Highlights of the RRP meeting/CME course at Johns Hopkins, 30 May 2014:
RRP patients/family members' perspectives

[*The following report is based on coordinated input from all those RRP families who attended the meeting]*

On Friday May 30, 2014, a CME course, "Updates in Recurrent Respiratory Papilloma: Clinical and Research Perspective", was held at Johns Hopkins in Baltimore, MD.

It was inspiring to see a novel symposium with CME credit offered for a discussion focused specifically on RRP and opened up to the RRP patient/family community. This offered a unique opportunity for an interaction among ENTs, RRP researchers and the patient community.

Some key "take away" points:

- Although this conference was organized by a surgical department, with much of the target audience being otolaryngologists, whose primary focus is voice and airway management; there was a clear message that the **cure for this disease is going to be medical and not surgical**.

- Based on need for surgery, US RRP (annual) **incidence** is estimated at 1:100000 with **prevalence** estimated to be a factor of 4-5 greater. However, both incidence and prevalence would be much greater if RRP impact on voice is considered.

- **KTP laser** is becoming the surgical tool of choice for managing RRP especially for those who can be treated in the office, but is also finding increased use in the OR. It has the capability of removing papillomas without impacting underlying epithelium.

- The speakers addressed these **adjunctive treatments** of interest:
  Avastin: Intralesional injections of the antiangiogenic agent bevacizumab (Avastin) continues to show promise for RRP patients. Systemic application may be effective in some cases of RRP more distally in the respiratory tract.

  Celebrex: The study of Celebrex was designed around sound theory of the relationship between COX-2 and PGE2. A clinical trial designed to measure the effectiveness of Celebrex on RRP is showing some very promising results. It wasn't clear if any of the responders had distal respiratory involvement.
  HPV Vaccine: The HPV L1 vaccine Gardasil generates antibodies that effectively prevent HPV 6,11,16,18 infections. This is being seen in new data that show a significant decline in HPV in young adults in countries, such as Australia, were inoculation compliance is high. This should result in a future reduction of RRP incidence. Gardasil is not designed to be effective for existing HPV infections, however, based on experimental treatment of dogs with persistent canine papilloma there is some evidence that an L1 vaccine could be used to treat persistent infection. [*Not clear why this should work? Thought that for therapeutic impact against existing infection there needs to be activation of T cells, which is more likely achieved by targeting E6 and/or E7 proteins?*]
  Artemisinin – An herbal medicine also known as sweet worm wood that is widely used to treat Malaria. It is cytotoxic to HPV expressing cell lines and along with iron-dependent

DHA-induced apoptosis, suggests that it may be useful for treating RRP. We are unaware of any coordinated/scientific study to investigate the efficacy of this potential RRP treatment and feel it deserves more attention.

- Some **new research directions**:
  Anti-PD1 therapy: Significant research as to why HPV evades the immune system indicates that the PD-1:PD-L1 pathway may inhibit host immune responses against HPV. This implies that anti-PD1 therapy may help RRP patients who express PD-1:PD-L1. A phase 1B study (MK-3475 Merck) using Merck's anti-PD1 drug currently involves head & neck cancer patients, but no efficacy results are available yet.
  Customized personalized treatments for RRP: The use of "conditionally reprogrammed cells" may offer the ability to provide personalized targeted therapy for RRP patients. By reproducing an individual's tumor cells and testing a variety of possible therapies, an optimal treatment may be determined.
  Another approach involves a xenograft model – growing RRP patients' tumors in NSG mice (immumo suppressed) to test a variety of potential treatments. Among other drugs, this approach has been used to successfully test systemic Avastin. (Note: possible immunotherapies cannot be tested in this way.)

- **RRP Specimen Biobank:** A formally coordinated effort between patients, doctors and researchers could allow a central research facility to collect pathology samples from patients, without the need for IRB approvals from each medical facility. Georgetown University Medical Center is presently taking initial steps to establish this biobank.

- **Pulmonary papillomas and malignant transformation:** Although there was a presentation acknowledging pulmonary papillomatosis and some discussions regarding screening, much more attention is needed to the issue of malignant transformation and new directions for treatment. Given the imperative for medical involvement and potential role of systemic therapy here, the absence of representation from medical oncology at the conference was disappointing. This manifestation of RRP involves about 95% of the disease morbidity/mortality and remains a major challenge which very much needs to be addressed by the RRP clinical / research community.

