Recurrent Juvenile Onset Respiratory Papillomatosis

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A five-year-old girl received the diagnosis of respiratory papillomatosis after an episode of respiratory distress in which the collapse of the right lung required intubation. During bronchoscopy, a single laryngeal papilloma and multiple tracheal papillomas (Panel A) were seen (up to a distance of 1.5 cm above the carina), which partially obstructed the lumen of the airway. In situ hybridization of the pathological specimen with a probe for human papillomavirus serotypes 6 and 11 confirmed that it contained the virus. The patient was treated with interferon and with periodic laser removal of the recurrent laryngotracheal papillomas. Sixteen months later, pulmonary involvement with papillomatosis was evident and was complicated by several pneumonias. Therapy with ribavirin and systemic cidofovir failed. A computed tomographic scan of the chest obtained when the patient was 10 years old showed discrete nodular papillomas (Panel B, arrow) and multiple cavitary lesions in the lung fields. She subsequently died of complications of pneumonia.
Recurrent Juvenile Onset Respiratory Papillomatosis

- Most common benign airway neoplasm in children
- Caused by human papilloma virus types 6 and 11
- Presumed to be acquired mainly by vaginal delivery
- Estimated incidence in children: 4.3/100,000
- 75% of children diagnosed by age 5 years
- Larynx most commonly affected, frequent recurrences, voice changes, airway compromise
- Often numerous surgical procedures, estimated 10,000 surgical procedures in the U.S.

Although benign in nature, chronic disease with significant morbidity and occasional mortality

Schraff et al. 2004; Derkay & Wiatrak 2008
Molecular Pathogenesis

- Preferential occurrence at epithelial transformation zones
- Entry into basal keratinocyte after microtrauma / abrasion
- Papillomas arise from disordered proliferation of differentiating keratinocytes
- High level of EGF receptors on affected cells
- Core of highly vascular connective tissue
- Malignant transformation may occur in association with HPV 11, molecular events unclear

Goon et al. 2008; Derkay & Wiatrak 2008
Molecular Pathogenesis

• Many exposed, only few get the disease

• Candidates:
  • MHC
  • Innate Immunity
    – Toll-like receptors
    – Cytokines regulating the inflammation
    – Transcription factors regulating immune response
  • Known Cell Biology Interactions
    – E5 inhibits H\(^+\)ATPase from acidifying vesicles
    – HPV cell receptor
  • Other Diseases
    – Epidermodysplasia verruciformis
    – Cervical Cancer

Buchinsky 2008
Clinical Presentation
and Diagnosis
Clinical Presentation and Diagnosis

• Progressive hoarseness, stridor, respiratory distress
• Less often chronic cough, recurrent pneumonia, failure to thrive, dyspnea and dysphagia

• Diagnosis made by
  – visualization of the papillomata via flexible naso-laryngoscopy or direct laryngo-bronchoscopy
  – Biopsies for histological confirmation and HPVtyping and exclusion of malignant transformation

• Natural history highly variable and unpredictable
  – Spontaneous remission
  – Stable state with only periodic surgical treatment
  – Aggressive with surgery every few days to weeks and consideration of adjuvant therapies

Derkay & Wiatrak 2008
ASPO Pediatric Otolaryngology Practice Survey 2002

- Experience with 700 children with RRP
  - 150 (21%) adjuvant therapies
    - Intralesional cidofovir (72)
    - Interferon (25)
  - 94 (13%) with distal spread
    - Trachea (53)
    - Trachea and bronchi (20)
    - Trachea, bronchi, and lungs (19)
    - Lungs only (2)
  - 25 fatal cases
    - Pulmonary failure (15; pneumonia, cavitary lung disease)
    - Anaesthesia-related (7)
    - Malignant transformation (3)

Schraff et al. 2004
Factors with Prognostic Impact

• Younger age at diagnosis associated with more aggressive disease and need for more frequent endoscopic surgical procedures and tracheotomy

• HPV 11 associated with more aggressive disease than HPV 6 and a higher rate of malignant transformation and death (36 and 24% vs. 0% at 20 years in an IFN-treated cohort of 42 pts)

• Tracheotomy associated with aerodigestive spread and lung involvement

• Lung involvement has dismal prognosis

1 Wiatrak 04; 2 Wiatrak 04; Gerein 05 3 Blackledge 00; Cole 89; Soldatskii 05; 4 Gelinas 08
Lung Involvement in RRP

Kramer et al. 1985
Lung Involvement in Juvenile Onset RRP

- Systematic review of studies investigating RRP with lung involvement in patients ≤ 20 years including 101 studies (23 cohorts, 4 case series, 72 case reports, 2 open trials) with 1666 pts and 55 cases

