Recurrent Respiratory Papillomatosis Update

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Human Papilloma Virus

- DNA virus
  - 7,900 bp long dsDNA
- Nonenveloped, icosahedral
- HPV type 6 and 11
  - Also cause genital warts
  - Type 11 = more severe
- Other types identified
  - Type 16 and 18 (most malignant potential)
  - Type 31 and 33 (intermediate malignant potential)

Epithelial Disease

- HPV infects basal cells
- Viral particles bind to cell-surface receptors
- Enter the cell
- Transported to nucleus
- Viral genome released and replicated
- Viral DNA transcribed into RNA → viral proteins

Epidemiology

- Childhood onset
  - Often dx 2-4 yrs old
  - 1.7-4.3 per 100,000
  - No gender/ethnic difference regarding surgical frequency
  - More aggressive
  - 19.7 surgeries per child
  - 4.4 per year

- Adult onset
  - Peaks btwn 20-40 yrs
  - 1.8 per 100,000
  - Slight male predominance
  - Less aggressive
  - 50% pts need < 5 procedures over their lifetime compared to <25% of children

Transmission

- Exact mode of transmission unclear
- Childhood disease thought to be transmitted during gestation or passage through birth canal
  - Vaginal delivery, firstborn, young mother, low socioeconomic status cited as risk factors
- Estimated risk of disease transmission from mother with active condylomata 1:400
- Adult onset RRP
  - Reactivation of latent infection
  - Newly acquired sexually transmitted disease

Lesion Characteristics

- Most often occur at sites where ciliated and squamous epithelium are juxtaposed

<table>
<thead>
<tr>
<th>Site</th>
<th>Single lesion</th>
<th>Multiple lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottic</td>
<td>1%</td>
<td>26%</td>
</tr>
<tr>
<td>Glottic</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>Subglottic</td>
<td>2%</td>
<td>58%</td>
</tr>
<tr>
<td>Tracheal</td>
<td>0%</td>
<td>14%</td>
</tr>
<tr>
<td>Bronchial, pulmonary</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
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Treatment

- Surgery is mainstay of therapy
  - Eradication of disease from airway
  - Improvement in voice quality
  - Control of disease spread
  - Decrease in number of OR trips
- Adjuvant therapies
  - Many agents, none FDA approved
  - No proven benefit in studies

Surgical Management

- Goals
  1. Ablate clinically involved epithelium
  2. Preserve uninvolved submucosal tissue
     - Sub-epithelium
     - Vocal fold lamina propria
- Surgical techniques
  1. Shaving/excision
  2. Ablation/vaporization
Microdebrider Versus CO₂ Laser Removal of Recurrent Respiratory Papillomas: A Prospective Analysis


Study of 19 patients with JORRP randomized by birth year

P<.388  P<.05

CO₂ Laser vs. Microdebrider

- Ablation or excision
- Shorter procedure time
- Precision
- Avoidance of risk for airway fire
- Hemostasis
- Better for sessile lesions
- Decreased cost

Shaving/Excision
Ablation/Vaporization

Pattern Generators
- Available for articulated arm delivery systems
- Require direct line-of-site
- Standard micromanipulators deliver a focused laser beam
  - Spot - 250 microns diameter
- Pattern generator uses a computer to create a pattern
  - Lines up to 5 mm in length and 250 microns in width
  - Circles up to 4 mm in diameter

Acublade™
- Focused Spot 250 microns
- Computer Generated Line 4mm long by 250 micron wide

Surgitouch™
- Focused Beam 250 micron diameter
- Pattern Generator 1.5 mm ablation circle
Pattern Generators

- Allows surgeon to choose relative depth of incision/ablation
- Computer generates pattern and calculates power
  - Each “pass” of the pattern penetrates tissue 200 to 250 microns
    - Variability due to
      - Focus of beam
      - Hydration/water content of tissue
- Surgeon chooses the number of “passes” or depth of ablation
  - 1 pass – 200 to 250 microns
  - 2 passes – 400 to 500 microns
  - 3 passes – 600 to 750 microns

Control of Depth

- Variability due to:
  - Focus of beam
  - Hydration/water content of tissue
- Surgeon chooses the number of “passes” or depth of ablation
  - 1 pass – 200 to 250 microns
  - 2 passes – 400 to 500 microns
  - 3 passes – 600 to 750 microns

Office-based Treatment

- Use of lasers through channeled distal chip endoscope

Laryngeal/Tracheal Anesthesia

- Patient seated with head up at 90\(^\circ\)
- Anesthetic dripped through working channel
Office-based Treatment
- Pulsed dye laser
  - Photoangiolytic effect, nonablative
- Pulsed potassium titanyl-phosphate (KTP) laser
  - 532 nm wavelength, photoangiolytic
- CO2 laser fiber
  - ablative

TNFE with KTP Ablation

Adjuvant Therapy
- Approx 20% of RRP patients treated
- Common criteria:
  - >4 surgeries per year
  - Distal spread
  - Rapid disease → airway compromise
- 2004 ASPO survey
  - 75 cidofovir
  - 25 interferon
  - 15 indole-3-carbinol
  - 11 heat shock protein E7

