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Initial Experience With Low-Dose Methotrexate as an Adjuvant Treatment for Rapidly Recurrent Nonvasculitic Laryngotracheal Stenosis

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IMPORTANCE Adult laryngotracheal stenosis (LTS) is typically managed surgically, but some patients fail treatment because of rapid restenosis or granulation tissue formation. The need for frequent surgery or tracheostomy reduces the quality of life in these patients and poses a significant challenge for the treating physician. New adjuvant treatments are required to reduce the surgical burden of this condition.

OBJECTIVE To examine whether patients with rapidly recurrent nonvasculitic LTS who fail surgical management of their stenosis (ie, requiring dilation more frequently than every 6 months) experience longer intervals between surgical procedures when receiving adjuvant treatment with low-dose methotrexate.

DESIGN, SETTING, AND PARTICIPANTS This study was a retrospective case series study of patients treated with methotrexate from January 2014 to January 2016 at a tertiary academic medical center. Participants were 10 patients with LTS without any diagnosis of vasculitis or granulomatous disease who underwent low-dose methotrexate therapy.

INTERVENTIONS Once-weekly treatment with oral methotrexate, 15 or 20 mg.

MAIN OUTCOMES AND MEASURES The mean number of days between operations before and after starting methotrexate therapy was compared. Clinical courses and adverse effects of each patient were also reviewed.

RESULTS Among 10 patients, the mean (SD) age at the outset of study inclusion was 52 (19) years; 8 were female and 2 were male. All 10 patients experienced some clinical improvement. Three patients who were previously tracheostomy dependent were able to be decannulated. Two other patients who were tracheostomy dependent and had failed endoscopic management of their granulation tissue had complete resolution. In 6 patients who underwent at least 1 surgical procedure before and after the initiation of methotrexate treatment, the mean (SD) interval between operations increased from 61 (35) days (95% CI, 26-96 days) before starting methotrexate therapy to 312 (137) days (95% CI, 175-449 days) after starting methotrexate therapy, for an absolute difference of 251 (58) days (95% CI, 193-309 days). The median number of days between surgical procedures was 44 days before starting methotrexate therapy and 289 days after starting methotrexate therapy. Adverse effects observed included mild hair thinning and onychomycosis in 2 patients and herpes zoster infection in 1 patient.

CONCLUSIONS AND RELEVANCE Low-dose methotrexate appears to be an effective adjunct to surgery in select patients with LTS that is resistant to surgical management and leads to a substantial increase in the number of days between surgical procedures. The patient and clinician must be aware of the adverse effects of methotrexate therapy and balance these factors against the risk of poorly controlled airway stenosis. Randomized, placebo-controlled, double-blind trials are needed to examine whether the clinical efficacy in this series of patients translates to a larger population.

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Adult laryngotracheal stenosis (LTS) is an acquired condition with significant morbidity and effects on the quality of life. Stenosis can arise because of vasculitis, postintubation trauma, or direct trauma, or it may be idiopathic in nature.[1] Management of this condition represents a particular challenge because most patients want to avoid a tracheostomy or other indwelling airway appliance. As a result, much effort is expended on managing LTS endoscopically or, when this method is not possible, via open tracheal resection to achieve decannulation or avoid cannulation in the first place.

Many patients with LTS have excellent surgical outcomes, and historical data suggest that the average patient has approximately 10 to 13 months between endoscopic dilations.[2,3] However, there is a subset of patients who for unclear reasons experience rapid restenosis and require immediate revision surgery. In the most severe of these cases, patients may need dilation as frequently as once every few weeks, risking potential loss of airway each time and leading to significant health care costs. Therefore, identification of risk factors and novel methods for treating these patients is of paramount importance.

In principle, all methods for medical therapy of LTS are treating the same mechanism: they are attempts to reduce localized airway inflammation, which should theoretically decrease the migration of fibroblasts and subsequent scar formation. Recent research has focused on the inflammatory component of LTS, and there has been speculation that more precisely targeting inflammation will lead to better outcomes.[4] One means is through the use of immunomodulating drugs, which is already done in autoimmune or vasculitic cases of LTS, such as in granulomatosis with polyangiitis (Wegener disease), typically using a combination of high-dose corticosteroids with cyclophosphamide, rituximab, methotrexate, mycophenolate mofetil, or azothioprine.

