

Recurrent Respiratory Papillomatosis

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Case Summary

An adolescent with a history of recurrent respiratory papillomatosis (RRP) and pulmonary involvement presented with progressive dyspnea on exertion.

Imaging Findings

Chest radiograph (Figure 1) and chest CT (Figure 2) showed both cystic and solid lesions. The cystic lesions had a variable appearance: Some had a thick, irregular wall while others had a thin, nearly imperceptible wall. A small nodule was visible in the posterolateral trachea on CT.

Diagnosis

Recurrent respiratory papillomatosis

Discussion

Recurrent respiratory papillomatosis is a rare disease characterized by recurrent benign papillomas that can occur anywhere along

the respiratory tract, most commonly the larynx and vocal cords. Globally, the incidence of RRP is 4 per 100,000 children and 2 per 100,000 adults.¹ Rates in the US have been steadily declining since the introduction of the human papillomavirus (HPV) vaccine in 2006.² The current estimated incidence of RRP in children is 4 per 100,000 children and 2 per 100,000 in adults annually.³

Specific types of HPV, most commonly HPV 6 and HPV 11, are associated with the wart-like papilloma characteristic of RRP.³ HPV 11 is associated with more aggressive disease, often seen in children less than 5 years old.⁴

Recurrent respiratory papillomatosis has a trimodal age distribution, with age peaks at 7, 35, and 64 years,³ and is classified as juvenile- or adult-onset. Patients with juvenile-onset RRP present between 2 and 6 years old with more aggressive disease⁵ transmitted vertically either in utero or during passage through an infected birth canal. The etiology of adult-onset RRP is unclear, with some sources favoring transmission via oral-genital contact while others favor genetic susceptibility, including adult activation of vertically transmitted disease.^{6,7,8} Upon infection, the virus remains latent within the host cells, causing recurrences even after the elimination of the initial papilloma.

Papillomas are found primarily in the larynx, although they

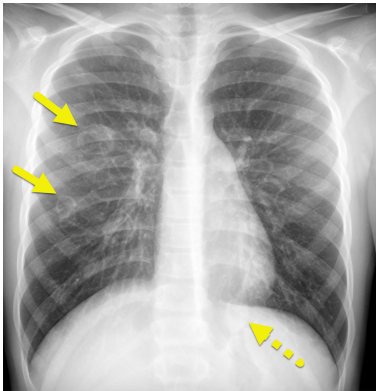
can occur anywhere in the airway, from the nasopharynx to the tracheobronchial tree and pulmonary parenchyma. Clinical presentation is nonspecific and dependent on the location of the lesions. Potential signs include voice changes, cough, dyspnea, wheezing, and stridor. In adults, hoarseness is the most common presenting sign. In children, presenting signs include progressive hoarseness, stridor, and breathing difficulties.⁵ Owing to the nonspecific signs, children are often treated for pharyngitis, asthma, or bronchitis, resulting in delayed diagnosis and potential for progression to respiratory distress.

Disease course is highly variable, ranging from spontaneous remission to malignant transformation. Squamous cell carcinoma resulting from RRP is rare but has a poor prognosis. Malignant transformation is more commonly associated with HPV 16 and 18, smoking, and radiation therapy.⁹ Disease recurrence is associated with diminished lymphocyte response, although it remains unclear whether this is causative or a result of infection.¹⁰

Recurrent respiratory papillomatosis is rarely diagnosed via chest radiograph, although it can be visualized as solid or cavitated pulmonary nodules if there is lung involvement. In severe cases, chest radiograph may demonstrate symptoms of bronchial

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Figure 1. Chest radiograph shows multiple cystic (solid arrows) and solid (dashed arrow) lesions in the lungs.



