

Chapter 40 – Management of Recurrent Respiratory Papillomatosis

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Recurrent respiratory papillomatosis (RRP) of the upper aerodigestive tract is a viral-induced benign neoplastic process. RRP occurs in a relatively small number of individuals but is a particularly vexing condition to treat due to its recurrent nature and the negative impact on voice, swallowing, and respiratory function. Although RRP can occur on any mucosal surface, it is most commonly found at mucosal transition zones in the larynx, specifically at the transition between ciliated pseudostratified (respiratory) epithelium and stratified squamous epithelium.[1] In recent years, significant scientific and clinical advances have resulted in an improvement in treatment outcome.

RRP is caused by the human papillomavirus (HPV), which is a double-stranded DNA, nonenveloped, icosahedral (20-sided) capsid virus. HPV is responsible for other medical conditions, including cervical condyloma and skin lesions (warts). Although many different HPV subtypes can result in clinical manifestations, the most common subtypes involved in RRP are HPV-6 and HPV-11. HPV infection typically produces an epithelial growth that can either be classified as a spreading or pedunculated pattern. Classically, these lesions have “fronds” with a central vascular subcomponent within each frond providing the “speckled” appearance typical of RRP (Fig. 40-1).[2]

RRP is a disease process limited to the epithelial layer. Interestingly, patients infected with HPV can have normal-appearing epithelial mucosa that contains HPV-infected cells.[3] This is particularly important to realize from a surgical standpoint wherein more aggressive surgical excision more often than not is detrimental to the patient and does not provide improved therapeutic benefit. In other words, a deeper excision with wide margins around the lesion will not benefit the patient, because the surrounding normal-appearing mucosa is already likely to be infected.[4]

