

Intratracheal Dilation-injection Technique in the Treatment of Granulomatosis with Polyangiitis Patients with Subglottic Stenosis

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ABSTRACT. Objective. An analysis of subglottic stenosis (SGS) occurrence frequency in patients with granulomatosis with polyangiitis (GPA) based on the time of appearance of clinical symptoms, and an assessment of treatment effectiveness, in particular with the intratracheal dilation-injection technique (IDIT).

Methods. Review and treatment with IDIT of 34 patients with SGS associated with GPA.

Results. SGS developed in 34 of 250 patients with GPA (13.6%) and was not reflective of disease activity in the organs in 15 of 34 patients (44%): 11 cases after and 4 cases during immunosuppressive therapy (IST) when patients did not have organ symptoms. All patients underwent IDIT and in total, the treatment resulted in immediate improvement. In addition, in 21 cases, IST was applied because of other organ involvement or of the lack of longterm efficacy of IDIT. The median time of response was 37 months and the median interval between sessions was 5 months. None of the patients required tracheostomy after beginning IDIT in our hospital.

Conclusion. SGS often occurs independently of other features of active GPA. IDIT is a safe and effective technique in the treatment of GPA-related SGS. It should be performed in all patients with GPA who develop significant SGS and in those with multiorgan disease concomitantly with IST. In patients with isolated SGS, IDIT also makes IST and tracheostomy unnecessary. (J Rheumatol First Release September 15 2016; doi:10.3899/jrheum.151355)

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Granulomatosis with polyangiitis (GPA) is a disorder of unknown etiology characterized by necrotizing granulomatous inflammation and vasculitis that affects predominantly small vessels of many organs¹. Airway involvement is found in 15%–55% of patients with GPA, but subglottic stenosis (SGS) is considered to be less common and is present in 16%–23% of adult patients^{2,3}. Symptoms of SGS range from nonspecific dyspnea, wheezing, stridor, and change in voice. Some patients with indolent disease onset may have been labeled “asthmatic” for many years before diagnosis, but in the majority, it is a potentially life-threatening presentation of GPA, necessitating surgical intervention (tracheostomy).

Intratracheal dilation-injection technique (IDIT) was initially used to treat non-GPA laryngotracheal stenosis. However, the results have been inconsistent⁴. The majority of non-GPA-SGS lesions are secondary to postintubation scarring and laryngotracheal trauma. These strictures may be fibrotic or calcified and difficult to treat in a conservative fashion. However, in further studies of GPA-related SGS,

intralesional corticosteroids injections and tracheal dilation proved remarkably effective^{5,6}.

The objective of our current retrospective study of patient data was to provide an analysis of SGS frequency occurrence in patients with GPA (based on the time of appearance of clinical symptoms) and to assess treatment effectiveness, particularly of IDIT.

MATERIALS AND METHODS

Data used in our retrospective study were taken from 34 patients with GPA-related SGS, from among 250 patients with GPA hospitalized in the National Research Institute of Tuberculosis and Lung Diseases in Warsaw, Poland, during 1989 to 2015 (23 women and 11 men, aged 18–78 yrs, median age 45 yrs). The diagnosis of GPA was applied according to current classification guidelines¹. Significant SGS was defined as the presence of symptomatic airway compromise, usually consistent with dyspnea, voice changes, or coughs, and objective tracheal narrowing (< 8 mm) visible in bronchoscopy and computed tomography targeted at the larynx and trachea (Figure 1 and Figure 2). Patients who had disease activity limited to the SGS underwent only IDIT without systemic therapy. Patients with SGS and active GPA affecting other than the subglottis also received standard immunosuppressive therapy (IST) with corticosteroids and a cytotoxic agent [cyclophosphamide (CYC) or methotrexate], according to the guidelines^{1,7}. In patients who failed to achieve longterm improvement through only local treatment, systemic therapy was also implemented. Pulmonary function was assessed using spirometry, blood gases, and the walking test. IDIT was performed during “rigid” bronchoscopy in the operating room, with the patient under general anesthesia and with jet ventilation. First, the trachea was examined and the overall appearance and tracheal diameter were noted. A biopsy was frequently performed. Then, tracheal dilation was performed, after which the stenotic area was injected with methylprednisolone acetate in a 4-quadrant submucosal pattern (total dose per procedure: 80 mg) using an

intratracheal approach. To lessen tracheal swelling from procedural trauma, intravenous (IV) dexamethasone was given immediately before surgery and 6–12 h afterward. The procedure was repeated every 3–4 weeks until the patient no longer displayed significant symptoms of SGS. The number of procedures was dependent on the severity and return of symptoms. In some cases, the procedure was continued to maintain efficacy. During 1 session, 2–4 procedures were performed (mean 2). Differences between the group required only 1 session, and the groups that required more than 1 session were tested using the Fisher’s exact test or the chi-square test, when appropriate. Numerical data between groups were compared using the Mann-Whitney U test and the chi-square test with Yates correction. A 2-sided p value of 0.05 was considered statistically significant.