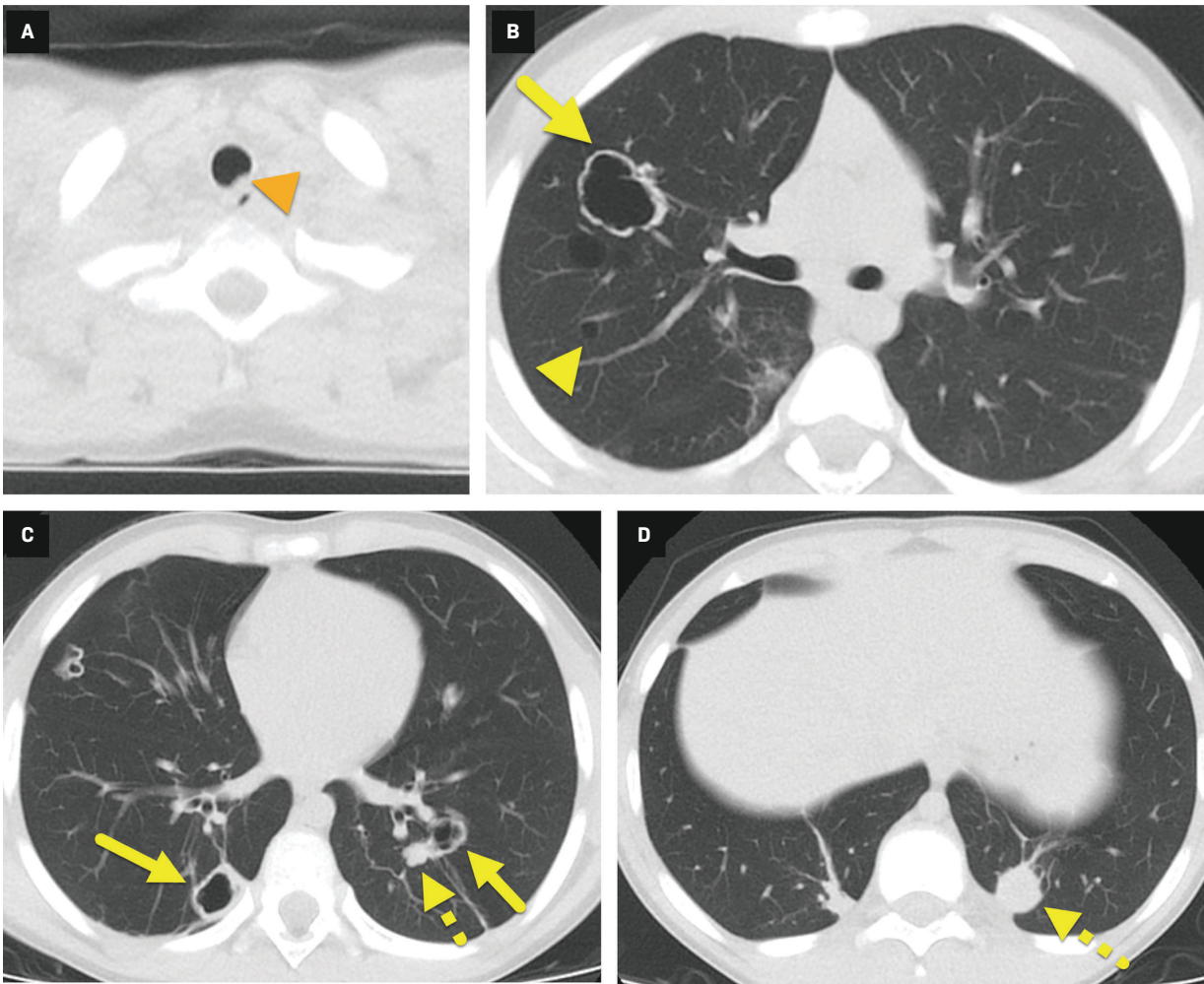
obstruction such as atelectasis and bronchiectasis.⁴

CT is the preferred imaging modality and can demonstrate the tracheal and bronchial lesions characteristic of RRP. Nodular lesions can present on CT as focal or diffuse large airway narrowing. Lung lesions may be single or multiple, nodular or polypoid, and of varying size and distribution.⁴ In some cases, lesions can present as enlarged air-filled cysts, and superimposed infection can cause air-fluid levels. CT find-

ings of airway obstruction include atelectasis and bronchiectasis.¹¹

Diagnosis is confirmed via laryngoscopy and bronchoscopy, allowing direct visualization of the vocal cords and airways, as well as biopsy for histopathological examination. Papillomas are often visualized as pale polypoid lesions along the respiratory tract. Definitive diagnosis is made via histopathological examination, which shows well-differentiated squamous epithelium with a central fibrovascular core.¹²

Figure 2. Chest CT through the trachea (A), subcarinal region (B), pulmonary vein insertion (C), and lung bases (D) shows multiple lesions in the airways. Some cystic lesions have a thick, irregular wall (arrows) while others have a barely perceptible wall (yellow arrowhead). Solid pulmonary nodules are also present (dashed arrows). A papilloma (orange arrowhead) is visible along the left posterolateral aspect of the trachea.



