Recurrent Respiratory Papillomatosis: A Case of Persistent Stridor in an 18 Month-Old Child

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Abstract

Recurrent respiratory papillomatosis (RRP) is characterized by non-cancerous, verrucous, polypoid, wart-like growths occurring at the junctions of the squamous respiratory and ciliary epithelium, particularly the larynx. It is thought to be caused by acquisition of human papilloma virus (HPV) during pregnancy or passage through the birth canal of an infected mother. This case report describes an 18-month-old female who presented to the emergency department due to persistence of biphasic stridor unrelieved with dexamethasone and racemic epinephrine nebulized treatments. Pediatric otorhinolaryngologist performed laryngoscopy, which revealed bilateral papillomatous lesions of the larynx causing airway obstruction.

Introduction

Recurrent respiratory papillomatosis (RRP) is the most common benign laryngeal tumor in children. RRP is characterized by verrucous, polypoid wart-like growths that usually affect the junctions of the squamous respiratory and ciliary epithelium, particularly the larynx.[1] This rare disease is divided into juvenile onset RRP (JORRP) and adult onset RRP (AORRP) depending on the presentation before and after the age of 12 years, respectively.[2] The juvenile onset form of RRP, the main focus of this case report, is caused by the acquisition of human papillomavirus (HPV) during pregnancy or passage through the birth canal of an infected mother.[3] The three major risk factors widely associated with juvenile onset RRP documented in PubMed literature review include being the firstborn child, vaginal delivery, and having a teenage mother who has genital condylomata (genital warts).[4] In a large retrospective cohort study, children born to mothers with a known history of genital warts were 231 times were likely to develop RRP than those born to mothers without such a history.[5] However, only 1 in 400 children born to mothers with genital warts will actually develop lesions later in life.[6] The overall incidence of RRP is relatively low, between one and four cases per 100,000; however, the recurrence is very common and can cause significant morbidity in affected children.[2] In rare instances, sudden death can occur if the child has respiratory compromise due to complete airway obstruction caused by these papillomatous lesions.[7] This case report aims to highlight the clinical features of RRP and to emphasize the importance of obtaining a detailed medical history and performing thorough physical examination in a child presenting with persistent biphasic stridor.

Case Report

The patient was an 18-month-old female who presented to the pediatric emergency department with eight days of nonproductive cough and persistent stridor. The stridor was reportedly worse at night when the patient was in the supine position and occurred during both inhalation and exhalation phases. Her mother reported a decrease in oral intake but denied fevers, dysphagia, vomiting, or diarrhea. Review of systems was negative for vocal cord damage or foreign body ingestion. Social history did not raise concerns for child sexual abuse. The patient was seen at a regional hospital four days prior and was discharged home after she received oral dexamethasone and nebulized racemic epinephrine treatment for a presumptive diagnosis of viral croup. She was not prescribed any antibiotics or other medications at that time.

Upon evaluation in the pediatric emergency department, the patient's vital signs revealed a heart rate of 148 beats/minute, respiratory rate of 32 breaths/minute, temperature of 96.8 °F , blood pressure of 116/65 mmHg, and oxygen saturation of 98% on room air. Examination revealed a well-nourished child with moderate subcostal retractions and inspiratory and expiratory stridor. She did not have any wheezes or crackles. There were no apparent otorhinolaryngological clinical manifestations (e.g., palatal injury, mouth sores, and condyloma acuminatus) to suspect sexual abuse. There was no physical evidence of bruises, trauma, or neurologic deficits. She received 3 racemic epinephrine nebulized treatments and intravenous dexamethasone with minimal symptomatic relief. Routine soft tissue x-rays showed findings of supraglottic narrowing (Figure 1).

