Seminar Series
Recurrent Respiratory Papillomatosis
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Recurrent respiratory papillomatosis is a frustrating and challenging disease for surgeons, patients, and patients' families. Although the voice and airway manifestations are managed surgically, a "cure" for this disease remains elusive. In this edition of the "Seminar Series," we endeavor to review the current literature regarding the epidemiology, etiology, clinical manifestations, and surgical and medical treatments of this disorder. The key to future management of recurrent respiratory papillomatosis may lie in its prevention, if current efforts to develop an effective vaccine come to fruition.

Key Words: cidofovir, human papillomavirus, interferon, microdebrider, recurrent respiratory papilloma, vaccine.

INTRODUCTION
Recurrent respiratory papillomatosis (RRP) is a disease of viral origin that is associated with exophytic lesions of the airway. Although it is a benign disease, RRP has potentially morbid consequences due to airway complications and to the risk of malignant conversion. The disease is often difficult to treat because of its tendency to recur and spread throughout the respiratory tract. The course of RRP is variable: some patients experience spontaneous remission and others suffer from aggressive papillomatous growth that requires multiple surgical procedures over many years. An estimated 15,000 procedures are performed in the United States each year for adults and children with RRP at a total annual cost of more than $150 million.1

ETIOLOGY
Until the 1990s, human papillomavirus (HPV) had been suspected but not confirmed as the causative agent in RRP. This uncertainty developed from an inability to culture the virus in vitro, and from the failure to demonstrate viral particles consistently in papilloma lesions with electron microscopy or HPV antibodies. Today, with the use of viral probes, HPV DNA has been identified in virtually every papilloma lesion studied.

The HPV is a small, DNA-containing, nonenveloped icosahedral (20-sided) capsid virus with a double-stranded circular deoxyribonucleic acid 7,900 base pairs long. The HPVs are grouped on the basis of genetic homology: viruses that exhibit less than 90% identity in specific regions of the viral genome are defined numerically as separate types. On this basis, nearly 100 different HPV types have been identified. These groupings correlate with tissue preference, disease severity, and clinical course. Among those that affect the aerodigestive and genital tracts, HPV types 6 and 11 are associated with the lowest malignant potential, whereas HPV 16 and 18 have the greatest malignant potential; HPV 31 and 33 have a malignant potential that lies somewhere in between. Children infected with HPV 11 appear to have a more obstructive airway course early in the disease and a greater need for tracheotomy.2,3

The induction of cellular proliferation is a fundamental property of HPV, although its mechanism of action remains unclear. The present understanding is that HPV establishes itself in the basal layer of the mucosa,4,6 in which viral DNA enters the cell and is transcribed into RNA; the RNA is, in turn, translated into viral proteins. After infection of the stem cells, the viral DNA either can be actively expressed or can exist as a latent infection in mucosa that remains clinically and histologically normal. During latency, very little viral RNA is present. In fact, HPV DNA can be detected in normal-appearing mucosa in patients with RRP who have been in remission for years, and its presence explains why reactivation and clinical recurrence can occur after many years of remission.7,9 Thus, reactivation of viral expression can occur at any time after establishment of a latent infection. Adult-onset respiratory papillomas could reflect either activation of virus present since birth or an

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infection acquired in adolescence or adult life.

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: the early (E) and late (L) regions. The E genes are involved in potent oncogenes that are responsible for the replication of the viral genome, interaction with host cell intermediate filaments, and transforming activities. The L region genes encode the viral structural proteins.10

Several factors are involved in the regulation of cell proliferation. The virus must have a means to reactivate the necessary host replication genes to facilitate its own DNA replication and must rely on the host DNA replication mechanism. One growth factor that is known to be associated with the proliferation of epithelial cells is the epidermal growth factor receptor. Human papillomavirus might induce epithelial proliferation by increasing the level of expression of epidermal growth factor receptor or its ligands. It may also induce cell proliferation by interacting with p53 or other tumor suppressor proteins, inhibiting their normal functioning.