Given the presumed importance of upper airway inflammation in the pathogenesis of LTS and its role in treatment failure, the ability to directly target inflammation with an effective therapeutic agent would be ideal. Many of the abovementioned immunomodulating medications have significant adverse effects or cost profiles. Of this group, methotrexate represents the most attractive option as an adjuvant treatment in LTS for several reasons. There is a long history of its safe use in many conditions, the adverse effect profile is favorable, and it is inexpensive compared with other options.[5] It also does not cause the same hyperglycemia, mood alteration, and facies seen with long-term corticosteroid use. Although methotrexate is used at high doses as a chemotherapeutic agent, with considerable toxic effects, lower doses are better tolerated. There is virtually no literature examining its use in the treatment of nonvasculitic airway stenosis: the only published study[6] to date, to our knowledge, is a case report describing the use of methotrexate for successful treatment of progressive idiopathic tracheobronchial stenosis.

The objective of this study was to examine whether low-dose methotrexate is an effective adjuvant therapy in patients with nonvasculitic LTS who fail surgical management of their stenosis (ie, requiring dilation more frequently than every 6 months) and have resistant, rapidly recurrent LTS and in whom rheumatologic disease has been ruled out. We sought to test the hypothesis that low-dose methotrexate, administered as an adjuvant therapy to traditional endoscopic surgical management, would increase the number of days between surgical procedures in this patient population such that this measure would be in line with historical controls.

Key Points

Question Does low-dose methotrexate improve the number of surgery-free days for patients with rapidly recurrent nonvasculitic laryngotracheal stenosis?

Findings In this case series study of 10 patients, a substantial difference in the number of surgery-free days was seen before vs after starting methotrexate therapy.

Meaning In patients with rapidly recurrent laryngotracheal stenosis, methotrexate may be used as an adjuvant treatment to reduce the frequency of surgical dilation.

Methods

Selection Criteria

The study was approved by the University of Miami Miller School of Medicine Institutional Review Board. A retrospective medical record review was performed for all adult patients with a history of LTS and no rheumatologic disease who were treated with low-dose methotrexate from January 2014 to January 2016. Patients were excluded from the study if, during treatment, they were found to have a vasculitic cause of their LTS.

Treatment

Patients who had failed surgical management of their stenosis (ie, requiring dilation more frequently than every 6 months) were started on methotrexate therapy at a dose of 15 mg, taken orally once weekly. Treatment was initiated immediately after surgical dilation. When appropriate for the patient's weight, dosing was titrated upward to 20 mg. All patients underwent routine monitoring of hepatic and hematologic function. Treatment with methotrexate was discontinued if serum test results revealed serious hepatic or hematologic dysfunction or if requested by the patient because of additional adverse effects. Otherwise, their treatment was still ongoing in 2016. All previous adjuvant therapies (eg, proton pump inhibitors, corticosteroid inhalers, and oral corticosteroids) were continued unchanged throughout the course of treatment, with the sole exception of a patient who had pronounced neurological adverse effects from oral corticosteroid use and requested to be weaned off of them.

Statistical Analysis

The dates of each patient's surgical procedures were recorded in a spreadsheet. The mean (SD) number of days (with 95% CIs) between surgical procedures before and after the initiation of methotrexate therapy was calculated for each population and for the difference in means. In addition, descriptive data from

