Iatrogenic Airway Stenosis With Recurrent Respiratory Papillomatosis

Jonathan A. Perkins, DO; Andrew F. Inglis, Jr, MD; Mark A. Richardson, MD

Objective: To describe the presentation of, factors contributing to, and treatment of iatrogenic airway stenosis (IAS) associated with recurrent respiratory papillomatosis (RRP).

Design: Retrospective case series.

Setting: Pediatric tertiary care center.

Patients: The charts of patients treated for RRP in our institution from 1980 to 1995 (N=50) were reviewed. Seven patients were identified as having IAS based on endoscopic findings.

Main Outcome Measures: Prevalence and types of IAS within our RRP patient population, methods used to treat IAS, and successful treatment of IAS.

Results: Of the 7 patients identified, 3 had isolated posterior glottic stenosis (PGS) and 1 had isolated subglottic stenosis. The other 3 had multiple areas of IAS as follows: PGS with bronchial stenosis, supraglottic stenosis with PGS, and tracheomalacia with tracheal stenosis from a suprastomal granuloma. The factors associated with IAS were extensive papilloma growth in the posterior glottis, prolonged periods of frequent laryngoscopies, and the use of nonstandard therapies, which in our series included topical podophyllum resin or photodynamic therapy. Six patients, all of whom had tracheal RRP at some point in their disease process, required tracheotomy. Five patients required laryngotracheal reconstruction. Laryngotracheal reconstruction permitted decannulation in all cases. Tracheal papillomas became sessile and nonobstructive after decannulation. Laryngotracheal reconstruction with rib grafting was most frequently performed. Of our 50 patients, none who did not have IAS required a tracheotomy. Of the 44 patients who did not require a tracheotomy, only 1 had tracheal papillomas.

Conclusions: Occasionally, therapy for RRP is complicated by IAS. In our series, PGS was most common. Tracheotomy was associated with the presence of both IAS and distal RRP. In selected cases, laryngotracheal reconstruction can be successfully accomplished when RRP is present, and subsequent regression of tracheal RRP is likely.


Recurrent respiratory papillomas are virally induced benign neoplasms involving the aerodigestive tract. Many different modalities of medical and surgical therapy have been tried, none of them curative. Antiviral therapies have been used to control recurrent respiratory papillomatosis (RRP), with varied success. Primary treatment remains repeated microlaryngoscopies with carbon dioxide laser excision or ablation. Most recent series reviewing surgical therapy for RRP in pediatric patients report complications associated with carbon dioxide laser use in up to 36% of patients. Various forms of laryngeal injury have been reported, but clinically significant iatrogenic airway stenosis (IAS) is uncommon. The medical literature contains few references to IAS, and most of these consist of isolated cases. The purpose of this study is to describe our experience with, and philosophy for, treating IAS associated with RRP. The correction of IAS in this setting is dependent on appropriate timing and individualized procedure selection.

RESULTS

The average age at presentation of the patients with IAS was 14 months, although most of the them had signs consistent with RRP at an earlier age. All patients were treated initially at outside institutions. All had periods of RRP growth requiring laser laryngoscopies every 2 months or less. A carbon dioxide laser coupled to an op-
erating microscope was used exclusively in all cases other than 6 and 7. All patients developed tracheal papillomas during the course of their disease, except patient 3, the only one without a tracheotomy. Only 1 of the 44 patients without tracheotomy had tracheal papillomas. Two tracheotomies were performed during treatment at our institution (cases 4 and 5); the rest were performed before our evaluation and treatment. Open surgical procedures were necessary for decannulation in 6 cases. Papilloma growth has not occurred in the areas of surgical airway expansion postoperatively. Patient 4 died of tracheostomy tube plugging. Six patients received interferon therapy; 2 had extremely favorable responses. The average length of follow-up for the patients in this series was 44 months.

Because the medical histories, examination findings, and methods used to correct the underlying IAS varied, we report the cases individually.