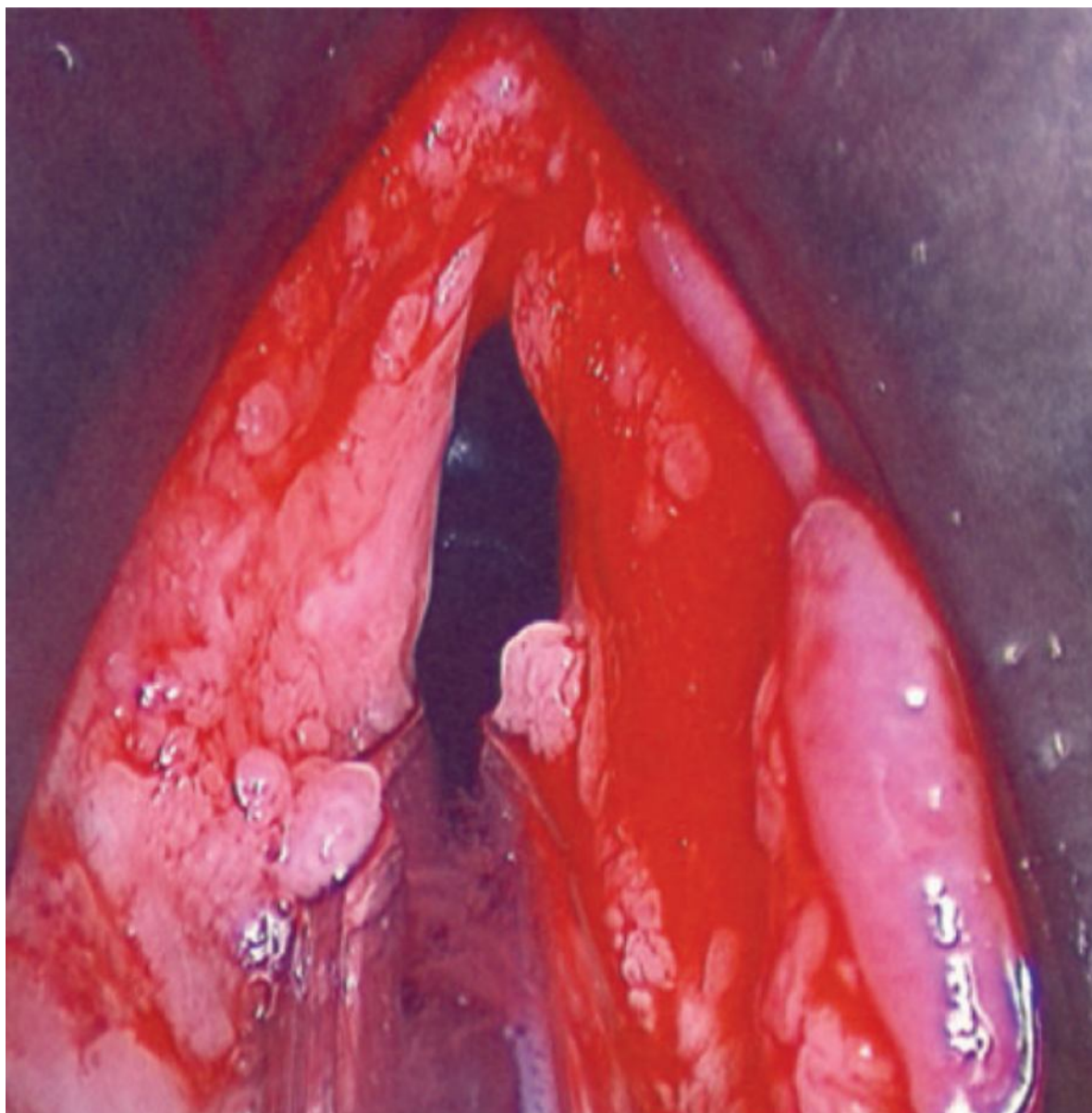



Figure 40-1 Recurrent respiratory papillomatosis (RRP) of supraglottis and true vocal folds. Notice the frondlike appearance of a typical RRP lesion.

PATIENT SELECTION

RRP occurs in a bimodal age distribution—young children and young adults—with symptoms and characteristics unique to each group. Young children typically present with a history of abnormal cry, chronic cough, or recurrent croup, or progressive respiratory obstruction often manifesting as stridor. Adult patients with RRP primarily complain of dysphonia at initial presentation.

Regardless of the age at presentation, a thorough physical examination of the head and neck, including both flexible fiberoptic laryngoscopy/stroboscopy and rigid stroboscopy, should be performed if possible. It may not be possible to adequately perform fiberoptic laryngoscopy in an outpatient setting in young children, so these patients may require microlaryngoscopy under general anesthesia to obtain a tissue biopsy, diagnosis, and determination of the extent of the lesions.^[5] Adults with epithelial lesions suggestive of RRP found on initial clinical evaluation should also undergo microlaryngoscopy with biopsy to rule out malignancy such as squamous cell carcinoma and to determine the extent of the disease.

Once a diagnosis of RRP has been established, it is important to discuss with the patient and family the fact that RRP is a chronic disease process and to provide information about all available treatment options. The patient and family should be informed that usually frequent surgical procedures may be necessary to debulk or excise the RRP lesions and, as such, the patient's quality of the voice may diminish from repeated surgery of the vocal folds. Additionally, patients and their families can often benefit from support groups such as the Recurrent Respiratory Papillomatosis Foundation, which is composed of both adults with RRP and the parents of children afflicted with

RRP (www.rpf.org ). The importance of providing the patient and family with adequate information as well as assisting them to develop appropriate expectations cannot be overemphasized in helping them to cope with the ramifications of the disease process.

PREOPERATIVE PLANNING

Prior to surgery, appropriate informed consent should be obtained from the patient (or parents if the patient is a child). This detailed process should include an explanation of the risks of surgery, which include: bleeding, infection, recurrence, chipped teeth, altered taste, numbness or weakness of the tongue, persistent or worsened dysphonia, and the likely need for additional surgical procedures. Patients should also be informed that some papilloma-covered areas of the larynx will not be removed, so that surgery will be staged for sites such as the anterior or posterior commissure to help prevent the formation of an anterior glottic web or posterior glottic stenosis. If the patient has any concomitant laryngeal irritation-producing conditions such as laryngopharyngeal reflux or tobacco use, he or she should be aggressively treated or eliminated. If available, the patient's video laryngoscopy examination should be viewed preoperatively, thereby providing a review of the locations of the lesions to assist in surgical planning.