- From the cohort studies, the incidence of lung involvement in RRP was estimated at 3.3%. The incidence of cancer in cases with lung involvement was 16%
  - The median interval between the diagnosis of RRP and that of lung involvement was 8 years (range <1—45 years)
  - The median interval between the diagnosis of RRP and that of cancer was 19 years, with a range of 4—45 years

- No conclusions feasible regarding treatment effectiveness
  - IFN appears not effective (40/51 failures; 1 responder)
  - IV cidofovir needs better evaluation (5/11 some response)

Gelinas et al. 2008
Management
Principles of Management

• At present, there is no cure for RRP, and no single treatment shown to be effective in eradicating RRP

• Surgical therapy is current standard of care with goal of complete removal of papillomas and preservation of normal structures and function

• Adjunctive therapies to surgical debulking may be needed in up to 20% of cases; consensus about their indications exists

• Interdisciplinary approach is mandatory and needs to be established at the time of initial presentation

Derkay 1995
Staging RRP Severity

• Several systems, none uniformly accepted

• Creates confusion regarding description of natural history and responses to interventions

• Staging system of Derkay
  – Based on area of involvement, severity, and functional parameters
  – Available as licensed software

Laryngoscopic and Clinical Assessment Scale for RRP

A. Clinical Score
1. Describe the patient’s voice today:
   normal__ (9), abnormal__ (1), aphonic__ (2)
2. Describe the patient’s stridor today:
   absent__ (9), present with activity__ (1), present at rest__ (2)
3. Describe the urgency of today’s intervention:
   scheduled__ (3), elective__ (1), urgent__ (2), emergent__ (3)
4. Describe today’s level of respiratory distress:
   none__ (9), 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___
• Supraglottis___

TRACHEA:
• Upper one-third___
• Middle one-third___
• Lower one-third___
• Branches:___ Right__ Left__

OTHER:
• Nose___
• Parotid___
• Pharynx___
• Esophagus___
• Lungs___
• Other___
Total Anatomical Score

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

Derkay 1998; Derkay 2004
Surgery
Surgical Approaches

• **Goal**
  – To remove disease
  – To preserve anatomical structure and function
    • Cold steel microinstrumentation
    • CO₂, flash dye or pulsed dye laser
    • Endoscopic microdebrider
    • Spontaneous ventilation preferred method of anesthesia

• Impossible to distinguish infected from noninfected epithelia
• Repeat recurrences frequent / repeat surgery may cause serious complications
• Tracheotomy may become necessary in extensive disease
  – Predominant risk factor for extension to lower airways *

Soldatskii et al. 2005
Surgical Approaches

Courtesy of S. Carter Wright, Jr. MD, Winston Salem, NC
Adjuvant Therapies
Adjuvant Therapies

• Criteria for initiation of adjuvant therapies *
  – > 4 surgical procedures / year
  – Distal spread of the disease
  – Rapid regrowth with airway compromise

• Interferon
• Intralesional cidofovir
• Systemic antiviral / antineoplastic agents; photodynamic therapy; dietary supplements; intralesional mumps vaccine; differentiating agents; cimetidine; artemisinine; COX-2 inhibitors; EGF/VEGF signal transduction; therapeutic vaccination; HspE7 fusion protein

* Derkay & Wiatrak 2008
Adjuvant Therapies: Recombinant Interferon alpha

• 12-month randomized crossover study in 66 pts with clinically severe juvenile-onset RRP to evaluate IFN alpha as an adjuvant to CO2 laser surgical excision

• Eligibility
  – disease onset to be before age 16
  – at least 3 endoscopic procedures in the 6 months prior to entry

• Randomization:
  – Observation versus IFN at 5 MU/m2 daily x 28 days and x 3/ week for 5 mo

• Evaluation:
  – Composite score (number of diseased anatomic sites / extent of disease)
  – endoscopic excisions every 2 months with evaluation of composite scores

• Significant lowering of score during IFN; CR in 9/ 57 evaluable pts vs. none during observation

