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Adult Subglottic Stenosis: Management With Laser Incisions and Mitomycin-C

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Objectives/Hypothesis: To assess the efficacy of endoscopic laser radial incisions with mitomycin-C application (ELRM) in managing adult subglottic stenosis (SGS).

Study Design: Retrospective case series review.

Methods: Fifteen consecutive cases of adult SGS treated with ELRM at a single tertiary referral center over three years were reviewed. Subjects with SGS secondary to Wegener's granulomatosis (WG) and idiopathic SGS were included. Patients with cartilaginous SGS were excluded. The primary outcome measure was postoperative reduction in symptoms. Secondary outcome measures included total number of procedures required to relieve symptoms, interval between procedures, and improvement in pulmonary function tests when available. In addition to surgery, 14 of 15 patients were treated medically for reflux.

Results: Ten women and five men with average age 48 years were identified. Ten patients had idiopathic SGS and five had WG. The predominant presenting symptom was dyspnea on exertion in all patients. All subjects reported at least a temporary postoperative reduction in symptoms. Six patients (40%) required only one ELRM and nine patients (60%) required repeat ELRM at an average interval of 9 months. The average interval for the six patients with idiopathic etiology requiring a second procedure was 9 months. One subject with WG required four procedures. His interval improved from 2.5 to 7 months between procedures. Evidence of extrathoracic airway obstruction resolved in three of four patients with pre and postoperative pulmonary function tests.

Conclusions: ELRM is an effective method of managing SGS associated with idiopathic causes. In patients with WG, ELRM reduced airway associated symptoms and avoided need for tracheotomy.

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INTRODUCTION

The most common cause of adult subglottic stenosis (SGS) in the modern era is mechanical trauma from prolonged intubation or tracheotomy.[1] Acquired SGS may also be caused by respiratory infections, external trauma, or rheumatologic disease, such as Wegener's granulomatosis (WG), a systemic vasculitis characterized by inflammation of the upper and lower respiratory tracts and kidneys.[2] SGS occurs in up to 20% of patients with WG and may be the presenting clinical feature.[2] Other, rarer, etiologies include scleroma, amyloidosis, and osteochondroid hamartoma.[3] Finally, multiple studies demonstrate that laryngopharyngeal reflux (LPR) is strongly associated with SGS regardless of etiology[4] and these studies suggest that LPR may be the primary etiology in some cases.

Because of multiple associated comorbidities and varied etiologies, adult SGS remains a challenging disease for the otolaryngologist to diagnose and treat. The primary difficulty for the surgeon is determining what structures are involved. The region of stenosis may involve only soft tissue scarring, only cartilage remodeling or some combination of both. Until recently, methods of assessing cartilage involvement were difficult as neither the commonly available methods of computed tomography (CT) scanning nor magnetic resonance imaging reliably image the cartilaginous framework of the airway. Therefore, patient history, related disease and direct endoscopy with palpation were considered the preferred method for determining cartilage involvement. When associated with external or internal trauma SGS is most likely to be associated with cartilage remodeling. When due to inflammatory conditions, such as WG or LPR, SGS is most commonly due primarily to soft tissue scar. The key to successful management is determining the degree of cartilage involvement. The recent advent of high resolution CT scanning with three dimensional reconstruction and virtual endoscopy is beginning to show promise in airway evaluation.[5] However, these types of studies are not widely available.

A wide array of surgical techniques for the management of SGS have been employed. These include various endoscopic and open operations. Endoscopic dilatation alone has proven to be ineffective in the majority of cases.[6] Segmental resection with primary anastomosis can achieve decannulation in the majority of patients with preexisting tracheotomy tubes[7–9] yet seems an aggressive option in patients with unknown causes of SGS, in those with ongoing sources of inflammation, or in those without cartilage involvement. Therefore, endoscopic techniques for this group of patients were developed to avoid the morbidity of open surgery and have evolved over time.[10–12]

Early work by Simpson et al.[13] demonstrated that endoscopic management was most successful in treating laryngotracheal stenoses that were not completely circumferential (CS), less than 1.0 cm in the vertical dimension, and not associated with significant loss of cartilage or remodeling. Ossoff and coworkers[14] introduced the use of laser radial incisions and dilation, and later, the adjunctive use of mitomycin-C, an antineoplastic agent that inhibits fibroblast proliferation and activity was reported first by Shapshay and coworkers.[15] Mitomycin-C is now routinely used in the endoscopic management of laryngotracheal stenosis. The concentration is usually 0.4 mg/mL and is applied topically on a cottonoid pledget. The length of application varies from two to three repeat applications of 2 minutes each to a single application of 5 minutes. The handling and disposal of the mitomycin-C should be per the hospital protocol for chemotherapeutic agents. Care should be taken to avoid contact with unprotected skin.

