
New alternative therapy for orofacial localized scleroderma

Xiao Song Liu, BDS, MDS, PhD,^a Yan Gao, BDS, MDS, PhD,^b
Li Wu Zheng, DDS, MD, PhD,^c and Hong Hua, BDS, MDS, PhD,^d Beijing and Hong Kong,
China

PEKING UNIVERSITY AND UNIVERSITY OF HONG KONG

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Scleroderma is an uncommon disorder characterized by thickening or hardening of the skin and fibrosis of the involved tissues. There are two distinct clinical categories: localized scleroderma and systemic scleroderma.^{1,2} Localized scleroderma refers to scleroderma primarily involving the skin and subcutaneous tissue, with minimal systemic features. Patients with localized scleroderma rarely progress to systemic disease. In systemic scleroderma, the fibrosis may extend to the internal organs, such as the heart, lungs, kidney, and gastrointestinal tract.

There are 2 major types of localized scleroderma: linear scleroderma and morphea.¹⁻³ Linear scleroderma is characterized by a band of sclerotic 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 localized scleroderma of the head and face is called *en coup de sabre*, and these lesions may result in hemiatrophy of the face. Morphea is characterized by small violaceous skin patches or larger skin patches that indurate and cause loss of hair and sweat gland function. Systemic scleroderma is divided into limited cutaneous scleroderma and diffuse cutaneous scleroderma. Patients with limited scleroderma often have a long history of Raynaud phenomenon before the appearance of other symptoms. They have skin thickening limited to the hands and frequently have problems with digital ulcers

and esophageal dysmotility. Diffuse scleroderma patients have a more acute onset, with constitutional symptoms, arthritis, carpal tunnel syndrome, and marked swelling of the hands and legs. They also characteristically develop widespread skin thickening and internal organ involvement. Systemic scleroderma may involve perioral tissues leading to restricted mouth opening and difficulties with oral hygiene and dental treatment. Localized scleroderma is generally benign, whereas systemic scleroderma can have life-threatening complications.¹⁻³ The mouth is often a mirror of the systemic conditions, and it is important for dental practitioners to recognize scleroderma at an early stage.

Although many therapeutic approaches have been reported, there are no universally effective treatments for localized scleroderma.^{4,5} Herein, we present 2 cases with localized scleroderma involving only oral mucosa and adjacent skin. Traditional Chinese medication was used to manage this rare condition.

CASES

Case 1

A 59-year-old female patient presented with a 4-month history of white patches at the right lower lip associated with progressive roughness and loss of sensation. Examination showed a sclerosed well defined band-like lesion extending from the skin of the right chin (Fig. 1, A) to the labial mucosa and eventually to the labial gingiva attached to the right mandibular canine and lateral incisor (Fig. 1, B). The lesion varied in width from 5 to 30 mm. Panoramic radiographic examination revealed alveolar bone resorption between the affected teeth (Fig. 2, A). The periodontal pocket depth of the right mandibular lateral incisor was 6 mm, deeper than that of the opposite tooth, which had normal bone structures (Fig. 2, B). Symmetric abrasions were noted in the right and left mandibular anterior teeth. Hematologic and biochemical investigations showed that the full blood count was normal, the anti-Scl-70 antibody, anti-CENP-B antibody, antinuclear antibody (ANA), antihistone antibody (AHA), and rheumatoid factor (RF) were negative, and anti-double-stranded DNA (ds-DNA) antibody was positive.

^aClinical Associate Professor, Department of Oral Medicine and Traditional Chinese Medicine, Peking University, School and Hospital of Stomatology.

^bProfessor, Department of Oral Pathology, Peking University, School and Hospital of Stomatology.

^cAssistant Professor, Department of Oral and Maxillofacial Surgery, Prince Philip Dental Hospital, University of Hong Kong.

^dProfessor, Department of Oral Medicine and Traditional Chinese Medicine, Peking University, School and Hospital of Stomatology. Received for publication Sep 3, 2009; returned for revision Mar 29, 2010; accepted for publication Apr 2, 2010.

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Fig. 1. Pretreatment appearance of case 1. A white band-like lesion (arrows) at the chin (A) and the lower labial mucosa (B).

Case 2

A 12-year-old girl presented with a 12-month history of slowly progressing white asymptomatic patch at the lower lip. Oral examination revealed a 6×15 mm well circumscribed homogeneous indurated lesion at the right lower labial mucosa (Fig. 3). Radiographic examination did not reveal any involvement of maxillomandibular complex and periodontal tissues. Hematologic tests were normal, and all autoantibody tests were negative.

