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Sub-lingual abnormalities in systemic sclerosis

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Abstract

Background—Sublingual frenulum abnormalities have been observed in systemic sclerosis (SSc) but the clinical significance of such features is not known. The goal of this project was to devise a reliable bedside tool to confirm the presence of sublingual frenulum abnormalities in SSc and explore potential associations with patient demographics and gastrointestinal (GI) clinical phenotype.

Methods—A working group was created to develop a semi-quantitative assessment tool for assessing sublingual abnormalities- the Sublingual Abnormalities Index (SAI). Sublingual frenulum thickness, frenulum length, sublingual buccal mucosa pallor, and the presence of oral telangiectasia were each individually scored using 0-2 Likert scales, and a composite score of the 4 domains created by summation of the individual scores. Assessment of the sublingual region of 21 patients with SSc and 8 healthy controls was undertaken. An image of the sublingual frenulum was obtained using pre-specified camera settings to allow assessment of inter-rater reliability with 2 independent blinded assessors.

Results—Scores for each of the SAI domains differed between healthy control and SSc ($p = 0.0003$). SSc patients had a composite SAI score of $4.3 (\pm 0.37)$. None of the healthy controls had a composite SAI score of >2 . There was excellent inter-rater reliability between clinician assessment and each blinded assessor (Cohen's Kappas of 0.72 and 0.82 respectively).

Conclusions—This feasibility study confirms the presence of clinical sublingual abnormalities in SSc, which can be categorized using a simple scoring chart with moderate to near perfect inter-

rater agreement. The functional significance and pathogenesis of this abnormality warrants further study.

Keywords

Scleroderma; systemic sclerosis; sublingual; gastrointestinal disease

Introduction

Systemic sclerosis (SSc, Scleroderma) is a connective tissue disease characterized by vasculopathy and fibrosis. While the etiology of this disease is unknown, ischemia and reperfusion injury is a component of the pathophysiology of gastrointestinal (GI) involvement[1]. The esophagus is the most commonly affected part of the GI tract reported in SSc.

Oral manifestations of SSc are an important cause of impaired quality of life [4]. However, the oral cavity is often overlooked when reporting of GI manifestations in SSc[1]. Thickening and shortening of the sublingual frenulum has been observed in SSc, but the prevalence of such abnormalities and clinical significance is not known[2, 3]. The lingual frenulum is soft tissue mucosa, which extends from the ventral surface of the tongue, in the midline, to the floor of the mouth, and influences the mobility of the tongue[5]. A shortened frenulum might impair the transition of the bolus from the oral cavity into the pharynx and speech quality in SSc. Of potential greater importance, sublingual frenulum thickening in SSc might portend distal gastrointestinal tract disease in SSc. We have observed increased pallor of the sublingual buccal mucosa along with the presence of telangiectases. To date, no clinical assessment tools exist to assess sublingual frenulum abnormalities in SSc. The specific objectives of this pilot study were to develop a novel bedside clinical assessment tool to confirm the presence of sublingual abnormalities in SSc compared with healthy controls. We have assessed inter-rater reliability of this tool and shall report the relationship between sublingual abnormalities with objective and subjective assessment of GI disease in SSc.

Methods

A working group was created to develop a semi-quantitative assessment tool for assessing sublingual abnormalities (the Sublingual Abnormalities Index). Sublingual frenulum thickness, frenulum length, sublingual buccal mucosa pallor, and the presence of telangiectasia were each scored using 0-2 Likert scales (0, normal; 1, intermediate abnormalities; 2, severe abnormalities). A composite score was calculated by summing the four domains. SSc patients were recruited and consented at their routine care visits to the University of Utah under IRB protocol 38705. Patients fulfilling the 2013 ACR/EULAR classification criteria for SSc and healthy controls (HC) were recruited from the SSc clinics at the University of Utah and the University of Pittsburgh. SSc participants completed the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) questionnaire. The presence of sicca symptoms and tobacco use was recorded. Case notes were reviewed to document participant demographics,

disease duration, auto-antibody status, and body mass index (BMI). An image of the sublingual frenulum was obtained using a Fuji film 16-megapixel camera with pre-specified settings. Images of the sublingual frenulum were assessed using the SAI. The images were assessed by the attending physician, in addition to blinded assessment of images obtained by 2 independent rheumatologists from SSc Centers.