Some presentation details:

- **RRP by the Numbers: Epidemiologic Gestalt**
  Farrel Buchinsky**,** Allegheny Health Network, Pediatric Otolaryngology

  Incidence ~ 1/100000 vs. 4/100000 (early estimates by RRP Task Force)
  prevalence ~ 4-5 times incidence
  Norway study indicates median age of diagnosis – children ~4, adults ~34
  Remission – 44% go into remission in < 4years
  HPV types in general population HPV6 ~2.3%, HPV11~0.3%
  28% of pregnant women have HPV, but 0.9% HPV6, 0.6% HPV11
  AORRP appears to relate to number of lifetime sexual partners
  In Australia, Gardasil compliance is high and new data shows significant decline in HPV in young adults

- **RRP in the 21st Century: A Patient's Perspective – Pulmonary Papilloma & Malignant Transformation**
  Jennifer Woo, Georgetown University School of Medicine ; RRP Foundation, President

  Pulmonary papilloma most common in younger diagnoses and HPV11 more so than HPV6, - extension to pulmonary is estimated to occur in up to 5%
  Aggressive pulmonary spread and carcinoma often develops in 20s & 30s
  Does HPV11 represent a "middle risk" for oncogenic progression?
  HPV related progression to lung cancer do not seem to be universally associated with smoking, prior irradiation or other environmental factors
  Are RRP-related lung cancers biologically distinct from other lung cancer?
  Need to develop and adopt consensus-based screening guidelines for pulmonary RRP.

- **Approaches to RRP Care: General Philosophies**
  Lee Akst, Johns Hopkins, Otolaryngology-Head and Neck Surgery

  The disease COMES BACK => this is a frustrating disease for everyone !
  Epithelial disease requires thorough, but superficial debridement
  Treatment = remove disease when active symptoms present.
  Goal during surgery – preserve the airway/ voice and minimize scarring
  Risk – cumulative scarring from multiple surgeries.
  KTP procedures are gaining more support from Doctors and Patients….
  Office visit vs. OR - patient's preference (when KTP is available)
  When there is an airway risk – should be operated on in OR instead of in office KTP

- **Unwieldy Workhorse: Operative Management of RRP with the CO2 Laser**
  Clint Allen, Johns Hopkins, Otolaryngology-Head and Neck Surgery

Use of CO2 laser for RRP has been declining recently. CO2 wavelength ~10600nm (targets water).
Early studies showed some thermal injury. Power and other parameters can be adjusted to minimize, but not completely eliminate, thermal injury.
CO2 laser may be more useful for disease located above vocal cords (in expert hands).

- **A Weapon of Minor Destruction: KTP Angiolytic Laser Use in the OR**
  Nazaneen Grant, Georgetown University Hospital, Otolaryngology-Head and Neck Surgery

  KTP is an angiolytic laser - selectively destroying microvasculature (this is relate to its operation at the wavelength of 532 nm), which enables it to "peel off " papillomas without impacting underlying epithelium.
  There is a retrogression or obliteration of blood vessels, as in embryologic development.
  KTP may not be appropriate for small children where considerable debulking is necessary and the microstructure is unclear.
  KTP lasers are also commonly used in ophthalmology, urology, and otology.

- **Office-based KTP Laser Treatment of Laryngeal Papilloma**
  Alexander Hillel, Johns Hopkins, Otolaryngology-Head and Neck Surgery

  No anesthetic, reduced post op pain
  84% in a study used no pain meds
  ~5% cannot tolerate the procedure
  Not as good for bulky disease
  Discomfort is usually mild
  You can use topical anesthesia
  Typically use the pulse setting epithelium can be preserved
  In office procedure - KTP laser allows patients to stay awake without general anesthesia , 87 % of patients prefer .

  Advantages of using KTP for doctors:
  Preserve epithelium
  Photocoagulation/ can adjust pulse widths of laser for more precision
  Thinner fiber
  Fast
  Bloodless procedure allows deeper removal of papillomas.
  Patient PROs:
    No General Anesthesia
    Total time less, more convenient. (Average time is 79 minutes in office vs. an average time of 300 minutes for the Operating Room)
    Reduce Post op pain
    Mild discomfort during procedure
  Patient CONS:

Lower threshold of recurrence
More frequent
Smell of tissue

Best Candidates – those who cannot tolerate anesthesia, less papilloma, secondary procedure
Other Considerations:

- **Treatment of RRP in Children: Strategies for Safe and Efficient Surgery**
  David Tunkel, Johns Hopkins, Otolaryngology-Head and Neck Surgery

  Identify the presenting signs and symptoms for children with RRP
  Discuss the surgical indications and goals for treatment of children with RRP
  Because considerable debulking is necessary in children, the microdebrider is more often used than KTP laser.

