CASE REPORT

A neoteric multidrug combination: novel approach to limited cutaneous systemic scleroderma involving the face

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SUMMARY

Limited cutaneous scleroderma is a subtype of scleroderma limited to the skin of the face, hands, feet and forearms. We present a case of a 45-year-old woman affected by limited cutaneous systemic scleroderma involving the orofacial region and causing restricted mouth opening. The patient showed noteworthy improvement of the skin lesion by use of a combination of intralesional corticosteroid with hyaluronidase and various multiantioxidants, resulting in amelioration of her mouth opening problem. The patient gave her full informed written consent to this report being published.

BACKGROUND

Systemic scleroderma is the most severe form of the disease and may ultimately lead to fibrosis of the skin and internal organs, such as the lungs, kidneys, heart and gastrointestinal tract. The systemic form may also be subdivided into limited and diffuse types. The limited form is usually manifested as skin thickening on the hands, which extends to the face and distal ends, under the knees and elbows. The involvement of internal organs is slower and less intense than that of the diffuse form, with a high frequency of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia (CREST) syndrome.¹

In most cases of limited cutaneous scleroderma, the initial complaint is Raynaud's phenomenon, whereas patients with diffuse cutaneous scleroderma often initially present with generalised swelling of the hands, skin thickening or arthralgias with or without Raynaud's phenomenon.²

Vascular injury, fibrosis and immune activation are the primary pathogenic factors responsible for the various clinical manifestations of systemic scleroderma. The fibrosis in systemic scleroderma is caused by increased production of collagen in subcutaneous tissue. The key cellular moderator of fibrosis is collagen-producing myofibroblasts.³

Usually, the diagnosis of systemic scleroderma is clinical. Effective treatment for scleroderma still remains inconclusive. Until now, no drug has effectively stopped the disease progression. Management of scleroderma is often challenging. The treatment of scleroderma depends on the severity, progression and functional deformity.

Treatment of scleroderma can be simply classified into topical and systemic therapy. Topical therapy consists of use of moderate to high-potency topical

corticosteroids, and in systemic therapy, systemic corticosteroids (0.5–1.0 mg/kg) are used daily for 3 months.

Treatment of systemic scleroderma is guided by cutaneous and organ-specific involvement. Corticosteroids are not used in the treatment of gastrointestinal and vascular manifestations of systemic scleroderma, including Raynaud's phenomenon and digital ulcers.⁴

Only a few articles describe the use of intralesional corticosteroids for limited cutaneous systemic scleroderma involving the orofacial region but, until now, there has been no literature on the use of a combination of intralesional corticosteroids and multiantioxidants for limited cutaneous systemic scleroderma.

Although many therapeutic approaches have been reported, there are no universally effective treatments for limited cutaneous systemic scleroderma.

In this case, the patient with limited cutaneous systemic scleroderma involving the orofacial region causing restricted mouth opening was successfully treated with an intralesional injection of Decamycin (dexamethasone sodium phosphate 4 mg) and Hynidase (hyaluronidase) for 5 months. The patient was also instructed to take oral multi-antioxidant capsules twice daily for 5 months.

CASE PRESENTATION

A 45-year-old woman reported to the dental clinic, with a 1-year history of restricted mouth opening. During anamnesis, the patient gave no history of drugs or chemicals, but she did report a positive history for Raynaud's phenomenon undergone 4 years prior. She had been diagnosed with systemic scleroderma by a rheumatologist. Since then, she had been managed with systemic corticosteroids, d-penicillamine and pantaprazole, however, she discontinued the medication in less than a year. No significant family history of connective tissue disorders was found. Dental history revealed that the patient had a history of extraction of right and left lower mandibular first molars at a private dental hospital 10 months earlier.

After extraction, her mouth opening had progressively decreased; within 6 months, she presented to our dental clinic with difficulty in mouth opening and also wanted to replace missing teeth in her lower jaw.

Extraoral examination revealed a loss of contour of facial skin (stiffening of facial skin), perioral skin

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puckering and incompetent lips with retracted mandible due to facial skin sclerosis. She was also noted to have a mask-like facies, with dense perioral fibrosis producing a fish-mouth appearance (figure 1). Her mouth opening was 25 mm.