It is likely that the host immune system plays an important role in the pathogenesis of HPV-induced lesions. Both humoral and cellular immune responses may be compromised in children with RRP, and a patient’s immunocompetence also may influence the clinical course of disease. Both children and adults with the acquired immunodeficiency syndrome or congenital immunodeficiencies and patients on immuno suppression after organ transplantation have been identified with RRP.11 The role of cytokines such as interleukin-2, interleukin-4, and interleukin-10 and expression of the major histocompatibility complex antigens in the malfunction of the cell-mediated immune response has been demonstrated in children with RRP.12 Papillomas with a reduced expression of these antigens may evade immune surveillance and allow the disease to progress more rapidly.

EPIDEMIOLOGY

Recurrent respiratory papillomatosis may have its clinical onset during either childhood or adulthood. Although juvenile-onset RRP is generally more aggressive, adult-onset disease may occasionally be severe as well. Among children, RRP is the most common benign neoplasm of the larynx, and the second most frequent cause of hoarseness.13

Incidence. The true incidence and prevalence of RRP are uncertain. In a Danish subpopulation incorporating 50% of the population of that country, the incidence of laryngeal papillomatosis was 3.84 cases per 100,000.14 The rate among children was 3.62 per 100,000; adult-onset cases occurred at a rate of 3.94 per 100,000. These figures are comparable with those found in a US survey, which estimated an incidence in the pediatric population of 4.3 per 100,000 children and 1.8 per 100,000 adults.1 Armstrong et al15 estimated the incidence of new cases of juvenile-onset RRP at between 80 and 1,500 per year and a prevalence of between 700 and 3,000 active cases based upon a 1999 epidemiological analysis of two US cities.

Recurrent respiratory papillomatosis may affect individuals of any age. The disease has been observed in patients as young as 1 day of age and as old as 84 years.1 Adult-onset RRP peaks between the ages of 20 and 40 years and has a slight male predilection. Juvenile-onset RRP (arbitrarily defined as patients with a diagnosis at less than 12 years of age) is most often diagnosed between 2 and 4 years of age; 75% of the children receive the diagnosis before their fifth birthday.16 Children with disease progression receive the diagnosis at younger ages than those who remain stable or become disease-free.17 The distribution among boys and girls is approximately equal.18

In most pediatric series, the diagnosis of RRP is established an average of 1 year after the initial onset of symptoms.19,20 Anecdotal observations suggest that most patients are firstborn, have young, primigravid mothers, and come from families of low socioeconomic status.1,11,21

The universality of HPV in the lower genital tract rivals that of any other sexually transmitted disease in humans. It is estimated that at least 1 million cases of genital papillomas occur per year in the United States, affecting about 1% of the population.22 These most often manifest as condylomata acuminata involving the cervix, vulva, or other anogenital sites in women or the penis of male sexual partners of affected women. In addition, it is estimated that colposcopic (subclinical) changes affect nearly 5 million US women. An additional 14 million women, or about 10% of the female population of child-bearing age, are DNA-positive but have no visible lesions; more than 80 million women, or 60% of the at-risk population, are HPV antibody-positive but DNA-negative. The incidence of HPV infection in young, sexually active college women is high, with a cumulative incidence of 43% over a 36-month period in a recent study.23 Clinically apparent HPV infection has been noted in 1.5% to 5% of pregnant women in the United States.24 As in RRP, HPV 6 and 11 are the most common subtypes identified in cervical condylomata.

Transmission. The precise mode of HPV transmis-
sion remains unclear. Several studies have convincingly linked childhood-onset RRP to mothers with genital HPV infections; among adults, circumstantial evidence suggests that the disease may be associated with oral-genital contact.