Diagnosis

Except for these lesions, there was no evidence of oral mucosal, cutaneous, vascular, or visceral abnormalities in both cases. Habits of chewing areca nut or tobacco, smoking or alcoholic consumption, and traumatic or family history were absent. After detailed history, physical examinations, and laboratory tests, both patients were diagnosed with localized scleroderma. Mucosal biopsy of both cases confirmed the clinical diagnosis of scleroderma (Fig. 4).

The traditional Chinese medicines oral *Salvia miltiorrhiza* (Tianjin Tasly Pharmaceutical Co., Tianjin, China)

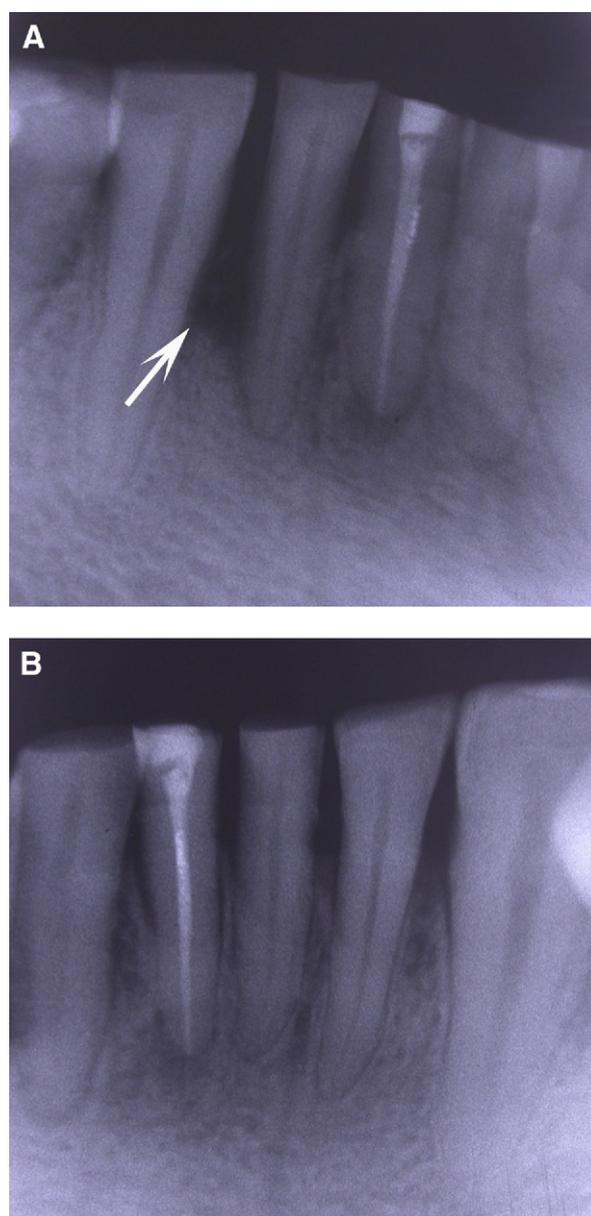


Fig. 2. Pretreatment panoramic radiograph of case 1. A, Alveolar bone resorption is evident between the right mandibular canine and lateral incisor (arrow). B, Opposite side shows normal bone structures.

in a dose of 750 mg/d and topical asiaticoside ointment (Shanghai Modern Pharmaceutical Co., Shanghai, China) were prescribed for both patients for long-term administration. At the 9-month follow-up, significant improvement was found in case 2. The size of the lesion reduced from 6×15 mm to 4×10 mm in association with a remarkable reduction of hypopigmentation (Fig. 5). Case 1 did not use topical asiaticoside as prescribed, thus *Salvia miltiorrhiza* alone. Softening and mild lightening of the lesion were found but the size remained unchanged (Fig. 6). Clinical assessments of



Fig. 3. Pretreatment appearance of case 2. A well circumscribed white lesion at the lower labial mucosa.

both cases were performed by 2 specialists of oral medicine independently.

DISCUSSION

The incidence of localized scleroderma is estimated to be 2.7 cases per 100,000 persons per year,⁶ and the prevalence of orofacial involvement in localized scleroderma is reported to be 7%.⁷ To our knowledge, no report in the literature had reported a scleroderma involving only oral mucosa and adjacent skin. Most patients with scleroderma in our clinic were referred by a dermatologist or rheumatologist to manage the problems in the oral cavity. Dental practitioners may be inexperienced in recognizing scleroderma, because of the rarity of this disease. Therefore reports regarding the scleroderma involving orofacial region are valuable for the dental practitioners. Localized scleroderma could be confused with other fibrotic conditions, such as scarring and oral submucosal fibrosis because of the similar clinically presentation. Usually, scarring or submucosal fibrosis has clear caustic factors, such as trauma or habit of chewing areca nut. Furthermore, most submucosal fibrosis lesions do not have a well defined border.