Again, patients with idiopathic SGS (IS) or those with SGS due to the inflammation of WG are more likely to have primarily soft tissue disease amenable to endoscopic management. Therefore, the present study was designed to assess the efficacy of endoscopic laser radial incisions and mitomycin-C application (ELRM) in treating adult SGS in these populations.

MATERIALS AND METHODS

A retrospective chart review was performed including all patients 18 years of age or older with SGS treated with ELRM at the University of California, San Francisco (UCSF) Department of Otolaryngology, Head and Neck Surgery between October 1, 2004, and January 21, 2008. Patients with IS and WG were included while those with cartilaginous SGS were excluded.

Fourteen of 15 patients were treated with twice daily proton pump inhibitors (PPIs) perioperatively. All patients underwent ELRM as described in the next paragraph with the following exceptions: the rigid bronchoscopic dilation step was not performed in one patient, and balloon dilation to 13.5 mm was performed instead of rigid bronchoscopic dilation in two other cases. Postoperative symptoms were recorded during routine follow-up. The total number of procedures and the interval between surgeries were noted. Four patients had pre and postoperative pulmonary function tests (PFTs) available for review.

Surgical Technique (ELRM)

General anesthesia with jet ventilation was used to provide adequate exposure for the intervention. After the induction of general anesthesia, an initial survey of the larynx and pharynx was performed with a monocular laryngoscope. Then an adult male or female subglottiscope was inserted into the larynx, positioned just above the true vocal folds, and suspended. Jet ventilation controlled by the anesthesiologist commenced. Photodocumentation of the stentotic segment was obtained with 0 degree and 70 degree Hopkins rod telescopes. The distance from the superior surface of the true vocal folds to the start of the lesion and the vertical length of the stenotic segment were measured by marking the telescope as it passed the edge of the viewing end of the subglottiscope.

The subglottiscope was rotated 90 degrees as it was carefully negotiated through the true vocal folds and advanced until it was seated just above the stenotic segment and resuspended. The patient's face was protected with saline-soaked towels and the microscope was positioned to view the larynx at 6.8 times magnification. A carbon dioxide (CO_2) laser with an AcuBlade^{TM} micromanipulator (Lumenis, Santa Clara, CA) was attached to the operating microscope. Laser energy was delivered in a pulsed (Ultrapulse^{TM}) mode. The Acublade^{TM} employs a computer to generate either a circular or linear pattern. The pulsed laser beam pattern is chosen by the surgeon and then shuttered to minimize overlapping areas of laser tissue impact and enhance surgical precision. Radial incisions were made through stenotic segments using the pattern generator to generate a line with a length of 1 to 3 mm and 0.5 to 1.0 mm deep. Delivery continued with the chosen pattern until the length of the entire stenotic segment was incised. Incisions were deep enough to reach the plane of the normal lumen of the adjacent trachea and larynx. Great care was taken to preserve intervening mucosa between the incisions (Fig. 1). Cottonoids soaked with mitomycin-C in a concentration of 0.5 mg/mL were then applied for 3 minutes to the incisions. Excess medication was wiped free using saline-soaked cottonoids.

Finally, the subglottiscope was removed, ventilation was maintained by the anesthesia team with mask-assisted respiration, and then size 6, 7, and 8 rigid bronchoscopes were sequentially passed through the segment for controlled dilation at the incision sites. The largest size bronchoscope that passed through the stenosis was noted.

RESULTS

Ten women and five men with average age 48 years were identified (Table I). Ten patients had IS (2 men, 8 women) and five had WG (3 men, 2 women). Presenting symptoms included dyspnea on exertion (all 15 patients), cough (3), dysphonia (3), stridor (2), globus sensation (2), and vocal fatigue (1). Most IS patients reported months to years of progressive dyspnea on exertion, and one patient's symptoms worsened during pregnancy. All five WG patients had previously been diagnosed with the rheumatologic disorder and were referred for suspected subglottic involvement or management of known SGS. Two IS patients had known gastroesophageal reflux disease and one of the two was taking twice daily PPIs before consultation.