Retrospective and recent prospective studies have confirmed that HPV may be passed by vertical transmission from mother to child. In addition, Kashiama et al found that patients with childhood-onset RRP were more likely to be firstborn and vaginally delivered than were control patients of similar age. The researchers hypothesized that primigravid mothers are more likely to have a long second stage of labor and that the prolonged exposure to the virus leads to a higher risk of infection in the firstborn child. They also suggested that newly acquired genital HPV lesions are more likely to shed virus than long-standing lesions, thus explaining the higher incidence of papilloma disease observed among the offspring of young mothers of low socioeconomic status, the same group that is more likely to acquire sexually transmitted diseases such as HPV. Despite the apparent close association between maternal condylomata and the development of RRP, few children exposed to genital warts at birth actually develop clinical symptoms. It is not well understood why RRP develops in so few children whose mothers have condylomata. The most likely method of maternal-fetal HPV transmission is through direct contact in the birth canal. This would explain the clinical observation that most children in whom RRP develops are delivered vaginally to mothers with a history of genital condylomata. Although HPV could be recovered from the nasopharyngeal secretions of 30% of infants exposed to HPV in the birth canal, the number of infants expected to manifest evidence of RRP is only a small fraction of this. Clearly, other factors (patient immunity; timing, length, and volume of virus exposure; and local trauma) must be important determinants of the development of RRP. Even though cesarean section would seem to reduce the risk of transmission of the disease, this procedure is associated with a higher incidence of morbidity and mortality for the mother and a much higher economic cost than elective vaginal delivery. Shah et al estimated that the risk of a child contracting the disease from a mother who has an active condylomatoses lesion and delivers vaginally is only about 1 in 400. The characteristics that differentiate this 1 child from the other 399 are elusive. In light of the uncertainty surrounding intrapartum exposure, there is presently insufficient evidence to support delivery by cesarean section for all pregnant women with condylomata.

However, there may be some benefit in managing condylomata during pregnancy if it can be accomplished without increasing the miscarriage rate. Reports of neonatal papillomatosis suggest that in at least some cases, development of the disease may occur in utero. Because cesarean section still does not prevent the development of papillomatosis in all cases, a better understanding of the risk factors associated with RRP is needed before the efficacy of cesarean delivery in preventing papillomatosis can be fully assessed. Discussion between the at-risk mother and her obstetrician regarding the issue of HPV transmission would seem appropriate.

Currently, a quadrivalent (HPV type 6, 11, 16, 18) vaccine is undergoing phase III clinical studies. The preliminary results regarding the HPV 16/18 vaccine for prevention of cervical dysplasia in women of child-bearing age were very encouraging. If similar results were obtained with the quadrivalent vaccine, one might expect to see a reduction in the susceptibility of neonates to the virus among vaccinated mothers.

**HISTOLOGY**

Histologically, RRP appears as sessile or pedunculated masses, pink to white in color, that often occur in irregular exophytic clusters (Fig 1). The masses consist of fingerlike projections of nonkeratinized stratified squamous epithelium supported by a core of highly vascularized connective tissue stroma (Fig 2). The basal layer may be either normal or hyperplastic, and mitotic figures are generally limited to this layer. Cellular differentiation appears to be abnormal, with altered expression and production of keratins. The degree of atypia may be a sign of pre-malignant tendency. Malignant transformation of RRP into squamous cell carcinoma has been documented in several case reports.

The RRP lesions occur most often at anatomic sites in which ciliated and squamous epithelium are juxtaposed. The most common sites for RRP are the limen vestibuli of the nose, the nasopharyngeal surface of the soft palate, the midline of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the undersurface of the vocal folds, the carina, and bronchial spurs. Areas of transition from ciliated respiratory epithelium to native or metaplastic squamous epithelium are commonly involved, as in patients with tracheotomies, in whom RRP is often encountered at the stoma and in the midhilar trachea. Similarly, children with bronchopulmonary dysplasia, in whom prolonged endotracheal intubation may result in interruption of the continuous respiratory mucosal surface, also may be at increased risk for the development of RRP. Injury to the respiratory mucosa may also explain the observation that RRP flourishes in the presence of un-
hoarseness may present somewhat later. Stridor is often the second clinical symptom to develop, beginning as an inspiratory noise and becoming biphasic with progression of the disease. Less commonly, chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, and acute life-threatening events may be the presenting symptoms.