SURGICAL TECHNIQUE

After general anesthesia has been induced, the airway should be secured by intubation with an endotracheal tube for adult RRP patients. A smaller tube such as a size 5.0 is preferable to allow more working space for excision of the lesions. In patients with extensive bulky RRP, a Hunsaker tube (Medtronic-Xomed, Jacksonville, FL) with jet ventilation may be required. For prepubescent pediatric patients, general anesthesia can be induced and maintained by intravenous infusion with spontaneous respiration.

Once the airway has been appropriately secured, the initial endoscopy should include a thorough examination of the oral cavity, oropharynx, hypopharynx, endolarynx, subglottis, trachea, and esophagus to accurately stage the sites and extent of the RRP. During suspension microlaryngoscopy, the largest laryngoscope possible is preferred for optimal visualization and ease of excision of the lesion.^[6] The use of angled telescopes is an important adjunct that helps visualize the full extent of and establish the precise locations of the lesions throughout the supraglottis and endolarynx.^[7] The undersurface of the vocal fold, as well as the ventricle and the anterior and posterior commissures, are best visualized with 30- and 70-degree telescopes. The angled telescopes are also useful for obtaining photodocumentation at the beginning and end of the procedure. After appropriate visualization of the lesions, submucosal infiltration of epinephrine (1:10,000) deep to the lesion, using a narrow gauge needle, is useful in elevating the lesions from important underlying structures such as the vocal ligament.^[8] Submucosal injection brings the lesion closer to the center of the laryngoscope, easing removal and providing hemostasis.

Historically, RRP has been excised with "cold steel" surgical instruments or the CO₂ laser. More recently, however, the microdebrider has been growing in popularity for the excision of RRP, because it provides the surgeon with the ability to rapidly remove bulky RRP with minimal trauma to the underlying structures.^[9,10] Cold steel instrumentation allows precise surgical excision with complete avoidance of thermal injury to deeper structures (see Chapter 37). The CO₂ laser has the advantage of allowing precise surgical excision of RRP in anatomic areas that are difficult to reach with hand-held instruments. The primary drawback of the CO₂ laser is the risk of thermal injury to surrounding tissue. The microdebrider is used to "skim" the surface, allowing the attached suction of the instrument to draw the RRP into the rotating head of the instrument. These different techniques for excision of these lesions can be optimally applied to the separate laryngeal subsites: supraglottis, glottis, and subglottis (see below).

Because RRP is a recurrent disease and is rarely cured by surgery, it is important that surgery be very conservative, precise, and restricted to the epithelium during excision of the lesions. As such, regardless of the method chosen for removal, the surgeon must always be cognizant of and strive to prevent damage to the critical structures of the vocal fold, including the lamina propria, vocal ligament, anterior and posterior commissures, and subglottis.

All efforts should be made to avoid tracheostomy in patients with RRP. The surgeon will likely find that disease tends to rapidly grow and recur around the tracheostomy sites in these patients, and may potentially lead to tracheal and pulmonary dissemination of disease, which is usually fatal.

Supraglottis

In the supraglottic larynx, RRP typically occurs on the laryngeal surface of the epiglottis and on the superior surface of the false vocal fold. When RRP is located in the laryngeal ventricle and the undersurface of the false vocal fold, excision of the lesion may be quite difficult. As such, removal of the medial portion of the false vocal fold may be required to optimize access to the ventricle.

Treatment of RRP on the laryngeal surface of the epiglottis is often challenging due to the anatomic constraints of achieving adequate visualization and exposure. Difficulty in achieving exposure may lead to prolonged operative times as the surgeon struggles with constant repositioning of the laryngoscope to provide optimal visualization. Due to the anatomic constraints, RRP in the supraglottis is often difficult to view and to ablate with the CO₂ laser.