• No dose-limiting or unexpected toxicity

Leventhal et al. 1988
Adjuvant Therapies:
Longterm follow up, Interferon

• Late-follow-up in 60 of the 66 subjects after median of 4 years:
  – 22 complete and 25 partial remissions; 13 pts no response
  – Median duration of the complete remissions was 550 days, and 15 pts continued to be in complete remission
  – Median duration of partial remissions was 400 days and seven pts were still in partial remission
  – Thirteen of 28 pts responded to a second course of IFN after an interruption in treatment of at least one month

• Patients with severe RRP may have a sustained or repeated response to treatment with IFN

Leventhal et al. 1991
Adjuvant Therapies: Longterm follow up of Interferon

- 20-year follow up of multicenter prospective series of 42 patients from 22 hospitals with RRP who were treated with IFN-alpha in doses of 3 MU/m² 3 times per week

- During mean +/- SD follow up of 172 +/- 36.8 months, event-free survival was 42.8%, and overall survival 82.6%

- HPV typing analysis
  - an association of HPV 11 with a more aggressive disease course (64% of HPV 11 pts versus 24% of HPV 6 pts),
  - a lower incidence of long-term response to IFN-alpha therapy (14% of HPV 11 pts versus 64% of HPV 6 pts),
  - and a higher incidence of malignant transformation and mortality during follow-up (36% and 24%, respectively, of HPV 11 pts versus 0% of HPV 6 pts).

Gerein et al. 2005
Adjuvant Therapies: Intralesional Cidofovir

- Cidofovir has activity against HPV in vitro
- 17 studies of intralesional cidofovir including 158 patients; various treatment schemes (1 to 22 injections over 1 to 54 months) and doses; various other adjunctive therapies
  - 90 (57%) complete responses
  - 55 (35%) partial responses
  - 13 (8%) no improvement
- Safety issue: Carcinogenicity / nephrotoxicity
Adjuvant Therapies: Safety of Intralesional Cidofovir

- Literature review including 31 articles with a total of 188 patients with RRP who received intralesional cidofovir
  - Five patients (2.7%) have developed dysplasia of the larynx during the treatment with cidofovir
  - This percentage is concurrent with the incidence of spontaneous malignant degeneration of RRP (2-3%)

- Authors conclusion: The use of intralesional cidofovir may not increase the risk of laryngeal dysplasia

Broekema & Dikkers 2008
Targeted Therapies and Therapeutic Vaccines
COX-2 as Target to Suppress Papilloma Growth

• COX-2 levels markedly overexpressed in papillomas, reflecting activation of EGFR->phosphatidylinositol 3-kinase signaling

• Treatment with prostaglandin E2 (PGE2) induced COX-2, whereas celecoxib, a selective COX-2 inhibitor, suppressed levels of COX-2

• Moreover, treatment with PGE2 stimulated papilloma cell growth, whereas celecoxib suppressed proliferation and induced apoptosis

COX inhibitors may be useful in the management of RRP
Very promising responses as AT in three adult patients

Wu et al. 2005
Clinical Celebrex® Trial Study Design

- Children > 4 years of age (approved for >2 years in RA)
- Study lasts 30 months for each patient
- Surgery every 3 months during the study, unless free of disease, then office evaluations every three months
- Blood tests every three months at time of surgery for biological studies
Targeted Therapies: Inhibition of EGF / VEGF Pathways

Human papillomatisis *E5 gene stimulates the transforming activity of EGFR* [Pim et al. 92]

Respiratory papilloma cells have *high levels of EGFR* [Vambutas et al. 93]

*EGFR is overexpressed* in respiratory papillomas compared with normal laryngeal epithelium [Johnston et al. 99]

Targeted disruption of the EGFR inhibits development of papillomas from human papillomavirus-immortalized keratinocytes [Woodworth et al. 00]

The angiogenic growth factor *VEGF-A is strongly expressed in the epithelium* of squamous papillomas in RRP. VEGFR-1 and VEGFR-2 mRNAs are *strongly expressed by underlying vascular endothelial cells* [Rahbar et al. 05]
Targeted Therapies: Inhibition of EGF / VEGF Pathways

- The EGFr signaling pathway is involved in cell growth and proliferation, and monoclonal antibodies and small-molecule inhibitors have been developed to inhibit EGFr pathways
- Targeted therapies based on inhibition of EGFr and angiogenesis are used in head and neck squamous cell carcinoma (HNSCC)
  - **Anti-EGFr antibodies**
    - Cetuximab (Erbitux®)
  - **Smallmolecule tyrosine kinase inhibitors**
    - Gefitinib (Iressa®)
    - Erlotinib (Tarceva®)
  - **Anti VEGF antibodies**
    - Bevacicubumab (Avastin®)
  - Combination of EGFR- and angiogenesis inhibition
  - Combination of TKIs with the COX-2 inhibitor celeceoxib