Because hoarseness in children is common and RRP is rare and slowly progressive, many cases are not recognized until respiratory distress results from papillomas obstructing the airway. Symptoms are typically present for a year before a diagnosis of RRP is made. Not uncommonly, children are treated for asthma, croup, allergies, vocal nodules, or bronchitis before a definitive diagnosis is arrived at.

A comprehensive medical history is critical in order to determine risk factors for papillomatosis and any comorbidities. Information regarding the time of onset of symptoms, prior airway trauma, including a history of previous intubation, and characteristics of the voice or cry is obviously important. A history of progressive inspiratory or biphasic stridor also suggests an expanding lesion of the glottis or subglottis. Although stridor that has been present since birth is more often associated with congenital airway anomalies, it should be realized that neonates also can present with papillomatosis. Associated symptoms such as feeding difficulties, allergic symptoms, vocal abuse, and the presence of hereditary congenital anomalies may help distinguish RRP from other diagnoses, including vocal fold nodules, vocal fold paralysis, subglottic cysts, subglottic hemangioma, and subglottic stenosis. In addition, parents should be questioned about any history of maternal or paternal condylomata. If the onset of stridor and dysphonia is gradual and progressive over weeks or months, then neoplastic growth compromising the airway must be consid-

Fig 1. Sessile papilloma lesions involving true vocal folds.

controlled gastroesophageal reflux, with an increased incidence of laryngeal scarring. Iatrogenic implantation of papilloma may be preventable by avoiding injury to nondiseased squamous or ciliated epithelium adjacent to areas of frank papilloma.

CLINICAL PRESENTATION

Although histologically the same lesion, a papilloma that produces hoarseness in one patient may produce stridor and obstruction in another, depending on the size and location of the lesion. Children with RRP most often present with some degree of dysphonia. Because of the precision of laryngeal mechanics, hoarseness may result from a remarkably small lesion and thus may be an early sign in the course of the disease process. On the other hand, if the origin of the lesion is remote from the vocal folds,
ered and investigated.

PHYSICAL EXAMINATION

Children who have symptoms consistent with RRP should undergo a thorough and organized physical examination. The physician should assess the child for tachypnea or signs of distress or fatigue that may indicate impending respiratory collapse, such as flaring of the nasal ala and the use of accessory neck or chest muscles. In the most acute cases, increasing cyanosis and air hunger may cause the child to sit with the neck hyperextended in an attempt to improve airflow. In such cases, additional examination should not be undertaken outside the operating room, the emergency room, or the intensive care unit, in which resuscitation equipment for intubation of the airway, endoscopic evaluation, and possible tracheotomy are readily available. In a stable, well-oxygenated child, additional examination can proceed. Auscultation with the aid of a stethoscope over the nose, open mouth, neck, and chest may help localize the site of the respiratory obstruction. In small children, the airway is best examined by pulling the bell off the stethoscope and listening with the open tube. Pulse oximetry can add an accurate quantitative analysis of the child’s respiratory status.

In most cases, the diagnosis of RRP can be made definitively by flexible fiberoptic nasopharyngoscopy and laryngoscopy. The procedure is useful in establishing the extent of involvement, the urgency of operative intervention, and the potential for airway compromise in the operating room, and should include careful, sequential inspection of the nasopharynx, oropharynx, hypopharynx, and supraglottic and glottic larynx. Although examination under spontaneous ventilation affords the best assessment of airway dynamics, endoscopy under anesthesia in the operating room is warranted in any child in whom RRP is suspected who cannot be fully examined in the outpatient setting because of poor cooperation or equipment limitations.

STAGING

Several scoring and staging systems for RRP have been proposed to aid in tracking the progression of a patient’s disease, communicating with other surgeons, and treating patients in a protocol format. Although no staging system has been uniformly adopted by clinicians and researchers, one such system numerically grades the extent of papillomatosis at defined aerodigestive subsites, assesses functional parameters, diagrammatically catalogs subsite involvement, and assigns a final numeric score to the patient’s current extent of disease (see Table 35). Using software designed at the University of Washington (Seattle) and licensed to the American Society of Pediatric Otolaryngology (ASPO), this staging system is now computerized and available to pediatric otolaryngologists and bronchoesophagologists. Use of encryption technology with this software will eventually allow clinicians from around the world to anonymously share their patients’ data, thereby enhancing our knowledge of this disease and its treatment through multi-institutional investigations while protecting patient confidentiality.