REPORT OF CASES

CASE 1

A male neonate delivered 32 weeks prematurely developed chronic lung disease and required a tracheotomy for ventilatory support. Laryngotracheal papillomas were diagnosed at 2 months of age. Monthly laser laryngoscopies were required. The patient’s first evaluation at our institution was at 4 years of age. Extensive laryngotracheal papillomatosis extending from the subglottis into the right mainstem bronchus was found, along with thick posterior and anterior glottic webs. Interferon therapy was initiated, but response was poor. Photodynamic therapy was performed at another institution. Following this, subsequent evaluations showed right bronchial stenosis, worsening of anterior glottic webbing, and posterior glottic stenosis (PGS) (Figure 1 and Figure 2). A bronchoplasty did not correct the bronchial stenosis. Subsequent serial balloon dilations of the bronchus failed. Since this patient’s left lung function is too poor to withstand a right pneumonectomy, there have been no further bronchial interventions. At 6½ years of age, the patient underwent laryngotracheal reconstruction (LTR) with lysis of the anterior glottic web and a posterior cricoid split with rib grafting. His laryngeal airway was improved, but decannulation was deferred for 8 months owing to the need for pulmonary toilet. The growth rate of the tracheal papillomas slowed markedly, and he has subsequently required laser therapy for nonobstructive tracheal papillomas every 4 to 6 months, instead of every 2 to 4 weeks.

CASE 2

A 3-month-old boy presented with RRP. Monthly laser laryngoscopies by 2 different physicians were necessary. Subglottic extension occurred after 10 months. A tracheotomy was performed at 11 months to maintain the airway. Progressive spread of papillomas into the distal trachea, which is frequently associated with partial obstruction of the distal tip of the tracheotomy tube, was noted on subsequent examinations. At 18 months of age,
the patient was referred to our facility for treatment. Initial endoscopy revealed PGS, anterior glottic papilloma, suprastomal papilloma, and distal tracheal papilloma (Figure 3). Interferon therapy was initiated, and the response was dramatic (Figure 4). The patient then underwent a single-stage LTR, using anterior and posterior rib grafting, at 2½ years of age. During the immediate postoperative period, he developed severe glottic edema, which required tracheotomy tube reinsertion. Decannulation was successful 6 months later (Figure 5). The residual tracheal papillomas were nonobstructive and did not require removal (Figure 6).

CASE 3

A 26-month-old girl presented to our institution with subglottic stenosis and RRP. At another institution, repeated laser laryngoscopies had been performed bi-monthly from the age of 4 months. Two months before our evaluation, the patient underwent topical podophylllum resin therapy for residual laryngeal papillomas. Progressive respiratory distress and hoarseness then developed. An anterior glottic web and subglottic stenosis were diagnosed. Serial laser laryngoscopies and dilations with steroid injections did not improve the airway. A single-stage LTR with anterior cricoid split and hyoid interposition was performed. No papillomas were found during this procedure. Subsequently, small nonobstructive supraglottic papillomas occurred, requiring laser removal every 4 to 6 months for 2 years. No further airway compromise has developed.

CASE 4

A 5-month-old boy who was born at 33 weeks' gestational age was diagnosed as having RRP. Monthly laser laryngos-
copies were performed. In 3 months, the papillomas involved the supraglottis, anterior glottis, posterior glottis, and left anterior subglottis. The patient was then transferred to our institution, where interferon therapy was begun. There was no response to interferon therapy. At 16 months of age, the patient developed PGS, which necessitated a tracheotomy at 19 months of age. Distal extension of papillomas occurred and glottic stenosis worsened, despite endoscopic interventions. Monthly laser laryngoscopies continued for the next 18 months. The patient died of tracheotomy plugging at 37 months of age.