We used relief of the clinical symptoms that remained after the last session as the criterion for judging improvement (response for treatment); factors were confirmed by a supplemental battery of objective pulmonary control tests (spirometry, walking test, blood gases). Further, the intervals between sessions (when patients were free from symptoms) were factored in and analyzed. The clinical characteristics of the patients are shown in Table 1.

RESULTS

In the available survey population, patients with SGS accounted for 13.6% of all patients with GPA (34/250). Patients in whom SGS symptoms were the first clinical manifestation of GPA accounted for about 15% of all patients with GPA-related SGS (7/34). The length of time between the onset of SGS symptoms to GPA diagnosis ranged from 5 months to 7 years. The number of patients with GPA who developed SGS had been increased together with longer survival times associated with more effective treatment of GPA.



Figure 1. Neck computed tomography scan (axial view) shows tracheal narrowing because of the thickening of the tracheal wall (arrow).



Figure 2. Computed tomography scan (coronal view) shows subglottic concentric tracheal wall thickening and stenosis in granulomatosis with polyangiitis (arrow).

Analysis of time intervals between appearance of SGS symptoms and evidence of pathology in major organs. From among 34 patients with GPA diagnosed with SGS, 17 (50%) displayed symptoms of organ involvement. In 15 (44%), SGS was diagnosed in the absence of symptoms of active GPA. In 11 of those cases, diagnosis was made after IST. In 4 cases, diagnosis was made during maintenance IST and absent of symptoms of organ pathology. In 2 patients (6%), SGS was the only symptom of GPA (confirmed by histological examination and/or the presence of antineutrophil cytoplasmic antibodies). In the group of 15 patients whose systemic GPA entered into clinical remission, the median time of SGS diagnosis was 4 years after the onset of GPA (range 5 mos–13 yrs) and 10 months from the end of IST (range 1–36 mos). In 2 patients displaying SGS as the only symptom, time to diagnosis of GPA ranged from 1–8 months (median 4.5 mos).

Dyspnea was the most common symptom in all patients; voice changes and cough were observed less often. The abnormality most often observed in pulmonary function tests was obstruction, with assessment made in 17 of 26 patients using spirometry. Prior to intervention, the mean percentage of forced expiratory volume in 1 s (FEV1) was 65.4%. Seven patients exhibited hypoxemia and 4 displayed desaturation in the walking test (Table 1).

Analysis of local treatment effectiveness. All patients underwent IDIT. In 13 cases, IDIT was the only treatment administered. In 17 cases with corresponding diagnosis of organ pathology, IDIT was administered in conjunction with

IST. In 4 cases, IST was added because of failure in longterm efficacy and corresponding procedural repetition/frequency. In all cases, patients displayed clinical improvement immediately following treatment.

The median duration of response to treatment was 37 months (range 2 weeks–14 yrs), and the median interval between treatment sessions was 5 months (range 3 weeks–3 yrs). In most cases (28 patients), from 1 to 4 sessions were performed. One patient needed 10 sessions, another needed 8, and another 5. The median number of sessions in all cases was 1, and in 19 cases (56%), 1 session was sufficient.

Seventeen patients receiving IDIT and IST displayed the longest median time of response (40 mos, range 2 weeks–12 yrs), a result that may be partly attributable to the longest followup period (median 7 yrs, range 2 weeks–20 yrs). The majority of these patients (12/17) needed only 1 treatment session. The median interval between sessions in the remaining 5 patients from this group was 11 months (range 5 weeks–34 mos).

In the 13 patients receiving only IDIT, the median response interval was 34 months (range 6 mos–9 yrs), but the median followup time was shorter (5 yrs, range 6 mos–15 yrs). Treatment failed to produce longterm efficacy in 4 cases (clinical symptoms returned repeatedly) and IST was added. While symptoms decreased significantly in 3 of those patients, 1 experienced frequent relapses and IDIT was repeated many times. Table 2 provides a summary of treatment results for all patients depending on the type of therapy.