Table 1. Clinical Information About 10 Patients Undergoing Methotrexate Therapy

Patient No./ Sex/ Age, y	Tracheostomy		Type of Surgery	Stenosis		Previous Medical Treatments	Medical Comorbidities	Notes
	Before Methotrexate	After Methotrexate		Etiology	Severity at the Initiation of Methotrexate Therapy			
1/F/40s	Yes	No	None (primary decannulation)	Postintubation	50%, 1-cm Length	Oral corticosteroids, PPI	None	Without problems 2 y after decannulation
2/F/60s	No	No	Tracheal resection, endoscopic dilation	Postintubation	60%, 1-cm Length	Corticosteroid inhaler	CAD, HTN, diabetes, COPD	Anastomosis line widely patent after 24 mo of treatment
3/M/20s	No	No	Endoscopic dilation	Neck trauma, postintubation	60%, 2-cm Length	Oral corticosteroids, H_2 antagonist	None	No adverse effects
4/F/60s	Yes	No	None (primary decannulation)	Postintubation	75%, Length NA	Oral corticosteroids, PPI	HTN, atrial fibrillation, psychosis	Failed dilation elsewhere. Without problems 19 mo after decannulation
5/F/80s	No	No	Endoscopic dilation	Idiopathic	30%, 1.5-cm Length	PPI, corticosteroid inhaler	GERD	Onychomycosis, hair thinning
6/F/50s	Yes	Yes	Tracheal resection	Postintubation	50%, 2-cm Length (granulation)	Antibiotics, PPI, corticosteroid inhaler	GERD, chronic bronchitis	Failed 2 tracheal resections elsewhere because of granulation tissue. Complete resolution of tracheal granulation tissue after 1 mo of treatment, no additional granulation tissue 15 mo later
7/F/50s	Yes	Yes	Tracheal resection, endoscopic dilation	Idiopathic	100%, 1-cm Length	PPI	GERD	Complete resolution of tracheal granulation tissue
8/M/70s	No	No	Endoscopic dilation	Postintubation	75%, 1.5-cm Length	Oral corticosteroids, H_2 antagonist	CAD	Onychomycosis, hair thinning, herpes zoster infection. Methotrexate drug rash. Able to discontinue prednisone and reverse significant neurological adverse effects
9/F/50s	No	No	Endoscopic dilation	Idiopathic	75%, 2-cm Length	Oral corticosteroids, PPI, corticosteroid inhaler	Morbid obesity, HTN, diabetes	Improved airway caliber at 2-mo visit, discontinued use as precaution because of elevated liver function test results
10/F/late teens	No	No	Tracheal resection, endoscopic dilation	Postintubation	50%, Length NA	None	Tracheomalacia	Decreased airway inflammation noted on endoscopic examination

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; H_2, histamine$_2$; HTN, hypertension; NA, not applicable; PPI, proton pump inhibitor.

each patient's treatment course, including comorbidities, previous treatments, and stenosis severity before methotrexate therapy, as well as endoscopic images and pathologic slides, were reviewed, and any adverse effects were tabulated.

Results

Demographics

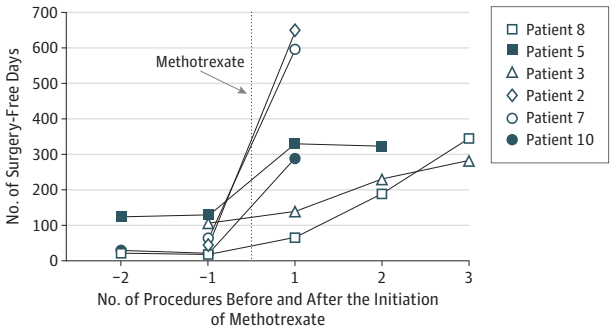
Eleven patients were identified who met initial inclusion criteria, 1 of whom was excluded after being diagnosed as having relapsing polychondritis during treatment. Therefore, 10 patients were included in the study, 5 of whom had failed primary endoscopic tracheal dilation without tracheostomy, 3 who had unsuccessful tracheal resection, and 2 with tracheotomies who did not undergo any surgery at our institution but failed dilation elsewhere (**Table 1**). There were 8 women and 2 men in the study cohort, with a mean (SD) age of 52 (19) years at the outset of study inclusion. Seven patients developed LTS after intubation, while 3 patients had idiopathic stenosis.

Adverse Effects

Of the 10 patients, 1 discontinued methotrexate therapy after 2 months because of the development of right upper quad-

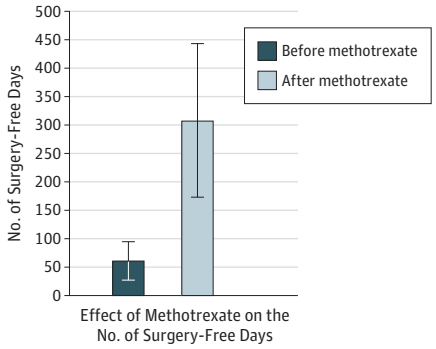
rant pain and elevated hepatic function study results. However, these findings were ultimately considered to be due to an incidentally discovered 10-cm renal cell carcinoma that impinged on the hepatobiliary system and predated methotrexate treatment. All other patients tolerated methotrexate therapy well, with 2 patients each reporting mild hair thinning and onychomycosis, 1 patient reporting a herpes zoster outbreak, and no patients experiencing abnormalities in serum testing results.