Patients with scleroderma might exhibit different dental and/or maxillo-mandibular abnormalities, including delayed tooth eruption, atrophic root development, widening of periodontal ligament space, shorter mandibular body, and resorption of mandibular angle, coronoid processes, condyles, and zygomatic arches.⁸⁻¹² Ischemia caused by limited mobility and extrinsic pressure from rigid tissues may be responsible for these abnormalities.^{13,14} Case 1 demonstrated a remarkable loss of alveolar bone associated with a deep periodontal pocket between the affected teeth. The bone resorption and the loss of periodontal attachment were localized without evidence of subgingival calculus or endodontic

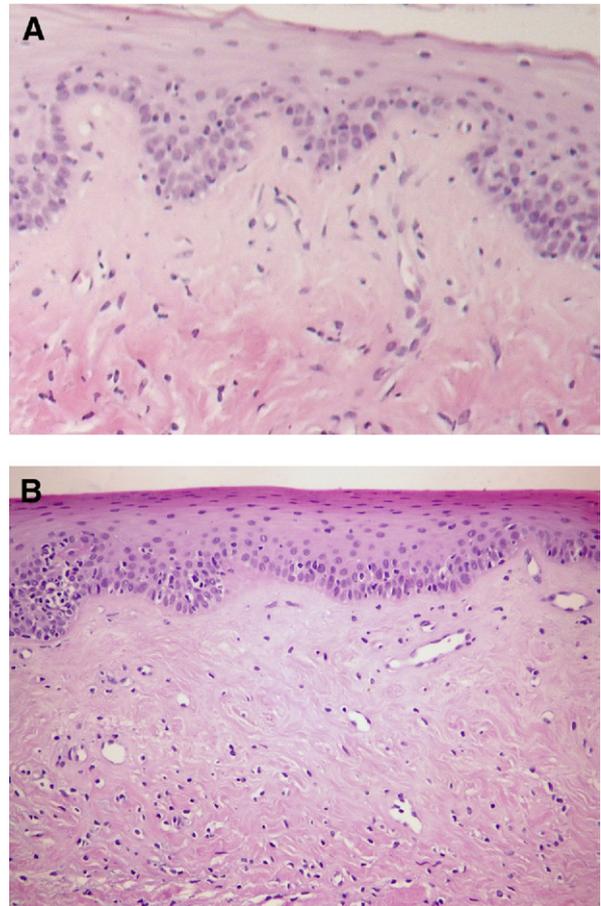


Fig. 4. Histologic sections from case 1 (A) and case 2 (B) demonstrate similar pathologic features: thinned epithelium, flattened epithelial peg, thickened collagen bundles, and lymphoplasmacytic infiltrate (hematoxylin and eosin staining, $\times 100$).

infection. The sclerosis of the affected gingiva might be the crucial factor responsible for the periodontal damage. Frequent dental assessment and management by the dental practitioner are essential to preserve the oral health of those affected with localized scleroderma.

Although laboratory evidence of autoantibody production is often seen in patients with localized scleroderma,⁴ no specific marker leading to a definitive diagnosis has been identified. Whether autoantibodies are pathogenic or merely epiphenomena is unclear. ANA, RF, and AHA are the most commonly detected autoantibodies in localized scleroderma, whereas anti-Scl-70 and anti-CENP-B antibodies are seen more often in systemic scleroderma. Anti-ds-DNA antibody is more frequently detected in adult patients with localized scleroderma than in pediatric patients.^{1,2,4,15} In the present report anti-ds-DNA antibody was not detected only in the adult patient, not in the 12-year-old girl.

Li et al.⁵ surveyed 195 pediatric rheumatologists in North America. Most respondents did not consider local-



Fig. 5. Case 2 at 9-month follow-up. Remission of the lesion along the mandibular labial mucosa.

ized scleroderma subtype to be a major factor in determining treatment. Nearly all respondents favored more aggressive treatment of lesions located on the face. About one-half of the respondents favored more aggressive treatment for recent disease onset (≤ 6 months duration).⁵ This may reflect a belief in a “window of opportunity” for treatment, with new lesions considered to be more “inflammatory” and more likely to respond to immunosuppressive medications. Uziel et al.¹⁶ reported earlier response to treatment in patients with more recent disease onset. However, Weibel et al.¹⁷ did not find any correlation between treatment response and disease duration. Case 1 revealed an irreversible periodontal damage up to 4 months’ duration after the white patch was noted at the lower lip. Although there is insufficient evidence to support the optimal time for treatment, the disease on the face and/or oral mucosa may need timely management to prevent subsequent cosmetic, functional, or dental issues.