Table 1. Clinical characteristics of 34 patients with GPA-related SGS.

Variable	No. Patients
Female	23
Male	11
Age, yrs	18–78
Median age, yrs	46
SGS diagnosis	
SGS as the only symptom of GPA	2
SGS diagnosed in clinical remission of GPA	15
SGS + activity of GPA in other organs	17
BVAS, organ involvement	34
0	15
1: sinus	9
2: ENT, sinus	1
3: sinus, kidney	3
4: sinus, ocular, kidney	4
5: sinus, skin, lung	1
9: sinus, ocular, lung, kidney	1
Trachea biopsy	26/34
GPA confirmation	16/26
Noncharacteristic pattern	10/26
ANCA present	24/34
Clinical symptoms	
Dyspnea	34
Cough	11/34
Hoarseness	10/34
Pulmonary function tests	
Desaturation in walking test	4/26
Hypoxemia, < 70 mmHg	7/34
Obstruction of spirometry, FEV1/FVC < 0.7	17/26
Treatment type	
Only IDIT	13
IDIT + IST, activity in other organs	17
IDIT + IST, persistent symptoms of SGS	4
Overall	34

GPA: granulomatosis with polyangiitis; SGS: subglottic stenosis; BVAS: Birmingham Vasculitis Activity Score; ENT: ear, nose, throat; ANCA: antineutrophil cytoplasmic antibodies; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; IDIT: intratracheal dilation-injection technique; IST: immunosuppressive therapy.

Table 2. Results of SGS therapy in 34 patients with GPA, depending on the type of treatment.

Treatment Type	No. Patients	No. Sessions	Time between Sessions, Mos, Median	Time of Response since the Last Session, Mos, Median or Range (Yrs)	Followup Period, Mos, Median or Range (Yrs)
IDIT + IST at the same time	12	1			
	3	2	12.6	40	7
	1	5		0.5–144 (12 yrs)	0.5–240 (20 yrs)
	1	10			
Only IDIT	7	1			
	5	2	5	34	5
	1	4		60–108 (9 yrs)	6–180 (15 yrs)
First IDIT	4	2–8	0.88		
IST added, reoccurring SGS	4	1–6	1.2	24	3
				6–48 (4 yrs)	6–96 (8 yrs)
Overall	34	1–10	5	37	7
				0.5–168 (14 yrs)	0.5–240 (20 yrs)

SGS: subglottic stenosis; GPA: granulomatosis with polyangiitis; IDIT: intratracheal dilation-injection technique; IST: immunosuppressive therapy.

The analysis comparing patients who required only 1 session of dilation versus those who required more than 1 session showed that in the first group, other organ involvement was significantly higher in comparison with the second group (79% vs 13%, $p = 0.00055$). Similarly, the median BVAS for the first group was higher ($p = 0.054$). These patients additionally received IST, which could have influenced these results. The number of sessions did not correlate with the age, sex of patients, and time of SGS diagnosis. The results of our analysis are shown in Table 3.

Five of 34 patients (15%) required tracheostomy before IDIT could be performed. None of the patients required tracheostomy after beginning IDIT in our hospital. In 2 patients (6%), complications after local treatment were observed in the form of cracking in the tracheal mucosa and were treated nonsurgically. In all cases, results of pulmonary function control tests improved. In addition, the mean percentage of FEV1 increased from 65.4% to 83.4%. Table 4 shows FEV1 values before and after treatment.

DISCUSSION

Because SGS can be a life-threatening manifestation of GPA, prompt diagnosis is essential. And because symptoms can be nonspecific, a high degree of vigilance is necessary. SGS should be considered in any patient with GPA displaying increasing dyspnea, voice changes, or cough. Although audible stridor is a helpful indicator, it is not always present. In addition, it is not always an indicator of SGS^{2,3,8}. The presence of SGS may be suggested by a flattening of the inspiratory curve in the flow-volume loop measurement of extrathoracic airway obstruction. However, this technique may not detect less severe SGS and should never be used as a primary means of diagnosis. Tracheal tomography and/or magnetic resonance imaging (MRI) appear useful in SGS diagnosis. With a sensitivity of 87.5% and a specificity of 60% in the detection of inflammatory activity, the use of MRI

Table 3. Analysis comparing patients with SGS-related GPA (n = 34) requiring only 1 session of dilation versus those requiring more than 1 session.