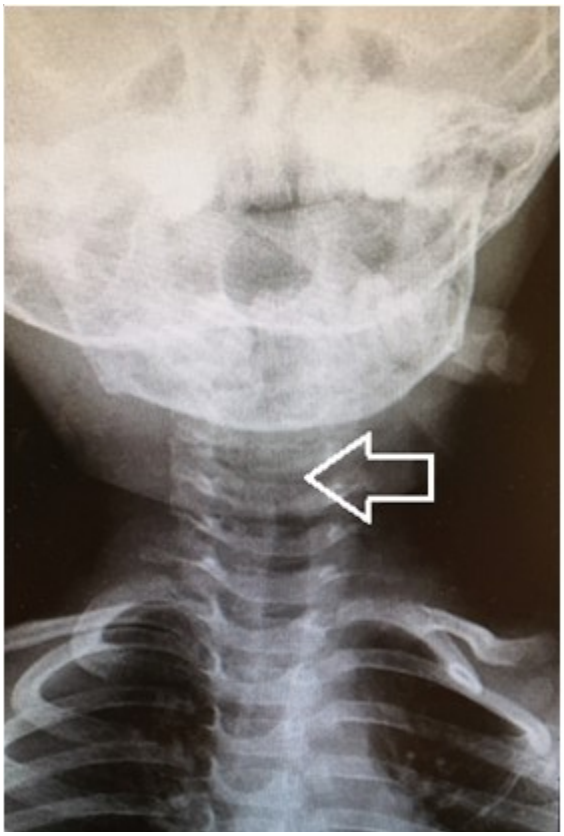
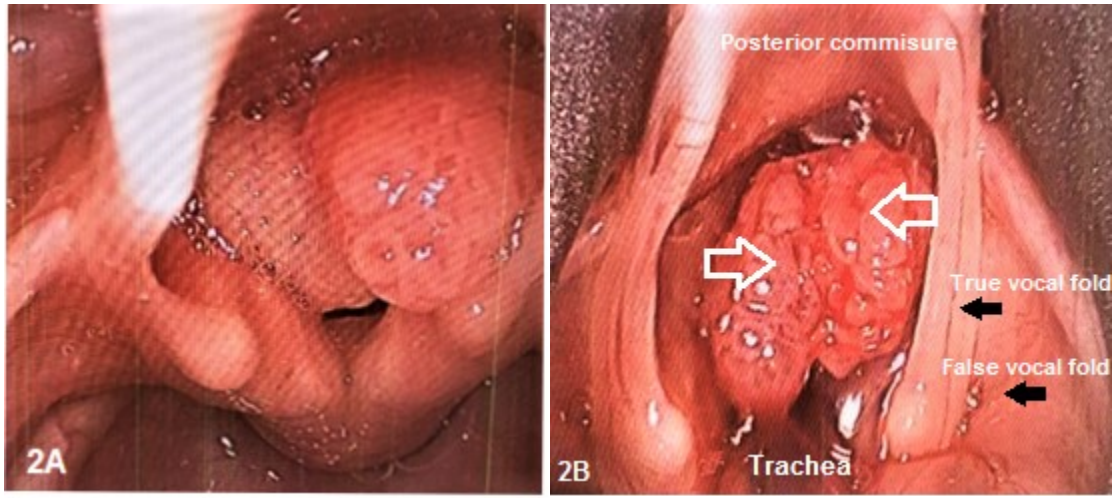


Figure 1. Mild supraglottic narrowing (white arrow) with distention of hypopharynx consistent with laryngotracheobronchitis without foreign body. Source: Patient Image

A nasopharyngeal aspirate did not identify any infectious organisms via direct polymerase chain reaction (PCR) amplification assay. The patient was started on scheduled racemic epinephrine nebulized treatments and inhaled and systemic steroids after she was admitted to the children's hospital.

Upon further questioning, the patient was a product of spontaneous vaginal delivery born without any complications at 38 weeks gestation. She was the firstborn child conceived in a monogamous family setting. Her mother received late-prenatal care because the family relocated to Oklahoma during the first trimester of pregnancy. The mother also endorsed having two small flesh-colored labial lesions during her pregnancy, but did not recall having any active lesions immediately prior to the delivery. These lesions did not require surgical resection and the mother did not take any medications aside from routine prenatal vitamins. The patient had received all of her age-appropriate vaccinations. She did not have any surgical history or congenital disorders. She had a normal developmental history.

Pediatric otorhinolaryngology consultation was obtained in the hospital due to the persistent biphasic stridor. Direct flexible laryngoscopy was performed under general anesthesia, which revealed sessile lesions involving the anterior left and entire right side of the patient's true vocal cords (Figures 2A-B).



