Introduction

Recurrent respiratory papillomatosis (RRP) is an enigmatic disease which can be devastating to those whom it affects. Much is poorly understood, and active research continues on the subject. Lesions affect various sites throughout the respiratory tract and can lead to hoarseness and airway obstruction sometimes requiring tracheotomy. Rarely it can degenerate into squamous cell carcinoma. This review will provide an overview of what is known about RRP and review what therapies lie ahead.

History

The scientific understanding of RRP has been a slow process. Ullmann in 1923 was the first to verify an infectious etiology by injecting homogenized papillomata from a child’s larynx into his own forearm and observing the development of papillomata there (21). It was not, however until 1956 that a pediatrician made an association between maternal condylomata and the risk of childhood infection(7). In 1973 an intranuclear icosahedral virus was identified in lesions by electron microscopy (2), and in 1980 human papillomavirus (HPV) DNA was identified in papillomata (15). Surgical debulking was advanced with the use of the CO2 laser and suspension microlaryngoscopy in 1972 (20) which remains the state of the art. Current areas of promise include the use of drugs to slow the disease progression. Originally called juvenile laryngeal papillomatosis, the disease has been increasingly recognized in adults and generally goes by the name recurrent respiratory papillomatosis.

Basic Science

The human papillomavirus is a naked, double-stranded, icosahedrally-shaped virus with circular supercoiled DNA that belongs to the Papovavirus family. "Papova" is an acronym for the three types of viruses in the family – papillomavirus, polyomavirus, and simian vacuolating virus. There are only three papovaviruses pathogenic to humans: HPV, and JC and BK viruses which are polyoma viruses (JC virus has been implicated in progressive multifocal leukencephalopathy and BK virus has been isolated from urine of kidney transplant recipients).

There are 90 subtypes of HPV known (12), but only a few commonly cause RRP. To be a subtype a strain has to exhibit less than 90% homology with other subtypes, and certain subtypes which behave...
in a similar fashion clinically have been found to have similar homology (1). These include 6 and 11, 16 and 18, and 31, 33, and 35. The original strains identified were labeled 6C-6F but 6C was later determined to be different enough to be classified as its own strain, HPV 11.

The subtypes which usually cause RRP 6 and 11, although other types have been found. Subtypes 6 and 11 are also the types which cause condyloma acuminata (genital warts), while 16 and 18 have been implicated as causative in cancer, particularly of the uterine cervix.

E6 and E7 are nuclear transforming proteins sometimes made by the virus. They are associated with malignant transformation. They may play a role in the future via molecular biological typing of individual lesions.

**Epidemiology**

Recurrent respiratory papillomatosis has been estimated to affect 15,000 total people in the United States, 6,000 of them being children. There are 2300 new cases among children and 3600 new cases among adults diagnosed each year, with an incidence of 4.3 and 1.8 per 100,000, respectively.

Diagnosis and treatment cost $151 million annually (3). Originally thought to be a disease of children it is now recognized that there is a bimodal distribution in ages. The first peak is in children, with the majority presenting by age five. Approximately 25% will present by age one, 75% by age five, and the remainder of juvenile onset RRP by puberty (9). Boys and girls are equally affected. There is a predilection for the firstborn child. In fact, the triad of the firstborn, vaginally-delivered infant of a teenage mother has been recognized as a risk factor for the disease. RRP is rare in non-twin sibling pairs. In the past it was thought that children with RRP would spontaneously remit at the onset of puberty due to hormonal changes, but this has not been found to be true.

Transmission is thought to be multifactorial, but in children the most common risk factor has been vertical transmission during birth from maternal HPV infection. Other postulated routes include hematogenous spread and ascending transplacental inoculation. Mothers of affected children can recall by history active or prior HPV infection 50% of the time. However, the understanding of the cause and effect is nebulous at best. It has been estimated that 10-25% of women of childbearing age have been shown to have evidence of latent or active HPV in cervical swabs, and HPV DNA has been found in one-third to one-half of aerodigestive tract swabs of children born to affected mothers. However, the majority of these children do not develop disease. The risk of developing disease is not precisely known but has been estimated at 1 in 400 (1).