Currently there is no cure for RPP. Papillomas are primarily treated surgically, with adjunct therapy recommended in approximately 20% of patients.⁴ Clinical criteria for adjunct therapy include greater than 4 surgical procedures per year, rapid regrowth with airway obstruction, or distal multisite spread.¹³ Adjunct therapy includes antiviral medications, COX-2 inhibitors, and chemotherapeutics.

Conclusion

Recurrent respiratory papillomatosis is a rare disorder of benign neoplasms of the respiratory tract, commonly located along the larynx and vocal cords. It is most commonly associated with HPV 6 and HPV 11 infection, and has a trimodal age distribution, with more aggressive disease in children. If left untreated, RRP can lead to significant respiratory distress and may lead to the development of squamous cell carcinoma. Although there is no cure, surgical excision improves symptoms. The HPV vaccine has helped decrease the incidence of RRP.

References

- 1) Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope*. 2008;118(7):1236-1247. doi:10.1097/MLG.0b013e31816a7135
- 2) Meites E, Stone L, Amiling R, et al. Significant declines in juvenile-onset recurrent respiratory papillomatosis following human papillomavirus (HPV) vaccine introduction in the United States. *Clin Infect Dis*. 2021;73(5):885-890. doi:10.1093/cid/ciab171
- 3) Sechi I, Muresu N, DiLorenzo B, et al. Pulmonary involvement in recurrent respiratory papillomatosis: a systematic review. *Infect Dis Rep*. 2024;16(2):200-215. doi:10.3390/idr16020016
- 4) Fortes HR, von Ranke FM, Escuisato DL, et al. Recurrent respiratory papillomatosis: a state-of-the-art review. *Respir Med*. 2017;126:116-121. doi:10.1016/j.rmed.2017.03.030
- 5) Benedict JJ, Derkay CS. Recurrent respiratory papillomatosis: a 2020 perspective. *Laryngoscope Investig Otolaryngol*. 2021;6(2):340-345. doi:10.1002/lio2.545
- 6) Gerein V, Schmandt S, Babkina N, et al. Human papilloma virus (HPV)-associated gynecological alteration in mothers of children with recurrent respiratory papillomatosis during long-term observation. *Cancer Detect Prev*. 2007;31(4):276-281. doi:10.1016/j.cdp.2007.07.004
- 7) Sabry AO, Papilloma PBC. Papilloma. [updated 2023 aug 14]. *StatPearls [Internet]*. StatPearls Publishing. 2024. <https://www.ncbi.nlm.nih.gov/books/NBK560737/>
- 8) Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. *Ther Clin Risk Manag*. 2015;11:731-738. doi:10.2147/TCRM.S81825
- 9) Katsenos S, Becker HD. Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat, with potential to lung cancer transformation: apropos of two cases and a brief literature review. *Case Rep Oncol*. 2011;4(1):162-171. doi:10.1159/000327094
- 10) Stern Y, Felipovich A, Cotton RT, Segal K. Immunocompetency in children with recurrent respiratory papillomatosis: prospective study. *Ann Otol Rhinol Laryngol*. 2007;116(3):169-171. doi:10.1177/000348940711600302
- 11) Pai SI, Wasserman I, Ji YD, et al. Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis. *Lancet Respir Med*. 2022;10(10):997-1008. doi:10.1016/S2213-2600(22)00008-X
- 12) Ko JM, Jung JI, Park SH, et al. Benign tumors of the tracheobronchial tree: CT-pathologic correlation. *AJR Am J Roentgenol*. 2006;186(5):1304-1313. doi:10.2214/AJR.04.1893
- 13) Torres-Canchala L, Cleves-Luna D, Arias-Valderrama O, et al. Systemic bevacizumab for recurrent respiratory papillomatosis: a scoping review from 2009 to 2022. *Children (Basel)*. 2022;10(1):54. doi:10.3390/children10010054