Figures 2A-B. Bilateral papillomatous lesions (white arrows) extending off false vocal cord and right true vocal cord. Images taken during diagnostic flexible laryngoscopy. Source: Patient Image

Gross histology report showed grey-pink soft tissues aggregating 0.6 x 0.4 x 0.3 cm, while microscopy revealed hyperplastic stratified squamous epithelium overlying a fibrovascular tissue, consistent with a diagnosis of benign squamous papilloma. Her respiratory symptoms resolved after the lesions were resected. We had the unique opportunity to observe this patient peripherally with pediatric ENT for about 12 months from the time of the initial diagnosis. She has since undergone four excisional surgeries ranging from 2 months to 4 months interval from recurrence.

Discussion

Recurrent respiratory papillomatosis (RRP) was first identified by Sir Morrell Mackenzie in the late 1800s when he recognized it as a distinct lesion of the larynx in children.[8] RRP has since been well-documented in medical literature and HPV was confirmed as the etiologic agent in the early 1990s via genetic technology.[2] To date, there are more than 200 serotypes of HPV discovered, with some serotypes classified based on their affected sites (e.g., anogenital, non-genital cutaneous, and non-

genital mucosa).[9] A few HPV serotypes are further classified as either "high risk" (i.e., when it is associated with malignant transformation) or "low risk" (e.g., condylomatosis).[10] The low risk HPV serotypes 6 and 11 are common causative agents of RRP.[2,11] The etiology of juvenile onset RRP is generally agreed to be vertical transmission either in pregnancy or at delivery, especially when the mother has active condylomatosis (genital warts) or is actively shedding disease from a recent HPV infection.[2] In contrast, adult onset RRP has been associated with sexual transmission, especially in those with multiple sexual partners and engaged in frequent oral sex activities.[12,13]

A literature review showed that hoarseness of the voice is the most common presenting symptom of RRP among pediatric patients.[12] Patients younger than 3 years old may sometimes present with other nonspecific signs and symptoms such as abnormal cry and failure to thrive.[14] Our patient was only 18 months old at the time of her RRP diagnosis, so she was not able to explicitly communicate any complaints of hoarseness in her voice. Stridor is the second most common initial symptom, which typically begins as inspiratory, and later progress to biphasic.[12,13] Persistent biphasic stridor in our patient was actually the key physical exam finding that helped narrow her differential diagnosis and workup. Stridor is a monophonic, high-pitched sound that is heard loudest over the anterior neck. Anatomically, the large upper airways can be divided into extrathoracic and intrathoracic regions. The extrathoracic region includes airways above the thoracic inlet: subglottic area (cricoid cartilage), glottis area (cricoid cartilage, incomplete tracheal rings), and supraglottic area (nasopharynx, epiglottis, larynx, aryepiglottic folds, and false vocal cords). The intrathoracic region includes airways below the thoracic inlet, which comprise the lower portion of the trachea (that lies within the thoracic cavity) and the mainstem bronchi.

The presence of stridor is suggestive of significant obstruction in the large upper or central airways. Stridor originating from the extrathoracic level is more pronounced during inspiration phase. Common diseases that can cause an inspiratory stridor sound (i.e., airway obstruction at the extrathoracic inlet level) are laryngomalacia, laryngotracheobronchitis (croup), retropharyngeal abscess, epiglottitis, and craniofacial malformations.[15] In contrast, stridor originating from obstruction in the intrathoracic level is more pronounced during exhalation phase since intrathoracic pressure rises on exhalation and causes airway collapse.[15] Compression of the trachea, congenital anatomic disorders (such as vascular rings and webs), and enlarged lymph nodes or bronchial tumors can all cause an expiratory stridor sound. Biphasic stridor (inspiratory and expiratory) is a fixed (rather than dynamic) central airway obstruction that may sound similar regardless of the intrathoracic or extrathoracic location.[15] Our patient had biphasic stridor because the papilloma lesions were causing obstruction to the glottis area (vocal cords). In the assessment of any pediatric patients with an unknown cause of persistent biphasic stridor, assuming that they have been stabilized from a respiratory standpoint, the clinician should consider the possibility of an underlying structural abnormality causing upper or central airways obstruction.

