at higher risk of obstructive airway disease and have a greater likelihood of needing a tracheotomy to maintain a safe airway.[10,16–20]

Two other major groups of HPV are associated with mucosal lesions. The group that contains HPV 16 and HPV 18 is associated with malignancies in the genital and aerodigestive tracts,[15] and the group that contains HPV 31 and HPV 33 exhibits malignant potential that lies between that of the group with HPV types 6 and 11 and that with types 16 and 18.[21]

HPV is thought to infect stem cells within the basal layer of mucosa.[22,23] After infecting the stem cells, the viral DNA can be actively expressed or it can remain latent, with mucosa appearing clinically and histologically normal. To produce viral proteins or to replicate the virus, the viral DNA reactivates the host replication genes. The viral genome consists of three regions: an upstream regulatory region and the two regions named according to the phase of infection in which they are expressed: early (E) and late (L) regions. The E-region genes are involved in the replication of the viral genome, interacting with the host cells, and transforming activities; they may also serve as oncogenes, depending on the HPV type. The L-region genes encode the viral structural proteins.[24]

How HPV induces cellular proliferation is unclear. Several of the viral E-region gene products bind and inactivate certain cellular tumor-suppressor proteins,[24,25] and HPV can activate the epidermal growth factor (EGF) receptor pathway, known to be associated with proliferation of epithelial cells.[26] Histologically, proliferation of HPV in the mucosa results in multiple "fronds" or finger-like projections with a central fibrovascular core covered by stratified squamous epithelium (Fig. 1).[22]

When papillomas are microscopic and spread, they give the mucosa a velvety appearance, and when macroscopic or exophytic, they appear as "cauliflower" projections (Fig. 2). These lesions may be sessile or pedunculated and typically appear pinkish to white. Ciliated epithelium undergoes squamous metaplasia when exposed to repeated trauma and is replaced with nonciliated epithelium, which may explain why RRP flourishes in patients with uncontrolled gastroesophageal reflux.[27]

RRP delays maturation of epithelium, resulting in significant thickening of the basal cell layer and nucleated cells in the superficial layers.[23] This is thought to be in part because of the interaction of HPV gene products with the EGF receptor pathway.[26] Although HPV-infected cells do not rapidly divide, there is a disproportionate increase in the number of dividing basal cells. Thus, expansion of

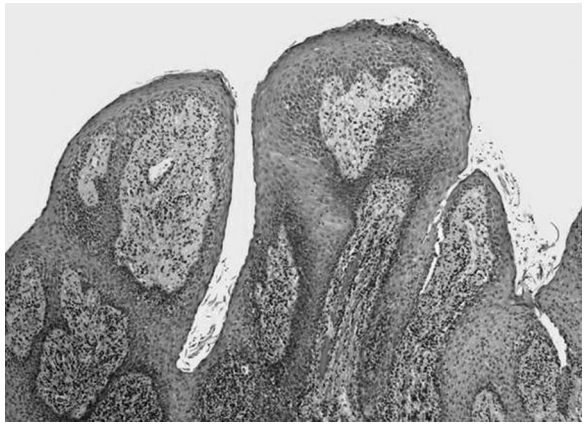

Fig. 1. Histopathology of laryngeal squamous papilloma demonstrating polypoid growth and small fibrovascular core containing few lymphocytes (hematoxylin-eosin; magnification, ×33).

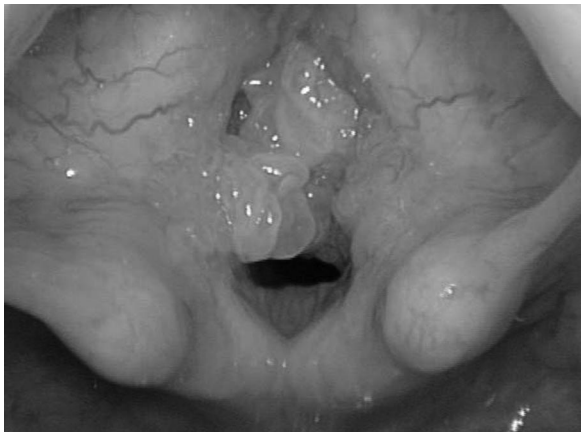

Fig. 2. Gross appearance of respiratory papillomas during laryngoscopy. Near-complete airway obstruction from glottic level papillomas.

the RRP tissue mass may occur very rapidly because of the large number of dividing cells.[5]

During viral latency, very little viral RNA is expressed. Nevertheless, HPV DNA can be detected in normal-appearing mucosa in patients with RRP that has been in remission for years, and unknown stimuli can result in reactivation and clinical recurrence.[28,29]

It is likely that the host immune system plays an important role in the pathogenesis of HPV-induced lesions. Both the humoral and the cellular immune responses may be compromised in children with RRP, and the patient's immunocompetence may be associated with the clinical course of the disease. The role of cytokines, such as interleukin-2, interleukin-4, and interleukin-10, and expression of the major histocompatibility complex antigens in the dysfunction of the cell-mediated immune response in children with RRP have been demonstrated.[30,31]

