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Review

Juvenile onset recurrent respiratory papillomatosis: possibilities for successful antiviral therapy

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Abstract

Recurrent respiratory papillomatosis (RRP) is a potentially devastating disease that can have significant morbidity, and can even result in mortality due to airway compromise or, less commonly, malignant transformation. Two distinct types of RRP exist: adult-onset RRP (AO-RRP) and juvenile-onset RRP (JO-RRP). Acquisition of human papillomavirus (HPV), the causative agent of RRP, is believed to occur in the peripartum period in the case of JO-RRP, with disease symptoms (primarily hoarseness) becoming apparent during the first several years of life. Treatment currently consists of surgical debulking of the papillomas to relieve airway obstruction. However, numerous antiviral therapies have also been evaluated, albeit primarily under uncontrolled settings. This article will review the biology, natural history and management of HPV infection, with particular emphasis on JO-RRP.

Keywords: Human papillomavirus; Laryngeal papillomatosis; Recurrent respiratory papillomatosis

1. Introduction

Papillomas (warts) have been recognized and described in human populations throughout the world since antiquity. Early clinicians realized that papillomas can be found in a number of anatomic locations, including both cutaneous (skin) and mucosal (genital tract, oral cavity, conjunctivae) sites. Near the end of the nineteenth century, the infectious nature of papillomas was confirmed when wart extracts were injected into humans and were found to produce disease. The viral etiology of warts was established by Ciuffo in 1907, when he successfully transmitted the infection to human volunteers using cell-free extracts (Ciuffo, 1907). Electron microscopy provided direct confirmation of the viral pathogenesis of papillomas beginning in the 1940s.

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However, further virologic characterization was impeded by two facts: (1) papilloma viruses are highly species specific, thereby limiting the utility of laboratory animals in the early research efforts; and (2) viral propagation in cell culture monolayers is not possible. Thus, even while tremendous advances were occurring during the 1940s and 1950s with such viral pathogens as polio and measles, investigation of the viral cause of papillomas was initially thwarted. Only with the advent of powerful molecular biology tools beginning in the 1970s was the understanding of the virology and pathophysiology propelled forward. Viral DNA analysis confirmed that, despite the prevailing view in the 1960s that a single species of papillomavirus accounted for all human papilloma (HPV) disease (Rowson and Mahy, 1967), in actuality scores of HPVs exist. At the current time, almost 100 HPVs have been detected utilizing polymerase chain reaction-based assays. Within this populous viral family, specific clinical manifestations of HPV are associated with specific HPV types.

Recent epidemiologic evaluations in the United States confirm that HPV infection is among the most prevalent of sexually transmitted diseases, with some reports suggesting that up to 75% of women in the US have genital HPV infection at some point in their lives (Syrjanen et al., 1990; Schneider et al., 1992). Between 500 000 and 1 000 000 new cases of genital HPV infection are estimated to occur each year in the US (Centers for Disease Control and Prevention, 1993), and at least 24 million persons in the US are genitally infected with HPV (Bonnez, 1997). Complications of genital HPV disease include the development of cervical carcinoma as well as HPV perinatal transmission, resulting in juvenile onset recurrent respiratory papillomatosis (JO-RRP). Though rare, JO-RRP can be a life threatening condition due to aggressive growth and re-growth of papillomas that can obstruct the patient's airway. In this review, the natural history of JO-RRP will be summarized, and potential treatment modalities discussed. Genital HPV infection will also be reviewed, as it relates to perinatal acquisition of HPV and subsequent development of JO-RRP.

2. Biology of human papillomaviruses

HPV are members of the Papillomavirus genus of the Papovaviridae family. The HPV genome consists of double-stranded circular DNA contained within an icosahedral capsid composed of 72 capsomeres. The genomes of approximately 75 types of HPVs have been completely sequenced and are available through the HPV sequence database at http://hpv-web.lanl.gov. The viral genome is divided into three regions: (1) the early region encodes gene products that are involved in viral DNA replication and cellular transformation; (2) the late region codes for both the major and the minor capsid proteins; and (3) the regulatory region contains the origin of replication and many control elements for transcription and replication (Pfister, 1984; Demmler, 1998).