Adult-onset RRP usually begins between ages 20 and 30, but any age may be affected. In adults it is thought that the virus is transmitted via sexual contact or via indirect contact with anogenital lesions. Typically the disease is more limited than the juvenile form and has a more indolent course. Males are usually slightly more affected than females by a ratio of 3:2 (1).

It is not known, then, why some individuals develop the disease and others do not. As mentioned before, even subsequent children of mothers with one affected child are only rarely affected themselves. A landmark study by Shah evaluated 109 children with RRP and found only one to have been born by cesarean section, much lower than would be predicted (18). However, cesarean section is not universally protective. Affected children have been born via cesarean, including one at this institution that has the added conundrum of being a twin whose sibling is unaffected. There is not a consensus regarding the role of cesarean section for prevention of disease in mothers with HPV
infection. Ultimately, the decision is one between a woman and her obstetrician, but the literature generally does not endorse prophylactic cesarean sections in the absence of other indications (10).

**Diagnosis & Course**

The most common presentation is of RRP is hoarseness. Young children may also present with weak cry, chronic cough, or stridor. Adults may present with other symptoms such as globus. The diagnosis is usually made upon the visualization of warty excrescences and confirmed by biopsy in the operating room. Histologically there is an epithelial projection with a fibrovascular core, and there is associated parakeratosis, koilocytosis, and acanthosis.

Although they can be found anywhere in the aerodigestive tract, there appears to be a predilection for areas where there is a junction of squamous and ciliary epithelium. This includes the limen vestibuli (junction of the nasal vestibule and the nasal cavity proper), nasopharyngeal surface of the soft palate, midzone of the laryngeal surface of the epiglottis, upper and lower margins of the ventricle, undersurface of the vocal folds, and the carina and bronchial spurs (12). Interestingly, virus can be detected in the normal mucosa adjacent to lesions. It is thought that this provides a reservoir for regeneration of new papillomata.

The typical course is of recurrent lesions requiring frequent debulking. However, every patient is different and treatment must be tailored to the individual. Some people require such frequent debulking that tracheotomy is necessary for airway protection. This unfortunately frequently leads to lesions around the tracheotomy site (in essence, an iatrogenic squamociliary junction), but traditional thinking has been that this predisposes to distal tracheal disease. A recent study of children, however, suggests that those who require tracheotomy have more aggressive disease and have distal disease prior to tracheotomy, and thus recommends that no child be subjected to a tenuous airway merely to avoid tracheotomy (19).

The natural history of the disease includes spontaneous remission. It is impossible to know to whom or when this will occur. The causes of remission are not known, and while the exact incidence is not known, it is thought that approximately one-third will remit by age forty. This makes clinical trials somewhat difficult inasmuch as it confounds the ability to tell who remitted due to treatment and who remitted due to the natural history of the illness.

Distal disease can develop and portends a poorer prognosis due to its inaccessibility. Clinically patients develop cavitary pulmonary lesions which can lead to atelectasis, chronic infection, post-obstructive pneumonia, and sepsis. It is thought distal disease is more common with HPV 11.

Rarely the lesions can undergo malignant degeneration which is almost uniformly fatal. One substantial risk factor is prior history of irradiation, a form of therapy no longer used to treat this disease.

**Treatment**

The mainstay of therapy has been repeated debulking. The goal is to eradicate disease without damaging normal structures. Traditionally this has been done with either cold steel or with the CO2 laser. A recent survey of otolaryngologists showed that 92% favored the laser (3). The KTP laser can be used for more distal disease. Care must be taken with the laser to avoid disastrous complications.
such as airway fire. Care must be taken to protect the operating room personnel as papillomata have been demonstrated in the laser plume. Good suction of smoke and laser operating masks are usually sufficient. Eye protection must be used to avoid laser damage to the globe.

Management of the airway is controversial. In the apnea technique the patient is intubated and administered 100% oxygen for a period of time. The tube is then removed for a period of time while the surgeon works. The patient is then reintubated and reoxygenated. This may be advantageous in pediatric airways in which there is not much room to work around a tube. Other methods include use of a laser-safe tube and spontaneous ventilation. Another common method is jet ventilation. Although this is generally felt to be safe, there is concern that this method may lead to distal inoculation of the virus. In patients with an existing tracheotomy, a metal tracheotomy tube can be placed to allow laser surgery to be carried out safely. A recent survey of otolaryngologists found the percent who favored the various techniques as follows: laser-safe tube 46%, jet ventilation 25%, apneic 16%, and spontaneous 12% (3).