- **Medical and Surgical Management of Severe Pediatric RRP**
  Diego Preciado, Childrens National Medical Center, Dept. of Otolaryngology

  Adjuncts used for treating invasive tracheobronchial papillomas:
  Cidofovir –very effective for many but might induce dysplasia, carcinoma?
  Interferon – alpha – effective but very high relapse rate; significant side effects
  I3C,DIM – no side effects, but not clear how effective
  Particular severe case has not responded well to these adjuvants
  [*We need some new approaches!]*

- **Avastin, Office-based Treatment, and the Future of RRP Care**
  Steve Zeitels, Mass. General Hospital, Ctr. for Laryngeal Surgery and Voice Rehabilitation

  Estimated RRP prevalence based on airway & voice impact:
  ~20000 Pediatric RRP: 80% airway & >95%voice; ~20000 Adult: 15% Airway & >95%voice

  RRP is an angiogenic lesion, so photoangiolytic lasers, particularly the pulsed-KTP (532 nm) is effective. The efficacy is enhanced by intralesional injection of an anti-angiogenic drug (Avastin) in combination with this angiogenic laser.

  For distal RRP involvement , i.e., tracheal and below, intralesional injection is difficult, so intravenous (IV) administration is suggested.
  There is a problem with IV Avastin if lung cancer is present because this cancer causes bleeding which can be a problem with Avastin. But this is not an issue with RRP. So, IV Avastin may be useful for **pulmonary RRP** if no cancer is involved.
  Perhaps other VEGF inhibitors (i.e., angiogenesis inhibitors) can be found that work better than Avastin.

- **The Biology of HPV and the Great Escape: How HPV Evades the Immune System**
  Sara Pai, Mass. General Hospital, Ctr. for Laryngeal Surgery and Voice Rehabilitation

  75% of sexually active people have or will be infected with HPV in their lifetime (only about 10% will present with disease).
  CD4+ (commanders) & CD8+(soldiers) are T-cells that play significant roles in controlling HPV. Some people express a high level of PD1/PD-L1 (receptor/protein), which appears to "turn off" some CD8+ T cell activity and inhibit host immune responses against HPV (and some cancers).
  Trials involving cancer patients who express PD1/PD-L1 are currently underway using anti-PD1 drugs that are designed to be effective in reducing PD1 expression thereby enhancing T cell activity. One such study is Merck's Phase 1B study of MK-3475. It is hoped that this approach can be extended to RRP patients with deep respiratory involvement.

- **Adjuvant Care of RRP**
  Simon Best, Johns Hopkins University School of Medicine

  Discussion of different drugs and compounds that have been used in RRP or are under investigation Evaluation of evidence for and against the use of various adjuvant treatments in RRP and future directions in RRP research

  Cidofovir – Based on Hopkins study involving 162 patients (15 JORRP), it has shown efficacy but should be used cautiously as it may produce significant vocal fold scarring with some risk of nephrotoxicity. The Hopkins study does not indicate a significant dysplasia risk.

  DIM – P450 inhibitor that affects the metabolism of estrogen. Rosen et al., phase 1 study – 35 patients, 1/3, 1/3, 1/3 complete, partial, no response. According to the RRPF website, DIM is the most common adjuvant therapy among RRP patients with ~55% overall positive response rate.

  Artemisinin - An herbal medicine also known as sweet wormwood that is widely used to treat Malaria. It has been used to treat some cancers by "starving" cancer cells of iron, which they need to proliferate. It may also be useful for treating RRP as a similar situation applies to HPV and there is some anecdotal evidence to support this.

  Avastin (systemic) – Based on the early positive responses in a German pilot study (not yet published) of RRP patients with deep respiratory involvement, IV Avastin was used in a particular case of tracheal papilloma using 4 cycles of IV Avastin. Proposed 3 week dosing, then 6 week and try to space it out to ~ 3months. 10mg/kg. Preliminary results are encouraging.

Xenograft Model – uses NSG mice (immumo suppressed) to grow individual RRP tumors with the goal of producing personalized and targeted therapies.

- **The Role of Prostaglandin E2 in RRP**
  Bettie Steinberg, , Laboratory of Papilomavirus Research, Hofstra North Shore-LIJ School of Medicine

  RRP patients have widespread latent infection, but it is the activation of the infection that causes the recurrence of RRP. Trauma, reflux are some possible triggers for activation.
  Specific defect in recognizing HPV might be associated with elevated COX-2 -> PGE2 levels. COX-2 appears to be generated by the RRP patient not from the papilloma cells.
  The virus turns up the receptors.
  Celebrex inhibits COX-2, so it may be able to reduce papilloma recurrence.
  EP4 appears to be the key.
  Preliminary results from a multi-center 24 month double-blinded clinical trial using Celebrex with RRP patients (1yr celebrex-1yr placebo) with cross over –
  52 patients (37 analyzable) – histories include ~ 2years of at least 3 surgeries/yr
  ~50% responded – 25% partial, 25% complete (These results are still blinded and the mechanism of response is still being studied)
  Does not eliminate latent viral DNA even after a clinical response

- **Treatment of Pulmonary Disease**
  David Feller-Kopman , Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine

  In most cases of pulmonary RRP, patients have undergone at least 20 recurrences.
  No new treatment options discussed for tracheobronchial papillomatosis, other than perhaps IV Avastin. Need new medicines and/or new ways to delivery adjuvants directly to lung tissues.