As noted above, papillomaviruses are highly species specific. Thus, while papillomaviruses are widespread among vertebrates, each type has a narrow species specificity. Experimental infection of animals with papillomaviruses not native to their species can produce malignant transformation. Examples of the oncogenic potential of papillomaviruses include the cottontail rabbit (Shope) papillomavirus (Shope, 1933; Lancaster and Olson, 1982) and bovine papillomaviruses (Lancaster and Olson, 1982). No papillomaviruses are known to cross species barriers in humans: human papillomaviruses infect only humans, and no animal papillomaviruses are known to infect people.

In addition to species specificity, HPVs also demonstrate significant cellular tropism. Specific viral types usually produce disease at distinct sites in the body. For example, HPV-1, -2, -3, -4, -7, -10, -26, -27, -28, -29, -49 and -57 are associated with cutaneous warts, while HPV-6, -11, -16, -18, -30, -31, -33, -34, -35, -39, -40, -42, -43,-44, -45, -51, -52, -54, -55, -56, -57, -58, and -59 are associated with genital tract infection (de Villiers, 1989). As discussed below, JO-RRP primarily is caused by HPV-6 and HPV-11 (Terry et al., 1987; Kashima et al., 1991).

Viral propagation in cell culture monolayers has not been possible to date. Likely, this is because full epithelial differentiation required for

production of infectious virions is not achieved in conventional cell cultures (Shah and Howley, 1996). In efforts to overcome this impediment, both in vivo and in vitro systems have been devised. When keratinocytes or other susceptible tissue such as cervical epithelium or foreskin are exposed to HPV and then transplanted into an appropriate animal model (SCID mice and athymic nude mice, respectively), viral replication has been achieved as the transplanted tissue differentiates to form a multilayer epithelium (Kreider et al., 1985; Bonnez et al., 1993). Keratinocyte differentiation within the organotypic raft system has also allowed for viral propagation in vitro (Dollard et al., 1992; Meyers et al., 1992; Chow and Broker, 1997).

The recurrence of localized disease in both the genital and laryngeal regions following periods of clinical inactivity suggests that viral persistence or latency is occurring. Indeed, the viral genome can be detected in normal-appearing cells that are adjacent to papilloma sites (Steinberg et al., 1983; Ferenczy et al., 1985). However, investigations to date have not clearly delineated whether virologic latency accounts for these clinical and laboratory findings, or whether viral persistence with low-level viral replication is occurring (Shah and Howley, 1996). Regardless, it has been shown that presence of residual HPV DNA after papilloma treatment may lead to recurrent disease (Steinberg et al., 1988).