Intraoral examination revealed multiple missing teeth in the maxillary and mandibular arch (figure 2) with a narrow maxillary palatal arch. Stiffening of right and left buccal mucosa, and of lower labial mucosa, was present. From the overall clinical features, we diagnosis our patient as having limited cutaneous systemic scleroderma involving the orofacial region.

INVESTIGATIONS

Laboratory investigations, including a complete haemogram, routine urine test, and renal and liver function tests, were normal. Panoramic radiographic examination showed widening of the periodontal ligament space in relation to 11, 12 and 13 (figure 3). Hand wrist radiograph showed generalised osteolysis (bone resorption) of distal phalanges (figure 4). On immunological studies, the patient was positive for antinuclear antibodies and anti-Scl-70 antibodies.

A punch biopsy was taken from the left buccal mucosa under local anaesthetic infiltration, and histopathological examination revealed acanthosis of the surface epithelium and subepithelial area. Thickened collagen bundles separated by oedema fluid were consistent with the diagnosis of localised scleroderma (figure 5). Finally, considering all the above features, we concluded the final diagnosis to be systemic scleroderma.

DIFFERENTIAL DIAGNOSIS

Lichen sclerosus, oral submucous fibrosis (OSF), rheumatoid arthritis and eosinophilic fasciitis may be considered.

TREATMENT

We used intralesional decamycin (dexamethasone sodium phosphate 4 mg) injection with hyaluronidase (Hynidase 1500 IU) and a multiantioxidant capsule (Riconia-LP) taken orally twice daily for 5 months. For delivering the intralesional injection, we used disposable 1 mL 30 gauge insulin syringes.

The first visit of treatment (first 2 months) (figure 6): After locally anaesthetising the area (buccal mucosa, lower labial mucosa), the Decamycin 1 mL intralesional corticosteroid was mixed with Hynidase and injected with the insulin syringe at multiple sites biweekly for 2 months. The oral multiantioxidant capsule (Riconia-LP) was taken twice daily for 2 months.

Second visit of treatment (next 10 weeks) (figure 7): After locally anaesthetising the area (perioral skin region), the Decamycin 1 mL intralesional corticosteroid was mixed with

Hynidase and injected with the insulin syringe at multiple sites once a week for 2 months. The oral multiantioxidant capsule (Riconia-LP) continued to be taken twice daily for 2 months.

Third visit of treatment (past 2 weeks) (figure 8A, B): During the visit patient showed a drastic change in mouth opening and the perioral skin puckering had completely disappeared (figure 8A). The mouth opening was 38 mm (figure 8B). The patient was started with 0.5 mg Dexona (dexamethasone) tablets and multiantioxidant capsules (Riconia-LP) twice daily orally for 10 days. The dexamethasone dosage (Dexona tablet) was tapered and stopped over the next 4 days.

Final visit of treatment: During this visit, prosthetic rehabilitation was initiated and the missing teeth in upper and lower jaw were replaced with a flexible removable partial denture.

OUTCOME AND FOLLOW-UP

During the third visit, the patient was happy about the drastic improvement in mouth opening, but she had developed gastritis due to the long-term Decamycin administration. So it was decided to lower the dosage of corticosteroid to 0.5 mg Dexona tablets twice daily and also advised the patient to take 20 mg pantaprazole capsules twice daily before food for 3 weeks. In the meantime, prosthetic rehabilitation was initiated. The missing teeth of the maxillary and mandibular arch were replaced with a flexible removable partial denture. After 3 weeks, the gastritis decreased completely. After 10-month follow-up, there was no sign of clinical relapse and the patient showed good improvement of the orofacial skin lesion (figure 9).

DISCUSSION

Scleroderma, or progressive systemic sclerosis (SS), an autoimmune rheumatic condition affecting the connective tissues, has a profound impact on oral health. Common orofacial findings include xerostomia, gastro-oesophageal reflux disease and limited mouth opening. SS is generally subdivided into limited and diffuse cutaneous subtypes. Patients with limited cutaneous SS typically have skin sclerosis that is restricted to the hands, and sometimes to the face and neck. The onset of the subtype SS is usually insidious; its most dramatic effects are cutaneous changes. Progressive tissue fibrosis ensues as normal types I and III collagen are deposited in extraordinary amounts, likely because of immunologically overactivated fibroblasts in various locations.⁵

Clinically, systemic scleroderma is divided into localised scleroderma and systemic scleroderma. There are two major types of localised scleroderma: linear scleroderma and morphoea. Linear scleroderma is characterised by a band of sclerotic

Figure 1 Extraoral examination reveals a loss of contour of facial skin with perioral skin puckering.