Figure 1. Number of Surgery-Free Days After Endoscopic Dilations Before and After the Initiation of Methotrexate Therapy



Details about the 6 surgical patients are listed in Table 1.

Figure 2. Number of Surgery-Free Days for All 6 Surgical Patients Before and After the Initiation of Methotrexate Therapy



Error bars indicate 95% CIs.

Number of Days Between Surgical Procedures

Six patients underwent at least 1 surgical procedure before and after the initiation of methotrexate treatment. The mean (SD) interval between operations was 61 (35) days (95% CI, 26-96 days) before starting methotrexate therapy and 312 (137) days (95% CI, 175-449 days) after starting methotrexate therapy. The mean (SD) absolute difference between the 2 groups was 251 (58) days (95% CI, 193-309 days) (**Figure 1**, **Figure 2**, and **Table 2**). The median number of days between surgical procedures was 44 days before starting methotrexate therapy and 289 days after starting methotrexate therapy.

Other Signs of Clinical Improvement

Two patients who were previously tracheostomy dependent were able to be decannulated after a short course of treatment with methotrexate. A third tracheostomy-dependent patient who initially failed decannulation after tracheal resection was successfully decannulated following initiation of methotrexate treatment. Two other patients who were tracheostomy dependent and had failed endoscopic management of their granulation tissue (potassium-titanyl-phosphate laser and microdebrider) had complete resolution when methotrexate was added as a postsurgical adjuvant therapy.

Discussion

Treatment with low-dose methotrexate appeared to have the desired effect in this population. All 6 patients who had operations before and after starting methotrexate treatment were noted to have a substantial increase in the number of days between surgical procedures after the initiation of methotrexate therapy. On average, the duration between operations in surgical patients decreased from 2 months to more than 10 months, which is in line with historical data for patients with LTS. Even for nonsurgical patients, success was seen in progressing to decannulation, despite failure elsewhere because of pronounced subglottic edema and stenosis, while a substantial reduction in the degree of subglottic inflammation was seen in some cases (**Figure 3** and **Figure 4**).

Recurrent LTS is a significant challenge for the global community of otolaryngologists. It is frequently misdiagnosed by

Table 2. Number of Surgery-Free Days for Patients at the Time of Each Surgical Procedure Before and After the Initiation of Methotrexate Therapy[a]

	No. of Surgery-Free Days					
No. of Procedures	Patient 8	Patient 5	Patient 3	Patient 2	Patient 7	Patient 10
Before Methotrexate						
−2	21	124	NA	NA	NA	28
−1	18	128	106	44	63	21
After Methotrexate						
1	66	329	139	651	597	289
2	188	322	231	NA	NA	NA
3	344	NA	282	NA	NA	NA

Abbreviation: NA, not applicable.

[a] Details about the 6 surgical patients are listed in Table 1.

practitioners in other fields as a pulmonary disorder, such as asthma, and proper endoscopic evaluation may not be sought until the condition has reached an advanced state. Furthermore, continued progress in critical care medicine has led to a steadily increasing population of patients who have been intubated and may subsequently develop LTS. While most patients are successfully managed with endoscopic dilation or open tracheal reconstructive techniques, some will fail rapidly. In a large cohort of 263 patients who underwent single-stage laryngotracheal reconstruction for idiopathic subglottic stenosis, 1.1% had restenosis by 1 month after surgery and 6.5% had granulation tissue present.[7]

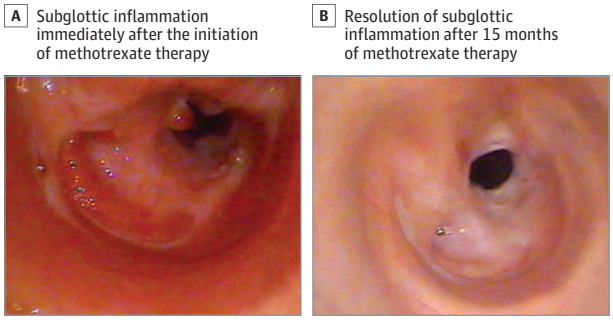
Few adjuvant treatment options are available for the treatment of LTS. Intraoperative therapy includes topical application of mitomycin C, as well as direct injection of corticosteroids into the stenotic segment. The latter therapy has begun to be applied in office settings, which may prove to be of some value.[8] Oral corticosteroids are the mainstay of postoperative and maintenance therapy, but this strategy is often not sustainable because of adrenal suppression, hyperglycemia, and other adverse effects. Some authors have advocated a combination of postoperative antibiotics and corticosteroids to lessen the degree of stenosis.[9,10] There also have been some efforts to prescribe inhaled corticosteroids for the same purpose, but deposition of medication in the laryngotracheal complex is generally only approximately 25% to 33% of the inhaled doses, and scant literature has examined this use specifically in stenosis.[11] A single-patient case study[12] recommends corticosteroid use in postintubation stenosis, and a retrospective review[13] of patients with tracheal resection found that inhaled corticosteroids helped alleviate granulation tissue.

