

## Progression of pulmonary cavities beyond HPV papillomatosis: A case report

Andrew Kim DO <sup>1,\*</sup>, Lily Liu <sup>2</sup>, Yi McWhorter DO <sup>3</sup> and Sapna Bhatia MD <sup>4</sup>

<sup>1</sup> Department of Internal Medicine, HCA Healthcare; Mountain View Hospital, Las Vegas, NV, USA.

<sup>2</sup> Kirk Kerkorian School of Medicine at University of Nevada, Las Vegas.

<sup>3</sup> Department of Medicine, HCA Healthcare; Mountain View Hospital, Las Vegas, NV, USA.

<sup>4</sup> Bhatia Pulmonary Center.

World Journal of Advanced Research and Reviews, 2023, 20(02), 670–673

Publication history: Received on 01 October 2023; revised on 09 November 2023; accepted on 11 November 2023

Article DOI: <https://doi.org/10.30574/wjarr.2023.20.2.2288>

### Abstract

The patient is a 22-year-old female with recurrent respiratory papillomatosis (RRP) requiring multiple laser ablations, presents for fiberoptic bronchoscopy due to worsening cavitory lesions of the right upper lobe seen on computed tomography (CT) scans. While these lesions were first attributed to her human papillomavirus (HPV) infection, bronchial cultures revealed a methicillin-sensitive *Staphylococcus aureus* (MSSA) infection. Not only is this case a unique presentation of concurrent RRP and MSSA cavitory lesions, it also highlights the importance of avoiding anchoring bias and initiating investigations for other differential diagnoses. We will review epidemiology, pathogenesis, and current therapeutics of RRP.

**Keywords:** Human papillomavirus (HPV); Papillomatosis; Cavitory lesion; Methicillin-sensitive *Staphylococcus aureus* (MSSA)

### 1. Introduction

Recurrent respiratory papillomatosis (RRP) is a disease caused by human papillomavirus (HPV) 6 and 11, and resulting papillomas present on vocal cords and larynx. It is most commonly seen in children by vertical transmission and often represents benign neoplasm.<sup>1</sup> However, HPV infections can induce cellular dysplasia and malignancy.<sup>2</sup> Lower airway involvement in RRP is in 1-2% of patients,<sup>3</sup> and 80% of them require tracheostomy.<sup>2</sup> 3.3% of patients develop lung involvement.<sup>3</sup> The prognosis after the involvement of lower respiratory tract tends to be poor. We present a 22 year-old female with longstanding RRP since birth who required bronchoscopy with brushing for newly developed tracheobronchial lesions.