The microdébrider can be quite useful to the surgeon for resecting lesions in the supraglottis given that in this area RRP is often bulky and the microdébrider can be angled to allow rapid removal.

Treatment of the superior surface of the false vocal folds is usually determined by the nature of RRP. If the disease is bulky, a microdébrider is the ideal method for rapid and controlled removal of the disease. If the RRP appears to be superficial and spreading, the defocused CO₂ laser at a low power setting is useful for vaporizing these lesions.

Angled 30- and 70-degree telescopes are also useful for providing visualization during excision of the lesion with a cup forceps.^[7] Borrowing from phonosurgery techniques, submucosal epinephrine injection into the lateral ventricle may help displace the lesions medially so that this area can be viewed through the laryngoscope, thereby improving ease and likelihood of complete removal.^[6]

True Vocal Folds

This region contains the true vocal folds and anterior and posterior commissures, and extends to a point approximately 1 cm below the true vocal folds anteriorly. RRP has a predilection for the true vocal folds (superior and infraglottic surface) as well as the anterior commissure. In this anatomic location, it is valuable to reemphasize that removal of RRP should be strictly isolated to the epithelium because RRP is a superficial disease, and deeper resection will likely result in scar formation and a worse voice without any improvement in the control of RRP. When excising RRP near or involving the anterior commissure, it is important to remove RRP in a staged unilateral fashion to prevent the formation of a glottic web (Fig. 40-2). This staged approach means that the patient will need scheduled surgery at a later date (approximately 30 days) to remove RRP from the contralateral side. This same staged approach is required for surgery in the posterior commissure. Retraction of the nonoperated contralateral vocal fold is also helpful for providing improved visualization of the anterior commissure.