  In addition to CT scans some other screening options that were mentioned are:
  Endobronchial ultra-sound – improved imaging (EBUS)
  Optical coherence Therapy (OCT)

  Some other guidance for ENT surgeons:
  Monitor signs of spreading into bronchial tubes with each RRP procedure.
  Avoid jet ventilation as there is a risk of downward spread of viral particles.

  Pulmonary RRP sometimes develop into calcified pulmonary nodules and often progress to cancerous tumors. No suggestions were presented on how best to treat these situations

- **HPV by the Millions; RRP by the Thousands: Susceptibility Insights**
  Farrel Buchinsky, Allegheny Health Network, Pediatric Otolaryngology

  Discussion of what can and what cannot be understood through genetic studies in recurrent respiratory papillomatosis.

RRP is a fairly rare disease that is not genetic but perhaps the susceptibility is. Family concurrence data (source?): 11/1859 had two people with RRP, i.e., never a spouse, identical twins, uncle/nephew, Siblings (years apart). The lack of "contact" in these family member occurrences, suggests genetics more likely than contagion. RRP Genetics study by Buchinsky, et al., has enrolled 608 patients and 797 parents between 2004 and 2012. Thus far they have completed genotyping of 94 families and have looked at **MHC/HLA typing** in hopes that it may help to **predict what adjunct therapies might be effective for individual RRP patients**. [Note: major histocompatibility complex (MHC) is a set of cell surface molecules encoded by a large gene family in all vertebrates and the human leukocyte antigen (HLA) system is the name of the locus of genes that encode for MHC in humans.]

Other misc findings:

In a Danish study over 15-20 years involving ~1.2 million mothers (Silverberg, 2003) there were 57 children born who developed RRP. Of this population of mothers 3012 had condyloma and from this much smaller subset 21 children were born who subsequently developed RRP. [Is this very significant increase in RRP births due to greater viral transmission or genetic factors affecting HPV susceptibility or a combination of the both?]

An HPV serology study in RRP patients indicates that most do not show a serologic response (lack of HPV antibodies in blood samples), especially JORRP patients. However, after Gardasil vaccination, RRP patients have a strong antibody response similar to people who do not have RRP.

- **The Development of the HPV Vaccine**
  C. Richard Schlegel, Department of Pathology Georgetown University Hospital

  The HPV shell contains L1 (95%) and L2 (5%) proteins. HPV vaccines, such as, Gardasil, target type specific L1 proteins to generate antibody immunity that effectively prevent new infections. Gardasil was designed to prevent HPV 6,11,16,18 and a recent new vaccine version adds HPV 31,33,52,58.

  Canine papilloma vaccine experiments:
  L1 vaccine developed that prevents mucosal CPV infections in dogs
  In a 4 dog trial with the L1 vaccine existing lesions cleared in 16 weeks
  In a 15 dog trial 50% of lesions were cleared
  Does this imply an L1 HPV vaccine might show efficacy clearing existing lesions in humans if L1 is expressed?

- **Use of Conditionally Reprogrammed Cells for RRP Studies**
  Hang Yuan, Molecular Oncology, Georgetown University Hospital

Discussion of new cell technology to analyze data from patients' cells with the goal of providing customized personalized therapy

Growing HPV cells in the lab via a new approach called "conditionally reprogrammed cells" that is an extension of HeLa cell research. [Note: the first time scientists were able to keep alive and grow cells cultured from other cells, used cells from cervical cancer patient Henrietta Lacks in 1951(Hence the abbreviation HeLa) .
After growing the tumor cells in the lab they can then be injected into a xenograft mouse which allows for testing a variety of drugs on the actual tumor.
In an actual clinical case of an RRP patient (type HPV 11) with a 20 year history of 350 surgeries, pulmonary disease was diagnosed in 2008 and did not respond to IV cidofovir. Using conditional reprogramming, cell cultures from the lung tumor tissue and normal lung tissue were generated. Drug testing with this approach identified vorinostat (an HDAC inhibitor drug approved for treating a form of Lymphoma) as a potential therapeutic agent. After 3 months of treatment, lung tumors had stabilized with continued impact after 15 months.

Georgetown researchers are seeking IRB approval to serve as a collection center for RRP tissue samples to further their study of testing adjuvant therapies to treat RRP.

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