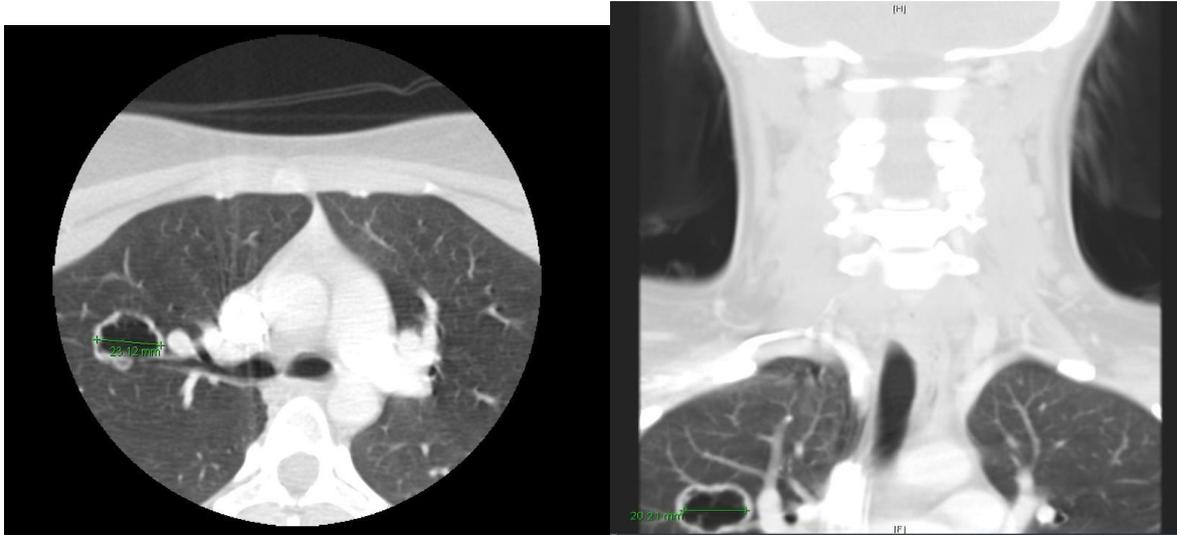
### 2. Case Presentation

Our patient is a 22-year-old female with a past medical history of RRP diagnosed at 6 months of age. She denies having received the HPV vaccine. She requires frequent laser ablations for lesions related to RRP in both upper and lower airways. In 2007, a tracheal culture taken showed growth of methicillin-sensitive *Staphylococcus aureus* (MSSA) and Group B streptococcus (GBS) pneumonia by bronchial cultures. This infection was treated with intravenous (IV) cefazolin 800 mg three times a day for 5 days.

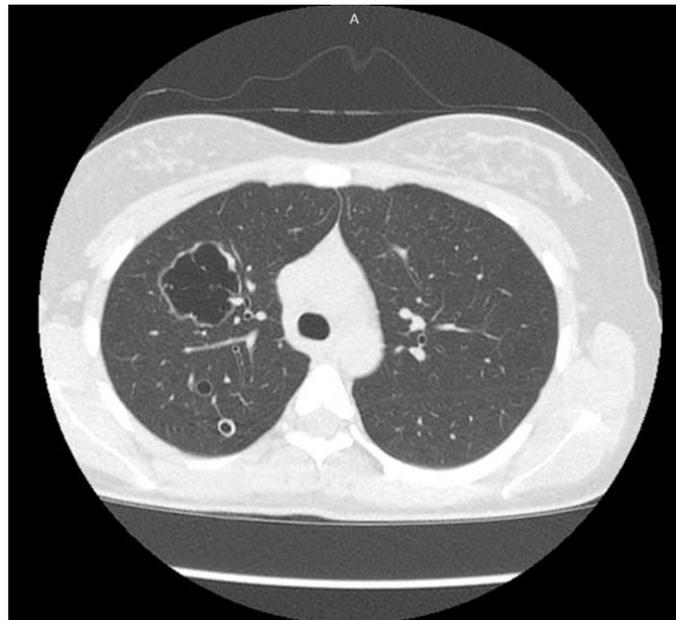
In 2014, her computed tomography (CT) scan of the chest revealed a 2.3 cm right upper lobe cavitory lesion (Figure 1A and 1B). Bronchial cultures at that time were positive for HPV. In early 2022, she underwent laryngoscopy which showed an anterior glottic scar and diffuse papillomatosis of the larynx, infraglottis, and anterior trachea. Serological

\* Corresponding author: Andrew Kim DO.

markers of autoimmune panel, antineutrophil cytoplasmic antibodies (ANCA), vascular endothelial growth factor (VEGF) levels, human immunodeficiency virus (HIV) were negative. In late 2022, she developed new satellite cavitory lesions requiring repeat bronchoscopy and brushing. Her bronchial cultures were positive for MSSA, but not HPV. The patient received oral trimethoprim/sulfamethoxazole 800-160 mg twice a day for 10 days. Her repeat CT scan in 2023 showed stable cavitation (Figure 2).



**Figure 1A and 1B** In 2014, CT scan demonstrates a 2.3 cm cavitation within the right upper lobe



**Figure 2** In 2023, CT showed numerous satellite pulmonary cavities as a result of MSSA pneumonia

### 3. Discussion

RRP is caused by HPV, naked double-stranded circular DNA viruses that are often associated with vulvar, cervical, and anal cancer<sup>5</sup>. HPV can be classified as high-risk when there is involvement of E6/E7 proteins impairing DNA repair pathways which increases likelihood of cancer, or low-risk with more common manifestations of anogenital papillomas and skin warts<sup>5</sup>. HPV 6 and 11 are most commonly associated with RRP, although other high-risk variants have been found to cause RRP as well.