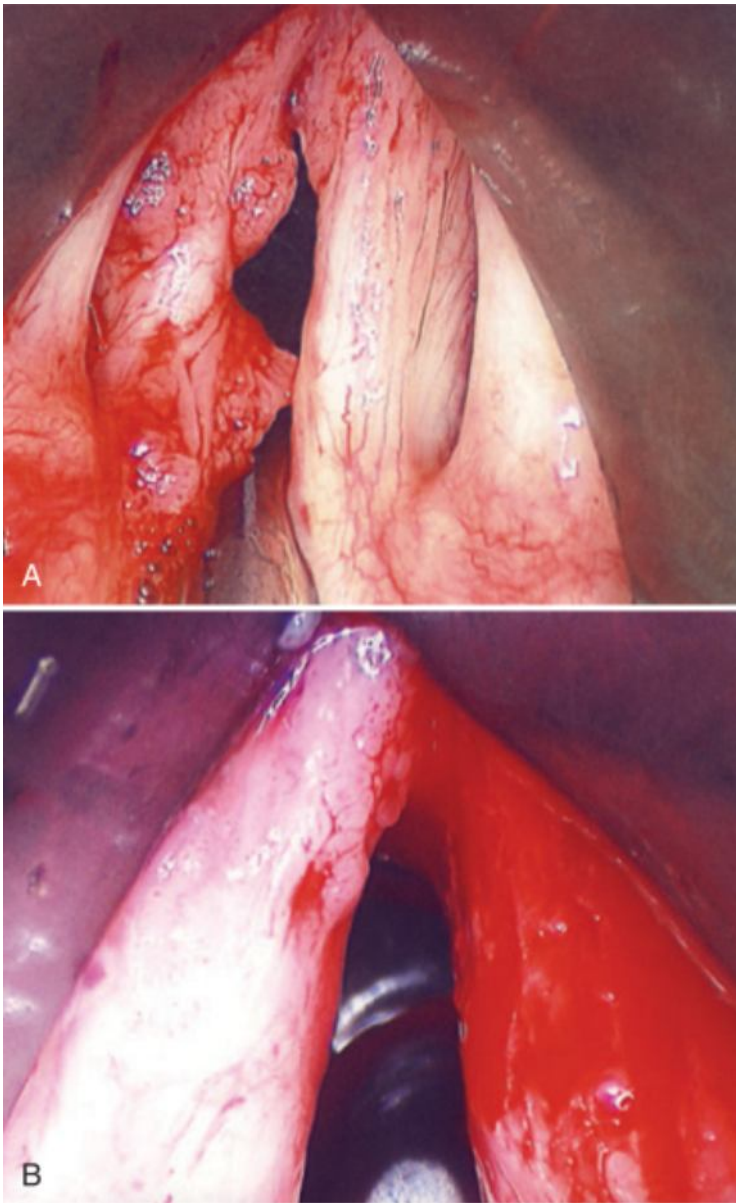


Figure 40-2 Staging of recurrent respiratory papilloma (RRP) removal from the anterior commissure. **A**, Intraoperative photograph before RRP removal. Notice bilateral anterior commissure lesions. **B**, After right-sided RRP removal. Lesions are intentionally not removed from the left anterior commissure to prevent formation of an anterior glottic web.

Cold steel instrumentation is ideal for excision of RRP lesions involving the true vocal folds. Using instruments and concepts of phonosurgery for removal of RRP in the glottis can be quite helpful (see Chapter 37). Bulky RRP can be quickly removed with a microdebrider from the true vocal folds (Fig. 40-3). Precision control similar to cold steel instrumentation, however, is not achieved. Great care is required to avoid injury to the lamina propria/vocal ligament. As such, the microdebrider should be considered only for patients with bulky lesions or who have already developed vocal fold scarring from repeated prior surgeries.