Four patients had a history of prior surgical intervention. One IS patient had undergone 19 prior microtrapdoor flap procedures. A second IS patient had been dilated once. One WG patient had been treated with multiple dilations, and a second WG patient had been unsuccessfully dilated once and had undergone tracheal resection with temporary relief. No patients had an indwelling tracheotomy tube at the time of consultation.

Twenty-eight total ELRMs were performed. All subjects in all cases reported at least a temporary postoperative reduction in symptoms. Overall, six patients (40%) required only one ELRM for symptomatic relief during the study period. The average follow-up for the entire study

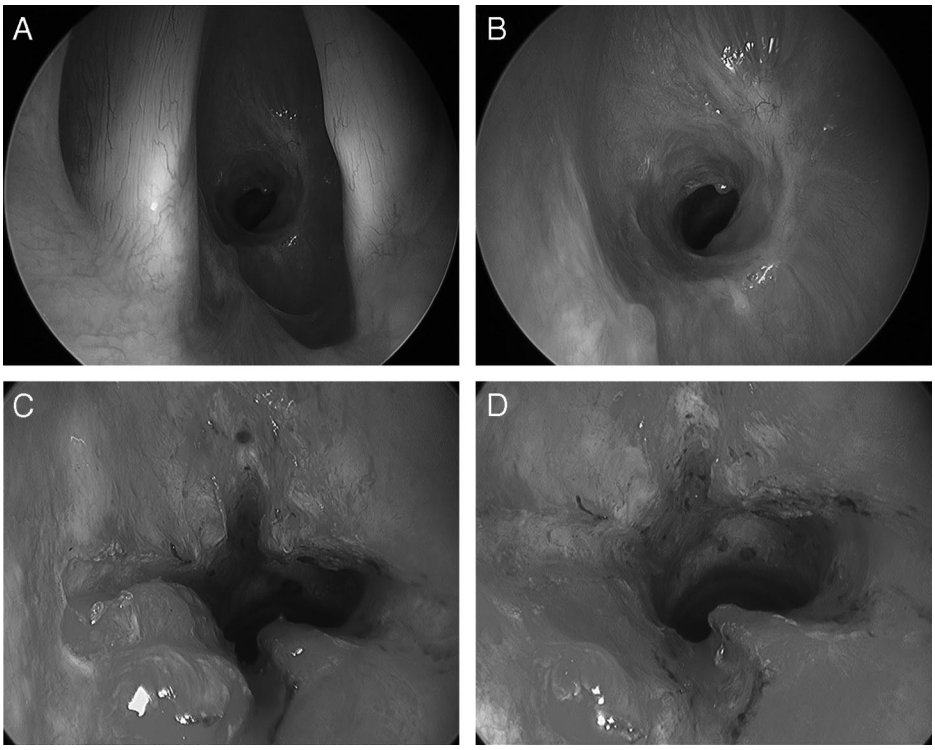

Fig. 1. (A–D) Endoscopic laser radial incisions. (A) Circumferential subglottic stenosis viewed with a 0-degree Hopkins telescope passed through a subglottiscope positioned just above the true vocal folds. (B) Closer view of the same stenotic segment. (C) Appearance after laser radial incisions have been made at 12, 3, 6, and 9 o'clock (where 12 o'clock is anterior) with preservation of intervening mucosa. (D) Enlargement of the incisions after controlled dilation.

group was 18 months (range 3–39 month). Nine patients (60%) required repeat ELRM at an average interval of 9 months. The percentage of patients requiring a second procedure was preserved within each group: 6/10 (60%) IS patients and 3/5 (60%) WG patients. Second procedures were performed at an average interval of 9 months for the six IS patients and 7 months for the three WG patients with recurrence of symptoms. The four IS patients who

TABLE I.
Patient Data.

Pt	Age	Sex	Dx	History	ELRMs (no.)	INT (mo.)	FU (mo.)
1	51	F	IS	Nineteen prior microtrapdoor flaps, most recently every 2–3 mo	3	4, 4	10
2	66	M	IS	Six-month history of progressive DOE and known history of GERD	1	n/a	21
3	63	F	IS	Several-year history of slowly progressive DOE	1	n/a	18
4	42	F	IS	Five-year history of slowly progressive DOE	1	n/a	11
5	33	F	IS	Prior history of DOE and one prior dilation at an outside institution	1	n/a	9
6	49	M	IS	Several-year history of slowly progressive DOE	2	10	16
7	57	F	IS	Several-year history of slowly progressive DOE	2	2	3
8	49	F	IS	Nine-month history of slowly progressive DOE	2	7	8
9	29	F	IS	Presented during pregnancy with a three-month history of progressive DOE	2	13	28
10	70	F	IS	Six-month history of slowly progressive DOE	3	21, 14	39
11	47	F	WG	Known WG with recurrent DOE after prior dilation and open tracheal resection	2	13	18
12	32	M	WG	Known WG with slowly progressive DOE	2	6	32
13	28	M	WG	Known WG with slowly progressive DOE and prior dilations	1	n/a	14
14	83	F	WG	Known WG with rapidly progressive DOE over one week	1	n/a	20
15	28	M	WG	Known WG with slowly progressive DOE	4	2.5, 7, 7	21

