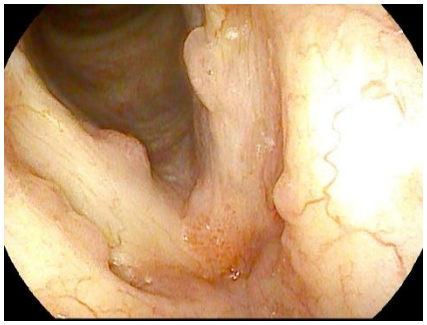
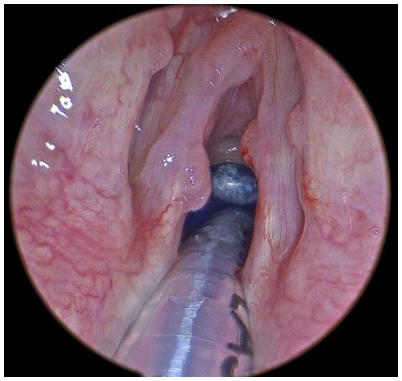
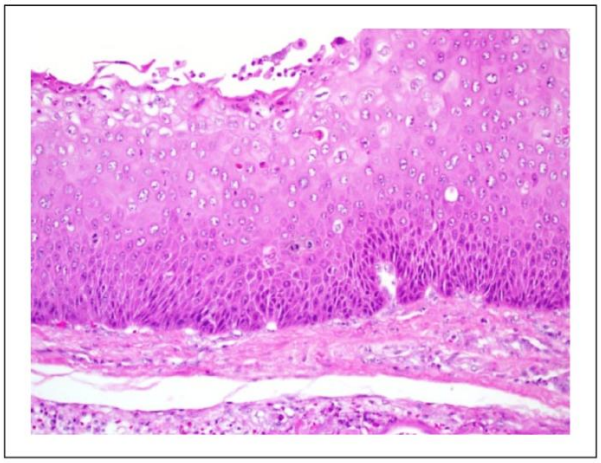
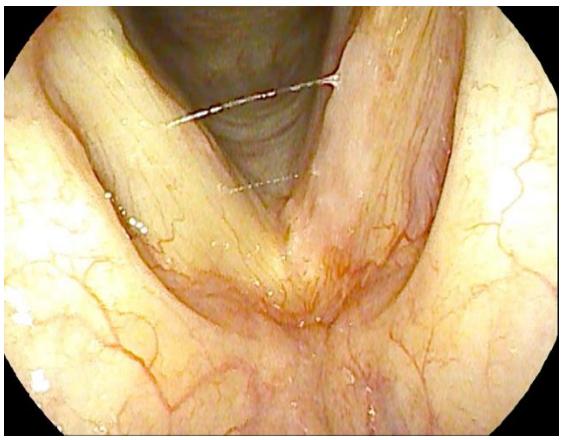
SOLVE THE PATIENT OF THE WEEK CASE

Topic: Recurrent Respiratory Papillomatosis

Patient's History	A 33-year-old male with a past medical history of ADHD presents for a 2-year history of progressive hoarseness. He has had a "crusty" voice as long as he can remember. He did have surgery on his vocal folds 5 years prior by another ENT that improved his voice. He smokes 0.5 packs of cigarettes a day. Denies hemoptysis, otalgia, dysphagia, sore throat, or weight loss.
Day 1	You obtain records from his prior surgeon's office who diagnosed him with Adult-Onset Recurrent Respiratory Papillomatosis (AORRP). Flexible laryngoscopy is shown below. What are the most common HPV subtypes responsible to the pathophysiology of AORRP.  **A. 6 and 11** B. 16 and 18 C. 31 and 33 D. 11 and 16 The two primary subtypes in RRP are 6 and 11, but high-risk subtypes 16, 18, 31, 33, and 39 have all been identified. The quadrivalent vaccine covers subtypes 6,11,16, and 18. The 9 valent HPV vaccine covers subtypes 6,11,16,18, 31,33,45,52, and 58.

	Benedict JJ, Derkay CS. Recurrent respiratory papillomatosis: A 2020 perspective. Laryngoscope Investig Otolaryngol. 2021 Mar 13;6(2):340-345. doi: 10.1002/lio2.545. PMID: 33869767; PMCID: PMC8035938.
Day 2	Given his progressive dysphonia and degree of laryngeal papillomas you recommend microdirect laryngoscopy with excision/ablation of papilloma. You counsel the patient about the risks of surgical intervention for his RRP including recurrence of disease. What is the most likely subsite for recurrence?  A. True vocal fold edge B. Epiglottis **C. Anterior Commissure** D. Subglottis Surgical intervention for RRP aims to completely excise or ablate the papilloma while minimizing laryngeal scarring and cicatrization. During direct laryngoscopy the anterior commissure is often a difficult access point which may lead to incomplete excision. In addition, the risk of two opposing raw surfaces causing a glottic web may lead to incomplete papilloma removal. Lastly papilloma is more likely to recur in the same region affected at the time of diagnosis or in regions adjacent to those affected at the time of diagnosis. Kim HT, Baizhumanova AS. Is recurrent respiratory papillomatosis a manageable or curable disease? Laryngoscope. 2016 Jun;126(6):1359-64. doi: 10.1002/lary.25795. Epub 2015 Nov 26. PMID: 26608928.
Day 3	