Bernier et al. 2009
Adjuvant Therapies: Tetravalent HPV Vaccine

- Tetravalent HPV vaccine Gardasil® induces neutralizing antibodies against capsid antigens of the HPV types 16, 18, 6 and 11
- It can efficaciously prevent new genital infections by one of the four vaccine types as well as the epithelial lesions induced by them
- However, the vaccine had no effect against pre-existing genital infections or lesions. Nevertheless, HPV vaccination may have a therapeutic effect in RRP by preventing new papilloma formation at additional sites or in patients who have achieved a remission
  - Two year old boy with RRP and simultaneous infection with the HPV-types 6/11
    - stable disease after 3rd injection
  - Four year old girl with RRP and infection with HPV type 11
    - no apparent response but progressive lung disease after 3 injections

Foerster 2008; Pawlita 2009; personal observation
Conclusions
Recurrent Juvenile Onset Respiratory Papillomatosis

- Multidisciplinary approach is needed
- Uncertainties about
  - Optimal surgical approach
  - Role of adjuvant therapies
  - Monitoring and follow up
- Low incidence poses significant problems in recruitment of subjects in sufficient numbers
- Universal or near universal use of an HPV vaccine with activity against HPV 6 and 11 may greatly reduce the global burden of the disease
Anecdotal Adjuvant Therapies
Anecdotal Adjuvant Therapies: Anticancer Agents / Isotretinoin

• Methotrexate
  Antimetabolite, anticancer agent
  – Responses as 3rd line adjuvant therapy in 3 patients (1 mg/kg 1-2x /week adjusted to blood counts) [Avidano 95]

• Cytarabin
  – 3/10 children with complete response [Hendrickse 85]

• Isotretinoin
  – Reverses abnormal differentiation of epithelial cells
  – No known direct antiviral properties; 1-2 mg/kg/day, BID
  – No response in 5 patients [Avidano et al. 1995]; no effects in placebo-controlled pilot study [Bell 1988]; responses in 3/5 patients [Alberts 1986] and very few individual cases
Anecdotal Adjuvant Therapies: Systemic Antiviral Agents

• Aciclovir
  – Action dependent on thymidine kinase (not encoded in HPVs)
  – Beneficial effects likely due to action on co-infectors
  – Three small case series including 22 patients, 15 reported to have responded in some way - difficult to assess

• Ribavirin
  – Inhibits cutaneous warts in rabbits infected with rabbit HPV
  – Responses in 3 of 5 reported patients

• Cidofovir
  – acyclic nucleoside phosphonate analogue; active in vitro and in vivo
  – 5 of 11 reported cases with some response (all lung involvement)

Chadha & James 2005; Chadha & James 2007; Gelinas 2008
Anecdotal Adjuvant Therapies: PEG-IFN plus Ribavirin

Treatment of Human Papillomavirus with Peg-interferon Alfa-2b and Ribavirin

- Medical Sciences School, University of Campinas; Campinas, SP, Brazil

HIV / HCV co-infected patient who had significant improvement of HPV lesions during the treatment of chronic hepatitis using peg-interferon alfa-2b and ribavirin

Pavan et al. 2007
Anecdotal Adjuvant Therapies: Nebulized Cidofovir

- **Nebulized Cidofovir**
  - CR 11 mo old girl with pulmonary involvement
  - Nebulized Cidofovir 20mg/mL: 4 mL x3/wk
  - Hemoptysis – 10 mg/mL x3/week
  - Responded with near complete response

Giles et al. 2006
Anecdotal Adjuvant Therapies: Indole-3 Carbinol

- Indole-3-Carbinol (I3C) is abundant in cruciferous vegetables and has been shown to decrease papillomatous growth in cell cultures and be effective in an animal model of RRP.
- In a prospective, open-label study design, pts with RRP received I3C (200 mg PO BID) after complete surgical removal. Further surgery was performed on an as-needed basis.
- 33 patients treated with I3C were available for long-term follow-up (mean=4.8 years), whereas 12 patients were lost to follow-up. Eleven (33%) patients experienced remission of papillomatous growth and did not require surgery while on I3C. Ten (30%) patients had a reduction in papillomatous growth that resulted in less frequent surgery. Twelve patients (36%) had no response.
- Of the 9 pediatric patients available, 1 experienced a complete response, 3 a partial response, and 5 had no response to I3C.
- Twelve pts with a positive response (partial or complete) to I3C are still taking I3C. Seven positive responders discontinued I3C, 3 of which have remained disease-free.
- No immediate or long-term side effects related to I3C were found.