Pt = Patient; Dx = diagnosis; IS = idiopathic subglottic stenosis; WG = Wegener's granulomatosis; DOE = dyspnea on exertion; GERD = gastroesophageal reflux; ELRM = endoscopic laser radial incisions and mitomycin-C application; INT = interval between procedures; FU = total follow-up.

did not require a second ELRM were followed for an average of 15 months (range 9–21 month). One subject with WG (patient #15) required four procedures during the study period. His interval improved from 2.5 to 7 months from his first to his third procedures. The interval between his third and fourth procedures was also 7 months. No patients progressed to require tracheotomy or open surgical intervention. Overall, each patient underwent an average of 1.9 ± 0.9 procedures.

All first procedures (15) were analyzed for factors predictive of surgical success, defined as not requiring a second procedure, because all patients showed an improvement in symptoms. The average length of stenosis (LOS) measured at the beginning of each case for the entire group was 1.46 ± 0.58 cm (range, 0.8–2.7 cm). Only two patients had a stenotic segment less than 1.0 cm in length. The mean LOS for IS patients, 1.7 ± 0.6 cm, was significantly greater than the mean LOS for WG patients, 1.0 ± 0.1 cm ($P < .03$), however, as noted previously, the percentage of patients proceeding to a second surgery was the same for both groups. The character of the stenosis was CS in 8 and eccentric (ES) in 7. Although the mean LOS for patients with ES (1.64 ± 0.60 cm) showed a trend toward being longer than those with CS (1.30 ± 0.55 cm) ($P < .3$), only 3/7 (43%) patients with ES underwent a second procedure compared with 6/8 (75%) patients with CS. Five first procedures were performed urgently for patients with critical airway narrowing on initial examination and evidence of extrathoracic airway obstruction on preoperative PFTs with flow volume loops. Three of these patients required a second procedure at an average interval of 3.3 months.

Four patients underwent PFTs before and after surgery. Evidence of extrathoracic airway obstruction resolved in three of four patients. The fourth patient was the gentleman with WG who required four procedures in the study period. He had PFTs between his first and second procedures which showed normal flow volume loops. He then stopped taking his PPIs and his WG medications. PFTs 1 year later (6 months after the most recent ELRM) showed the development of extrathoracic upper airway obstruction, reflecting progression of the underlying disease.

The majority of procedures (17/28, 61%) were performed on an outpatient basis. The remainder (11/28, 39%) required a one-night hospital stay, largely because of the extensive catchment area of UCSF; these patients resided an average distance of 175 miles from the medical center. Only one patient stayed for medical reasons, a 73-year-old woman with IS (patient #10, who also lives 200 miles away from UCSF) who developed postoperative nausea and subsequently, increased pulmonary secretions with difficulty clearing the secretions. She was treated with intravenous steroids and racemic epinephrine with complete resolution of her symptoms by postoperative day four, and she was discharged home breathing more easily than she had been preoperatively. A second patient (#7), was admitted urgently from clinic for severe airway narrowing, underwent an uncomplicated ELRM, and stayed one night in the hospital. She was discharged home then returned to a scheduled visit on postoperative day 6 with mild dyspnea, stably improved from her preoperative condition, and subglottic crusting that required a two-night stay in the hospital for monitoring while corticosteroids were administered. The patient's symptoms resolved completely before discharge. The prolonged hospital stay and the readmission were the only complications that occurred in all 28 procedures (7%). No cervical emphysema, bleeding, infection, or loss of cartilaginous support was seen in any of the study patients.