Usually a patient who requires multiple procedures develops a regular interval at which time he or she returns for elective debulking. This interval can be quite variable and depends on the patient. Care must be taken especially around the anterior and posterior commissures to avoid the formation of webs. It is better to be more conservative on one side and leave behind disease than to be aggressive and develop a web. At the next procedure one addresses the other side more aggressively and the former more conservatively.

Due to the nature of the disease adjunctive measures and alternative treatments have been sought out. Therapies which have been explored but rejected include steroids, estrogens, cryotherapy, cautery, ultrasound, radiation, vaccines, resin of podophyllum, transfer factor, levamisole, suction diathermy, lymphokines, escarotics, calandine, magnesium, and antibiotics (1,12). Newer therapies which have been tested include alfa-interferon, indole-3-carbinol, acyclovir, retinoic acid, ribavirin, methotrexate, cidofovir, and photodynamic therapy.

Interferon is a product of human leukocytes, although it is now produced via recombinant technology. It has been shown to reduce the growth rate at which the papillomata grow, although Healy demonstrated that the initial benefit seen at six months was gone by one year (8). Current standard of care includes therapy for patients requiring surgery greater than four times per year (3). The dose is increased to a target of 3 MU/m² body surface area. It is continued for at least six months. Side effects include flu-like symptoms, elevation of hepatic enzymes, renal insufficiency, anorexia, seizures, GI distress, and transient numbness (1). There is some suggestion that neutralizing antibodies may blunt its beneficial effect and that this may vary by brand (6). Results may vary considerably from patient to patient.

Indole-3-carbinol is a naturally-occurring product of cruciferous vegetables. It affects estrogen metabolism, shifting production to anti-proliferative estrogens. Only 25% of mice who were injected with papillomata and then fed I3C developed disease as compared to 100% of controls (13). As with interferon some patients have a much more pronounced response than do others. A recent phase I trial showed a third of patients undergoing remission, a third slowing their rate of growth, and a third with no response (17). Dosage is 200-400 mg for adults and 100-200 mg for children weighing less than 25 kg (1). It is a non-prescription drug and may be ordered by patients. It is well-tolerated.
Acylovir is a nucleoside analog which inhibits thymidine kinase, which is present in Herpesviruses but not HPV. A recent study has shown that some adults with RRP have molecular evidence of coinfection with other viruses, particularly HSV. It is felt that acyclovir acts to decrease disease by treating HSV which may potentiate HPV. However, HSV was not found in papillomata of children in one study (14,16).

Retinoic acid is a Vitamin A derivative which has been shown to modulate epithelial differentiation. It is used clinically in a variety of different settings, but its use in RRP is still limited. Side effects include dry skin and chelitis.

Photodynamic therapy involves the administration of a photosensitizing agent, dihematoporphyrin, which is concentrated in rapidly growing tissues. Following administration of this agent, the lesions are then excised with a tunable argon pump dye laser which preferentially destroys the tissues which concentrated the dye. The main side effect is photosensitivity which lasts weeks to months, and has sometimes led to hospitalizations for cutaneous burns.

Ribavirin is also a nucleoside analog which has been shown to be efficacious in respiratory syncitial virus. Preliminary data are under investigation.

Methotrexate inhibits DNA synthesis and repair by affecting folate metabolism. It has been used with some success in some patients.

Cidofovir inhibits DNA polymerase and has been used successfully in AIDS-related infections. Investigation is currently underway and has been complicated by the fact that this drug may be carcinogenic.

Conclusion

In conclusion, RRP is a disease which causes a substantial human and financial cost to the public. HPV has been shown to be the etiology. It affect people of all ages. Life-threatening airway obstruction may develop. The natural history is poorly understood but is characterized by spontaneous remission in some patients. Treatment is essentially palliative with surgical debulking. Various adjunctive drugs have been developed which slow but do not eradicate the progression of disease in some patients. Currently there is ongoing research aimed at improving the treatment of this insidious disease.

Bibliography