Variables	1 Session	More than 1 Session	p
Age, yrs*	32 (27–49)	48 (36–62)	NS
Male**	8 (42)	3 (25)	NS
Time from diagnosis**	24 (3–78)	24 (0–90)	NS
BVAS*	1 (0–3.5)	0 (0–1)	0.054
SGS as sole sign**	0 (0)	2 (13)	NS
SGS diagnosed during remission**	5 (26)	6 (40)	NS
SGS diagnosed during therapy**	4 (21)	0 (0)	NS
Organ involvement***	15 (79)	2 (13)	0.00055

* Median (interquartile range), p in Mann-Whitney U test. ** n (%) of positive cases (for age and men), p in Fisher's exact test. *** n (%) of positive cases, p in chi-square test with Yates correction. SGS: subglottic stenosis; GPA: granulomatosis with polyangiitis; BVAS: Birmingham Vasculitis Activity Score; NS: not significant.

Table 4. Pre- and post-treatment values of FEV1 in 17 patients with GPA-related SGS with preliminary obstruction in spirometry. Values are liters (%).

Patients, Sex/Age, yrs	FEV1 before Treatment	FEV1 after Treatment
1. F/54	1.45 (61)	1.45 (61)
2. M/23	2.16 (49)	3.28 (73)
3. F/32	0.88 (26)	2.94 (89)
4. F/36	1.75 (53)	2.15 (65)
5. F/30	2.94 (88)	3.6 (108)
6. F/36	2.07 (63)	2.55 (72)
7. F/22	1.73 (51)	2.31 (68)
8. F/44	2.48 (75)	2.92 (91)
9. M/48	2.49 (70)	3.06 (87)
10. F/22	1.99 (60)	3.38 (101)
11. M/58	2.51 (65)	3.74 (97)
12. F/23	2.72 (78)	4.3 (125)
13. F/40	1.56 (51)	2.37 (78)
14. M/27	2.74 (52)	3.31 (63)
15. F/27	1.88 (57)	3.05 (93)
16. F/31	2.04 (62)	2.92 (94)
17. F/46	1.59 (74)	2.29 (115)

FEV1: forced expiratory volume in 1 s; GPA: granulomatosis with polyangiitis; SGS: subglottic stenosis.

recently has grown as a key, noninvasive method of diagnosing SGS, which can differentiate between regional or circumferential wall thickening and can detect circumscribed intramural “granulomatous” lesions⁹.

In our survey, SGS was a symptom of GPA and not reflective of disease activity in the organs¹⁰. That it often occurs or progresses independently of GPA was also visible in the results. In 15 of the 34 patients studied (44%), SGS occurred in the absence of other symptoms of GPA. In 11 of those cases, it occurred after IST. In 4, SGS occurred during IST, when disease in other organs was in clinical remission.

Intratracheal injection of long-acting corticosteroids with mechanical dilation of stenotic segments has been proven to be an effective therapy in patients who develop SGS in the course of GPA^{5,6,11,12}. This was also confirmed in our study.

Immediate improvement after IDIT was observed in all patients. The median time between sessions was 5 months and the median period of response was 37 months, longer than observed in comparable studies^{13,14,15}. More than half of the patients (19/34, 56%) required only 1 treatment session. In this group, other organ involvement was significantly higher in comparison with patients who needed more sessions (79% vs 13%, p = 0.00055); similarly, the median BVAS for the first group was higher (p = 0.054). It should be noted that these patients received multiple treatments, which could have influenced these results. Also, in this group (receiving IDIT and IST because of accompanying organ pathology), symptom-free time posttreatment was longer; however, the time of observation of these patients was the longest compared with other groups, a factor that could affect the results. The shorter duration of posttreatment observation for the group treated with IDIT only could also have implications for efficacy. None of the patients required tracheostomy after beginning IDIT. To our knowledge, our study is the first to compare the results of treatment types in patients with GPA-related SGS.

Some studies reported that in patients with GPA who had isolated SGS, the treatment rationale is to avoid IST as the primary treatment, an approach supported by the frequent lack of association of SGS with other features of disease activity and the evidence that the subglottic lesion is not universally responsive to systemic agents^{5,6}. Our results confirm this approach. In our study, symptoms of SGS occurred between 1 month and 36 months after IST was administered in 32% of patients (11/34). In 12% of patients (4/34), symptoms occurred as they were undergoing IST. In the 4 cases without longterm improvement after IDIT, we decided to implement IST. In spite of this, 1 of the patients required repeated procedures. In another study, from among 26 cases of GPA with tracheobronchial stenosis, CYC induction therapy was effective only in 1 patient with SGS among 7 who were treated¹⁰. Despite conventional GPA therapy, 62% of patients in this group experienced at least 1 stenosis relapse¹⁰. While