Many drug regimens have been tried, with variable success, in the treatment of localized scleroderma, including D-penicillamine, cyclosporine, oral corticosteroids, low-dose methotrexate, psoralen, vitamin D analogs, tacrolimus, and mycophenolate mofetil.^{5,18-23} *Salvia miltiorrhiza* is a well known Chinese herbal medicine that has been used to inhibit tumor cell growth, inflammation, and oxidation.²⁴⁻²⁶ Recent studies demonstrated that *Salvia miltiorrhiza* can suppress fibroblast proliferation.^{27,28} Asiaticoside is extracted from the traditional herbal medicine, *Centella asiatica*, a plant of the Umbelliferae family, which has been used for many years for the treatment of dermal disorders, rheumatism, venous insufficiency, and microangiopathy.²⁹ Previous studies demonstrated that asiaticoside can stimulate the maturation of scar, decrease the inflammatory reaction, and enhance wound and ulcer healing.³⁰⁻³² As early as 1972, asiaticoside had been



Fig. 6. Case 1 at 9-month follow-up. Moderate remission of the lesion at the chin (A) and lower labial mucosa (B).

reported to be effective in treating systemic scleroderma by strongly inhibiting the biosynthesis of acid mucopolysaccharides and collagens in carrageenin granulomas,³³ but subsequent clinical reports were very rare.^{34,35} After 9 months’ treatment with combined application of oral *Salvia miltiorrhiza* and topical asiaticoside, significant clinical improvement was noted in case 2. Case 1 treated with *Salvia miltiorrhiza* alone demonstrated only moderate improvement.

The present study suggests that *Salvia miltiorrhiza* together with the asiaticoside may represent a valid alternative in treatment of localized scleroderma. Both medications are extracted from natural herbs which are safe for long-term administration. A limitation of the present report is the lack of objective measurement of discomfort, which could have biased our observations. Further randomized controlled clinical trials with large sample size are warranted to optimize the therapeutic approach to this rare condition.