MANAGEMENT

Approaches to Surgery: Once the diagnosis of RRP has been made, the clinician must determine the urgency for surgical debridement of the papillomas. Because there is currently no therapeutic regimen that completely eradicates HPV from the airway, the aims of therapy in extensive disease should be to reduce the tumor burden, decrease the spread of disease, create a safe and patent airway, improve voice quality, and increase the time interval between surgical procedures. Even with the removal of all clinically evident papilloma, latent virus may remain in adjacent tissue, which may explain the recurrent nature of RRP. Therefore, it is prudent to accept some residual papilloma rather than risking spread of disease or damage to normal tissue and excessive scarring. Ideally, the procedure should be performed before the lesions become so large or numerous that the patient is in respiratory distress; conversely, shortening the interval between surgeries may place the patient at more risk for complications from anesthesia, web formation, stenosis, and fibrosis in the larynx.

It is incumbent upon the surgeon to discuss with the anesthesiologist before the operation the means by which anesthesia will be delivered and by which the patient will be ventilated during the procedure. Most otolaryngologists prefer to remove gross disease with an endotracheal tube in place, followed by extubation and apneic excision. When the laser is used, initial placement of a laser-safe endotracheal tube is required. Apneic excision with the patient extubated is useful in removing smaller and more posterior lesions that are poorly visualized with an endotracheal tube in place. This technique, however, may require intermittent interruption of the surgery for reinsertion of the tube and ventilation of the patient. Alternatively, the procedure may be performed under spontaneous ventilation or Venturi jet ventilation.

Until recently, the laser had been favored over cold instruments in the treatment of RRP involving the airway.1 Light from the carbon dioxide (CO2) laser is absorbed by water in tissues, resulting in controlled destruction and cauteryization of tissue surfaces. When
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COLTRERA-DERKAY STAGING AND SEVERITY SCHEME

A. Clinical Score
1. Describe the patient’s voice today:
   normal____(0), abnormal____(1), aphonie____(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

coupled to an operating microscope, the laser vaporizes the lesions with precision, reducing collateral tissue damage, bleeding, and scarring. The newest generation of laser micropoint micromanipulator enables the surgeon to debulk papilloma initially in a defocused mode and then focus to a 250-nm spot size to excise papillomas from potentially problematic areas, such as the anterior and/or posterior commissure and true vocal folds. Although their absorption characteristics are less favorable, the potassium titanyl phosphate (KTP) laser and the argon laser are also used occasionally, especially in cases in which fiber-delivered laser light is preferable.

A recent survey of members of the ASPO found that the microdebrider is now favored over the use of laser and cold steel microlaryngoscopy techniques. The technique uses a small, protected oscillating blade coupled to suction, which allows papillomas to be brought into the blade for shearing and removal. Several recent prospective and retrospective reviews have demonstrated that patients whose papillomas were treated with the microdebrider experienced a shorter operating time, less pain, and less expense than did patients treated with the laser.37,38 This technique may also be less likely to cause laryngeal scarring than the CO2 laser.

Cold steel excision involves the lowest risk of scar formation in the true vocal folds, and can be used successfully by adherence to the principles of phonomicrosurgery, submucosal infusion, and microinstrumentation. This approach may have treatment advantages over CO2 laser surgery, especially in adult patients with RRP.39,40 Zeitels and Sataloff reported no papilloma recurrence at 2 years of follow-up among 6 adults who underwent resection for primary disease. Of those who underwent surgery for recur-
rent papillomatosis, 6 of 16 (38%) continued to have recurrence after their microflap procedure. The Voice Committee of the American Academy of Otolaryngology—Head and Neck Surgery pronounced in 2002 that cold steel excision is the preferred technique for adults with RRP.