Three patients that were determined to have a severe sublingual score were referred to an Ears, Nose, Throat (ENT) physician to have subsequent oropharyngeal, speech, and swallow assessment in order to assess whether the frenulum affected swallow function and if frenulectomy was indicated. A flexible laryngoscopy, which evaluated the anatomy and functioning of the larynx and hypopharynx, was performed. Subsequently a swallowing study was completed according to protocol with 1cc, 3cc, and 20cc liquid barium swallows followed by paste and cracker swallow. All swallows were reviewed in detail with frame by frame analysis. Quantitative measures of timing and structural displacement were reviewed for all liquid bolus sizes. Overall transit time, size of the upper esophageal sphincter (UES), maximal pharyngeal constriction size, hyoid displacement, and timing of airway closure relative to arrival of bolus at the UES were measured. An esophageal screen was performed at baseline to assess dilation of the distal esophagus and retention of material.

Statistical analysis was performed by an independent assessor using SAS version 9.4. We used frequency to summarize and describe categorical variables. Means were used to describe normally distributed continuous data. Median and interquartile range was used to describe skewed continuous data. Cohen's Kappa (weighted) was used to assess agreement of frenulum assessments.

Results

Twenty-one patients with SSc (19 female) and 8 healthy controls (6 female) were recruited to the study. The mean age of the SSc population was 55.1 (SD 13.7) years. Median SSc disease duration from first non-Raynaud symptom was 9.9 years (SD 9.9), the median BMI was 20 (19.8-23.6) and all were ANA positive. Nine SSc patients reported xerostomia and two used tobacco (Table 1).

All SSc patients assessed had the presence of buccal telangiectases and/or a least one of the following of abnormalities of their frenulum: thickening, shortening, pallor, or vessel engorgement. Each of the frenulum measures differed between healthy control and SSc ($p=0.0003$). The SSc patient population had a composite SAI score of 4.3(+ 0.37). No healthy control had a composite score of greater than 2. Assessment of the frenulum in the SSc patients and healthy controls revealed excellent agreement between the reference scorer and the two assessors for the frenulum (Table 2). The overall agreement of the reference scorer with the other scorers (0.72 for one assessor and 0.82 for the other assessor) indicated strong agreement. The lowest agreement was seen for buccal telangiectases (0.51 for one assessor and 0.47 for the other assessor).

For SSc patients the GIT 2.0 median score was 0.26 (0.2-0.54 IQR), with the majority of the patients ($n=15$) having mild overall GIT severity. The most common symptom reported was

bloating, which was reported in all patients and had a GIT score of 0.75 (0.5-1), which was followed by reflux 0.5 (0-0.63).. There was a positive association was identified between severity of clinical frenulum assessment and total GIT 2.0 score (spearman $r=0.44$, $p=0.04$) as well as disease duration (spearman $r=0.61$, $p=0.003$).

Three SSc patients with high 3SAI composite sublingual score reported oropharyngeal dysphagia and had very abnormal esophageal screens, with dilation of the distal esophagus and retention of material that eventually cleared. Each had normal vocalization, flexible laryngoscopy, and swallow study measures.

Discussion

This pilot study confirms a high prevalence of sublingual frenulum abnormalities in SSc. Our novel semi-quantitative scoring tool (the 3SAI) was feasible, successfully differentiated SSc patients from healthy controls and reliable with excellent agreement following independent assessment by 2 SSc clinicians. We have demonstrated the capacity to capture images using digital photography that would facilitate centralized blinded assessment of the 3SAI in future cross-sectional and longitudinal studies. Correlation with disease duration suggests sublingual frenulum abnormalities might represent a late manifestation of SSc. There was an apparent association between sublingual abnormalities and patient-reported assessment of GI disease using the GIT 2.0 questionnaire that warrants further investigation. Lingual frenulum protocols in infants include a range of motion or mobility component, which we have not currently incorporated into our protocol [6]. As such, we referred our severe sublingual abnormality patients to ENT for expert dynamic evaluation of the oral cavity, speech, and swallow. Three patients with a severe sublingual score had abnormal swallow screens with delayed esophageal transit and poor emptying. Each patient had normal anatomy and functioning of the larynx and hypopharynx as well swallow evaluations (with regards to the size of the UES, maximal pharyngeal constriction size, hyoid displacement, and timing of airway closure). This suggests there might not be a role for frenulectomy to improve function in SSc patients since the standard indications by ENT were not met for this procedure. However, only three patients were referred, thus definitive conclusions cannot be made. Furthermore, the contribution of xerostomia and tobacco use to sublingual abnormalities was not adequately evaluated by ENT.