CASE 5

A 4-year-old girl presented with biphasic stridor and severe respiratory distress after a lifelong history of upper airway compromise and vocal dysfunction. Endoscopy revealed papillomas involving all areas of the larynx, especially the posterior commissure. Monthly laser laryngoscopies were performed, and interferon therapy was initiated. Response to medical therapy was poor. Six months later, the patient temporarily relocated and underwent a tracheotomy at another institution because of airway obstruction from anterior and posterior glottic webbing as well as subglottic papillomas. Distal extension of papillomas occurred. After 18 months of interferon therapy, the papillomas involved only the anterior commissure, but PGS was present. Endoscopic procedures were unsuccessful in relieving this stenosis. Laser laryngoscopy for subglottic and vocal cord papillomas continued to be required every 6 months. An LTR using anterior and posterior rib grafts was performed when the patient was 11 years old. Decannulation was deferred several months because of persistent glottic and supraglottic edema. The residual glottic papillomas were nonobstructive and required no treatment.

CASE 6

A 27-month-old girl presented to another institution with laryngeal papillomas that involved the anterior portions of the false and true vocal cords. These growths were removed on 2 occasions with microlaryngeal instrumentation. Nine months after diagnosis, the patient underwent a tracheotomy. Care was then transferred to our institution. Endoscopy revealed extensive papillomas extending into the subglottis and distal trachea, thick anterior glottic webbing, and PGS extending superiorly to involve the proximal arytenoids and aryepiglottic folds, resulting in both PGS and supraglottic stenosis. The patient was treated with interferon, as well as monthly laser laryngoscopies. No response to medical therapy was noted, and the PGS worsened. Recombinant interferon therapy was administered when the patient was 8 years old, with a good response (Figure 7). At the age of 9 years, the patient underwent a complete laryngofissure with lysis of posterior glottic scarring and Y-V advancement of posterior laryngeal mucosa into the posterior glottis, as described by Montgomery. Decannulation was not accomplished until 3 months later because of prolonged postoperative laryngeal edema and the continued presence of obstructive tracheal papillomas. Residual tracheal papillomas regressed after decannulation.

CASE 7

An 8-month-old girl presented with severe respiratory distress and laryngeal papillomas. She had never cried normally, and aphonia had developed. Initial treatment consisted of sharp excision of papillomas. Subsequent treatment occurred at 2 separate institutions, with laser laryngeal procedures performed every 2 to 6 weeks for the first 5 years of the patient’s life. A tracheotomy tube was placed when the patient was 2 years old. After the age of 5 years, the papillomas resolved, but 1 year earlier, a distal tracheal stenosis with associated papillomas had been noted, along with a segment of significant tracheomalacia. This segment required stenting with a long tracheotomy tube. Repeated endoscopic laser procedures were attempted to relieve the area of obstruction and dynamic collapse. The patient was evaluated at our institution at the age of 10 years. Tracheal granulation tissue with associated mild tracheal stenosis was found at the distal end of the tracheotomy tube, along with suprastomal granulation tissue. The tracheomalacia no longer caused airway compromise. Decannulation was attempted, but rapidly failed. The suprastomal granuloma was subsequently removed through an open procedure. After serial tracheotomy tube downsizing and no recurrence of tracheal granulomas, the patient underwent decannulation, with success, at the age of 12 years.

COMMENT

Our series of 7 patients all demonstrated aggressive RRP. This is evidenced by the fact that all 7 had extraglottic spread of papillomas and required extended periods of frequent surgical procedures. This spread of the papillomas outside the glottis occurred early in the disease process in all cases. Maintaining a patent, safe airway in this setting is difficult, necessitating frequent surgical procedures. The frequency of laser laryngoscopies has been
correlated with an increase in iatrogenic laryngeal complications.3 However, these treatments are necessary to maintain airway patency and to avoid tracheotomy.

Reported iatrogenic complications associated with carbon dioxide laser use in cases of pediatric RRP vary significantly.3,6 Ossoff et al6 have postulated that the variation is attributable to differing surgical philosophies regarding total disease removal vs limited disease removal. Our own approach is similar to that of Benjamin and Parsons6: frequent operations are performed with conservative papilloma removal. In all series, reported complications mainly involve formation of anterior glottic webbing; IAS is uncommon. These webs are managed conservatively with observation or endoscopic lysis.