the place of systemic treatment in isolated SGS remains unclear, our assumption is that adding something at the time of the procedure (for example, steroids) could lead to further benefit. Terrier, *et al*¹⁶ analyzed factors potentially associated with time to endoscopic treatment failure. Their data suggested that high-dose systemic corticosteroids (prednisone 30 mg/day or more) administered at the time of the procedure was associated with a better event-free survival, whereas a shorter time from GPA diagnosis to endoscopic intervention was associated with a higher cumulative incidence of treatment failure. In our study, patients received IV dexamethasone directly before and 6–12 h postoperatively to prevent tracheal swelling related to the mechanical trauma of the procedure. Its effect on reduction of tracheal inflammation in our patients cannot be excluded.

Whether and when to intervene is always a question in GPA-related SGS cases. Schokkenbroek, *et al*¹⁷ proposed 2 main indicators in these patients: complaints and physical signs. Progressive complaints and progressive decline of peak flow values (+/+) indicate the need for IDIT. Absence of progressive complaints and unchanged peak flow values (–/–) indicate watchful waiting. Absence of progressive complaints with decline of peak flow values (–/+) needs to be addressed when the values reach a critical level, when it can be expected that a common cold might lead to severe stenosis of the airway. Finally, progressive complaints with unchanged peak flow values (+/–) indicate that pulmonary function tests should be performed and if negative, indicate that the patient has an incorrect perception of his physical potentials. The decision about when to perform IDIT should be based mainly on the presence of clinical symptoms, particularly in evidence of tracheal narrowing. However, every patient should be viewed individually.

IDIT is the primary recommended treatment in patients with isolated GPA-related SGS. Owing to the potential ineffectiveness of cytotoxic agents, IDIT is also preferred for patients with multiorgan GPA and SGS. This is a difficult technique that requires a lot of experience to properly administer. Still, it is highly effective. It is also attractive for other reasons. Intralesional corticosteroid injections have been shown to reduce inflammation and to impair both fibroblast production of collagen and scar formation, possibly through inhibition of cytokine-mediated fibroblast stimulation. Corticosteroids may also bring about collagen resorption and atrophy. Additionally, this procedure was also found to be safe. Langford, *at al*⁵ reported only 1 complication occurring in 113 procedures in 20 patients. In our study, complications were observed in 2 cases (6%).

Other techniques are also used in the local treatment of SGS, such as laser resection, stenting, and topical mitomycin¹⁸. Gouveris, *et al*¹⁹ suggested that endoscopic laser surgery combined with intraoperative local mitomycin and triamcinolone application may provide an effective treatment regimen in patients with idiopathic and GPA-related hard and

short SGS. In the cited study of 11 patients, in which only 4 had GPA-related SGS, the sample population was too small to permit valid conclusions. The authors concur that their promising results require further investigation. Nonetheless, although most of the literature suggests that the use of topical mitomycin around the airway improves surgical outcomes (bronchoscopy and dilation), there is still uncertainty surrounding the use of mitomycin²⁰ because no large randomized and controlled trial has yet been performed to determine whether mitomycin prevents airway scarring.

Our study, too, has some limitations. Although it represents a fairly large series of patients with GPA who had SGS that required endoscopic interventions, it is limited by the retrospective approach. Patients received systemic corticosteroid directly before and 6–12 h postoperatively to prevent tracheal swelling related to the mechanical trauma of the procedure; however, the treatment's efficacy remains questionable. We used relief of the clinical symptoms that remained after the last session as the criterion for judging improvement, but their reappearance indicated renewed endoscopic intervention. Although subjective, these are relevant criteria in daily practice.

Our study offers experiential insight into the treatment of GPA-related SGS, particularly with IDIT. It shows that SGS frequency in patients with GPA increases in parallel with patient survival time. Often patients required only IDIT. Therefore, IDIT is an important and an effective technique in the treatment of GPA-related SGS. In patients with isolated SGS, this technique permits healthcare practitioners to avoid the use of IST and spares patients its side effects. This procedure has been proven to be safe and makes tracheostomy unnecessary. It should be performed in all patients with GPA who develop significant SGS. In addition, in conjunction with IST, IDIT is advised for patients in whom GPA has spread to major organs because of the questionable efficacy of cytotoxic agents in the treatment of the subglottic lesion. It should be undertaken in specialized centers where there is extensive experience with both the disease and bronchoscopy interventions.

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