Case report

Oro-facial fibrosis in systemic sclerosis: a reconstructive journey

Faith Hyun Kyung Jeon 1,2, Michelle Griffin,1,2,3 Jajini Varghese,1,3
Peter Edward Michael Butler1,2,3

SUMMARY

Oro-facial fibrosis presents a significant disease burden in patients with systemic sclerosis, but there remains no established treatment modality. Autologous fat grafting is a minimally invasive surgical procedure that is now increasingly recognised for its regenerative capacity, propagating an expansion of heterogeneous indications beyond volume restoration, including fibrotic diseases such as systemic sclerosis. We present a 42-year-old woman with oro-facial involvement of systemic sclerosis leading to severe limitation in mouth opening and closure, with marked retraction of the lower lip and gingival display. We describe the reconstructive journey over a 12-year period, where the antifibrotic effect of autologous fat grafting served as the basis on which a series of surgical procedures were performed to achieve functional and aesthetic improvement. Autologous fat grafting provides a novel treatment modality for orofacial skin fibrosis, previously considered a non-treatable disease manifestation of systemic sclerosis.

BACKGROUND

Systemic sclerosis (SSc), also known as scleroderma, is a rare complex multisystem disorder involving vascular, immunological and fibrotic pathological components.1 Cutaneous fibrosis is a near-universal feature in patients with SSc, and involvement of the face and perioral regions carries a significant disease burden, yet is often overlooked in contrast to consequences of visceral fibrosis, which is associated with higher mortality.2 Oro-facial manifestations of SSc as a result of progressively adherent fibrotic skin to the underlying tissues include reduced facial expression described as ‘Mauskopf faces’, reduction in mouth opening and closure (microstomia) with characteristic perioral furrowing and reduction in labial thickness of the lips (microcheilia). Together, these lead to a decline in aesthetic appearance, facial expression, reduced oral access with impact on nutrition, maintenance of oral hygiene, saliva control and speech phonation, posing a complex multifactorial disease burden manifesting as aesthetic, functional and social compromise.3 Current available therapies focus on treating life-threatening complications arising from organ involvement, and a disease-modifying therapy targeting skin fibrosis is still lacking. We describe the reconstructive journey of a patient with oro-facial fibrosis secondary to SSc. Consent was obtained from the patient to present this case study.

CASE PRESENTATION

A 42-year-old woman with anti-Scl-70 antibody-positive limited cutaneous SSc presented to our plastic surgery outpatient clinic. She had evidence of significant oro-facial fibrosis with clear restriction in mouth opening and inability to achieve oral competence. In particular, there was marked retraction of the lower lip with gingival display, leading to symptoms of dry mouth (xerostomia) and salivary incontinence (figure 1). She reported that limitations of mouth opening and mastication directly impacted her nutritional status, activities of daily living and quality of life. She had a background of stable pulmonary fibrosis that did not require immunosuppressive therapy and had a history of renal cell carcinoma with previous nephrectomy. In order to improve the functional and aesthetic sequelae of oro-facial fibrosis, the patient underwent a series of surgical procedures over a 12-year period, with a goal to increase mouth opening, achieve oral competence and address soft tissue fibrosis.

TREATMENT

To lengthen the lower lip and facilitate mouth closure, a full-thickness skin graft was harvested from the abdomen and inserted into the lower lip mucosa following intraoral contracture release. Scar releases were performed and reconstructed with free mucosal grafts harvested from the buccal and abdominal mucosa. Subsequent scar releases used Z-plasties and V-Y mucosal lip advancement flaps. Further support for the lower lip was provided through static suspension techniques. Mitek bone anchors and then bilateral tensor fascia lata facial slings were used to resuspend the mentalis and depressor labii oris. A mental silicone implant was used to augment the chin and facilitate volume suspension.

To reverse fibrosis and restore soft tissue volume, multiple autologous fat grafting (AFG) procedures were performed simultaneously or in between the aforementioned surgical procedures at monthly intervals of approximately 6–12. The technique described by Coleman was used.4 Fat was harvested from the abdomen using a blunt cannula connected to a 10 mL Luer Lock syringe. The lipoaspirate was centrifuged at 3000 rpm for 3 min, the oil and blood were discarded, and the remaining portion containing fat was injected using a cannula connected to 1 mL syringes. Fat grafts were injected...
Novel treatment (new drug/intervention; established drug/procedure in new situation)

Figure 1 A female patient aged 49 years presenting features of oro-facial fibrosis secondary to systemic sclerosis, including perioral skin furrowing, thinning of the lips and restriction in mouth opening and closure (microstomia), causing lower lip retraction and gingival display. As a result of severe microstomia, she reported symptoms of dry mouth, salivary incontinence and difficulty in mastication that impacted her nutrition and activities of daily living.

in multiple passages to the upper and lower lips, nasolabial folds, cheeks and chin. Table 1 presents all the surgical procedures in chronological order.