Acid reflux also has been found to be a significant comorbidity in adult LTS and is generally thought to have some role in its pathogenesis, although the degree to which it contributes is not clear.[2,7,14-16] Some authors have argued for aggressive control of laryngopharyngeal reflux as a means of preventing disease recurrence and minimizing surgical failures but has similarly not been studied in a controlled, prospective fashion.[17,18]

There also have been anecdotal reports of clinical success using mycophenolate mofetil in the treatment of nonvasculitic cases of LTS, but, to our knowledge, none have been published to date. However, a study[19] showed that mycophenolate mofetil can successfully be used to treat idiopathic fibrosis of the retroperitoneum, suggesting that this therapy could be applied to the upper airway.

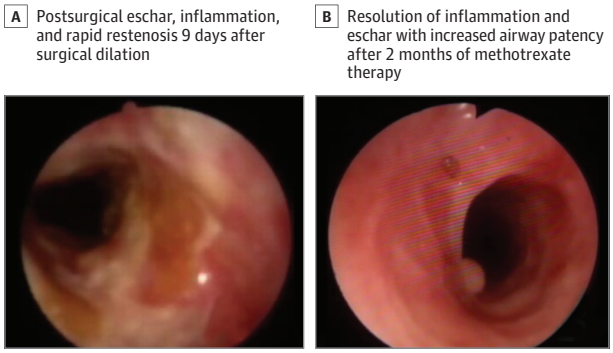
The theoretical foundation for the present study was that the underlying mechanism for treatment failure in these patients is an inflammatory process, as yet poorly understood. Endoscopic evaluation of the patients before and after surgery typically reveals an inflamed, erythematous stenotic segment. In theory, improved control of inflammation in the diseased area should allow the airway to scar in a more favorable, dilated configuration rather than immediately narrowing due to proliferative tissue growth. Some authors have advocated aggressive adjuvant therapies in the postoperative period as a means of controlling this inflammation and use a combination of corticosteroids, proton pump inhibitors, and antibiotics.[10]

Figure 3. Laryngoscopic Examination of Patient 8



Details about patient 8 are listed in Table 1.

Figure 4. Laryngoscopic Examination of Patient 9



Details about patient 9 are listed in Table 1.

One question raised by this study is when to discontinue the use of methotrexate, which is currently unclear. Given its apparent positive effect on controlling inflammation, methotrexate might be best suited for use just before and after surgery, which would help minimize undesired adverse effects by reducing the duration of treatment to when it is most needed.

Limitations

This study is limited by its small sample size and retrospective nature. It is also possible that the clinical improvement seen herein could represent regression to the norm given the overall poor status of these patients at the outset of study inclusion. There did not appear to be any significant contribution in any patient from improved management of the underlying medical comorbidities, such as type 2 diabetes, obesity, or coronary artery disease (Table 1). However, in all cases, the observed improvement seemed to correlate with the initiation of methotrexate therapy. An 18-year-old patient who had failed tracheal resection and was requiring monthly dilations noted immediate improvement in her breathing and was able to resume high school. Another patient who was experiencing severe debilitation while undergoing a prednisone regimen was able to taper off of it after starting methotrexate therapy and returned to his full-time employment.

Conclusions

Our study establishes low-dose methotrexate as a new, potentially useful adjunct to surgery for patients with rapidly recurrent nonvasculitic LTS. Methotrexate is well tolerated, easily accessible, and affordable, and it can prolong the number of days between surgical procedures in patients who may not have any other viable alternatives. Further studies are needed to examine the use of methotrexate in this patient population, including randomized, placebo-controlled double-blind trials.

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Study concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Rosow.
Drafting of the manuscript: Rosow.
Critical revision of the manuscript for important intellectual content: Both authors.
Statistical analysis: Both authors.

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