The main purpose of this pilot study was to develop a feasible and reliable tool that could be applied to future larger studies designed to better understand the clinical significance and likely pathophysiology of sub-lingual abnormalities in SSc. Further work is planned to explore the relationship between the 3SAI (both composite score and individual domains) and patient demographics, clinical phenotype and more extensive patient- reported assessment of oral health, quality of life and gastrointestinal tract symptoms. The chief limitations of the study were its small size and prior knowledge of underlying disease state by our independent assessors upon scoring obtained images.

The healthy controls were selected based on there absence of health problems, but were not age and gender matched. In this pilot study, we identified certain challenges in our assessments, which provide guidance for future directions. Firstly, standardization of

measurement of vascular engorgement likely should capture fasting status, menstrual cycle, and timing of vasodilator medications, which are known affect vascular measurements. This may have contributed to the lack of agreement among investigators; subtleties in vascular size may require perfusion imaging to better assess this finding. Secondly, microstomia can make assessment of the sublingual region challenging. Some subjects reported difficulty extending their tongue to allow photographic assessment. Movement of the patient's tongue during image acquisition sometimes resulted in blurring of the image. These factors may have underestimated sublingual changes such as the telangiectases count.

Conclusions

Sublingual abnormalities are frequently present in SSc and can be assessed and semi-quantitatively scored in the clinical setting using the scoring tool we have developed. The ability to reliably quantify this disease feature of SSc with the 3SAI requires further study and will potentially allow clinicians to monitor progression of disease and guide appropriate referral to speech therapy and ENT treatment intervention. The potential to image the sublingual region for subsequent blinded assessment might be of value in future long-term observational studies. Assessment of sublingual abnormalities is not included in existing recommendations on gastrointestinal screening tools in SSc [7]. Further work to establish the clinical significance, disease associations and aetiology of sublingual abnormalities in SSc is warranted.

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1

Systemic Sclerosis Disease Features (n=21)

Female	19
Male	2
Age (years)	55.1 ± 13.7
Non Raynaud Disease Duration (years)	9.9 ± 9.9
Presence of oral sicca	9
Antibody Type	
• PM-SCL	1
• RNA Polymerase III	3
• RNP	1
• SCL 70	2
• Th/To	1
• Centromere	12
Tobacco Use	2
BMI	24.4 ± 5.6
Sublingual Assessment Index (SAI)	4.3 ± 0.37
•Sublingual frenulum thickening	0.90 ± 0.62
•Sublingual frenulum length	0.95 ± 0.8
•Sublingual buccal pallor	0.90 ± 0.7
•Sublingual venous engorgement	0.90 ± 0.7
•Buccal and lingual telangiectases	0.62 ± 0.59

Table 2

Sublingual Frenulum Assessment

Parameter	Score			Inter-rater Agreement Cohen's Kappa (95% CI)		
	0	1	2	Rater 1 vs 2	Rater 1 vs 3	Rater 2 vs 3
Sublingual frenulum thickness	Normal	Intermediate thickening	Severe thickening	0.85 (0.66-1.0)	0.93 (0.80-1.0)	0.79 (0.56-1.0)
Sublingual frenulum length	Normal	Intermediate shortening	Severe Shortening	0.59 (0.29-0.88)	0.87 (0.69-1.0)	0.58 (0.28-0.88)
Sublingual buccal mucosa	Normal	Intermediate pallor	Severe pallor	.63 (0.35-0.90)	0.94 (0.82-1.0)	0.55 (0.25-85)
Buccal and labial telangiectases	None visible	1-6 visible	>7 visible	0.51 (0.13-0.88)	0.47 (0.15-0.79)	0.48 (0.15-0.80)
Total Score	0-2	3-5	5 +	0.72 (0.48-0.98)	0.82 (0.60-1.0)	0.53 (0.21-0.84)