TRANSMISSION

The mode of HPV transmission is still not clear.[32] Approximately a million cases of genital papillomatosis are diagnosed each year in the United States.[33] One study reported finding HPV infections in 43% of sexually active college women over a 36 month period.[34] Most manifest as condylomata acuminata of the cervix, vulva, or other anogenital sites in women or the penis of male sexual partners of affected women. Colposcopic (subclinical) changes are seen in approximately 4% of women, and approximately 10% of women have biopsy specimens positive for HPV DNA but no visible lesions. It has been estimated that approximately 60% of women (81 million) might test positive for HPV antibody, and the virus may be present in the genital tract of up to 25% of all women of child-bearing age worldwide.[33]

Vertical transmission occurring during delivery through an infected birth canal is presumed to be the major mode of transmitting the infection to children. Clinically apparent HPV infection has been noted in 1.5% to 5% of pregnant women in the United States,[35,36] and overt maternal condyloma are seen in more than 50% of mothers who give birth to children with RRP.[37] The same subtypes (HPV 6 and 11) are involved, and cesarean delivery appears to lower the risk of infection in the child.[38]

Patients with childhood-onset RRP are more likely to be firstborn and vaginally delivered than are control patients of similar age.[39,40] One hypothesis is that primigravid mothers are more likely to have a long second stage of labor, and this results in prolonged exposure of the fetus to the virus. If newly acquired genital HPV lesions are more likely to shed virus than long-standing lesions, this would explain the higher incidence of papilloma disease among offspring of younger mothers.[39,40]

Although in one study HPV could be recovered from the nasopharyngeal secretions of 30% of infants exposed to HPV in the birth canal, only a small portion of children developed clinical RRP.[28] Clearly, other factors (patient immunity, timing, length and volume of virus exposure, local trauma) must be important in the development of RRP. Although delivery by cesarean section might reduce the risk of HPV transmission, surgery has higher morbidity and mortality and economic cost. Furthermore, in at least some cases, transmission may occur in utero.[32,7]

The risk of a child contracting the disease from a mother who has an active genital condyloma lesion during vaginal delivery is 1 in between 231 and 400 cases.[38,41,42] However, the characteristics that distinguish this 1 child from the other 230 to 399 remain elusive. Clearly, the risk factors for HPV transmission and RRP need to be better understood before elective cesarean delivery can be recommended. In addition, if the HPV vaccine becomes effective in reducing the incidence of genital warts and oral cavity lesions, vaccination could all but eradicate RRP in future generations.[43–45]

CLINICAL FEATURES

In most pediatric series, the time from onset of symptoms to diagnosis of RRP is approximately 1 year,[3,7] although the duration of symptoms before diagnosis varies. The vocal fold is usually the first and predominant site of papilloma lesions, and hoarseness is the principal presenting symptom.[46] Unfortunately, particularly in very young children, changes in voice may go unnoticed. Stridor is often the second clinical symptom to develop, initially inspiratory, then becoming biphasic. Less common presenting symptoms include chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with an upper respiratory tract infection. Not uncommonly, a diagnosis of asthma, croup, allergies, vocal nodules, or bronchitis is entertained before a definitive diagnosis is made.

The natural history of RRP is highly variable and unpredictable. The disease may undergo spontaneous remission, persist in a stable state requiring only periodic surgical treatment, or may be aggressive, requiring surgical treatment every few days to weeks and consideration of adjuvant medical therapy.

When RRP presents as respiratory distress caused by papillomas obstructing the airway, tracheotomy often must be performed. Shapiro et al.[47] noted that these patients tend to be younger and to have more widespread disease, often involving the distal airway. However, it has been suggested that tracheotomy may activate or contrib-

ute to the spread of disease lower in the respiratory tract,[48] and, in one series, tracheal papillomas developed in half of patients with tracheotomy.[49] Thus, most authors agree that tracheotomy is a procedure to be avoided unless absolutely necessary, and, when a tracheotomy is unavoidable, decannulation should be considered as soon as the disease is managed effectively with endoscopic techniques. Boston et al.[50] from Cincinnati noted successful laryngotracheal reconstruction in a cohort of children with RRP who also had severe subglottic stenosis.

Children with bronchopulmonary dysplasia who require prolonged endotracheal intubation may also be at increased risk for development of RRP. If interruption of the respiratory mucosa is a risk factor for RRP, endotracheal tube irritation may have the same effect as tracheotomy.