The reported cases of IAS in association with RRP are listed in Table 1. These cases are derived from larger series of patients with RRP. In these series, IAS correction, when attempted, required open procedures, either to remove or reconstruct the larynx. Interpretation of these cases is difficult because a clear delineation of the stenotic areas is not always reported and the timing and type of corrective procedures are not well described.3,5,17 In some reports, it is stated that no corrective surgery was attempted.3,4 The laryngectomies were done for “non-functional” larynges in patients with long-standing RRP.11,16 Of the 27 patients identified as having IAS, 8 had anterior glottic webbing that required a laryngofissure to obtain decannulation.11,14,15,18 Suction diathermy is not frequently used today, but severe IAS was associated with its use.11,14,18 It is in these reports and one other that reconstructive laryngeal surgery other than laryngofissure with keel placement is described as being used for the treatment of IAS with RRP. Rinne et al14 report 3 cases of LTR that did not involve grafting, only stenting. Decannulation was successful in their cases, but postoperative dilation was necessary. Wiatrak and Cotton12 describe 2 patients who developed tracheal stenosis after reanastomosis of a diversionary procedure as described by Tucker.19 These patients developed tracheal stenosis at the anastomotic site: one was helped by open reconstruction and the other still has severe RRP with tracheal stenosis.

In our series, IAS was most common in the posterior glottis. In these cases, it appeared that frequent removal of posterior glottic papillomas caused posterior glottic webbing that progressed to PGS with impairment of arytenoid movement. It is our observation that the PGS seen in this setting is different from that seen after intubation trauma: in the latter, cricoarytenoid joint ankylosis is common, whereas in the former, interarytenoid webbing is more common. Once PGS was present, endoscopic techniques directed at either division of scar or division of scar with keel was helpful by open reconstruction and the other still has severe RRP with tracheal stenosis.

Table 1. Reported Cases of Iatrogenic Airway Stenosis (IAS) Associated With Recurrent Respiratory Papillomatosis*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Cases of IAS</th>
<th>No. of Surgical Corrections of IAS</th>
<th>Type of Papilloma Removal</th>
<th>Area of Stenosis</th>
<th>Type of Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiatrak and Cotton,12 1992</td>
<td>2</td>
<td>1</td>
<td>CO2 laser</td>
<td>Glottic</td>
<td>LTR with keel</td>
</tr>
<tr>
<td>Morgan and Zitsch,1 1986</td>
<td>4</td>
<td>Not reported</td>
<td>CO2 laser</td>
<td>Glottic and subglottic</td>
<td>LTR with keel</td>
</tr>
<tr>
<td>Irwin et al,19 1986</td>
<td>2</td>
<td>1</td>
<td>Suction diathermy</td>
<td>Glottic</td>
<td>No corrective surgery</td>
</tr>
<tr>
<td>Harries et al,15 1995</td>
<td>1</td>
<td>1</td>
<td>Suction diathermy</td>
<td>Glottic</td>
<td>Postoperative serial dilation</td>
</tr>
<tr>
<td>Rinne et al,14 1983</td>
<td>3</td>
<td>3</td>
<td>Forceps, cryotherapy, and suction diathermy</td>
<td>Glottic and subglottic</td>
<td>Laryngofissure with keel</td>
</tr>
<tr>
<td>Shapiro et al,13 1996</td>
<td>1</td>
<td>1</td>
<td>CO2 laser</td>
<td>Glottic</td>
<td>Laryngofissure with keel</td>
</tr>
<tr>
<td>Saleh,7 1992</td>
<td>7</td>
<td>7</td>
<td>CO2 laser</td>
<td>Glottic and tracheal</td>
<td>Laryngofissure with keel</td>
</tr>
<tr>
<td>Robbins and Howard,11 1983</td>
<td>2</td>
<td>2</td>
<td>Suction diathermy</td>
<td>Glottic and subglottic</td>
<td>Laryngofissure with keel</td>
</tr>
<tr>
<td>Cohen et al,17 1980</td>
<td>4</td>
<td>0</td>
<td>Forceps</td>
<td>Glottic</td>
<td>LTR with anterior and posterior rib grafts</td>
</tr>
<tr>
<td>Crockett et al,3 1987</td>
<td>1</td>
<td>Not reported</td>
<td>CO2 laser</td>
<td>Glottic</td>
<td>LTR with posterior rib grafts</td>
</tr>
</tbody>
</table>

*CO2 indicates carbon dioxide; ellipses, not applicable; and LTR, laryngotracheal reconstruction.