OUTCOME AND FOLLOW-UP
Postoperatively, after each procedure the patient was reviewed in the plastics dressing clinic at 7 days and in the outpatient department at 6 weeks to 3 months. Full active mouth closure and oral competence was achieved (figure 2), with significant improvement in lower lip ptosis at rest (figure 3). At maximal mouth opening, an increase of approximately 5 mm was observed. The patient reported an improvement in mastication and easier oral access for dental care.

DISCUSSION
Oro-facial fibrosis is a cause of significant concern in patients with SSc, yet there are no established treatment pathways. Scattered reports of improvement derived from specialised exercise programmes to stretch the perioral soft tissues tend to be short-lived and are unlikely to be offered in routine physiotherapy regimes. Furthermore, poor patient compliance and continued disease progression contribute to the lack of longevity of perceived benefits.

Surgical correction of microstomia in the context of postsurgical or traumatic sequelae has been well documented and

Figure 2 A female patient aged 54 years at the end of a 12-year reconstructive journey to treat microstomia secondary to systemic sclerosis, showing significant improvement in lower lip ptosis at rest. Procedures included intraoral mucosal grafts, multiple scar releases, mucosal advancement flaps and facial suspension surgery, supplemented with multiple autologous fat grafting procedures.

Table 1 Summary of surgical procedures and fat graft volumes

| Date of surgery | Surgical procedure | Total volume of fat transferred |
|-----------------|---------------------|--------------------------------|
| 20/12/2007      | Full-thickness skin graft to lower lip and autologous fat transfer | 5 mL |
| 13/03/2008      | Autologous fat transfer to both lips | 9.7 mL (5.7 mL to upper lip, 4 mL to lower lip) |
| 26/06/2008      | Autologous fat transfer to both lips and cheeks | 11.5 mL (4.5 mL to upper lip, 3 mL to lower lip, 1 mL to chin, 1.5 mL to left cheek, 1.5 mL to right cheek) |
| 12/02/2009      | Autologous fat transfer to both lips and cheeks | 11.5 mL (3.5 mL to upper lip, 3.5 mL to lower lip, 0.25 mL to right nasolabial fold, 0.25 mL to left nasolabial fold, 2 mL to right cheek, 2 mL to left cheek) |
| 04/06/2009      | Free buccal mucosal graft to lower lip and autologous fat transfer to upper lip and cheeks | 6.9 mL (1.8 mL to upper lip, 2.4 mL to right cheek, 2.7 mL to left cheek) |
| 02/10/2010      | Free abdominal mucosal graft with V-Y mucosal advancement flap to lower lip and autologous fat transfer to lips and chin | 10.25 mL (5.5 mL to upper lip, 1.75 mL to lower lip, 3 mL to chin) |
| 16/04/2014      | Facial suspension with Mitek to chin and lower lip | NA |
| 04/06/2014      | Autologous fat transfer to face | 11 mL (4 mL to upper lip, 2 mL to lower lip, 1 mL to philtrum, 4 mL to chin) |
| 14/05/2015      | Autologous fat transfer to face | 15.5 mL (2 mL to upper lip, 3 mL to lower lip, 1 mL to chin, 1 mL to right and left nasolabial folds, 3 mL to right and left cheeks, 1.5 mL to nose) |
| 20/04/2016      | Tensor fascia lata graft to chin and autologous fat transfer to face | 21 mL |
| 29/06/2016      | Autologous fat transfer to face | Volume not specified |
| 21/12/2016      | Mental silicone implant, Z-plasty to lip and autologous fat transfer to face | 7.5 mL (1.5 mL to upper lip, 3 mL to each nasolabial fold) |
| 18/10/2017      | Z-plasties and V-Y advancement flap to lip and autologous fat transfer to face | 4 mL (1 mL to upper lip, 1 mL to lower lip, 0.25 mL to philtrum, 0.25 mL to perioral ridges, 0.5 mL to each nasolabial fold, 0.25 mL to each nasal ala) |
| 16/01/2019      | V-Y lip advancement, replacement of mental implant and autologous fat transfer to face | 2 mL |
Novel treatment (new drug/intervention; established drug/procedure in new situation)

A female patient aged 54 years at the end of a 12-year reconstructive journey to treat microstomia secondary to systemic sclerosis, demonstrating full active mouth closure which was previously not possible. Procedures included intraoral mucosal grafts, multiple scar releases, mucosal advancement flaps and facial suspension surgery, supplemented with multiple autologous fat grafting procedures.