Several publications have highlighted the potential benefits of alternative surgical technologies in managing RRP. Bower et al evaluated the feasibility and safety of the flash pump dye laser in 9 children and found good early results. McMillan et al published preliminary results regarding their positive experience with the 585-nm pulsed dye laser in 3 patients. Bergler et al reported on the successful use of argon plasma coagulation to treat a 3-year-old with recalcitrant RRP.

Revision Surgery. No surgical technique has consistently accomplished long-term eradication of RRP. As a result, most patients with RRP make numerous trips to the operating room for surgery to maintain the patency of the airway and improve vocal quality. A national RRP registry, composed of children from the clinical practices at 22 pediatric otolaryngology sites (arguably a skewed population of more severely affected children), contains a mean lifetime number of procedures of 19.7 per child, with an average of 4.4 procedures per year. Children in whom RRP was diagnosed before 3 years of age were found to be 3.6 times more likely to require more than 4 surgical procedures per year, and 2.1 times more likely to have 2 or more anatomic sites involved than those in whom RRP was diagnosed after their fourth birthday. There were no apparent differences in surgical frequencies by gender or ethnicity. Other investigators have also found that younger children are more likely to have persistent disease and more often experience an increased number of surgeries in the first year after diagnosis.

The reoperation rate among adults has also been studied in a survey of practicing otolaryngologists in the United States. Whereas more than 75% of children required 5 or more procedures over their lifetime, only 50% of adults required the same frequency of surgery. Approximately equal percentages of children and adults (17% of children versus 19% of adults) had aggressive RRP requiring more than 40 lifetime operations, although adults had more years to accumulate these operations.

Tracheotomy. In patients with aggressive RRP and in those who do not have easy access to medical care in an airway emergency, tracheotomy may be desirable. However, it has been suggested that prolonged tracheotomy, and the presence of subglottic papilloma at the time of tracheotomy, may be associated with an increased risk of distal tracheal spread. Cole et al reported that tracheal papillomas developed in half of their tracheotomy patients, and that despite attempts to avoid this procedure, 21% of their patients still required long-term tracheotomy. Conversely, Shapiro et al noted that RRP tracheotomy patients presented at a younger age and with more widespread disease, often involving the distal airway before tracheotomy. In their experience with 13 patients, they did not feel that tracheotomy itself led to spread of disease outside the larynx. In the Centers for Disease Control and Prevention (CDC) registry, children with tracheotomy received the initial diagnosis of RRP at a younger age (2.7 years) than did those without tracheotomy (3.9 years). Although the risk of tracheotomy remains controversial, most researchers agree that it is a procedure to be avoided unless absolutely necessary. When tracheotomy is unavoidable, decannulation should be considered as soon as the disease is managed effectively with endoscopic techniques.

PROGRESSION

Extralaryngeal spread of respiratory papillomas has been identified in 13% to 30% of children and in 16% of adults with RRP. The most frequent sites of extralaryngeal spread are, in order of frequency, the oral cavity, the trachea, and the bronchi. In a recent review of the experience at 3 academic medical centers, 12% of children with RRP had distal tracheal spread of their disease and 7% had pulmonary dissemination. One common thread in the children with distal spread was the use of jet ventilation anesthesia techniques in the surgical management of their disease.

Half of the respondents in a recent ASPO survey of practices in the United States related at least 1 death from RRP within their practice. When death occurs, it usually is associated with a complication of frequent surgical procedures or is caused by respiratory failure due to distal disease progression. Recurrent respiratory papillomatosis presenting in the neonatal period is thought to be a negative prognostic factor, with a greater likelihood of death and need for tracheotomy.

