

BMJ Case Reports

TITLE OF CASE

Oro-facial Fibrosis in Systemic Sclerosis: A Reconstructive Journey

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 which 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 female 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 anti-fibrotic effect of autologous fat grafting served as the basis upon which a series of surgical procedures were performed, to achieve the functional and aesthetic improvement. Autologous fat grafting provides a novel treatment modality for oro-facial 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, immunologic and fibrotic pathological components.[1] Cutaneous fibrosis is a near universal feature in SSc patients, and involvement of the face and perioral region 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 facies', 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.[2-3] 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 systemic sclerosis. Consent was obtained from the patient to present this case study.

CASE PRESENTATION

A 42-year old female patient with Anti-Scl-70 antibody positive limited cutaneous systemic sclerosis presented to our Plastic Surgery outpatients 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 the soft tissue fibrosis.

TREATMENT *If relevant*

To lengthen the lower lip and facilitate mouth closure, a full thickness skin graft was harvested from the abdomen and inset into the lower lip mucosa following intra-oral contracture release. Scar releases were performed and reconstructed with free mucosal grafts harvested from the buccal and later abdominal mucosa. Subsequent scar releases used z-plasties and V-Y lip mucosal lip advancement flaps. Further support for the lower lip was provided through static suspension techniques. Mitek bone anchors and later 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 in volume suspension.

To reverse fibrosis and restore soft tissue volume, multiple autologous fat grafting procedures were performed simultaneously or in between the aforementioned surgical procedures at approximately six to twelve monthly intervals. The technique described by Coleman was used.[4] Fat was harvested from the abdomen using a blunt cannula connected to a 10ml Luer Lock syringe. The lipoaspirate was centrifuged at 3000 rpm for 3 minutes, the oil and blood discarded, and the remaining portion containing fat was injected using a cannula connected to 1ml syringes. Fat grafts were injected in multiple passages to the upper and lower lip, nasolabial folds, cheeks and chin. Table 1 presents all the surgical procedures in chronological order.

| Date of Surgery | Surgical Procedure | Total volume of fat transferred |
|------------------------|--|---|
| 20/12/2007 | Full thickness skin graft to lower lip & autologous fat transfer | 5ml |
| 13/03/2008 | Autologous fat transfer to both lips | 9.7ml (5.7ml upper lip, 4ml lower lip) |
| 26/06/2008 | Autologous fat transfer to both lips and cheeks | 11ml (4.5ml upper lip, 3ml lower lip, 1ml to chin, 1.5ml L cheek, 1.5ml R cheek) |
| 12/02/2009 | Autologous fat transfer to both lips and cheeks | 11.5ml (3.5ml upper lip, 3.5ml lower lip, 0.25ml R nasolabial fold, 0.25ml L nasolabial fold, 2ml R cheek, 2ml L cheek) |
| 04/06/2009 | Free buccal mucosal graft to lower lip & autologous fat transfer to upper lip and cheeks | 6.9ml (1.8ml upper lip, 2.4ml R cheek, 2.7ml L cheek) |
| 02/10/2010 | Free abdominal mucosal graft with V-Y mucosal advancement flap to lower lip & autologous fat transfer to lips and chin | 10.25ml (5.5ml upper lip, 1.75ml lower lip, 3ml chin) |
| 16/04/2014 | Facial suspension with Mitek to chin and lower lip | NA |
| 04/06/2014 | Autologous fat transfer to face | 11ml (4ml upper lip, 2ml lower lip, 1ml philtrum, 4ml chin) |
| 14/05/2015 | Autologous fat transfer to face | 15.5ml (2ml upper lip, 3ml lower lip, 1ml chin, 1ml R and L nasolabial folds, 3ml R and L cheek, 1.5ml nose) |
| 20/04/2016 | Tensor fascia lata graft to chin and autologous fat transfer to face | 21mls |
| 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 | 7.5ml (1.5ml upper lip, 3ml to each nasolabial fold) |
| 18/10/2017 | Z-plasties and V-Y advancement flap to lip and autologous fat transfer to face | 4ml (1ml upper lip, 1ml lower lip, 0.25ml philtrum, 0.25ml to perioral ridges, 0.5ml to each nasolabial fold, 0.25ml to each ala) |
| 16/01/2019 | V-Y lip advancement, replacement of mental implant and autologous fat transfer to face | 2ml |

Table 1. Summary of surgical procedures and fat graft volumes

OUTCOME AND FOLLOW-UP

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

DISCUSSION *Include a very brief review of similar published cases*

Oro-facial fibrosis is a cause of significant concern in patients with systemic sclerosis, yet there are no established treatment pathways.[3] Scattered reports of improvement derived from specialised exercise programs to stretch the perioral soft tissues tend to be short lived, and unlikely to be offered in routine physiotherapy regimes. Furthermore poor patient compliance and continued disease progression contribute to the lack of longevity of the perceived benefits.[5]