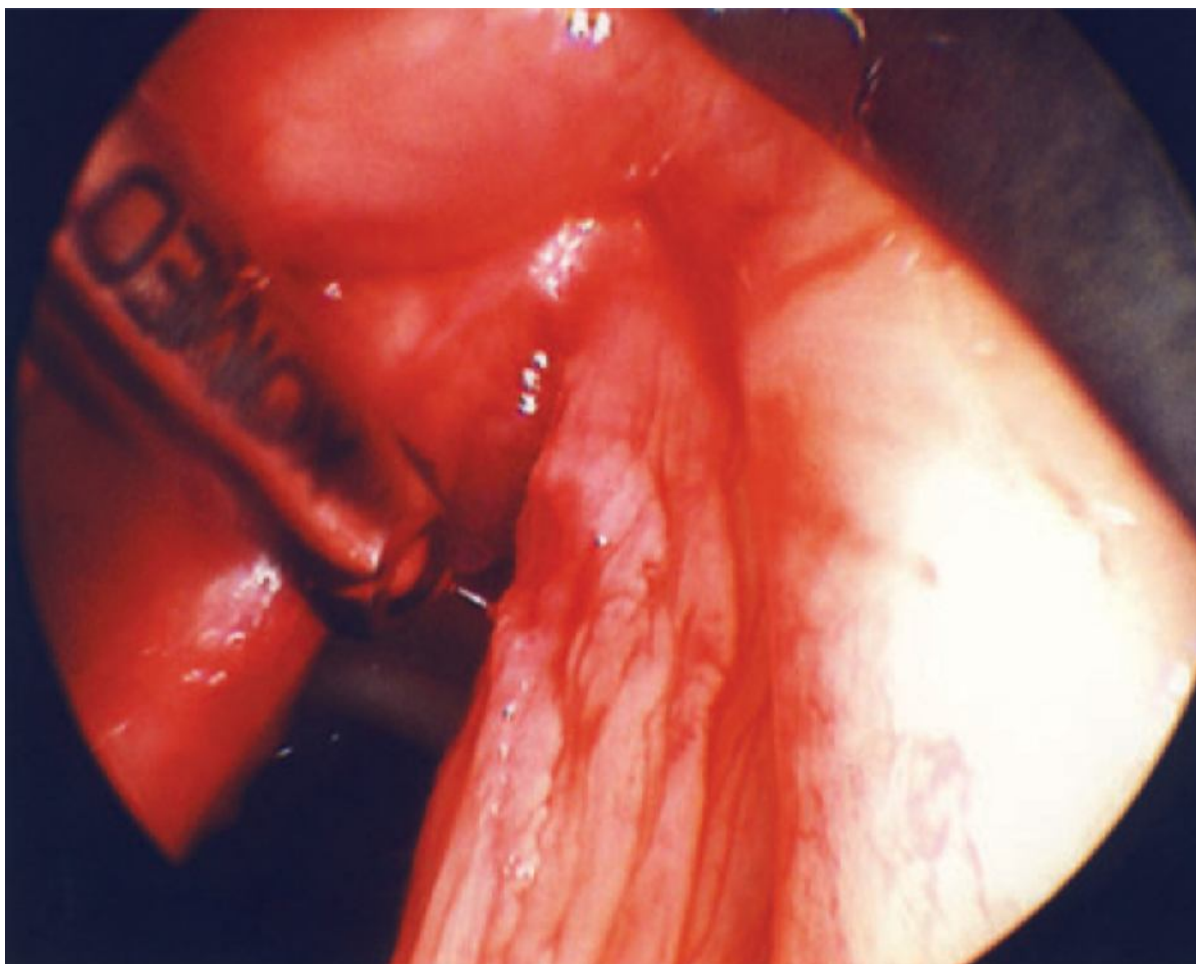


Figure 40-3 Bulky glottic recurrent respiratory papilloma being removed with a microdebrider.

Posterior Commissure

The endotracheal tube (ETT) poses a challenge to proper exposure of the posterior commissure during microlaryngoscopy. For exposure in this area, the laryngoscope is positioned to hold the ETT anteriorly, providing a clear view of the posterior commissure. A posterior commissure laryngoscope can be quite helpful in providing appropriate visualization and exposure, because the laryngoscope has a notch to secure the ETT in anterior position. As in the rest of the larynx, angled telescopes can also be quite beneficial in helping to determine the extent of the RRP lesions.

A feared complication of operating in the posterior commissure is the formation of a posterior glottic web, which is a difficult problem to treat (Fig. 40-4). To prevent glottic web, the same principles of surgery at the anterior commissure apply to surgery at the posterior commissure, for example, RRP should be excised from one side at a time using a staged approach for removal. Cold steel instrumentation is the preferred method for resecting RRP from the posterior commissure. Resection using a microdebrider can also be performed for bulky RRP in this area.