The possible association between HPVs and malignancy has been pursued for many years. Increasingly, the body of evidence confirms such a correlation. Papillomaviruses occupy an interesting historical place in the link between viruses and cancer, with the Shope papillomavirus of the rabbit providing one of the first experimental examples of a mammalian cancer virus and of an oncogenic DNA virus (Shope, 1933). More recent studies of the oncogenic potential of HPVs have concentrated on genital tract malignancies. The possibility that an infectious agent plays a role in the development of cervical cancer, for instance, has been suggested in numerous clinical and epidemiological studies (Fraumeni et al., 1969; Graham et al., 1979; Brinton, 1992). Evidence that HPVs might be such an infectious agent are several fold (Bonnez and Reichman, 1995): (1) more than 90% of cervical malignancies contain HPV DNA, usually HPV-16, HPV-18 and HPV-31; (2) these same HPV types are found in cervical intraepithelial neoplasias (CIN), which are premalignant lesions; and (3) HPV mRNA can be detected in the tissues of cervical malignancies, indicating that the HPV genome is being expressed (zur Hausen, 1985; Stoler and Broker, 1986; Anderson et al., 1991; Lorincz et al., 1992). Laboratory investigations of HPVs further support their role as an etiologic agent of cervical cancer. The genomic DNAs of the high-risk HPVs, HPV-16 and HPV-18, are capable of immortalizing human keratinocytes in cell culture, while those of low-risk HPVs are not (Durst et al., 1987; Storey et al., 1988; Woodworth et al., 1989; Kawashima et al., 1990; Shah and Howley, 1996). The viral genome is transcriptionally active in all HPV-associated lesions (Tsunokawa et al., 1986; Shirasawa et al., 1987; Stoler et al., 1992; Shah and Howley, 1996) and is found in both primary and metastatic tumors (Lancaster et al., 1986). The HPV open reading frames (ORFs) which convey transforming capabilities are the E6 and E7 ORFs. The E6 and E7 ORFs are consistently expressed in HPV-transformed cells and in HPV-associated tumors, with the degree of transcription correlating directly with the grade of the tumor (Durst et al., 1992; Stoler et al., 1992; Shah and Howley, 1996). Additional epidemiologic investigations provide further evidence of the role of HPVs in the development of cervical cancer (Campion et al., 1986; Koutsky et al., 1992). Human papillomaviruses may also be involved in the pathogenesis of other malignancies, both within the genital tract (Daling and Sherman, 1992; Demeter and Reichman, 1994) and in areas such as the larynx (Chang et al., 1992).

3. Clinical manifestations

3.1. Genital HPV infection

The majority of patients with anogenital warts present to their physician with asymptomatic growths on their genitalia (Chuang et al., 1984),

though occasionally patients will complain of pruritis, burning, pain, or bleeding. The warts are slightly hyperkeratotic, firm, exophytic papules that are flesh to dark gray in color. They can be either sessile or attached by a broad short peduncle, and are typically from 1 mm to 2 cm in size.

In circumcised men, the papillomas typically are found on the shaft of the penis, whereas in uncircumcised men they are most frequently located at the preputial cavity (Oriel, 1971; Chuang et al., 1984; Bonnez, 1997). Less commonly involved sites include the urethra, scrotum, perineum, groin, and pubic area. In women, the vast majority of clinically apparent lesions are located over the posterior introitus, including the fourchette, spreading toward the labia minora, labia majora, and clitoris. Less common sites of involvement include the perineum, vagina, anus, cervix, and urethra (Oriel, 1971; Bonnez, 1997). During pregnancy, genital papillomas can increase in both size and number (Osborne and Adelson, 1990). Regardless of anatomic location, most genital warts are caused by HPV-6, and to a lesser extent HPV-11 and other HPV types (Bauer et al., 1991; Sugase et al., 1991; Langenberg et al., 1993).

3.2. Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is characterized by the growth of papillomas at sites in the respiratory tract. While the papillomas can be found from the nasal vestibule to the peripheral lung, the larynx is the most common site of involvement. Two distinct groups of patients with RRP exist, namely those whose disease presents during childhood (juvenile onset recurrent respiratory papillomatosis, or JO-RRP) and those whose disease becomes apparent during adulthood (adult onset recurrent respiratory papillomatosis, or AO-RRP). By definition, patients with JO-RRP are diagnosed by 12 years of age, prior to the onset of consensual sexual activity. However, most children will have their JO-RRP detected within the first 5 years of life. The diagnosis of AO-RRP, on the other hand, peaks in incidence during the third and fourth decades of life. While in JO-RRP viral transmission probably occurs during the peripartum period (Hajek, 1956), the mode of transmission in AO-RRP is unclear.