ADJUVANT TREATMENT METHODS

Although surgical management remains the mainstay of therapy for RRP, ultimately as many as 20% of patients with the disease will require some form of adjuvant therapy. The most widely adopted criteria for initiating adjuvant therapy are a requirement of more than 4 surgical procedures per year, distal multisite spread of disease, and/or rapid regrowth of papilloma disease with airway compromise.
Cidofovir (Vistide) is a nucleoside analog that has antiviral activity against the herpesvirus family and is approved by the US Food and Drug Administration for the treatment of cytomegalovirus retinitis in patients with human immunodeficiency virus disease. It has also been shown to induce apoptosis in HPV-positive cells. Snoek et al. demonstrated a complete initial clinical response in 14 of 17 adult patients with laryngeal RRP who had local injection of cidofovir, and 10 of the 14 remained disease-free. Although Pransky et al. were unable to reproduce these results in terms of complete responses, they were able to markedly improve the airway and increase the interval time between surgical procedures in 10 children severely affected by RRP without the development of significant adverse events. Off-label use of cidofovir to treat RRP has become the most commonly used adjuvant therapy, despite an alarming lack of well-controlled studies to demonstrate its safety and efficacy. Animal studies have raised the possibility of nephrotoxicity and carcinogenesis at doses currently used in humans. Additionally, in pediatric patients, the drug requires repeated infiltration into the larynx under general anesthesia, which raises the risk of airway compromise and increases the cost and potential morbidity of this therapy. In adults, office use of cidofovir in less severely affected patients is gaining favor. Reports of its use in small cohorts of patients by Chhetri et al. and Co and Woo have all been favorable, citing minimal side effects in select groups of adult patients.

Interferons are a class of proteins that are manufactured by cells in response to a variety of stimuli, including viral infection. 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. When used to treat RRP, α-interferon therapy is initiated at 5 million units per square meter of body surface area administered by subcutaneous injection on a daily basis for 28 days and then 3 days per week for at least a 6-month trial. After 6 months in children with excellent responses, or if side effects are severe, the dosage can be decreased to 3 million units per square meter administered 3 days per week, with further slow weaning as tolerated. Common interferon side effects fall into two categories: acute reactions (fever and generalized flu-like symptoms, chills, headache, myalgias, and nausea, which seem to decrease with prolonged therapy) and chronic reactions (decrease in the growth rate of the child, 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. Acetaminophen has been found to effectively relieve the fevers, and interferon injections are best tolerated at bedtime. Interferon produced by recombinant DNA techniques appears to have fewer side effects and better efficacy than blood bank–harvested interferon.

Photodynamic therapy in the treatment of RRP has been studied extensively at Long Island Jewish Hospital by Shikowitz et al. Photodynamic therapy is based on the transfer of energy to a photosensitive drug. The original drug used was dihematoporphyrin ether (DHE), which has a tendency to concentrate within papillomas more than in surrounding normal tissue. Patients are typically treated intravenously with 4.25 mg/kg of DHE before photoactivation with an argon pump dye laser. A small but statistically significant decrease in RRP growth, especially in those patients with the worst disease, was seen with the use of photodynamic therapy and DHE. The drawback of this therapy is that patients become markedly photosensitive for 2 to 8 weeks. A new drug, m-tetra (hydroxyphenyl) chlorine (Foscan, Scotia Holdings, London, England), has shown efficacy in HPV-induced tumors in rabbits with minimal tissue damage and less photosensitivity. A parallel arm, randomized trial with a single photodynamic therapy has recently been completed in 23 adults and children who had required surgery at least 3 times a year. Only 5 of 15 patients who completed the study achieved remission, and several of these experienced recurrences after 3 to 5 years.

Recent interest has focused on chemically pure indole-3-carbinol (I3C), a dietary supplement not approved by the US Food and Drug Administration, which has been shown to inhibit papilloma formation in mice. This compound is found in high concentration in cruciferous vegetables such as cabbage, broccoli, and cauliflower. A small dietary study at Long Island Jewish Hospital (unpublished observations) showed promise, although there were concerns regarding how much active drug the patients were actually receiving. Indole-3-carbinol is now available in pure chemical form, and a clinical trial centered at the University of Pittsburgh demonstrated cessation of papilloma growth in 6 of 18 patients who were given the medication and a reduced papilloma growth rate in another 6 individuals. Six patients showed no clinical response to I3C. There are some concerns regarding whether the pure I3C will maintain its effectiveness when taken with antacids or histamine (H2) blockers; a new product, Phytosorb-DIM (BioResponse, Boulder, Colorado), is purported to overcome this limitation.