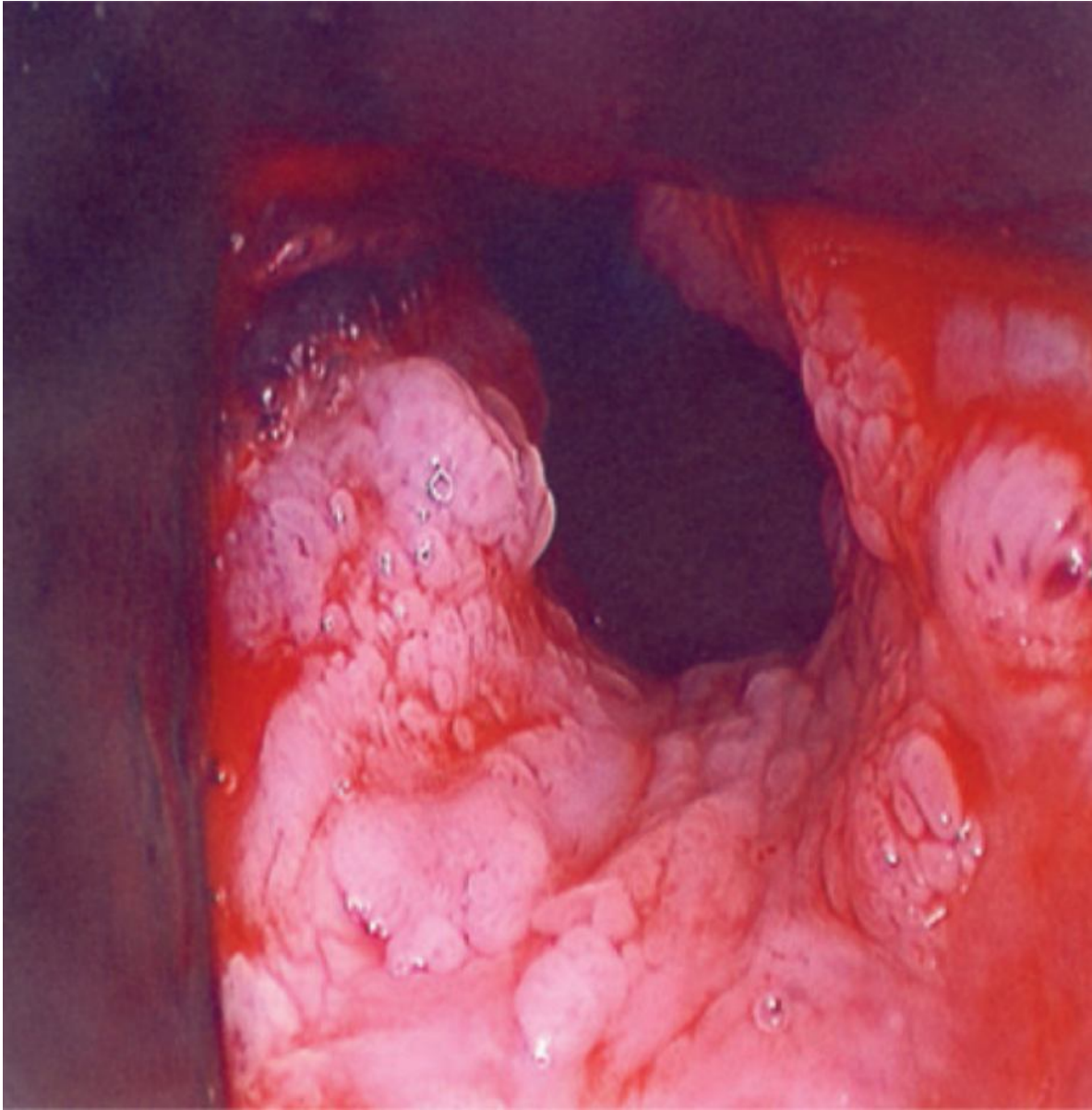


Figure 40-4 Recurrent respiratory papilloma at the posterior commissure. Excision of lesions must be unilateral and staged to avoid developing posterior glottic stenosis.

Subglottis

The subglottic larynx has its superior border at the inferior border of the glottis and extends inferiorly to the trachea. As such, removal of RRP from the subglottis can be challenging due to the difficulty of obtaining access, as well as airway and anatomic limitations. Optimal removal of RRP is through a two-handed approach, using an angled telescope in one hand and using either cold steel instruments such as cup forceps or a microdébrider in the other hand. When exposure is difficult, the CO₂ laser can be used to ablate the lesions, whereas hand-held instruments can be used for retraction to provide improved visualization. It is important to be very conservative and judicious in the use of the CO₂ laser to prevent damage to surrounding structures or cause deep tissue thermal injury. To that end, a laser set at intermittent, low power provides improved safety and resection ability for lesions in the subglottis.[2]

Adjunctive Therapy for RRP

Because patients with RRP frequently require multiple surgical procedures for control, finding adjunctive treatment options is important. The goals of adjunctive treatment options is to eradicate the disease, reduce the number of surgical procedures, increase the symptom-free interval, increase the average time period between surgical procedures, and decrease the overall extent and severity of disease. These additional treatment options are usually directed toward the viral etiology of RRP.