Extralaryngeal spread of respiratory papillomata has been identified in approximately 30% of children and in 16% of adults with RRP.[51] The most frequent sites of extralaryngeal spread were, in decreasing order of frequency, the oral cavity, trachea, and bronchi and esophagus (Fig. 3).[7,46,51]

Pulmonary papilloma lesions begin as asymptomatic, noncalcified, peripheral nodules.[52] These lesions enlarge and undergo central cavitation, liquefaction, and necrosis, often with evidence of an air-fluid level on radiograph (Fig. 4). Patients may present with recurrent bronchiectasis, pneumonia, and declining pulmonary status. The clinical course of pulmonary RRP is insidious and may progress over years but eventually manifests as respiratory failure caused by destruction of lung parenchyma. To date, no treatment has been found effective for pulmonary RRP.[53] An RRP Task Force survey reported malignant transformation of RRP into squamous cell carcinoma in 26 cases,[51] and Dedo and Yu[54] reported malignant transformation in 4 of 244 (1.6%) patients treated over 2 decades.

STAGING RRP SEVERITY

A staging system is helpful to track disease in individual patients and communicate with other professionals. Although several systems to stage RRP have been proposed, none has been uniformly accepted. This has created confusion in the literature and in physician-to-physician communications regarding patients' responses to therapies and abilities to accurately report the natural course of RRP and the results of using adjuvant therapies.

A new staging system for RRP[55,56] incorporates the best qualities of existing systems by assigning numeric grades for the extent of papillomatosis at specific sites along the aerodigestive tract and for functional parameters and assigns a final numeric score to the extent of disease at each assessment (Figs. 5 and 6). This system has now been computerized using software designed at the University of Washington (Seattle, WA) and licensed to the ASPO and is available to pediatric otolaryngologists and bronchoesophagologists. The software encrypts data to be compliant with the U.S. Health Insurance Portability and Accountability Act, allowing clinicians from around the world to pool anonymous data for multi-institutional investigations.

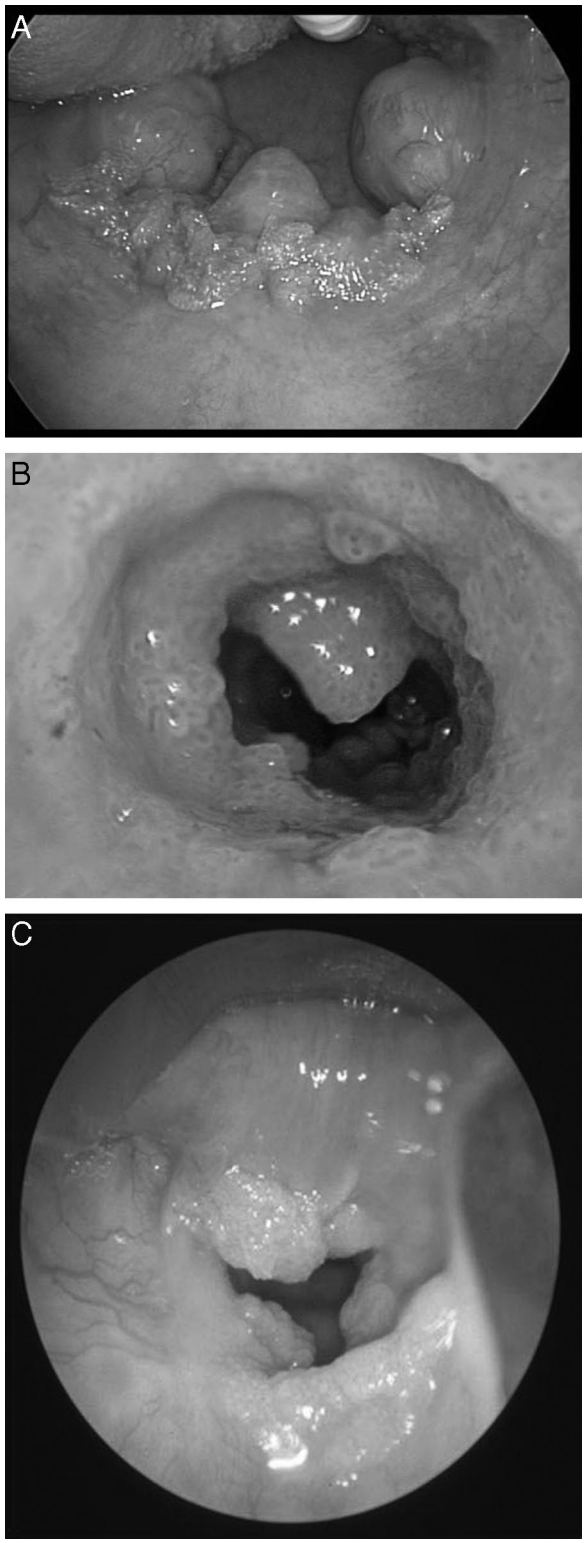

Fig. 3. (A) Diffuse papillomatous involvement of soft palate. (B) Obstructive papillomas in mid-tracheal region. (C) Papillomas involving upper trachea and cricopharyngeal region.