Although accurate data regarding the prevalence and incidence of recurrent respiratory papillomas are not available, a task force on recurrent respiratory papillomas queried 1346 board certified otolaryngologists practicing in the US as of 1 January 1993 (Derkay, 1995). Based on a questionnaire survey, annualized incidences of 2354 new pediatric cases and 3623 new adult cases were reported. The incidence of the disease was estimated at 4.3 per 100 000 children younger than 14 years of age, and approximately 1.8 per 100 000 persons older than 15 years of age. Approximately 5970 active pediatric cases existed in the US in 1993, requiring 16 597 surgical procedures at a cost of $109 000 000. Since only 315 of the total 1346 questionnaires were returned, these data are likely a significant under estimation of disease prevalence and cost to the health care system.

Approximately one-half to two-thirds of patients with RRP have onset of illness during childhood, and thus have JO-RRP (Shah and Howley, 1996). The highest incidence of JO-RRP occurs in patients under 5 years of age (Strong et al., 1979). Most patients with JO-RRP come to medical attention due to hoarseness or voice changes. Indeed, RRP is the second most common cause of hoarseness in this age group, and is the most common benign neoplasm in the larynx (Jones and Myers, 1985; Morgan and Zitsch, 1986).

Papillomas most commonly are located in the larynx and most frequently involve the vocal folds where it interferes with normal closure during phonation and results in hoarseness (Figs. 1 and 2). Other sites commonly involved in JO-RRP include the vestibular fold and epiglottis. Papillomas may also occur throughout the respiratory tract, with or without laryngeal involvement. Other sites that may be involved include the trachea, lungs, nose, and oral cavity. The specific etiologic factors that predispose certain children to the development of aggressive and debilitating disease have not been defined. Children with very aggressive HPV disease may develop distal airway spread of the papillomas into the tracheobronchial tree and/or the pulmonary parenchyma; in these latter patients, the disease is fatal (Kramer et al., 1985; Cole et al., 1989). Although controversy

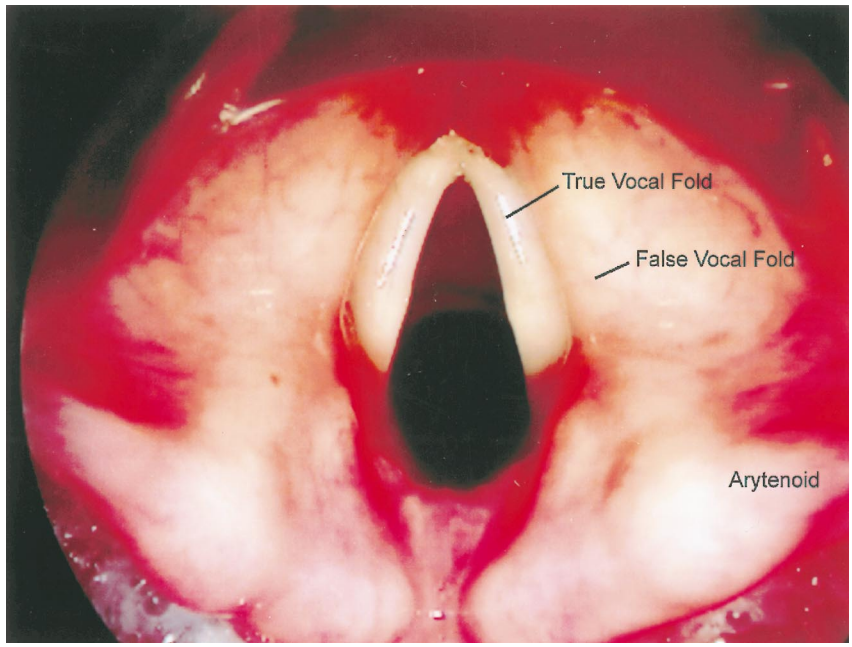

Fig. 1. Normal airway. (Photograph provided by David Malis.)