Rosen et al. 2004
Anecdotal Adjuvant Therapies: Photodynamic Therapy

- Dihematoporphyrin ether led to a small but significant decrease in RRP growth, especially in pts whose disease was worse
  - patients become markedly photosensitive for 2 to 8 weeks after treatment

- M-tetra(hydroxyphenyl)chlorine was effective in rabbits with minimal tissue damage and less photosensitivity

- A randomized clinical trial of this drug in 23 pts with severe RRP resulted in improvement in laryngeal disease
  - papillomas recurred in 3 to 5 years, and the therapy was poorly tolerated by a quarter of the patients.

Shikowitz 98; Shikowitz 05
Anecdotal Adjuvant Therapies: Intralesional Mumps Vaccine

- Initially, 11 children with RRP treated in a pilot study with laser excision at regular intervals for at least a year without adjuvant therapy; later, a series of 18 children and 20 adults with RRP, some of whom had used various adjuvant therapy with interval laser excision. INTERVENTIONS: Both patient groups continued their same interval laser excision with the same or similar laser, same clinical setting, and same surgeon. Locally injected mumps vaccine was then administered into the excision site after each laser removal of papilloma. OUTCOME MEASURES: Larynx and trachea were microphotographed with each treatment. Two consecutive disease-free intervals and a follow-up of at least 1 year were required criteria for remission. RESULTS: In the pilot study, remission was induced in 9 (82%) of 11 patients by 1 to 10 injections, with follow-up of 5 to 19 years. In the subsequent series, remission was induced in 29 (76%) of 38 patients by 4 to 26 injections, and follow-up was 2 to 5 years. CONCLUSIONS: Combined with serial laser excision, mumps vaccine positively influences induction of remission in children with RRP. The mechanisms of this effect are unclear.

Pashley 2000
Anecdotal Adjuvant Therapies: Miscellaneous Interventions

• Artemisinin
  – Immunomodulatory / apoptotic effects
  – Anecdotal experience

• Ranitidine/cimetidine
  – Gastroesophageal reflux may have a role in aggravating papillomatosis [Borkowski 99; Harcourt 99; Mc Kenna 05]
  – Control of GERD may improve RRP, cimetidine may have additional immunomodulatory properties
Inhibiting COX-2 Reduces Papilloma Cell Proliferation and Increases Apoptosis

Wu et al. 2005
Three Patients Treated in Pilot Study

Shikowitz et al. 2007
Targeted Therapies: Inhibition of EGF / VEGF Pathways

• Human papillomatosis E5 gene stimulates the transforming activity of EGFR, dramatically increasing proliferation in agar [Pim et al. 92]

• Respiratory papilloma cells have high levels of EGFR and respond to epidermal growth factor by a decrease in epithelial differentiation [Vambutas et al. 93]

• Epidermal growth factor receptor is overexpressed in respiratory papillomas compared with normal laryngeal epithelium, and it is recycled to the surface after stimulation with epidermal growth factor [Johnston et al. 99]

• Targeted disruption of the EGFR inhibits development of papillomas and carcinomas from human papillomavirus–immortalized keratinocytes [Woodworth et al. 00]

• The angiogenic growth factor VEGF-A is strongly expressed in the epithelium of squamous papillomas in RRP. VEGFR-1 and VEGFR-2 mRNAs are strongly expressed by underlying vascular endothelial cells, suggesting a role in the pathogenesis of RRP [Rahbar et al. 05]
Adjuvant Therapies: Targeted Therapies

• Gefitinib Therapy for Life-Threatening Laryngeal Papillomatosis in a 14 year old boy
  – Therapy with gefitinib showed an immediate and dramatic response, which stopped on discontinuation of the therapy and resumed on its reintroduction [Bostrom et al. 2005]

• Cetuximab therapy for aggressive recurrent respiratory papillomatosis in a neonate
  – Control with repeat debulking, systemic therapy with cetuximab and intralesional cidofovir [Loyo et al. 2008]