REFERENCES

- Albilla JB, Lam DK, Blanas N, Clokle CM L, Sandor GKB. Small mouths . . . big problems? A review of scleroderma and its oral health implications. *J Can Dent Assoc* 2007;73:831-6.
- Hawk A, English JC III. Localized and systemic scleroderma. *Semin Cutan Med Surg* 2001;20:27-37.
- Wood RE, Lee P. Analysis of the oral manifestations of systemic sclerosis (scleroderma). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1988;65:172-8.
- Vierra E, Cunningham BB. Morphea and localized scleroderma in children. *Semin Cutan Med Surg* 1999;18:210-25.
- Li SC, Feldman BM, Higgins GC, Haines KA, Punaro MG, O'Neil KM. Treatment of pediatric localized scleroderma: results of a survey of North American pediatric rheumatologists. *J Rheumatol* 2010;37:175-81.
- Arkachaisri T, Vilaiyuk S, Torok KS, Medsger TA Jr. Development and initial validation of the localized scleroderma skin damage index and physician global assessment of disease damage: a proof-of-concept study. *Rheumatology (Oxford)* 2010;49:373-81.
- Marzano AV, Menni S, Parodi A, Borghi A, Fuligni A, Fabbri P, et al. Localized scleroderma in adults and children. Clinical and laboratory investigations of 239 cases. *Eur J Dermatol* 2003;13:171-6.
- Dervis E, Dervis E. Progressive hemifacial atrophy with linear scleroderma. *Pediatric Dermatology* 2005;22:436-9.
- Rushton M. Asymmetry of tooth size in congenital hypoplasia of one side of body. *Br Dent J* 1953;95:309-11.
- Foster TD, Fairburn EA. Dental involvement in scleroderma. *Br Dent J* 1968;124:353-6.
- Foster TD. The effects of hemifacial atrophy on dental growth. *Br Dent J* 1979;146:148-50.
- Mazzeo N, Fisher BS, Mayer MH. Progressive hemifacial atrophy (Parry-Romberg syndrome). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:30-5.
- Nestal-Zibo H, Rinne I, Glükmann M, Kaha H. Calcinosis on the face in systemic sclerosis: case report and overview of relevant literature. *J Oral Maxillofac Surg* 2009;67:1530-9.
- Lewkonja RM, Lowry RB. Progressive hemifacial atrophy (Parry-Romberg syndrome) report with review of genetics and nosology. *Am J Med Genet* 1983;14:385-90.
- Matucci-Cerinic M, Steen V, Nash P, Hachulla E. The complexity of managing systemic sclerosis: screening and diagnosis. *Rheumatology (Oxford)* 2009;48(Suppl 3):iii8-13.
- Uziel Y, Feldman BM, Krafchik BR, Yeung RS, Laxer RM. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000;136:91-5.
- Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JJ. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children. *Br J Dermatol* 2006;155:1013-20.
- Falanga V, Medsger TA. D-Penicillamine in the treatment of localized scleroderma. *Arch Dermatol* 1990;126:609-12.
- Hunzelmann N, Anders S, Fierlbeck G, Hein R, Herrmann K, Albrecht M, et al. Double-blind, placebo-controlled study of intralesional interferon gamma for the treatment of localized scleroderma. *J Am Acad Dermatol* 1997;36:433-5.
- Hulshof MM, Bouwes Bavinck JN, Bergman W, Masclee AA, Heickendorff L, Breedveld FC, et al. Double-blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. *J Am Acad Dermatol* 2000;43:1017-23.
- Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphea. *Br J Dermatol* 2005;153:815-20.
- Badea I, Taylor M, Rosenberg A, Foldvari M. Pathogenesis and therapeutic approaches for improved topical treatment in localized scleroderma and systemic sclerosis. *Rheumatology (Oxford)* 2009;48:213-21.
- Martini G, Ramanan AV, Falcini F, Girschick H, Goldsmith DP and Zulian F. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology* 2009;48:1410-3.
- Hao Y, Xie T, Korotcov A, Zhou Y, Pang X, Shan L, et al. Salvianolic acid B inhibits growth of head and neck squamous cell carcinoma in vitro and in vivo via cyclooxygenase-2 and apoptotic pathways. *Int J Cancer* 2009;124:2200-9.
- Wang X, Morris-Natschke SL, Lee KH. New developments in the chemistry and biology of the bioactive constituents of Tanshen. *Med Res Rev* 2007;27:133-48.
- Zhu YZ, Huang SH, Tan BK, Sun J, Whiteman M, Zhu YC. Antioxidants in Chinese herbal medicines: a biochemical perspective. *Nat Prod Rep* 2004;21:478-89.
- Lu XY, Li M, Weng MW. Inhibition effects of constituents of *Radix Salvia Miltiorrhizae* on proliferation and procollagen transcription of dermal fibroblasts in systemic scleroderma. *Natl Med J Chin* 2007;87:2426-8.
- Zheng L, Zhou LP, Jiang LL, Gao J, Wang YX. Influences of Danshen (*Salvia*) and Chuanxiong (*Ligusticum chuanxiong*) on fibroblasts proliferation in scleroderma. *J Hubei Univ Chin Med* 2009;11:15-6.
- Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha DK, Dhawan BN. In vitro and in vivo wound healing activity of asiaticoside isolated from *Centella asiatica*. *J Ethnopharmacol* 1999;65:1-11.
- Cheng CL, Guo JS, Luk J, Koo MW. The healing effects of Centella extract and asiaticoside on acetic acid induced gastric ulcers in rats. *Life Sci* 2004;74:2237-49.
- Xie JL, Qi SH, Li TZ, Huang B, Tang JM, Xu YB, et al. Effect of asiaticoside on hypertrophic scar in the rabbit ear model. *J Cutan Pathol* 2009;36:234-9.
- Kimura Y, Sumiyoshi M, Samukawa K, Satake N, Sakanaka M. Facilitating action of asiaticoside at low doses on burn wound repair and its mechanism. *Eur J Pharmacol* 2008;584:415-23.
- Sasaki S, Shinkai H, Akashi Y, Kishihara Y. Studies on the mechanism of action of asiaticoside (Madecassol) on experimental granulation tissue and cultured fibroblasts and its clinical application in systemic scleroderma. *Acta Derm Venereol* 1972;52:141-50.
- Szczepański A, Dabrowska H, Błaszczuk M. Madecassol in the treatment of scleroderma (preliminary study). *Przegl Dermatol* 1974;61:701-3.
- Guseva NG, Starovoitova MN, Mach ES. Madecassol treatment of systemic and localized scleroderma. *Ter Arkh* 1998;70:58-61.

Reprint requests:

Li Wu Zheng
Department of Oral and Maxillofacial Surgery
Prince Philip Dental Hospital
University of Hong Kong
Hong Kong
China
lwzheng@hku.hk

Hong Hua
Department of Oral Medicine and Traditional Chinese Medicine
Peking University
School and Hospital of Stomatology
22 Zhongguancun Nandajie
Peking, 100081, China
honghua1968@yahoo.com.cn