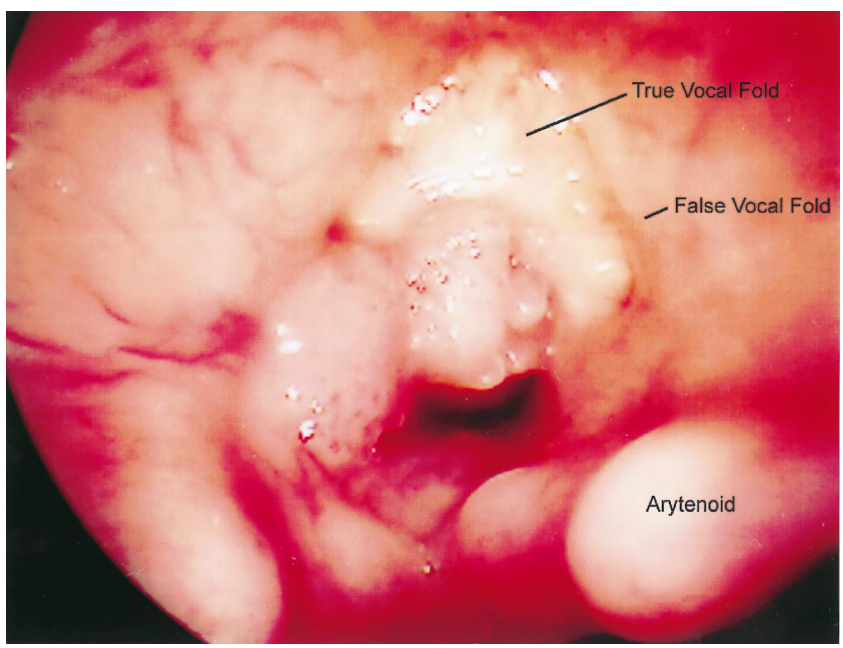

Fig. 2. Laryngeal papilloma. (Photograph provided by David Malis.)

remains as to whether performing a tracheotomy in those patients with life-threatening proximal airway disease (i.e. laryngeal obstruction) potentiates distal (i.e. tracheobronchial and/or pulmonary parenchymal) airway seeding, there is some evidence that tracheotomy is an independent risk factor in the development of subsequent distal airway spread (Cole et al., 1989).

There is extensive evidence to support the theory that viral transmission in JO-RRP occurs during the peripartum period as the neonate passes through an infected birth canal (Hajek, 1956). Evidence for this likelihood is several fold (Shah and Howley, 1996): (1) 30–60% of mothers of JO-RRP patients have a known history of genital warts, compared with $< 5\%$ of mothers whose children do not have JO-RRP (Cook et al., 1973; Quick et al., 1980; Abramson et al., 1987); (2) the vast majority of children with JO-RRP are born vaginally and thus have a potential exposure to an infected birth canal, though cases of JO-RRP have been reported among children delivered by cesarean section (Shah et al., 1986); and (3) HPVs can be detected for several weeks in the oropharynx of infants born to mothers with genital warts (Fredericks et al., 1993). However, of those children who develop JO-RRP, not all have mothers with evidence of vaginal HPV disease. Clinicians should consider the possibility of sexual abuse in children who acquire RRP outside the peripartum period (Yoshpe, 1995).

HPV types 6 and 11 are primarily responsible for RRP, with HPV-6 being the most common (Terry et al., 1987; Kashima et al., 1991). However, other viral types have been implicated as well, including HPV-16 and -18 (Chang et al., 1992). Infection by HPV-11 has been correlated with the most severe form of RRP disease, including extension into the trachea and lungs (Mounts and Kashima, 1984; Hartley et al., 1994; Rimell et al., 1997). Clinically, the disease course exhibits extreme intra- and inter-patient variability with some patients experiencing periods of relatively accelerated disease activity admixed with periods of relative quiescence. Although controversial, some patients and clinicians have observed that the disease becomes less aggressive (as manifest by less frequent surgical interventions) as a child with JO-RRP enters puberty. Whether this is strictly because the diameter of the airway has increased as the patient has grown, or whether there are hormonal factors at work, remains to be fully elucidated. In very rare instances, patients with RRP may undergo spontaneous remission, with AO-RRP patients being more likely to experience this than are JO-RRP patients (Bjork and Teir, 1957; Holinger et al., 1968).