Figure 3  A female patient aged 54 years at the end of a 12-year reconstructive journey to treat microstomia secondary to systemic sclerosis, demonstrating full active mouth closure which was previously not possible. Procedures included intraoral mucosal grafts, multiple scar releases, mucosal advancement flaps and facial suspension surgery, supplemented with multiple autologous fat grafting procedures.

tends to be reserved to those with severe functional restrictions. Commissuroplasties increase the horizontal length of oral aperture and are combined with local techniques to reconstruct the oral lining and to minimise postoperative contracture. Suggested techniques include Y-V mucosal advancement flaps and rhomboid flaps, which have been found to be superior to full-thickness or split-thickness skin grafts.3–9 Adjunctive postoperative splinting is advocated, but the risk of relapse remains a challenge, and often patients require multiple scar revisions.10 Adaptation of these techniques for SSc has been reported, but risk of relapse is further compounded by fibrotic progression of the disease.11 Moreover, there is a higher risk of poor wound healing and postoperative infection in these patients. Together with the creation of extensive and discernible scarring, surgical correction does not present a favourable method of choice.

Several non-surgical procedures have been suggested to confer benefit through the modulation of collagen architecture or metabolism. Methods include intense pulsed light therapy,12 ultraviolet A1 phototherapy13 and pulsed carbon dioxide laser therapy.14 Hyaluronidase injections are also proposed to have antifibrotic effects through hydrolysis of bonds within hyaluronic acid (HA), a component of the extracellular matrix, which has increased cutaneous deposition in patients with SSc.15 Despite their suggested improvement for microstomia, these have not been adopted into routine care, with limited reports advocating their use.

AFG is an established minimally invasive surgical procedure that is being adapted to a growing number of indications that expand beyond volume restoration. The lipid grafts contain a heterogeneous cell population including adipocytes, adipose-derived stem cells (ADSCs), endothelial cells, pericytes, smooth muscle cells and immune cells.16 Together, these cells prevent fibroblast to myofibroblast conversion and promote angiogenesis, anti-inflammatory and immunomodulatory effects.17–18 It is increasingly recognised that antifibrotic effects are mediated by ADSCs, attributed to its secretion of antifibrotic factors, matrix metalloproteinases and modulation of profibrotic factors. AFG is finding a role in the treatment of burns, radiation-induced dermatitis, hypertrophic scarring and scleroderma19 20 and was the basis by which our patient’s microstomia was addressed. We have found that injection of fat to the upper and lower lips, nasolabial folds and chin in consecutive procedures has improved mouth opening in our patient, with stable results at 1 year. This is reflected in the literature where treatment of orofacial fibrosis secondary to SSc with AFG significantly improved mouth opening with corresponding decrease in the Mouth Handicap in Systemic Sclerosis Scale, a validated scale assessing mouth disability including mouth opening, dental issues, mouth dryness and aesthetic components.3 21–22 Del Papa et al.18 did not find a significant change in mouth opening from baseline at 1 month assessment, but a statistically significant increase was observed at 3 months after procedure, and this correlated to a significant decrease in skin hardness, assessed using a durometer, and an increase in labial microvascularity, observed using videocapillaroscopy. Our group reviewed a cohort of 62 patients with SSc treated with perioral AFG performed by the senior author and found a significant improvement in mouth function that was maintained 100% at 6 months, 94% at 7–12 months and 66% at 1-year follow-up.17 Other studies have also reported significant improvement in mouth function up to 1 year postoperatively21 22; however, further long-term studies are required to understand sustainability of results. Our cohort also demonstrated a cumulative benefit with sequential procedures,17 postulated to be a result of neovascularisation of capillaries in the fibrotic dermis, allowing for better survival of sequential fat grafts.18 This was explored by Denadai et al.24 who compared outcomes of initial fat grafting procedures with sequential procedures and found significantly better fat retention in the latter.