	At your post-operative follow-up visit you review the pathology report with the patient. The final diagnosis is squamous papilloma consistent with RRP. The report also comments on low grade dysplasia based on the 2017 WHO classification. You counsel the patient that dysplasia occurs in 10-50% of patients with AORRP. The patient then asks what is his lifetime risk of malignant transformation?  **Figure 2.** This papilloma with moderate dysplasia exhibtis atypia in the form of mitotic figures above the basillar layer, dyskeratosis, and nuclear pleomorphism beyond what is encountered in a typical papilloma. Figure from: Karatayli-Ozgursoy S, Bishop JA, Hillel A, Akst L, Best SR. Risk Factors for Dysplasia in Recurrent Respiratory Papillomatosis in an Adult and Pediatric Population. Ann Otol Rhinol Laryngol. 2016 Mar;125(3):235-41. doi: 10.1177/0003489415608196. Epub 2015 Oct 8. PMID: 26453486. A. <0.001% **B. <3%** C. 10% D. 25% While dysplasia can be a common finding in RRP histology in 10-50% of patients, malignant transformation remains uncommon. When malignant transformation does occur in <3% of patients it is associated with a more favorable clinical course. Taliercio S, Cespedes M, Born H, Ruiz R, Roof S, Amin MR, Branski RC. Adult-onset recurrent respiratory papillomatosis: a review of disease pathogenesis and implications for patient counseling. JAMA Otolaryngol Head Neck Surg. 2015 Jan;141(1):78-83. doi: 10.1001/jamaoto.2014.2826. PMID: 25393901.
Day 4	

	The patient remembers that his first surgeon used cidofovir during his RRP surgery. He wants to know if the cidofovir caused his dysplasia? Which of the following is the strongest predictor of dysplastic transformation in patient with RRP? A. Young age at disease onset **B. Older age at disease onset** C. Smoking D. Prior cidofovir use In a study of 159 patient with AORRP and JORRP, 10% of patient were found to have dysplasia or carcinoma in-situ in addition to papilloma. They examined gender, age at disease onset, and prior cidofovir use and found that older age at disease onset was predictive of developing dysplasia (56 vs 45 years old; *P* = .0005). Note that cidofovir use was not predictive of developing dysplasia. Karatayli-Ozgursoy S, Bishop JA, Hillel A, Akst L, Best SR. Risk Factors for Dysplasia in Recurrent Respiratory Papillomatosis in an Adult and Pediatric Population. Ann Otol Rhinol Laryngol. 2016 Mar;125(3):235-41. doi: 10.1177/0003489415608196. Epub 2015 Oct 8. PMID: 26453486.
Day 5	Post-operatively the patient is pleased with his voice outcome. Flexible laryngoscopy is shown below. The patient asks what he can do to prolong the amount of time until he may need another surgery?  A. Strict adherence to reflux medication B. Smoking cessation **C. Vaccination against HPV** D. Voice therapy

	The dogma that smoking cessation and reflux management are important to decrease disease recurrence has yet to be supported in studies. Multiple recent studies have shown a significant increase in time between surgeries and number of surgeries after HPV vaccination. Ponduri A, Azmy MC, Axler E, Lin J, Schwartz R, Chirilă M, Dikkers FG, Yang CJ, Mehta V, Gangar M. The Efficacy of Human Papillomavirus Vaccination as an Adjuvant Therapy in Recurrent Respiratory Papillomatosis. Laryngoscope. 2023 Sep;133(9):2046-2054. doi: 10.1002/lary.30560. Epub 2023 Jan 18. PMID: 36651338; PMCID: PMC10859188.
Case summary	This case follows a 33-year-old male with a history of adult onset RRP now with dysphonia. The etiology of RRP is infectious from the human papilloma virus specifically most commonly subtypes 6 and 11. One of the most common risks with surgical excision of papilloma is recurrence of disease which is most common at the anterior commissure and at the same region affected by papilloma at the time of diagnosis. While dysplasia can occur in RRP, malignant transformation is still uncommon, <3% lifetime risk. Older age at diagnosis for AORRP is predictive for development of dysplasia. Lastly while reflux management and smoking cessation are commonly recommended to patient with AORRP, only HPV vaccination has been shown to increase time between surgeries and number of surgeries.
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