CLASSICAL SURGICAL MANAGEMENT

At present, there is no "cure" for RRP, and no single treatment has consistently been shown to be effective in

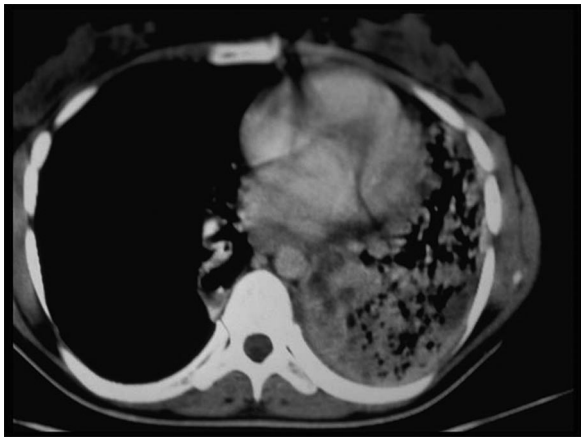

Fig. 4. Pulmonary spread of recurrent respiratory papillomatosis. Note lytic, cavitary lesions on computed tomography scan.

eradicating RRP. The current standard of care is surgical therapy with a goal of complete removal of papillomas and preservation of normal structures. In patients who have anterior or posterior commissure disease or highly aggressive papillomas, the goal may be sufficient removal to clear the airway while preserving normal structures so as to avoid complications of subglottic and glottic stenosis, web formation, and resulting airway stenosis.

The carbon dioxide (CO_2) laser has replaced "cold" instruments for removal of RRP involving the larynx, pharynx, upper trachea, and nasal and oral cavities.[51] When used with an operating microscope, the laser can be used with precision to vaporize RRP lesions with minimal bleeding. Multiple procedures performed over time are recommended in an attempt to avoid tracheotomy and permit the child to develop good phonation with preservation of normal vocal cord anatomy.

The CO_2 laser has an emission wavelength of 10,600 nm and converts light to thermal energy that is absorbed by intracellular water; the result is controlled destruction of tissues by cell vaporization and cautery of tissue surfaces. The latest generation of a laser microspot micromanipulator enables the surgeon to use a spot size of 250 mm at 400 mm focal length and 160 mm at 250 mm focal length. The newest application of the CO_2 laser allows it to be used through a flexible bronchoscope, providing access for its use in the distal airway. In one series of 244 patients with RRP treated with the CO_2 laser every 2 months, "remission" was achieved in 37%, "clearance" in 6%, and "cure" in 17% of cases.[54]

The drawbacks of the CO_2 laser relate to safety: the laser beam may glance off nearby metal, such as a retractor, and injure the surgeon or areas on the patient that are not protected by a wet towel to absorb the laser energy. In addition, the laser smoke or "plume" has been found to contain active viral DNA, a potential source of infection,[57–59] so smoke evacuators are necessary when this type of laser is used. The most serious safety concern with the CO_2 laser is that the laser beam generates heat that, if the beam inadvertently strikes the endotracheal tube in the oxygen-rich environment provided by anesthetic gases, could lead to an explosion or fire in the airway. Laser-generated heat could also cause injury to deeper tissues, leading to scarring with complications such as abnormal vocal cord function, spread of viral particles to previously unaffected areas, and delayed local tissue damage.

EMERGING SURGICAL TECHNIQUES

To minimize the risk of scar formation in the true vocal folds, cold steel excision using microinstrumentation may have treatment advantages over CO_2 laser surgery, especially in adults.[60–62] Zeitels and Sataloff[62] reported that all 6 adults who had undergone resection for primary disease were still free of papillomata at the 2 year follow-up visit; of those who presented with recurrent papillomatosis, 6 of 16 (38%) had recurrence after a microflap procedure.

Although the CO_2 laser is the most commonly used laser for RRP in the larynx, the potassium titanium phosphate (KTP), 585 nm flash dye, or argon laser could also be used. When papillomata are present in the tracheobronchial tree, it is often necessary to use a KTP or pulse dye laser coupled with a ventilating bronchoscope or a ventilating resectoscope. Bower et al.[63] evaluated the feasibility and safety of the flash pump dye laser in nine children and found good early results. McMillan et al.[64] reported good preliminary results with the 585 nm pulsed dye laser in three patients.

Rees et al.[65] performed 328 pulsed dye laser treatments in the office in 131 adult patients and reported that the patients overwhelmingly preferred the in-office surgery to a procedure under general anesthesia. Zeitels et al.[66,67] reported that use in the office of a 532 nm pulsed KTP laser to treat recurrent glottal papillomatosis and dysplasia led to 75% regression of disease in two thirds of patients and good results with a solid-state fiber-based thulium laser that functions similarly to a CO_2 laser with the benefit that the laser beam is delivered through a small glass fiber.