Table 2. Successful Corrective Procedures

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Area of Stenosis</th>
<th>Open Procedure Performed*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posterior glottis</td>
<td>LTR with posterior rib graft</td>
</tr>
<tr>
<td>2</td>
<td>Posterior glottis</td>
<td>LTR with anterior and posterior rib grafts</td>
</tr>
<tr>
<td>3</td>
<td>Subglottis</td>
<td>LTR with anterior hyoid graft</td>
</tr>
<tr>
<td>4</td>
<td>Posterior glottis</td>
<td>LTR with anterior and posterior rib grafts</td>
</tr>
<tr>
<td>5</td>
<td>Posterior glottis and supraglottis</td>
<td>Laryngofissure with mucosal advancement</td>
</tr>
</tbody>
</table>

*LTR indicates laryngotracheal reconstruction.
procedures were necessary for decannulation. Our experience is similar to that of other investigators. The type of procedure is directed at the specific area of airway stenosis, as in any other situation. In our experience, when there is a period of spontaneous or medically induced RRP quiescence, defined as the absence of obstructive laryngeal papilloma growth 8 or more weeks after ablation, open laryngeal procedures can be performed as would be for a similar lesion in the absence of RRP. The 8-week interval allows sufficient time for postoperative healing of the single-stage reconstructive procedures before removal of obstructing papillomas is necessary. Since these reconstructive procedures were performed, there has been no evidence of RRP occurrence over the graft or flap site. It was not uncommon for extubation and decannulation to be delayed by prolonged laryngeal edema, perhaps as a result of altered lymphatic drainage related to the repeated prior surgical procedures or to the disease process itself. This prolonged laryngeal edema limits the probability of successful extubation after a planned single-stage procedure.

The 2 patients with distal IAS were treated, with varied success. Patient 7 had extensive RRP as an infant and subsequently developed mild tracheal stenosis with granulomas at the distal tracheotomy tube tip and the tracheotomy site. Decannulation was accomplished with serial tracheotomy tube downsizing and granuloma excision during a time of RRP quiescence. A similar case has been reported, and the same conservative treatment was successful. The bronchial stenosis in case 1 has progressed to subtotal bronchial occlusion despite attempted bronchoplasty and balloon dilatation. Correction of PGS in this case permitted decannulation, but the patient tempted bronchoplasty and balloon dilatation. Correction progressed to subtotal bronchial occlusion despite at-

ternative tracheotomy tube downsizing and granuloma excision during a time of RRP quiescence. A similar case has been reported, and the same conservative treatment was successful. The bronchial stenosis in case 1 has progressed to subtotal bronchial occlusion despite attempted bronchoplasty and balloon dilatation. Correction of PGS in this case permitted decannulation, but the patient has minimal airflow through the stenotic bronchus.

Rates of tracheotomy as high as 61% have been reported in pediatric patients with RRP. The overall 12% rate reported over the past 16 years at our institution is consistent with the rates reported from some other centers. It should be stressed that 5 of our 6 patients with a tracheotomy had significant laryngeal IAS, compared with only 1 of the 44 patients without a tracheotomy, suggesting that laryngeal IAS may be the final airflow insult leading to tracheotomy in some cases.