Figure 2 Intraoral examination reveals multiple missing teeth in the maxillary and mandibular arch.

Figure 3 Panoramic radiographic examination showed widening of the periodontal ligament space in relation to 11, 12 and 13.

induration and hyperpigmentation occurring on a limb or the side of the face. This form of the disease may run along the entire length of the extremity, involving underlying muscle, bones and joints. When the disease crosses a joint, it may cause limitation of motion along with growth abnormalities. The lesion of linear localised scleroderma of the head and face is called en coup de sabre, and these lesions may result in hemiatrophy of the face. Morphoea is characterised by small violaceous skin patches or larger skin patches that indurate and cause loss of hair and sweat gland function.⁶

Parry-Romberg syndrome has been linked with many systemic manifestations, including dermatological, neurological, ophthalmological, cardiac, rheumatological, infectious, endocrine and maxillofacial fields.⁷

Panniculitis of the face is a rare manifestation of connective tissue disorder such as localised scleroderma. The lipoatrophy in the course of connective tissue diseases is usually preceded by the inflammation, painful phase and may cause a deep contour loss of facial tissues.⁸

Figure 4 Hand wrist radiograph shows generalised osteolysis (bone resorption) of the distal phalanges.

Figure 5 Histopathological examination revealed acanthosis of the surface epithelium and subepithelial area.

Recent research suggests that reactive oxygen species (ROS) represent a hallmark of the pathogenesis of systemic scleroderma, both at the fibroblast and at the endothelial cell levels, and the cellular redox state may play a significant role in the progression of scleroderma fibrosis.⁹

The free radical release process is as important in the pathogenesis of morphoea as it is in SS.¹⁰

In practice, the diagnosis of scleroderma is clinical and made by the presence of Raynaud's phenomenon, typical skin thickening and visceral involvement. Laboratory investigations are supportive.¹¹

Autoantibodies are seen in approximately 95% of patients with scleroderma and more than 30 specificities have been described. Most of these can be detected with screening anti-nuclear antibody (ANA) using indirect immunofluorescence. The antigen specificity may be detected with enzyme immunoassay or multiplexed bead assay. Recently, antiplatelet derived growth factor receptor antibodies were described in SS.¹²

Scleroderma is a multisystem disease with variable expression; thus any treatment plan must be holistic yet at the same time focus on the dominant organ disease. The goal of therapy is to improve quality of life by minimising specific organ involvement and minimising subsequent life threatening disease. At the same time, the many factors that alter daily function need to be

Figure 6 Intralesional injection (in lower labial mucosa) at first visit.

Figure 7 Intralesional injection (in perioral skin region) at second visit.

addressed, including nutrition, pain, deconditioning, musculoskeletal disuse, co-morbid conditions and the emotional aspects of the disease such as fear, depression and the social withdrawal caused by disfigurement.¹³

In majority cases of systemic scleroderma, methotrexate, cyclosporin, tacrolimus, relaxin, low-dose penicillamine, and intravenous Ig may be beneficial in improving the skin tightness. Calcium channel blockers, the angiotensin II receptor type 1 antagonist losartan, prazosin, the prostacyclin analogue iloprost, N-acetylcysteine and the dual endothelin-receptor antagonist bosentan may be beneficial for Raynaud's phenomenon. Epoprostenol and bosentan are approved for therapy of pulmonary hypertension.¹⁴

OSF is in many aspects similar to scleroderma, where continuous and uncontrolled fibrosis accompanies a chronic

Figure 9 At 10-month follow-up, there was no sign of clinical relapse.

inflammatory reaction. In scleroderma, sclerosis is histologically characterised by an inflammatory cellular infiltrate composed of lymphocytes, macrophages, mast cells, eosinophils and plasma cells, and the collagen bundles are oriented parallel to the epidermis. Fibrosis is the pathological hallmark of scleroderma, which leads to induration of the skin and fixation of the epidermis to deeper subcutaneous tissue. Fibrosis in the oral cavity causes induration and stiffness of mucous, which ultimately leads to inability to open and close the mouth. Similar changes occur in OSF, where increased thickened collagen deposition leads to restricted mouth opening.¹⁵

The treatment followed in the present case was a combination of intralesional Decamycin (dexamethasone sodium phosphate 4 mg) injection and Hynidase (hyaluronidase), with multiantioxidant capsule (Riconia-LP). This treatment regime is commonly followed by patients with OSF. Since OSF shares features similar in many respects to those of scleroderma, we followed the same regimen for this patient.

