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The Clinical Picture

A 35-year-old man with recurrent hoarseness

Q: A 35-YEAR-OLD MAN who does not smoke presents with recurrent hoarseness. He has undergone laser photoresection of a tracheal mass three times in the past 2 years. **FIGURE 1** depicts a tracheal mass detected during a recent bronchoscopy.

What is the correct diagnosis?

- Carcinoid tumor
- Squamous cell carcinoma
- Recurrent respiratory papillomatosis
- Wegener granulomatosis
- Invasive aspergillosis

A: Carcinoid tumor, the most common benign endobronchial lesion, has a smooth, pedunculated, and vascular appearance. This patient's lesion has a "mulberry" or "bunch-of-grapes" appearance, which would be unusual for a carcinoid tumor.

Squamous cell carcinoma is also unlikely, as the patient is young and does not smoke.

Wegener granulomatosis is unlikely, because he has no history of sinus symptoms or hematuria. In addition, endobronchial Wegener granulomatosis usually presents as an ulcerative and not an exophytic mass lesion.

Invasive aspergillosis of the airways occurs only in immunosuppressed patients.

Recurrent respiratory papillomatosis is the most likely diagnosis.

■ RECURRENT RESPIRATORY PAPILOMATOSIS

This is the most common benign neoplasm of the larynx and the most common tumor of the upper respiratory tract in children, and more than 20,000 people in the United States have active disease.



FIGURE 1. Tracheal mass

Human papillomavirus types 6 and 11, which cause genital warts, also cause recurrent respiratory papillomatosis.

Juvenile onset vs adult onset

Recurrent respiratory papillomatosis can be categorized by the patient's age at the onset of disease, and the juvenile-onset form almost seems like a different disease from the adult-onset form.

Juvenile-onset infection is transmitted vertically from mothers with active genital human papillomavirus infection or latent infection to their newborns through the birth canal. In contrast, the cause of adult-onset recurrent respiratory papillomatosis is either reactivation of virus present since birth or infection in the form of a sexually transmitted disease. Its incidence is higher in people practicing oral sex.



The juvenile-onset form is usually more aggressive and recurs with multiple lesions, whereas adult-onset lesions are usually singular and recur less frequently.

Juvenile-onset recurrent respiratory papillomatosis usually manifests when the patient is 2 to 4 years old, whereas the adult-onset form arises between the third and fifth decades of life. Males and females are equally affected in both forms of the disease.

Vocal cords most often affected

Recurrent respiratory papillomatosis classically presents with laryngeal involvement, most often on the true vocal cords. Other areas often affected are the limen vestibuli of the nose, the nasopharyngeal area of the soft palate, the midline of the epiglottic margins of the larynx, the under-surface of the vocal cords and false cords, the carina, and the upper trachea, especially tracheostomy sites. Five percent to 10% of patients have bronchopulmonary involvement in the form of pneumatoceles and parenchymal masses.

Significant controversy surrounds the role of tracheotomy in activating the disease and spreading it to the lower respiratory tract. Most experts agree that tracheotomy should be considered only if absolutely necessary and also suggest early decannulation to limit disease spread.

Symptoms

Adults with recurrent respiratory papillomatosis almost always present with dysphonia or lesions of the oral cavity or nasal vestibule, which may be discovered incidentally. In contrast, in children the disease is the second most common cause of hoarseness (the most common cause being viral upper respiratory tract infection). The second symptom to develop after dysphonia is stridor, which includes both inspiratory and expiratory components as the disease progresses.

Other clinical manifestations include chronic cough, recurrent postobstructive pneumonia, failure to thrive in children, worsening dyspnea, and acute respiratory failure.

Histologic appearance

Grossly, papillomas appear as flesh-colored, pedunculated, exophytic lesions, typically described as having a mulberry or bunch-of-grapes appearance.

Light microscopy of the papilloma reveals finger-like projections of stratified squamous epithelium overlying a vascular connective tissue stroma.

In about 3% of cases the papilloma progresses to

cancer, usually squamous cell carcinoma. Smoking and radiation exposure have been reported to be significant risk factors contributing to malignant transformation.

Treatment

Although surgery remains the mainstay of therapy, new developments in medical therapy can provide other options. But there is no cure for recurrent respiratory papillomatosis as it is still not possible to eradicate human papillomavirus.

Surgical management involves removal of symptomatic papillomas and avoiding excessive scarring. Today, carbon dioxide laser is the preferred method of removing papillomas from the oral and nasal cavities, larynx, and upper trachea. Other types of lasers used include argon, neodymium:yttrium aluminum garnet (Nd:YAG), pulse-dye, and potassium titanyl phosphate. Phonosurgery, submucosal infusion, and microinstrumentation, including microdebriders with miniaturized shavers, are believed to limit airway and vocal cord scarring in adults and are currently the preferred method of therapy by many clinicians. Bronchoscopic examination might be needed as frequently as every 2 to 4 weeks.

Ten percent of patients require adjuvant therapy as a result of failure to surgically control the disease. The most commonly used adjuvant therapy is alpha-interferon. Other options are cidofovir, indole-3-carbinol (I3C), cis-retinoic acid (isotretinoin), and HspE7, a recombinant protein. In a recent prospective trial, all 13 patients who received intralesional injections of cidofovir entered long-term remission.

In addition, speech and language therapy should be offered to preserve phonation. Families should be encouraged to engage in frank and open discussions of this challenging and often frustrating disease and should be offered further support through resources such as the Recurrent Respiratory Papilloma Foundation (609-530-1443).

Current research regarding vaccine therapy for pediatric recurrent respiratory papillomatosis has shown promise and revived hope.

SUGGESTED READING

Alkotoob ML, Budev MM, Mehta AC. Recurrent respiratory papillomatosis. *J Bronchol* 2004; 11:132-139.

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