In this series, IAS led to tracheotomy, and tracheotomy was implicated with distal spread of disease. In the 2 patients we saw before and after tracheotomy (cases 4 and 5), there were no tracheal papillomas before tracheotomy, but there were extensive tracheal papillomas after tracheotomy. We suspect that the same thing happened in cases 2, 6, and 7. Patient 1 had tracheal papillomas prior to tracheotomy, but these were associated with several weeks of endotracheal intubation, which can be considered a tracheotomy tube equivalent in terms of tracheal trauma. We concede that there is a legitimate question as to whether tracheotomy actually causes distal spread of papillomas or is merely a marker for more aggressive disease; however, we interpret our clinical findings as supporting the former argument, because while many of our 44 patients without tracheotomy had very aggressive RRP growth, only 1 had tracheal papillomas. This result is in keeping with the theory of Kashima et al, that papillomas tend to grow at squamociliary junc- tions that can be induced in the trachea by traumatic metaplasia from a tracheotomy tube. Some investigators have argued that the tracheal papillomas seen with tracheotomy are not a significant problem and that tracheotomy should not be viewed with extra trepidation in patients with RRP. However, it is our experience that an indwelling tracheotomy tube does not necessarily make the treatment of aggressive RRP easier or safer. The bulky distal papillomas seen in case 2 frequently led to partial obstruction of the tracheal cannula, and the only death in our 50 patients with RRP was the result of tracheotomy tube plugging (case 4). In light of the difficult treatment dilemmas that patients with laryngotracheal papillomas pose, and the excellent regression in tracheal papillomas seen in all our patients following decannulation, it is highly desirable, from a safety standpoint, to avoid producing IAS or, failing that, to reverse the stenosis and to restore the natural airway.

Adjuvantive medical measures to treat RRP are many. Few aside from interferon therapy have shown significant clinical utility. When interferon was used in our case series, it was intermittently effective. We had a striking response in cases 2 and 6. Both these patients had been treated with nonrecombinant interferon, without effect, but when purified recombinant interferon was used, papilloma regression occurred, facilitating LTR. Patients 1 and 3 developed significant complications as a result of adjunctive medical treatment (photodynamic therapy and podophyllum resin), underscoring the need for caution when attempting to use nonstandard treatments. Appropriate dosing is difficult to determine for both photodynamic therapy and podophyllum resin. While podophyllum resin is not commonly used today for this reason, hematoporphyrins show promise if the therapeutic index can be improved.

Recurrent respiratory papillomatosis presents between 2 and 3 years of age in most patients. The average age at presentation in our 7 cases was 14 months. There was evidence of early RRP in several of the cases, but the diagnosis was delayed. The combination of aggressive RRP and presentation at a young age may have predisposed these patients to the development of IAS. A younger patient with aggressive RRP will undergo more laser laryngoscopies than an older child. Frequent laser laryngoscopies in a small larynx and airway make the risk of IAS high, as others have shown.

The tracheotomy likely fosters tracheal RRP. Decannulation depends on reduced aggressiveness of the laryngotracheal papillomas and correction of the IAS. Usually, these 2 conditions can be met and decannulation can be achieved, although occasionally catastrophic events may supervene, as in our patient who died of tracheotomy tube plugging.

**CONCLUSIONS**

Iatrogenic airway stenosis occurs infrequently in association with RRP. Aggressive RRP leads to frequent surgical procedures and to the temptation to use nonstandard therapies. These interventions may result in IAS. In our series, IAS, in combination with aggressive RRP, often led to tracheotomy, and tracheotomy was associated
with distal tracheal RRP. Recombinant interferon therapy was effective in producing papilloma regression in some cases. Iatrogenic airway stenosis can be successfully treated with standard endoscopic and open laryngeal surgery when laryngeal RRP growth is quiescent. Decannulation following LTR was frequently delayed by glottic edema and by bulky tracheal lesions. All cases of IAS with tracheal spread of RRP demonstrated regression of distal papillomas with decannulation. Iatrogenic airway stenosis in association with RRP can be devastating, but with careful endoscopic and open surgical management, it can be successfully corrected. Prevention of IAS requires “gentle” endoscopic excisions as often as necessary to maintain the airway and avoidance of therapies that may result in indiscriminate tissue destruction in the airway.

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