Surgical correction of microstomia in the context of post-surgical or traumatic sequelae has been well documented and tends to be reserved to those with severe functional restrictions. Commissuroplasties increase the horizontal length of the oral aperture, and are combined with local techniques to reconstruct the oral lining and minimize post-operative contracture. Suggested techniques include Y-V mucosal advancement flaps and rhomboid flaps, which have been found to be superior to full or split thickness skin grafts.[6-9] Adjunctive post-operative splinting is advocated, but the risk of relapse remains a challenge, and often patients require multiple scar revisions.[10] Adaptation of these techniques for systemic sclerosis 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 post-operative infection in these patients. Together with the creation of extensive and discernable 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 (IPL) therapy,[12] ultraviolet A1 (UVA1) phototherapy [13] and pulsed carbon dioxide laser therapy.[14] Hyaluronidase injections are also proposed to have antifibrotic effects through hydrolysis of bonds within hyaluronic acid, a component of the extracellular matrix, which have increased cutaneous deposition in SSc patients.[15] Despite their suggested improvement for microstomia these have not been adopted into routine care, with limited reports advocating their use.

Autologous fat grafting (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 angiogenic, 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 treatment of burns, radiation-induced dermatitis, hypertrophic scarring, and in scleroderma,[19-20] 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 have improved mouth opening in our patient, with stable results at 1 year. This is reflected in the literature where treatment of oro-facial fibrosis secondary to SSc with AFG significantly improved mouth opening with corresponding decrease in the Mouth Handicap in Systemic Sclerosis Scale (MHSS), a validated scale assessing mouth disability including mouth opening, dental issues, mouth dryness and aesthetic components.[3, 21-23] 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 post-procedure, and this correlated to a significant decrease in skin hardness, assessed using a durometer, and increase in labial microvasculature, as observed using videocapillaroscopy. Our group reviewed a cohort of 62 SSc patients treated with peri-oral AFG performed by the senior author, and found a significant improvement in mouth function that was maintained 100% at 6 months, 94% at 7 to 12 months and 66% at 1 year follow-up.[17] Other studies have also reported significant improvement in mouth function up to 1 year post-op,[3, 21-22] 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 compared to sequential procedures and found significantly better fat retention in the latter.

Besides functional improvement, studies have reported a high patient satisfaction and improved subjective aesthetic evaluation, mostly using pre- and post-operative 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 a challenge, with no evidence to support superiority in mode of fat processing. This is demonstrated in the disparate methods used by the authors, including Coleman technique,[17-18] gravity separation method,[3,21] microfat [23] and ADSCs suspended in HA gel.[22] The lip subunit exhibited the greatest fat resorption,[17] 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 systemic sclerosis 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 the suboptimal recipient bed and progressive nature of disease,[25] however fat grafting in the active state of disease has been suggested to inhibit or slow disease progression.[26] 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.[25] Concurrent use of immunosuppressants was found not to affect surgical outcomes.[17]

In addition to AFG, numerous surgical techniques were adapted to address the patient's microchelia 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 utilizes 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.[27-28] 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 mucositis and development of fibrous bands leading to trismus.[29] The multitude of surgical techniques described to treat this disease attests to the current lack of effective treatment modality. Static facial suspension techniques were employed to elevate the lower lip and chin and improve oral competence, demonstrating how fibrotic and atrophic facial soft tissues adherent to underlying structures and restricting facial expression in SSc patients draw parallels to that of facial paralysis.[30] Finally the mental implant facilitated in volume suspension of the lower lip.

LEARNING POINTS/TAKE HOME MESSAGES 3-5 *bullet points*

- Surgical correction of oro-facial fibrosis in systemic sclerosis 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 utilised to counteract fibrosis and form the basis of surgical reconstruction.
- Autologous fat grafting provides a novel treatment modality for oro-facial skin fibrosis, previously considered a non-treatable disease manifestation of systemic sclerosis.
- Surgical techniques can be adapted from trauma, facial reanimation and cosmetic surgery to address SSc patients' functional and aesthetic concerns.

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FIGURE/VIDEO CAPTIONS

Figure 1. Female patient aged 49 presenting features of oro-facial fibrosis secondary to systemic sclerosis, including peri-oral 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 the severe microstomia she reported symptoms of dry mouth, salivary incontinence, and difficulty in mastication that has impacted her nutrition and activities of daily living.

Figure 2. Female patient aged 54 at the end of a 12-year reconstructive journey to treat microstomia secondary to systemic sclerosis, showing significant improvement of lower lip ptosis at rest (**Figure 2a**) and full active mouth closure which was previously not possible (**Figure 2b**). Procedures included intra-oral mucosal grafts, multiple scar releases, mucosal advancement flaps and facial suspension surgery, supplemented with multiple autologous fat grafting procedures.

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