In 3–5% of RRP patients, spontaneous malignant transformation/degeneration of previously benign papillomas to squamous cell carcinoma occurs and appears to be independent of the apparent risk factors of tobacco use or exposure to radiation therapy (Solomon et al., 1985; Kashima et al., 1988). This malignant degeneration is most commonly associated with HPV types of high-malignant potential (i.e. HPV-16 and HPV-18), occurs in both JO-RRP and AO-RRP, and carries a dismal prognosis.

4. Treatment of JO-RRP

4.1. Surgical therapies for RRP

Numerous treatment modalities have been utilized for the management of RRP. At the present time, the most common intervention is laryngoscopy with surgical debulking of the papillomas. Unfortunately, the papillomas recur following surgical resection, frequently necessitating repeated ablative efforts to maintain a patent airway. In younger pediatric patients, a smaller caliber airway, associated with aggressive disease, occasionally necessitates surgical debridement as frequently as every 2 weeks to maintain the airway. Such frequent surgical intervention can have a tremendously deliterious psychological impact on the pediatric patient, their family, and the clinician.

The surgical management of proximal airway (i.e. laryngeal) papillomas has involved either the mechanical debulking of the papillomas with microlaryngeal instruments or with the CO_2 laser, though sharp dissection techniques, cauterization, and the application of acetic acid or podophyllum have also been described (Bauman and Smith,

1996). Although extremely precise, the CO_2 laser is not without its own inherent problems, including: (1) thermal injury to adjacent normal soft-tissues, resulting in permanent laryngeal scarring; (2) aerosolization of HPV viral particles into the laser plume thereby posing potential risks to the patient and operating room team; and (3) risk of a laser-induced airway fire. Fortunately, the development of a laryngeal microdebrieder, a technology adapted from orthopedic arthroscopic equipment, has seemingly overcome some of the shortfalls of the CO_2 laser.

As previously noted, papilloma regrowth occurs at variable rates of time after any of these procedures, with no therapy being curative; similarly, the average number of operative procedures annually is highly variable from patient to patient. Unfortunately, the aforementioned surgical treatment modalities have not resulted in curing this virally-mediated recurrent disease, and therefore several adjuvant therapies have been evaluated.

4.2. Adjuvant therapies for RRP

The most commonly accepted adjuvant therapy for RRP is the systemic use of interferon α-2a. Multi-institutional human trials of interferon α-2a have shown variable efficacy in patients with aggressive RRP (Healy et al., 1988; Leventhal et al., 1991). Unfortunately, in those patients who experience a good clinical benefit (e.g. partial or complete response), a significant rebound phenomena (i.e. resurgence of the lesions with discontinuation of treatment) was reported in approximately one-third of patients. Anecdotal reports of adjuvant therapy combining interferon with methotrexate in patients with pulmonary parenchymal disease have found some benefit in a few patients (Avidano and Singleton, 1995). Unfortunately, recent reports have now implicated interferon in the development of spastic diplegia (Barlow et al., 1998).

Although thought to be potentially beneficial in epithelial maturation, *cis*-retinoic acid has been ineffective in the management of HPV infection in humans (Bell et al., 1988; Avidano and Singleton, 1995).

Similarly, non-controlled studies suggesting that acyclovir decreases the extent of respiratory papillomatosis in patients with recalcitrant disease have been reported (Endres et al., 1994). However, the beneficial effect of acyclovir appears to be insufficient to counteract the rebound phenomenon when interferon was stopped abruptly.

Photodynamic therapy, based on the selective uptake of hematoporphyrins by neoplastic cells, was shown to decrease the rate of laryngeal papilloma growth following treatment of human subjects (Abramson et al., 1992, 1994). However, latent infection has been noted to persist after photodynamic therapy, and photosensitivity can persist for weeks after the therapy has been discontinued.