Besides functional improvement, studies have reported high patient satisfaction and improved subjective aesthetic evaluation, mostly using preoperative and postoperative photographs on a global scale.18 21–23 Volumetric analyses using three-dimensional photography found a reduction in perioral wrinkling and appearance of ridges with augmentation in lip volumes and improvement in lip ratios, presenting a plausible explanation for the improvement in aesthetic evaluation.17 Fat retention rates, however, remain unpredictable and are a challenge, with no evidence to support superiority in the mode of fat processing. This is demonstrated in the disparate methods used by the authors, including Coleman technique,17 18 gravity separation method3 21 microfat23 and ADSCs suspended in HA gel.22 The lip subunit exhibited the greatest fat resorption17; however, maintenance of improved mouth opening and function is reported despite complete fat resorption.21

The relationship of autologous fat grafting in autoimmune diseases such as SSc is yet to be established. As immune activation is key in the pathophysiology of fibrosis, it can feasibly influence surgical outcomes and determine optimal timing of surgical interventions. Hemifacial atrophy, a variant of localised scleroderma, was found to be a negative predictor of fat retention due to suboptimal recipient bed and the progressive nature of disease21; however, fat grafting in the active state of disease has been suggested to inhibit or slow disease progression.28 This may advocate for earlier intervention in patients exhibiting features of oro-facial fibrosis before it reaches a state of functional impairment. This is further supported by independent findings of superior fat retention rates associated with younger age at surgery.23 Concurrent use of immunosuppressants was found not to affect surgical outcomes.17

In addition to AFG, numerous surgical techniques were adapted to address our patient’s microcheilia and marked lower lip retraction, which was compounded by a contracted
previous full-thickness skin graft to the lower lip mucosa. Scar revisions with mucosal full-thickness skin grafts and Z-plasties were combined with V-Y mucosal lip advancement flaps, a local technique that uses intraoral incisions to manoeuvre tissues and augment the thickness and projection of the lips, used in the context of trauma, cleft deformity and aesthetic surgery. Mucosal grafts are also used for oral submucous fibrosis, a chronic and insidious scarring disease limited to oral tissue, often termed ‘idiopathic scleroderma of the mouth’, characterised by mucosal insidious scarring disease limited to oral tissue, often termed ‘idiopathic scleroderma of the mouth’, characterised by mucosal and fibrous bands leading to trismus. The ‘idiopathic scleroderma of the mouth’, characterised by mucosal insidious scarring disease limited to oral tissue, often termed ‘idiopathic scleroderma of the mouth’, characterised by mucosal

Learning points

- Surgical correction of oro-facial fibrosis in systemic sclerosis (SSc) requires consideration of the progressive nature of the disease, which can complicate long-term outcomes.
- The regenerative capacity of adipose-derived stem cells in fat grafts can be used to counteract fibrosis and forms the basis for surgical reconstruction.
- Autologous fat grafting provides a novel treatment modality for oro-facial skin fibrosis, previously considered a non-treatable disease manifestation of SSc.
- Surgical techniques can be adapted from trauma, facial reanimation and cosmetic surgery to address the functional and aesthetic concerns of patients with SSc.

Contributors All authors have seen and approved the final manuscript. All authors have made substantial contributions to all of the following: (1) conception and design of the study (MG, PEMB), or acquisition of data (FHKL, IV); (2) drafting the article or revising it critically for important intellectual content (FHKL, MG, IV); (3) final approval of the version to be submitted (FHKL, MG, IV, PEMB).

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Faith Hyun Kyung Jeon http://orcid.org/0000-0002-7166-5611