Other investigators used an endoscopic microdebrider to quickly debulk laryngeal disease. Pasquale et al.[68] reported improved voice quality, less operating room time, less mucosal injury, and a cost benefit for the microdebrider compared with the CO_2 laser. Patel et al.[69] and El-Bitar and Zalzal[70] also reported improved outcomes with an endoscopic microdebrider. A Web-based survey of members of the ASPO found the majority of respondents now favoring the use of "shaver" technology.[51] Safety advantages include no risk of laser fire or burns and no risk of aerosolized viral DNA particles.

Even with the removal of all clinically evident papilloma, latent virus remains in adjacent tissue. Therefore, it is prudent to leave residual papillomas when their removal might damage normal tissue and produce excessive scarring. In cases of extensive disease, the goals should be to reduce the tumor burden, decrease the spread of disease, create a safe and patent airway, optimize voice quality, and increase the time interval between surgical procedures. Staged papilloma removal for disease in the anterior commissure is appropriate to prevent the apposition of two raw mucosal surfaces. Boston et al.[50] reported

Laryngoscopic and Clinical Assessment Scale for RRP

A. Clinical Score

1. Describe the patient's voice today:
   normal___(0), abnormal___(1), aphonic___(2)
2. Describe the patient's stridor today:
   absent___(0), present with activity___(1), present at rest___(2)
3. Describe the urgency of today's intervention:
   scheduled___(0), elective____ (1), urgent___(2), emergent___(3)
4. Describe today's level of respiratory distress:
   none___(0), mild___(1), moderate___(2), severe___(3), extreme___(4)

Total Clinical Score (Questions 1 through 4) = _____

B. Anatomical Score

For each site, score as: 0=none, 1=surface lesion, 2=raised lesion, 3=bulky lesion

LARYNX:
- Epiglottis: Lingual surface___ Laryngeal surface___
- Aryepiglottic folds: Right___ Left___
- False vocal cords: Right___ Left___
- True vocal cords Right___ Left___
- Arytenoids: Right___ Left___
- Anterior commissure_____
- Posterior commissure_____
- Subglottis_____

TRACHEA:
- Upper one-third_____
- Middle one-third_____
- Lower one-third_____
- Bronchi: Right___ Left___
- Tracheotomy stoma____

OTHER:
- Nose_____
- Palate_____
- Pharynx_____
- Esophagus___
- Lungs_____
- Other_____ **Total Anatomical Score** _____

C. Total Score = Total Anatomical Score plus Total Clinical Score

Fig. 5. Staging assessment sheet for recurrent respiratory papillomatosis (RRP).[55]

on successful laryngotracheal reconstruction in children with subglottic stenosis and RRP.

ADJUVANT TREATMENT MODALITIES

Although surgical management remains the mainstay therapy for RRP, some form of adjuvant therapy may be needed in up to 20% of cases.[51] The most widely accepted indications for adjuvant therapy are a need for more than four surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease.[7]

Antiviral Modalities

Interferon. The first widely used adjuvant therapy was α-interferon.[71,72] Interferons are a class of proteins that are manufactured by cells in response to a variety of stimuli, including viral infection. The exact mechanism of interferon action is unknown but appears to involve modulation of host immune response by increasing production of a protein kinase and endonuclease, which inhibit viral protein synthesis.[73] The enzymes that are produced block the viral replication of RNA and DNA and alter cell membranes to make them less susceptible to viral penetration.

Common interferon side effects include acute reactions (fever and generalized flu-like symptoms, chills, headache, myalgias, and nausea that appear to decrease with prolonged therapy) and chronic reactions (decrease in a child's growth rate, elevation of liver transaminase levels, leukopenia spastic diplegia, and febrile seizures). Thrombocytopenia has been reported, as have rashes, dry skin, alopecia, generalized pruritus, and fatigue. Side effects can be minimized