Ribavirin, an antiviral drug used to treat respira-
tory syncytial virus pneumonia in infants, has also shown some promise in the treatment of aggressive laryngeal papillomatosis. McGlennen et al at the University of Minnesota completed a small trial in 8 patients using ribavirin in an oral form at 23 mg/kg per day divided 4 times daily after an initial intravenous loading dose. An increase in surgical interval was seen in those treated.

Another antiviral treatment that has been advocated in the treatment of RRP is acyclovir. Although 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, conflicting clinical results have been seen in several small series. It has been postulated that in those cases in which acyclovir has been effective, co-disease factors susceptible to the drug may be present. Viral coinfections with herpes simplex virus type 1, cytomegalovirus, and Epstein-Barr virus have been demonstrated in patients with RRP, and adult patients with viral coinfections appear to have a more aggressive clinical course.

Optimal control of extraesophageal reflux disease has been advocated as a means of improving patient outcomes along with surgical therapy. In a prospective evaluation of 31 children with RRP, antireflux treatments in patients who were undergoing surgery for laryngeal RRP reduced the soft tissue complications, especially scarring and web formation. Prophylactic antireflux therapy may be warranted in any patient who undergoes surgery during which laryngeal mucosal disruption is anticipated.

Heat shock protein (Hsp) E7, a recombinant fusion protein of Hsp65 from Mycobacterium bovis BCG and E7 protein from HPV 16, is under development for treatment of HPV-related diseases. In a study conducted in 8 university-affiliated medical centers, 27 children were enrolled and followed up to 60 weeks. Before enrollment, these patients required surgery at an average interval of 55 days. After a baseline debulking surgery, patients received 3 doses of HspE7 500 µg subcutaneously 30 days apart. Treated patients demonstrated a longer mean first posttreatment intersurgical interval (ISI; 106 days; p < .02), a longer median ISI for all surgeries (107 days; p < .02), and a significant decrease in the number of required surgeries (p < .003). Unexpectedly, the treatment effect was most striking in the 13 female patients, with statistically significant increases in both first posttreatment ISI (142%; p < .03) and median ISI (147%; p < .03).

OTHER CONSIDERATIONS

Children in whom RRP is newly diagnosed 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 (www.rrpf.org; PO Box 6643, Lawrenceville, NJ 08648-0643) and the International RRP ISA (www.rerpwebsite.org; PO Box 30821, Seattle, WA 98113-0821) can be a vital resource for information and support.

Patients with RRP require frequent office visits and endoscopic procedures at the outset to establish the aggressiveness of their disease. They are encouraged to return to the office or call as often as necessary while family members and the health care team become familiar with the child’s symptoms and level of distress. Repeat flexible fiberoptic laryngoscopy may be useful in the office setting, although it is reasonable to return to the operating room with children whose symptoms have recurred once the diagnosis has been established. Speech and language therapy consultation should be obtained early in the course of the disease. Control of comorbidities such as reflux and asthma should be aggressively pursued.

It should be stressed that participation in national and regional protocols of adjuvant treatment methods is essential for the scientific community to learn more about RRP. A national registry of patients with RRP has been formed through the cooperation of the ASPO and the CDC. The registry has tracked more than 600 children at 22 sites, and has data on more than 11,000 surgical procedures. It is hoped that the national registry will aid in the identification of patients suitable for enrollment in multi-institutional studies of adjuvant therapies and will help better define the risk factors for transmission of HPV and the cofactors that may determine the aggressiveness of RRP.

A multicenter initiative organized through the RRP Task Force is currently ongoing in an attempt to identify the host genes that govern susceptibility to RRP. It is hoped that by determining the host genes that govern susceptibility, we will enhance our understanding not only of RRP but also of host-viral interaction in general. Ultimately, this may lead to additional innovative treatment methods.

REFERENCES


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