Indole-3-carbinol (I3C) is a chemical found in cruciferous vegetables such as cauliflower, Brussels sprouts,

cabbage, and broccoli. It has been found to be active in regulating estrogen metabolism and has been studied for breast and colon cancer prevention. In an in vitro experiment, I3C was found to suppress growth of RRP in an animal model. A prospective clinical trial showed that approximately one third of patients with RRP who took oral I3C had a significant reduction in new RRP growth.[11] During the last decade, I3C has been used in clinical practice with moderate success in treating patients with RRP.[12,13]

Systemic interferon has been studied and used extensively in the past with good control of the disease. However, multiple significant side effects of treatment as well as rapid rebound of RRP once treatment is stopped limit clinical usefulness.[14,15] Photodynamic therapy has also been extensively studied for the treatment of RRP. However, so far, no clinical study has conclusively demonstrated a significant improvement in disease control.[16]

Cidofovir is a cytosine nucleotide analog antiviral medication approved by the U.S. Food and Drug Administration for treatment of cytomegalovirus retinitis. This medication is currently being used in an "off-label" fashion as an adjunctive treatment of RRP. In vitro studies have demonstrated that cells infected with HPV type 16 are more uniformly sensitive to cidofovir than cells infected with HPV type 6.[17] Clinically, however, intralesional injection of cidofovir for the treatment of RRP has proven to be very promising for controlling recurrence and severity, and for increasing the time period between surgical procedures, particularly in studies on pediatric patients[18]; however, the response may be unpredictable between patients.[19] There is also a suspicion that repeated cidofovir use can cause the development of dysplasia and the possible subsequent development of carcinoma.[20] Additionally, there is clinical suspicion that cidofovir may increase the possibility of scar formation of the true vocal folds, and thus is reserved for patients with extensive lesions who require frequent and multiple surgical procedures for control of the RRP.[21] Intralesional cidofovir can be injected superficially in the area of RRP disease, either during microlaryngoscopy or under local anesthesia in the office via either a per-oral approach or using a flexible laryngoscope with a working channel.

An HPV vaccine is a future adjunctive treatment option that may potentially lead to eradication of this disease. An HPV vaccine has recently been approved by the U.S. Food and Drug Administration for the prevention of cervical carcinoma, which is also caused by HPV.[22,23] This vaccine, however, will most likely not work for patients with active HPV infection as it is designed for the initial prevention of acquiring HPV. It is hoped that with widespread implementation of the HPV vaccine, the number of individuals who develop RRP will be dramatically reduced.

POSTOPERATIVE MANAGEMENT

When RRP is excised from the area of the anterior commissure and the patient may be at risk for developing an anterior glottic web, "sniffing" exercises for 1 week postoperatively should be prescribed. These sniffing exercises may help reduce the formation of the web. Pain in the immediate postoperative period is usually well controlled with acetaminophen.

COMPLICATIONS

Because RRP is a chronic disease for which patients may require multiple surgical procedures, the progressive deterioration of voice quality can occur. In patients with limited mouth opening, or in cases with prolonged operative times, patients may develop numbness of the tongue from the position of the laryngoscope. This is usually self-limited and resolves over a period of several weeks.[24]

The most feared complication of RRP surgery is the formation of a glottic web or stenosis in patients with lesions at the anterior or posterior commissure. These complications are challenging to treat and may have a significant impact on the patient's voice and breathing.

PEARLS

- It is important for patients and their families to understand that RRP is a chronic disease.
- Careful, superficial dissection using cold steel instruments for excision of RRP lesions from the area of the true vocal folds helps minimize vocal fold scar formation and subsequent dysphonia.
- For RRP involving the anterior or posterior commissure, excision of lesions should be unilateral and staged to avoid formation of a glottic web or stenosis.
- All efforts should be made to avoid tracheostomy.
- Oral indole-3-carbinol and intralesional cidofovir injection should be considered for patients with extensive RRP requiring multiple and frequent surgical procedures for disease control.

PITFALLS

- Failure to review preoperatively the patient's video laryngoscopy examination may result in "missing" difficult-to-visualize sites of disease.
- Injudicious or aggressive use of the CO₂ laser or microdébrider can result in damage to vital surrounding structures.
- It is important to stay superficial during surgical excision in that deeper and more extensive excision will not prevent RRP recurrence and may cause scarring.
- Tissue should always be sent for pathologic analysis to prevent missing a diagnosis of carcinoma.
- Failure to aggressively treat or eliminate concomitant laryngeal irritation-producing conditions, such as laryngopharyngeal reflux and tobacco use, will adversely impact the patient's outcome.

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