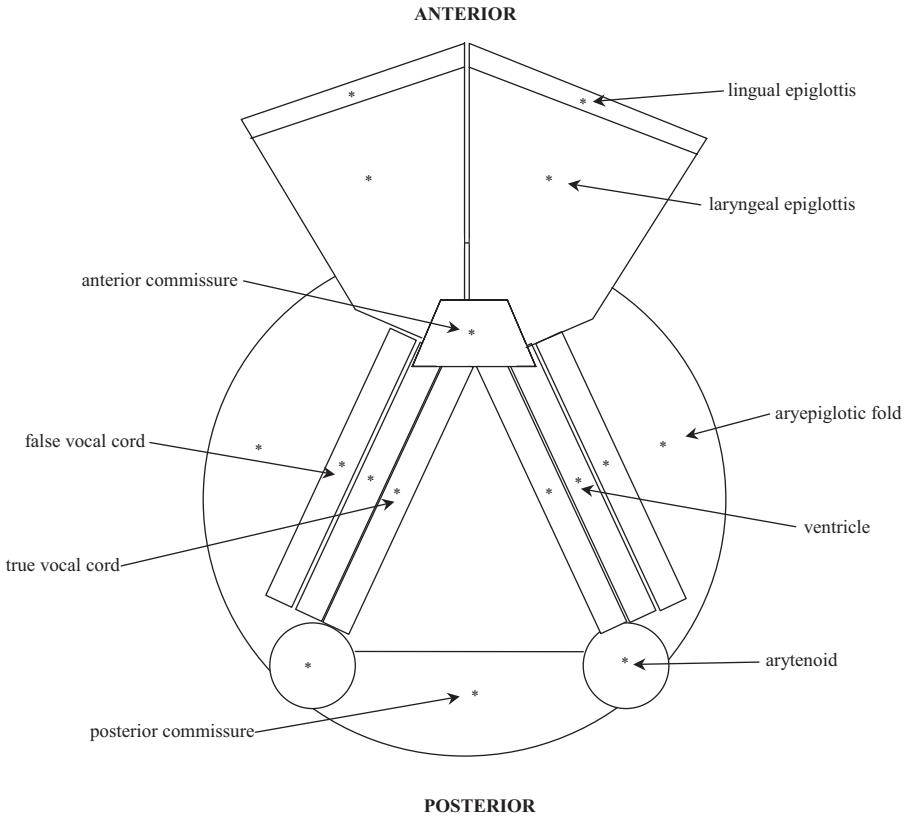

Fig. 6. Diagram of laryngeal sites that may be scored.[55]

by giving interferon injections at bedtime and using interferon produced by recombinant DNA techniques rather than interferon harvested from donated blood.

The typical dose of interferon for children with RRP is 5 million units/m^2 body surface area administered by subcutaneous injection on a daily basis for 28 days, then 3 days per week for at least a 6 month trial. After 6 months, if there is good response and side effects are tolerable, the dosage can be decreased to 3 million units/m^2 for 3 days a week, followed by slow weaning.

Ribavirin. Ribavirin, an antiviral drug used to treat respiratory syncytial virus pneumonia in infants, has shown some promise in the treatment of aggressive laryngeal papillomatosis. McGlennen et al.[74] reported that an intravenous loading dose followed by oral doses of 23 mg/kg/day in four divided doses led to an increase in the intervals between surgery in eight patients.

Acyclovir. Another antiviral treatment that has been advocated for RRP is acyclovir. The activity of acyclovir is dependent on the presence of virally encoded thymidine kinase, an enzyme that is not known to be encoded by papillomavirus. Nevertheless, acyclovir was found effective in some cases. It appears more likely to be effective when there are concurrent viral infections, and viral co-infections with herpes simplex virus-1, cytomegalovirus, and Epstein-Barr virus have been demonstrated in both adult[75] and pediatric[16] RRP patients. Adult patients with viral co-infections appear to have a more aggressive clinical course.[75]

Cidofovir. Recent reports have stimulated interest in the intralesional injection of cidofovir (Vistide, Gilead, Foster City, CA)(S)-1-[3-hydroxy-2-(phosphonylmethoxyethyl)-propyl]-cytosine—a drug approved by the U.S. Food and Drug Administration for use in those infected with HIV who also have cytomegalovirus infection. Although most reports of cidofovir for RRP are of cases or case series, the results are encouraging enough to consider this a treatment option in patients severely affected by RRP. Cidofovir is currently the most frequently used adjuvant drug in children with RRP.[51]

Snoeck et al.[76] reported that, in a series of 17 patients with severe RRP, injection of cidofovir (2.5 mg/mL directly into the papilloma bed) after laser surgery was followed by a complete response in 14 days. Pransky et al.[77–79] used this therapy in 10 children with severe RRP and reported both a short-term and long-term response in all 10 patients. One case of pulmonary multicystic papillomatosis was treated successfully with systemic cidofovir.[80] Naiman et al.[81] found cidofovir effective in a small cohort of adults and children given high doses of cidofovir at 2 week intervals. Co and Woo[82] found intralesional injections of cidofovir to be effective in a small cohort of adults with RRP. McMurray et al.[83] were unable to demonstrate improved outcomes with cidofovir administered at a relatively low dose in the only blinded, randomized trial reported to date.

Because animal studies demonstrated a high level of carcinogenicity for cidofovir and there have been case reports of progressive dysplasia in patients with RRP who received cidofovir,[84] the RRP Task Force has published guidelines for clinicians interested in using cidofovir to treat RRP.[85] Extensive pretreatment counseling with the

patient's family is absolutely necessary before embarking on this treatment regimen.

Photodynamic Therapy

Photodynamic therapy (PDT) for RRP has been studied extensively by Shikowitz et al.[86,87] The first drug used for PDT of RRP was dihematoporphyrin ether (DHE). Patients are typically given 4.25 mg/kg of DHE intravenously before PDT of papillomata. This treatment led to a small but statistically significant decrease in RRP growth, especially in patients whose disease was worse.[86] The drawback of PDT with DHE is that patients become markedly photosensitive for 2 to 8 weeks after treatment.