Juvenile onset RRP is a rare disease which affects males and females in equal proportions, while males are more affected with adult onset RRP.[12] Age at onset of the RRP is a well-known factor in estimating aggressiveness and severity of the disease-younger age at diagnosis is associated with an increased need for more frequent surgical procedures.[16] As a result, juvenile onset RRP may often lead to multiple hospitalizations due to the rapid growth and recurrence of the papilloma lesions, even after surgical resection and adjuvant therapies.[17] At present, there is no cure for RRP and no single treatment modality has consistently been shown to be effective in eradicating RRP.[11] Surgery is the mainstay of treatment for RRP. There are several surgical methods available including direct resection with operating laryngoscopes (as was the case for our patient), endoscopic debulking with microdebridders, laser ablation, and most recently, shaver technology.[2,11] Surgical intervention aims to

remove papillomatous lesions and maintain safe airways, but it does not prevent future recurrence.

Adjuvant therapeutic options have been shown to yield a modest decrease in the frequency and severity of lesion recurrence.[11,18,19] General criteria for commencement of adjuvant therapy include: 1) > 4 surgical procedures annually, 2) rapid re-growth of papilloma with airway compromise, 3) and remote multi-site spread of the disease.[20] Current adjuvant medical therapy include antiviral agents (acyclovir, ribavirin, cidofovir), interferon, retinoid, photodynamic therapy, zinc, cyclooxygenase-2-inhibitor, methotrexate, preventive vaccines (mumps, MMR, quadrivalent HPV), and gene therapy.[4,5,11] All of these treatment modalities focus on mechanisms like immunomodulation, disruption of molecular signaling cascade or HPV replication, and inhibition of proliferation/growth arrest of HPV infected cells.[20] Interferon has been extensively investigated as an adjuvant treatment for RRP. The exact mechanism of action is unknown; however, interferon modulates the immune system and epithelial development by increasing production of protein kinase and endonucleases, which inhibits viral protein synthesis.[11] Although interferon therapy has shown promising results to reduce severity of papilloma growth, it also carries significant side effects (e.g., flu-like symptoms, chills, headaches, elevated liver functions, leukopenia, thrombocytopenia, febrile seizures, and alopecia).[11] For children, the duration of interferon treatment is usually 6 months.

Perhaps the most specific HPV-directed adjuvant therapy is the use of the HPV vaccines.[21] There are two commercially available HPV vaccines on the market: 1) Gardasil from Merck and 2) Cervarix from GlaxoSmithKline. Both vaccines were developed with virus-like particles (VLP) that simulate the surface of HPV. Gardasil is a quadrivalent vaccine with VLP for serotypes 6, 11, 16, and 18. Preliminary studies have shown that patients who received 3-doses of the Gardasil vaccine may experience prolonged time to recurrence in the RRP population (i.e., increase in inter-surgical interval resulting in a slower disease progression and decreased morbidity).[21,22] In girls aged 15-19 years, a previously published meta-analysis indicated that genital warts decreased significantly by 31%, which may indirectly reduce the RRP incidence by preventing vertical HPV transmission to newborns.[4] The current Advisory Committee on Immunization Practices (ACIP) recommendation is that vaccination of females with HPV vaccine beginning at 11 or 12 years of age (the series can begin as early as age 9). The CDC also states that, "Ideally, vaccine should be administered before potential exposure to HPV through sexual contact".[23] However, it is not clear if there is a role for the HPV vaccines in children less than 9 years old. Longer-term monitoring will reveal whether current decline in genital warts are mirrored by declines in RRP.[24]

Conclusion

In summary, recurrent respiratory papillomatosis is a benign neoplasia of the respiratory epithelium that occurs in both children and adults. It is a potentially life-threatening disease that deserves immediate attention, particularly in pediatric patients who present with persistent biphasic stridor refractory to conventional medical interventions. Surgical excision is the mainstay of treatment for RRP. The hallmark of RRP is a high frequency of surgeries in the years following a formal diagnosis of the disease, particularly for the youngest patients. RRP can cause significant emotional and economic burden for the patient and their family. Numerous adjuvant pharmacologic therapies have been used to treat RRP with some success. The greatest optimism for future prevention of RRP lies with the successful widespread implementation of HPV vaccines, with a reduction in all HPV-associated diseases in general.