Adjuvant Therapy
- α-Interferon
- Indole-3-carbinol
- Photodynamic therapy
- Cidofovir
- Acyclovir
- Ribavirin
- Retinoic acid
- Mumps vaccine
- Methotrexate
- Hsp E7
α-Interferon

- Proteins produced by cells in response to stimuli (i.e., viral infection)
- Block viral replication and make cell membranes less susceptible to penetration
- Leventhal BG et al. 1988
  - Randomized crossover trial of 66 patients with severe JORRP
  - Statistically significant improvement in disease burden, worsening of disease after discontinuation
- Unfavorable side effects: acute flu-like reactions, chronic hepatic and renal dysfunction


Cidofovir

- Nucleoside analog of deoxyctydine monophosphate
- Once converted, becomes incorporated into DNA and produces toxicity against herpesvirus family
- FDA approved for IV use in HIV patients with CMV retinitis
- Used “off-label” as intralesional treatment for severe RRP

Cidofovir

- Chadha and James 2007
  - 10 year systematic review of RRP treated with cidofovir
  - Reported complete resolution in 57%
  - Partial response in 35%
  - Variability in dosage, interval of administration, number of injections


Cidofovir

- McMurray 2008
  - Prospective, blinded, placebo-controlled study
  - 19 patients
  - No statistical difference in Derkay severity score, VHI, quality of life survey between groups
  - Both groups had statistically significant improvement in all measures
  - Criticisms: small n, low dose of cidofovir (0.3-5mg/ml), and short follow up

Cidofovir Risk

- Studies in rats
  - IV Cidofovir
    - Higher dose – 22/37 female rats → adenocarcinoma of the breast, 6/32 male rats → Zymbal's gland carcinoma
    - Lower dose – 20% rats developed cancer
  - Subcutaneous injection
    - 26 week toxicology study of 1/wk injection terminated at 19 weeks
    - Induction of palpable masses, mammary adenocarcinoma
    - Equivalent to 0.04 times human systemic exposure with recommended IV dose

- Naiman et al. 2004
  - Blood concentration of cidofovir after intralesional injection was 0.01-0.1 times recommended dose for CMV retinitis in 35 patients

- Lindsay et al. 2008
  - Retrospective review of 96 OR specimens of JORRP patients treated with cidofovir
  - No dysplasia identified

RRP Taskforce Recommendations

- Should be routinely offered as a treatment option in moderate-severe cases of RRP patients
  - Frequent surgery, airway compromise, poor communication/voice, pts who would otherwise be considered for tracheostomy
- Dysplasia/malignancy should be reported
- Should be discouraged in patients with mild disease until results of long term use established.
- Informed consent obtained prior to use
- Adverse responses should be reported

Celecoxib (Celebrex)

COX-2 and PGE2 Are Expressed in Respiratory Papillomas

Inhibiting COX-2 Reduces Papilloma Cell Proliferation and Increases Apoptosis

![Graph showing relative proliferation and apoptosis](image)

**Response to Celebrex (Pilot Study)**

![Graph showing growth rate](image)

**Bevacizumab (Avastin)**

- Humanized monoclonal antibody
- Inhibits angiogenesis by binding to VEGF
- Substantial vascular and renal complications with systemic treatment
- Few adverse events with intravitreal injections for variety of disorders

**Avastin**

- Zeitels et al. 2009
  - Pilot study of 10 patients with recalcitrant bilateral glottal RRP
  - 5 injections + KTP treatments
  - 4/10 patients resolved
  - 4/10 have limited disease, treated with Avastin only
  - 2/10 continued with Avastin and KTP

HPV Vaccine

- Currently 2 vaccines in development:
  - Gardasil® (Merck)
    - Quadrivalent: types 6,11,16,18
  - Cervarix® (GlaxoSmithKline)
    - Bivalent: 16, 18
- Phase II trials have demonstrated excellent safety without major side-effects
- Phase III trials have shown effective prevention of genital wart expression and progression to CIN II/III.
  - 98% efficacy in preventing CIN in HPV naïve women

Case 1- JORRP

- 20 year old male
- Numerous surgeries since 9 mo, at least every 4 months
- Tracheal disease
- Tried interferon, cidofovir
- Video

Case 1- JORRP

- MDL with CO2 laser excision/ablation
- Video
- Enrolled onto celebrex trial
- Surgery q 3 months
Case 2 - AORRP

- 74 year old author, professor, public speaker
- 6 month history of gradual voice change
  - Rough – cannot focus voice
  - Increased effort
  - Difficult to be heard

Case 2 - 1 Month Postoperative
Case 2 – 3rd Recurrence

Case 2 – TNFE with KTP Ablation

Case 2 – TNFE with KTP Ablation

Case 2 – 1 Month post KTP Ablation
Conclusions

- RRP is a disease that causes significant mortality
- Surgery is mainstay of treatment
- Regardless of instrument, preserve normal mucosa
- Future directions
  - Vaccine for prevention
  - Medical therapy

References