A new drug, m-tetra(hydroxyphenyl)chlorine (Foscan, Biolitec Pharma, Ltd., Dublin, Ireland), was effective in treating HPV-induced tumors in rabbits with minimal tissue damage and less photosensitivity. A randomized clinical trial of this drug in 23 patients ages 4 to 60 with severe RRP resulted in improvement in laryngeal disease; however, papillomas recurred in 3 to 5 years, and the therapy was poorly tolerated by a quarter of the patients.[87]

Indole-3-Carbinol

The dietary supplement indole-3-carbinol, which is found in high concentrations in cruciferous vegetables such as cabbage, cauliflower, and broccoli, has been evaluated for treating RRP. The rationale is that RRP lesions exhibit increased binding of estrogen,[88] and a study in immunocompromised mice showed that inhibition of estrogen metabolism using indole-3-carbinol reduced the formation of HPV-induced papilloma tumors by nearly 75%.[89] In an open-label, multicenter study in children with RRP, Rosen and Bryson[90] found that after 8 months or more of treatment, one third of patients had cessation of papilloma growth and did not require further surgery, one third had reduced papilloma growth rate, and one third had no evident response. Longer follow-up in a larger, blinded, controlled trial of this therapy appears warranted.

Celebrex

Cox-2 inhibitors have been shown to have antipapilloma activity in rabbits.[91] Preliminary results in a study of Celebrex (Pfizer, New York, NY) in a small cohort of adults with RRP were encouraging and led to National Institutes of Health funding of a multicenter trial that is currently enrolling adults and children with RRP.

Retinoids

Retinoids (metabolites and analogues of vitamin A) modulate cellular proliferation and differentiation of diverse histologic cell types. There are a variety of retinoids, and their effects on epithelial cell metabolism differ. In the aerodigestive tract, excess vitamin A has been found to suppress squamous differentiation and may cause mucous metaplasia, and vitamin A deficiency may lead to hyperkeratinization and squamous metaplasia.[92] These findings have led to 13-cis-retinoic acid (Accutane, Roche, Nutley, NJ) being tried as a treatment for RRP.[93] The dosage for retinoic acid is 1 to 2 mg/kg/day for 6 months or until the patient develops side effects he or she cannot tolerate. Accutane must be used with extreme caution in sexually active patients because it is teratogenic. In addition, its psychiatric side effects may lead to complications in teenage patients.

Mumps Vaccine

Injection of mumps vaccine or measles-mumps-rubella vaccine into RRP lesions led to moderate success in inducing remission in an open-label, single-center trial.[94] These positive results, however, have not been reproduced by other investigators.

RRP and Reflux

The role of gastroesophageal reflux in exacerbation of RRP deserves special mention. Recent case reports have shown that the rate of recurrence of respiratory papillomatosis in children may decrease significantly after antireflux therapy.[27,95,96] The H_2-antihistamine cimetidine (ranitidine) has been shown to have immunomodulatory effects,[97,98] leading to its use against various virally based diseases, including RRP.[95] Its effectiveness in a small series of children with RRP resistant to previous therapies led to the recommendation for optimal control of extraesophageal reflux disease as adjunctive therapy for RRP.[96]

Gene Therapies

Emerging strategies for treating RRP include gene therapies. Gene therapies target genes that are expressed exclusively in pathologic tissues and not by normal cells. For RRP, targets would be HPV type 6 and 11 early genes E2, E5, E6, and E7.[21,24–26] The gene therapy strategies are based on our current understanding of the differentiation of RRP epithelium.

Expression of normally high levels of EGF receptor has been reported in RRP.[26] In vitro, these cells respond to EGF by decreased differentiation. Conversely, withdrawal of EGF allows them to differentiate normally.[26] Inhibitors of the EGF receptor kinase are reported to induce growth arrest and differentiation in HPV 16-infected keratinocytes.[97] Therefore, one goal of treatment for RRP may be to induce differentiation of RRP epithelium, as has been reported in response to some of the retinoid therapies.[98] Indeed, some of the differentiation effects of retinoids may be manifest as a result of their effects on the EGF receptor. A promising new chemotherapeutic agent, gefitinib (Iressa, AstraZeneca, Wilmington, DE), has been reported in the treatment of life-threatening RRP with extensive tracheobronchial involvement.[99] A topical or aerosol application of EGF receptor inhibitors might induce epithelial differentiation and reduce growth of RRP.