Animal studies utilizing the cottontail rabbit papillomavirus model have found that intradermal ribavirin administration reduces the number of lesions, decreases the time of first appearance of lesions, and reduces the overall mass of the lesions when administered prior to infection (Ostrow et al., 1992). However, no reports of the use of ribavirin in human subjects exist at this time.

Finally, cidofovir has demonstrated promise as an effective treatment of HPV infections in pediatric and adult patients with laryngeal papillomatosis in several small, uncontrolled reports (Snoeck et al., 1996, 1998; Pransky et al., 1999). Cidofovir is a cytosine nucleotide analog with potent in vitro and in vivo activity against a broad spectrum of viruses, including cytomegalovirus, herpes simplex virus types I and 2, varicella-zoster virus, Epstein-Barr virus, human herpesvirus-6, human herpesvirus-8, polyomaviruses, adenovirus, and HPV. It has been approved by the Food and Drug Administration (FDA)for the treatment of CMV retinitis. The major dose-limiting toxicity experienced by recipients of cidofovir is nephrotoxicity. Product labeling by the FDA indicates that cidofovir should be considered a potential carcinogen in humans due to its propensity to cause tumors, primarily mammary adenocarcinomas, in rats.

Intralesional administration of cidofovir to patients with RRP, with or without initial surgical debulking of the lesions, has been reported to produce dramatic improvement in some patients.

However, these anecdotal studies were not controlled and the role of inter- and intra-patient disease variability was not scientifically excluded. Thus, while the initial reports of the efficacy of intralesional cidofovir are encouraging, caution should be maintained in how these limited data are interpreted. Furthermore, the safety of intralesional cidofovir administration has yet to be established: the development of adenocarcinomas in animal models suggests that controlled studies of this compound are warranted, as opposed to the widespread use of cidofovir outside of a study setting. Validating this concern was a recent report of three patients in a European study treated with intralesional cidofovir who subsequently developed squamous cell carcinoma at the injection site; though each of these patients had associated risk factors for the development of laryngeal cancer, the use of intralesional cidofavir was, at the least, a confounding variable (Pransky et al., 1999). The mechanism of cidofovir's potential activity against HPV is unclear.

Although intralesional cidofovir is the most promising modality to date for the treatment of severe RRP, the above clearly highlights the need for a prudent, careful, and rigorously scientific evaluation of this compound. Currently, the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) is conducting a controlled Phase I/II investigation of intralesional cidofovir for the treatment of pediatric laryngeal papillomatosis, with close supervision by the FDA. It is anticipated that this controlled trial will determine what further investigation of cidofovir, if any, is warranted in the management of JO-RRP.

Finally, RRP remains an orphan disease with a relatively miniscule prevalence. Further complicating the study of this disease is the geographically wide-spread location of the patients and their treatment by otolaryngologists in community, tertiary care, and academic institutions. Unfortunately, due to these aforementioned confounding factors, most of the antiviral trials for the treatment of RRP have been dramatically limited by their uncontrolled nature. Although extensive networks have been established by patient groups, in which anecdotal research information is shared (primarily over the internet), this has actually served to further erode the ability of large, controlled studies to be performed. It is only through the conduct of large, multicentered, controlled studies in which uniform scoring systems and outcome measures are employed that the potential efficacy of any given treatment modality can be established. Diligence, therefore, must be maintained, both by investigators and by patients, in order for any treatment modality to be proven effective and of benefit to future patients with this devastating disease.

5. Summary

Much has been learned in recent years about the pathophysiology of JO-RRP. As new antiviral therapies are developed and evaluated, it is hoped that this disease can be better controlled and possibly even cured. Recognition of these shared goals of all persons involved in the care of affected children, be they parents or physicians, will undoubtedly assist in our common efforts to minimize the impact of this chronic infection and improve upon its management and treatment.

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