Corticosteroids are a class of steroid hormones released by the adrenal cortex; these regulate a vast array of physiological processes, and synthetic derivatives of these molecules are widely used in the clinic for treating inflammatory disorders and autoimmune diseases.¹⁶

The role of corticosteroids in systemic scleroderma is controversial. Steroids inhibit collagenase activity.³

Corticosteroids also prevent new blood vessel formation by inhibiting expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells.¹⁷

Scleroderma, or SS, is characterised by increased deposition of hyaluronic acid (HA) and collagen. Both processes ultimately result in the formation of fibrotic scar tissue.¹⁸

HA as proteoglycan is involved in a variety of physiological control processes within the skin. It affects the firmness and plasticity of tissue, is involved in the transport of substances, and affects the proliferation and differentiation of different cell types.¹⁹

Hyaluronidase is a naturally occurring enzyme that degrades HA, one of the four main glycosaminoglycans that constitute the dermal extracellular matrix and regulate its permeability.

Figure 8 (A) Disappearance of perioral skin puckering at third visit. (B) Improved mouth opening (38 mm).

Since hyaluronidase digests hyaluronic acid, it has been used to treat skin disorders, such as diabetic scleroderma, scleroderma and pretibial myxoedema.²⁰

In scleroderma, the metabolism of free radical nitric oxide appears to be profoundly disturbed. There is considerable evidence implicating overproduction of free radical nitric oxide and ROS such as superoxide anions (O₂⁻) and peroxynitrite (ONOO⁻) in the pathogenesis of systemic scleroderma. Evidence suggests that antioxidants can counteract Transforming Growth Factor β (TGF β)-induced ROS in human dermal fibroblasts and also help in decreasing the fibrotic effects associated with scleroderma.²¹

Studies have also shown that a natural antioxidant such as epigallocatechin-3-gallate, an active polyphenol constituent of green tea, may directly regulate multiple signal transduction pathways such as MAP kinases (PI3-kinase, ERK), thereby reducing oxidant stress and the fibrotic effects associated with SS.²²

Lycopene possesses robust antioxidant activity that is twice as effective as β carotene and 10 times more effective than tocopherol, in its ability to trap singlet oxygen.²³

The improved mouth opening and reduced burning sensation in patients with OSF is due to the curative effect of lycopene, which acts by inhibiting abnormal fibroblast activation.²⁴

Zinc plays a role as an antioxidant in protecting sulfhydryl groups from oxidation and prevents superoxide anions (O₂⁻)

and hydroxyl radical production by pro-oxidant metals, copper and iron. Therefore, zinc deficiency may increase oxidative stress-induced tissue damage by decreasing the antioxidant functions.²⁵

Copper is essential for wound repair; indeed, lysyl oxidases are extracellular copper enzymes that initiate the cross-linking of collagen and elastin, and their activities decline to inadequate copper status.²⁶

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Patient perspective

One year ago I was really scared about why my mouth opening was progressively decreasing and after being diagnosed with scleroderma I was really upset. But after 5 months of medical treatment and following prosthetic rehabilitation, I felt great relief in mouth opening. Owing to the good teamwork of the doctors, today I am able to smile and share my story.

Learning points

- Localised scleroderma (morphea) is an autoimmune disorder of unascertained origin causing restricted mouth opening in most cases. The combination of intralesional corticosteroid with hyaluronidase and multi-antioxidants appears as a pristine approach for treating the restricted mouth opening in lip morphea.
- The combination of intralesional corticosteroid with hyaluronidase prevents abnormal collagen formation and antioxidants such as lycopene prevent abnormal fibroblast activation in scleroderma.
- New evidence suggests that oxidate stress and free radicals such as (reactive oxygen species, (ROS)) play a vital role in pathogenesis of scleroderma. Antioxidants such as epigallocatechin-3-gallate, lycopene, β carotene, selenium, α lipoic acid, α tocopherol acetate and zinc, prevent free radical (ROS) formation thereby preventing the progression of scleroderma.
- We believe this new combination treatment offers a promising approach for preventing progression of scleroderma.

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