HPV Vaccines

Vaccines have been devised that elicit an immune response against HPV gene products. Some of these have shown promise as immunotherapies for HPV-associated cancers.[100–102]

A multicenter clinical trial was conducted involving 27 children with severe RRP of a biological modifier based on an HPV 16 heat-shock protein fusion product. The children who received the vaccine had a 93% (statistically significant) increase in the first intersurgical interval

(ISI) (time from vaccination to the next required surgery for RRP) and prolongation by 107 days of the median ISI for all surgeries after treatment ($P < .02$). A prospective, randomized, placebo-controlled trial is currently in the planning phase.[103]

Recently, a quadrivalent HPV vaccine, Gardasil (Merck, Whitehouse Station, NJ), was approved for the prevention of cervical cancer, adenocarcinoma in situ, and cervical intraepiethlial neoplasia 1 to 3, vulvar and vaginal intraepithelial neoplasias grades 2 to 3, and genital warts associated with HPV 6, 11, 16, and 18. The CDC Advisory Committee on Immunization Practices has recommended vaccination for all girls ages 11 to 12, girls and women ages 13 to 26 who have not yet been vaccinated, and girls as young as age 9 in whom the physician believes it would be appropriate.[104] If the vaccine proves effective in reducing the incidence of cervicovaginal HPV disease, it may also decrease the incidence of RRP, possibly eradicating RRP in future generations.[43–45]

A bivalent HPV vaccine is currently in phase 3 trials.[105] This vaccine provides protection against HPV 16 and 18 but not 6 and 11. Early phase 2 data for this vaccine suggest that it is 100% effective in preventing incident and persistent cervical HPV 16 and 18 infections. This vaccine's efficacy against HPV 16 and 18 suggests that, similar to the quadrivalent vaccine, it may reduce the incidence of HPV-associated head and neck cancers. However, because the bivalent vaccine does not protect against HPV 6 and 11, it will not likely affect the vertical transmission of HPV 6 or 11 from mother to child.

RRP REGISTRY AND TASK FORCE INITIATIVES

For the scientific community to learn more about RRP, patients with RRP should be enrolled in a national registry. Such a registry has been formed through the cooperation of the ASPO and the CDC.[8,9,13] The registry includes data on more than 11,000 surgical procedures performed in nearly 600 children at 22 sites. Data from the national registry aided in the identification of patients suitable for enrollment in multi-institutional studies of adjuvant therapies and better defined the risk factors for transmission of HPV and the cofactors that may determine the aggressiveness of RRP. An RRP Task Force, made up of the principal investigators at each of the registry sites and representatives from the adult RRP research community and patient/parent advocacy groups, meets twice yearly to facilitate research initiatives. The RRP Task Force wrote a set of practice guidelines to help clinicians diagnose and manage RRP in children, wrote public health guidelines regarding RRP, wrote statements on the use of cidofovir, is providing a statement on the value of viral typing, and is facilitating investigation of the genes responsible for aggressive RRP.[106] They have also facilitated the development of similar groups of RRP investigators in Canada and Europe and are currently working with their colleagues outside of the United States to study the benefits of the quadrivalent HPV vaccine for treatment and prevention of RRP.

RRP SUPPORT GROUPS

Children newly diagnosed with RRP warrant a substantial time commitment on the part of the otolaryngologist to engage the family in a frank and open discussion of the disease and its management. Support groups such as the Recurrent Respiratory Papilloma Foundation (http://www.rrpf.org) and the International RRP ISA Center (http://www.rrpwebsite.org) can be a vital resource for information and support. Educational information, research updates, discussion groups, and announcements regarding new treatment modalities are just a few of the issues covered on these Web sites.

SUMMARY

RRP is a seemingly capricious and potentially fatal disease that is frustrating to treat. The goals of surgical therapy are to maintain a safe airway while avoiding excessive scarring and maintaining useful vocal cord function. No single type of therapy has been consistently effective in eradicating RRP. When children need surgical therapy more frequently than four times in 12 months or have evidence of distal spread of RRP outside of the larynx, adjuvant medical therapy should be considered. Many adjuvant therapies have been investigated, including dietary supplements, control of extra-esophageal reflux disease, potent antiviral and chemotherapeutic agents, and PDTs. Although several of these modalities have shown promise, no adjuvant therapy to date has "cured" RRP.

Strides are being made in learning more about the natural history of the disease. A registry of RRP patients has been developed, and software has been made available to clinicians to facilitate follow-up and sharing of treatment data. Future research is needed regarding prevention of transmission of HPV from mother to child. Specifically, the roles of caesarean section and gynecologic surgery during pregnancy need to be elucidated. Universal or near-universal use of an HPV vaccine that provides protection against HPV 6 and 11 may do for RRP what the *Haemophilus influenzae* type B (HiB) vaccine has done for *H. influenzae* type B epiglottis, virtually eliminating new cases in less than a decade.

Further refinements in surgical techniques, including the use of new office-based lasers to minimize laryngeal scarring, need to be studied. Surgical therapy for RRP requires a skilled team consisting of otolaryngologists, anesthesia providers, and operating room personnel working together in a facility properly equipped to manage difficult pediatric airways. Because of the recurrent nature of RRP and the potential for airway obstruction, parental support and education can be invaluable in maintaining a safe airway in the child with RRP.

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