While vaccination efforts against HPV have decreased the incidence of RRP, it is still estimated to be 4.3 per 100,000 children, with 75% of the cases presenting before age 3<sup>1</sup>. Juvenile-onset RRP tends to be the more aggressive form of the disease with a higher likelihood of recurrence<sup>6</sup>. Juvenile-onset RRP is obtained via vertical transmission during delivery when the neonate is passed through an infected genital tract<sup>6</sup>. In fact, births with a maternal history of genital warts corresponded to a 231.4 times higher risk of disease in the offspring compared to births without a maternal history of genital warts<sup>7</sup>. Furthermore, the mode of delivery has shown correlation to transmission as neonates delivered by Cesarean deliveries were found to have significantly lower rates of HPV infection compared to those delivered by vaginal deliveries<sup>8</sup>. In our patient, Cesarean section by birth could have prevented her RRP infection caused by HPV.

Currently, there is no definitive cure for RRP. The most important preventative method is HPV vaccination. A systematic review revealed that adjuvant HPV vaccination reduced disease recurrence and need for surgical intervention in patients with active disease<sup>9</sup>. Patients with aggressive RRP who received 3 doses of the quadrivalent prophylactic HPV vaccine showed an increased time between surgical procedures<sup>10</sup>. If our patient received HPV vaccination as a teenager, it could have increased her time in remission, reduced the number of necessary procedures performed, and increased her quality of life.

For patients with active RRP, surgery remains the most common treatment. The goal of treatment is to remove the papilloma and preserve an adequate airway. The most common surgical modalities include cold metal instruments, micro debridement, and CO2 laser. However, patients that undergo surgical intervention commonly require multiple surgeries, resulting in scarring of the larynx and glottis. Another treatment option is cidofovir, an antiviral agent that is primarily used to treat cytomegalovirus retinitis in patients with human immunodeficiency virus; it has been used off-label for RRP since 1998<sup>11</sup>. A systematic review of RRP treatment with cidofovir reported complete resolution in 57% of patients and no improvement in only 8% of patients<sup>12</sup>. However, no randomized controlled trials with cidofovir have been conducted. Bevacizumab is another adjuvant therapy used against aggressive RRP that is refractory to treatment. Bevacizumab is a recombinant monoclonal antibody that inhibits the binding of VEGF to its receptor that has been shown to increase time between surgical interventions and decrease disease severity<sup>13</sup>.

Anchoring bias is commonly seen in medicine as physicians tend to focus on previous diagnoses to explain new conditions. In this patient's case, the cavitations were thought to be explained by her known HPV diagnosis until the positive MSSA culture. MSSA is known to cause cavitory lesions in the lung, particularly if the bacteria can produce the Pantan-Valentine leukocidin (PVL)<sup>14</sup>. The main distinction in the diagnosis of our patient is the positive culture of MSSA found within the sample of the right upper lobe. Appropriate antimicrobial treatment of infection has been shown to lead to radiological resolution<sup>15</sup> of cavitations.

---

#### **4. Conclusion**

HPV infection can cause RRP through vertical transmission, leading to recurring papilloma requiring laser therapy and pulmonary cavities needing surveillance and treatment. Vigilance in monitoring disease progression and detecting additional pathological processes can help patients stay in remission and improve quality of life. Patients with RRP may be susceptible to opportunistic infections, especially as adjuvant therapies with immunosuppressive agents such as bevacizumab become more widely used.

---

#### **Compliance with ethical standards**

##### *Acknowledgments*

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

##### *Disclosure of conflict of interest*

The above listed authors, Drs. Kim, Liu, McWhorter, Bhatia, have no conflicts of interest to declare.

##### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

---

**References**

- [1] Derkay Craig S. and Wiatrak Brian. Recurrent Respiratory Papillomatosis: A Review. *The Laryngoscope*. 2009 Jan;118(7): 1236-1247
- [2] Blackledge FA, Anand VK. Tracheobronchial extension of recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2000 Sep;109(9):812-8. doi: 10.1177/000348940010900905. PMID: 11007082.
- [3] Yu JP, Barajas RF Jr, Olorunsola D, Sugrue LP, Hernandez-Pampaloni M. Heterogeneous 18F-FDG uptake in recurrent respiratory papillomatosis. *Clin Nucl Med*. 2013 May;38(5):387-9. doi: 10.1097/RLU.0b013e3182868af9. PMID: 23486321.
- [4] Soldatski IL, Onufrieva EK, Steklov AM, Schepin NV. Tracheal, bronchial, and pulmonary papillomatosis in children. *Laryngoscope*. 2005 Oct;115(10):1848-54. doi: 10.1097/01.mlg.0000173155.57491.2a. PMID: 16222208.
- [5] Ouda AM, Elsabagh AA, Elmakaty IM, et al. HPV and Recurrent Respiratory Papillomatosis: A Brief Review. *Life*. 2021;11(11):1279. doi:10.3390/life11111279
- [6] Benedict JJ, Derkay CS. Recurrent respiratory papillomatosis: A 2020 perspective. *Laryngoscope Investigative Otolaryngology*. 2021;6(2):340-345. doi:10.1002/lio2.545
- [7] Silverberg M. Condyloma in pregnancy is strongly predictive of Juvenile-Onset recurrent respiratory papillomatosis. *Obstetrics & Gynecology*. 2003;101(4):645-652. doi:10.1016/s0029-7844(02)03081-8
- [8] Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clinical Otolaryngology and Allied Sciences*. 2002;27(4):237-243. doi:10.1046/j.1365-2273.2002.00555.x
- [9] Dion GR, Teng S, Boyd LR, et al. Adjuvant Human Papillomavirus Vaccination for Secondary Prevention. *JAMA Otolaryngology–Head & Neck Surgery*. 2017;143(6):614. doi:10.1001/jamaoto.2016.473
- [10] Hočevnar-Boltežar I, Matičič M, Šereg-Bahar M, et al. Human papilloma virus vaccination in patients with an aggressive course of recurrent respiratory papillomatosis. *European Archives of Oto-Rhino-Laryngology*. 2014;271(12):3255-3262. doi:10.1007/s00405-014-3143-y
- [11] Ballestas SA, Shelly S, Soriano RM, Klein A. Tendencias en el tratamiento de la papilomatosis respiratoria recurrente. *Acta Otorrinolaringológica Española*. 2021;72(2):109-120. doi:10.1016/j.otorri.2019.11.001
- [12] Chadha NK, James AL. Antiviral agents for the treatment of recurrent respiratory papillomatosis: A systematic review of the English-language literature. *Otolaryngology–Head and Neck Surgery*. 2007;136(6):863-869. doi:10.1016/j.otohns.2006.09.007
- [13] Maturo S, Hartnick CJ. Use of 532-nm Pulsed Potassium Titanyl Phosphate Laser and Adjuvant Intralesional Bevacizumab for Aggressive Respiratory Papillomatosis in Children. *Archives of Otolaryngology–Head & Neck Surgery*. 2010;136(6):561. doi:10.1001/archoto.2010.81
- [14] Adler A, Temper V, Block C, Abramson N, Moses A. Panton-Valentine Leukocidin-producing *Staphylococcus aureus*. *Emerging Infectious Diseases*. 2006;12(11):1789-1790. doi:10.3201/eid1211.060726
- [15] Takigawa Y, Fujiwara K, Saito T, et al. Rapidly Progressive Multiple Cavity Formation in Necrotizing Pneumonia Caused by Community-acquired Methicillin-resistant *Staphylococcus aureus* Positive for the Panton-Valentine Leukocidin Gene. *Internal Medicine*. 2019;58(5):685-691. doi:10.2169/internalmedicine.1454-18