REFERENCES

1 Denton CP, Black CM, Abraham DJ. Mechanisms and consequences of fibrosis in systemic sclerosis. Nat Clin Pract Rheumatol 2006;2:134–44.
2 Veale B, Jablonski R, Fitch T, et al. Orofacial manifestations of systemic sclerosis. Br Dent J 2016;221:305–10.
3 Blezius O, D’Andrea F, Nicolletti GF, et al. Effects of fat grafting containing stem cells in Microstomia and Microcheilia derived from systemic sclerosis. Aesthetic Plast Surg 2017;41:839–44.
4 Coleman SR. Structural fat grafting: more than a permanent filler. Plast Reconstr Surg 2006;118:1085–20.
5 Yuen HK, Marlow NM, Reed SG, et al. Effect of orofacial exercises on oral aperture in adults with systemic sclerosis. Disabil Rehabil 2012;34:84–9.
6 Converse JM. Techniques for the repair of defects of the lips and cheeks. In: Converse JM, ed. Reconstructive plastic surgery. 2nd edn. Philadelphia: Saunders, 1977;3: 1544–94.
7 Kazanjian VH, Roopenian A. The treatment of lip deformities resulting from electric burns. Am J Surg 1954;88:884–90.
8 Zak M, Means O, Cason B, et al. Management of severe burn Microstomia. Eplasty 2016;16:e45.
9 Zweifel CJ, Guggenheim M, Jandali AR, et al. Management of microstomia in adult burn patients revisited. J Plast Reconstr Aesthet Surg 2010;63:e151–7.
10 Bedard J-F, Thonghammachat S, Toljanic JA. Adjunctive commissure splint therapy: a revised approach. J Prosthet Dent 2003;89:408–11.
11 Koymen R, Gulse A, Karacayli U, et al. Treatment of microstomia with commissuroplasties and semidynamic acrylic splints. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:503–7.
12 Comstedt LR, Svensson A, Trolius A. Improvement of microstomia in scleroderma after intense pulsed light: a case series of four patients. J Cosmet Laser Ther 2012;14:102–6.
13 Tewari A, Garibaldinos T, Lai-Cheong J, et al. Successful treatment of microstomia with UVA1 photostimulation in systemic sclerosis. Photodermatol Photoinmunol Photomed 2011;27:113–4.
14 Benniani I, Lopez R, Bonnet D, et al. Improvement of Microstomia in scleroderma after carbon dioxide laser treatment. Case Rep Dermatol 2016;8:142–50.
15 Melvin OG, Hunt KM, Jacobson ES. Hyalurondine treatment of Scleroderma-Induced Microstoma. JAMA Dermatol 2019;155:857–9.
16 Simonacci F, Bertolzi N, Griece MP, et al. Procedure, applications, and outcomes of autologous fat grafting. Ann Med Surg 2017;20:49–60.
17 Almodair A, Griffin M, Ryan CM, et al. Stem cell enriched lipotransfer reverses the effects of fibrosis in systemic sclerosis. Plast Surg 2019;140:50e–61.
18 Del Papa N, Caviggioli F, Sambataro D, et al. Autologous fat grafting in the treatment of fibrotic perioral changes in patients with systemic sclerosis. Cell Transplant 2015;24:63–72.
19 Griffith M, Ryan CM, Pathan Q, et al. Characteristics of human adipose derived stem cells in scleroderma in comparison to sex and age matched normal controls: implications for regenerative medicine. Stem Cell Res Ther 2017;8:23.
20 Strong AL, Rubin JP, Kozlov JH, et al. Fat grafting for the treatment of scleroderma. Plast Reconstr Surg 2019;144:1498–507.
21 Ghetsi M, Almadzhadeh A, Nobari N, et al. Autologous fat grafting in the treatment of facial scleroderma. Dermatol Res Pract 2018;2018:6568016.
22 Onesti MG, Fioramponti P, Carella S, et al. Improvement of mouth functional disability in systemic sclerosis patients over one year in a trial of fat transplantation versus adipose-derived stromal cells. Stem Cells Int 2016;2016:2416192.
23 Saurerau N, Daumas A, Truillet R, et al. Efficacy of autologous Microfat graft on facial handicap in systemic sclerosis patients. Plast Reconstr Surg Glob Open 2016;4:e660.
24 Denadai R, Raposo-Amaral CA, da Silva SA, et al. Complementary fat graft retention rates are superior to initial rates in craniofacial contour reconstruction. Plast Reconstr Surg 2019;143:823–35.
25 Denadai R, Raposo-Amaral CA, Pinho AS, et al. Predictors of autologous free fat graft retention in the management of craniofacial contour deformities. Plast Reconstr Surg 2017;140:50e–61.
26 Hurstad JP, Shiriha DA, Kortesi BG. Successful treatment of Parry-Romberg syndrome with autologous fat grafting: 14-year follow-up and review. Ann Plast Surg 2011;67:423–5.
27 Samian MR. Lip augmentation for correction of thin lips. Plast Reconstr Surg 1993;91:162–6.
28 Jacomo AA, Quatela VC. Quantitative analysis of lip appearance after V-Y lip augmentation. Arch Facial Plast Surg 2004;6:172–7.
29 Mehrotra D, Pradhan R, Gupta S. Retrospective comparison of surgical treatment modalities in 100 patients with oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:61–10.
30 Liu YM, Serras DA. Static procedures for the management of the midface and lower face. Facial Plast Surg 2008;24:211–5.

Novel treatment (new drug/intervention; established drug/procedure in new situation)