DISCUSSION

Determining the proper management of adult laryngotracheal stenosis has intrigued otolaryngologists throughout modern history. Our recent evaluation and management of two patients referred for recurrent disease after only temporary relief from open tracheal resection spurred our interest in evaluating our own outcomes. Despite a wide array of approaches described in the literature, no single method has been proven to be significantly more effective than the others. Conversely, with the exception of dilation, which has been proven to be ineffective,[6] many approaches have shown acceptable rates of success, variably defined as symptomatic relief or decannulation of previously tracheotomy-dependent patients.

Several prior studies have reported heterogeneous patient populations with varying degrees of glottic, subglottic, and tracheal stenosis. The present series focused on a subset of adult laryngotracheal stenosis patients with SGS secondary to either unknown inflammatory causes or WG and no cartilaginous contribution to the stenosis. All patients were managed effectively with ELRM and treatment of reflux, with 60% of patients requiring a second procedure, an acceptable mean interval between procedures (9 month) for patients with idiopathic causes, and no requirement of tracheotomy or open surgical intervention. These results compare favorably with other published case series of endoscopic management.[10–19]

In 1982, Simpson et al. described five factors predictive of poor results or failure with endoscopic management of laryngotracheal stenosis: CS scarring with cicatricial contracture, scarring longer than 1 cm in vertical dimension, tracheomalacia and loss of cartilage, previous history of severe bacterial infection associated with tracheostomy, and posterior laryngeal inlet scarring with arytenoid fixation.[13] The design of the present study excluded patients with the latter three factors but allowed for examination of the first two: the pattern and length of the stenotic segment. Our data support Simpson's first conclusion, that CS lesions lead to poorer outcomes, because more patients with CS stenosis required a second ELRM than those with ES stenosis (75% vs. 43%). However, the majority of patients in this study had stenotic segments exceeding 1 cm in length but still reported an improvement in symptoms postoperatively and did not progress to require open surgery or tracheotomy. In addition, one of the two patients with short (<1.0 cm) LOS required a second ELRM. Therefore, although LOS has been shown previously to be an important factor to consider in endoscopic management,[13] predominantly soft tissue stenoses such as those in IS and WG may be treated effectively even when longer than 1.0 cm. In addition,

the use of mitomycin-C to inhibit fibroblast proliferation and modulate wound healing has been shown to improve success rates, even in complex lesions.[18]

The complication rate in the present study (7%) was acceptably low. One patient had postoperative nausea and increased secretions which resolved with conservative management and observation, whereas a second patient required readmission for two nights of observation and corticosteroid administration. This finding has significant implications when considering open surgical intervention and the attendant perioperative risks of edema or granulation tissue formation requiring reintubation or tracheotomy, cervical emphysema, anastomotic dehiscence, recurrent laryngeal nerve injury, tracheoesophageal fistula, and death.[7–9]

Despite these risks, cricotracheal resection and primary thyrotracheal anastomosis have been shown to be highly effective in managing laryngotracheal stenosis secondary to prolonged intubation or trauma.[7–9] Open surgery as the primary treatment modality in patients with ongoing inflammatory diseases, such as IS or WG, has not been studied in a large series. Recent studies of airway reconstruction continue to report predominantly intubation-related disease, with idiopathic and autoimmune diseases as additional subsets.[20] Although not utilized in the present study, open surgical management is a reasonable consideration for patients who fail endoscopic management of SGS. However, the criteria that define failure of endoscopic management continue to be debated. Valdez and Shapshay reported their algorithm of offering primary resection and reanastomosis to patients with disease refractory to three endoscopic procedures,[15] whereas Dedo and Catten describes repeated microtrapdoor flap procedures for "palliation" of what he terms idiopathic progressive SGS.[19]

Furthermore, the best treatment modality for any given patient with SGS is predicated on the results of upper aerodigestive tract endoscopy. Office-based indirect laryngoscopy, high resolution CT scans, and PFTs give supportive evidence but only the detailed view afforded by intraoperative microdirect laryngoscopy, subglottoscopy, and tracheoscopy can accurately diagnose the location, extent, and character of the stenosis. The initial endoscopy should not be limited to diagnostic maneuvers; intervention should be considered for all patients, since ELRM, as the current series demonstrates, can be highly successful with a low complication rate.

CONCLUSION

Adult SGS remains a challenging disease to treat. Endoscopic management continues to evolve, providing an effective alternative to open surgical approaches for patients with inflammatory causes of SGS, such as IS and WG. Airway-associated symptoms are reduced and tracheotomy can be avoided. Endoscopic management can be performed safely, with an acceptably low complication rate, in the outpatient setting or with an overnight stay for patients traveling long distances to the hospital. Further study of this treatment modality is warranted.

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