References

1. Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 1993;102:580-583.

2. Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. AP MIS 2010;118:450-454.

3. Shah KV, Stern WF, Shah FK, et al. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infec Dis J 1998;17:372.

4. Wangu Z, and Hsu K. Impact of HPV vaccination on anogenital warts and respiratory papillomatosis. Human Vaccines and Immunotherapeutics 2016;12(6):1357-1362.

5. Silverberg MJ, Thorsen P, Lindeberg H, et al. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645.

6. Shah KV, Stern WF, Shah FK, et al. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infec Dis J 1998;17:372.

7. Balazic J, Masera A, Poljak M. Sudden death caused by laryngeal papillomatosis. Acta Otolaryngol Suppl 1997;527:111-113.

8. Ahmed PA, Ulonnam CC, Undie NB. Recurrent respiratory papillomatosis: a report of two cases and review of literature. Niger J Ped 2014;41(1):7-73.

9. Hager WD. Human papilloma virus infection and prevention in the adolescent population. Journal Pediatric Adolescent Gynecology 2009;22:197.

10. Freed GL, Derkay CS. Prevention of recurrent respiratory papillomatosis: role of HPV vaccination. International Journal of pediatric otorhinolaryngology 2006;70:1779-1803.

11. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. The Laryngoscope. The American Laryngological, Rhinological and Otological Society, Inc. 2008;118:1236-1247.

12. Harman EM, Mosenifar Z, Sarma S, et al. Recurrent respiratory papillomatosis. Medscape reference. 2011. Web link: emedicine.medscape.com/article/302648.

13. Quin FB, Ryan MW, et al. Recurrent respiratory papillomatosis. Grand round presentation at UTMB, department of otolaryngology. 2003. Web link: www.utmb.edu.otoref/grnds/papillomatosis-2003-0265/papillomatosis2003-0625.htm.

14. Tasca RA, Clarke RW. Recurrent respiratory papillomatosis. Archives of Disease in Childhood 2006;91(8):689-691.

15. Sly PD, Collins RA. Physiological basis of respiratory signs and symptoms. Pediatric Respiratory Review 2006;7:84.

16. Izadi F, Hamkar R, Ghanbari H, Abdolmotallebi F, Jahandideh H. The role of human papilloma

virus (HPV) genotyping in recurrent respiratory papillomatosis in Rasoul Akram Hospital. Med J Islam Repub Iran 2012;26(2):90-93.

17. Carifi M, Napolitano D, Morandi M, and Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. Therapeutics and Clinical Risk Management 2015;11:731-738.

18. Fusconi M, Grasso M, Greco A, Gallo A, et al. Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir. Acta Otorhinolaryngologica Ital 2014;34 (6):375-381.

19. Rogers DJ, Ojha S, Maurer R, Hartnick CJ. Use of Adjuvant Intralesional Bevacizumab for Aggressive Respiratory Papillomatosis in Children. JAMA Otolaryngol Head Neck Surg. 2013;139 (5):496-501.

20. Katsenos S, Berker HD. Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat with potential to lung cancer transformation: apropos of two cases and brief literature review. Case Rep Oncol 2011;4(1):162-171.

21. Sullivan C, Curtis S, and Mouzakes J. Therapeutic use of the HPV vaccine in Recurrent Respiratory Papillomatosis: A case report. International Journal of Pediatric Otorhinolaryngology 2017;93:103-106.

22. Baumanis MM, and Elmaraghy CA. Intersurgical interval increased with use of quadrivalent human papillomavirus vaccine (Gardasil) in a pediatric patient with recurrent respiratory papillomatosis: A case report. International Journal of Pediatric Otorhinolaryngology. 2016;91:166-169.

23. Centers for Disease Control and Prevention (CDC) FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP) MMWR Morb Mortal Wkly Report 2010;59:626.

24. Wangu Z, Hsu KK. Impact of HPV vaccination on anogenital warts and respiratory papillomatosis. Hum Vaccin Immunother 2016;12(6):1357-1362.

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