Hyaluronidase injections for treatment of symptomatic pansclerotic morphea-induced microstomia

Laila F. Abbas, BA, Jennifer Coias, BA, Heidi T. Jacobe, MD, MSCS, and Rajiv I. Nijhawan, MD
Dallas, Texas

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INTRODUCTION

Morphea, or localized scleroderma, is a rare autoimmune disorder that causes sclerosis and inflammation of the skin and subcutaneous tissue. Management can be challenging, as unchecked disease activity can lead to severe sclerosis, resulting in functional impairment.[1] Sclerosis involving the face can lead to microstomia, leading to difficulties with mastication, phonation, and oral hygiene.[2]

Mainstays of treatment include a combination of topical steroids, ultraviolet phototherapies (UVA-1 or UVB), and systemic immunosuppressive agents such as methotrexate or mycophenolate mofetil.[1] Most treatments are primarily aimed at reducing inflammation and are ineffective for sclerosis and resulting disability; however, off-label use of hyaluronidase has been reported to improve sclerosis in both morphea and other sclerosing disorders.[2-4] We report on a patient with pansclerotic morphea involving the jawline and affecting the muscles of mastication, with resultant microstomia, who experienced notable improvement with hyaluronidase injections.

Abbreviations used:

SSc: systemic sclerosis
UV: ultraviolet

CASE REPORT

A 60-year-old woman presented with an 18-year history of deeply sclerotic plaques consistent with morphea. Over the last 3 years, the lesions became more diffuse, involving her legs, abdomen, arms, chest, neck, and jaw. The lower extremity involvement resulted in limited range of motion in the ankles and toes, requiring physical and occupational therapy. The patient also experienced marked functional impairment because of jaw involvement, with severe spasms causing trismus, jaw thrusting, microstomia, and ticks. The transient spastic events occurred 5 to 6 times daily and were accompanied by intense sharp pain. Unable to open her mouth completely, she reported trouble swallowing, talking, and smiling. She lost 110 pounds over 3 years due to eating difficulties; for example, she was only able to eat strawberries cut into twelfths. Her symptoms caused her substantial distress, and she suffered from concurrent anxiety and depression. She was treated with UVA-1 phototherapy, methotrexate, hydroxychloroquine, and steroids, which resolved the inflammatory component of the lesions. However, the fixed and deeply sclerotic plaques around her jaw persisted despite treatment, and she continued to have significant disability.

Clinically, this patient had gingival recession and tongue atrophy as well as a decrease in oral aperture because of deeply sclerotic plaques around her jaw,

From the Department of Dermatology, University of Texas Southwestern Medical Center.

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Correspondence to: Rajiv I. Nijhawan, MD, University of Texas Southwestern Medical Center, 5939 Harry Hines Blvd, Suite 400, Dallas, TX, 75390-9191. E-mail: rajiv.nijhawan@utsouthwestern.edu.

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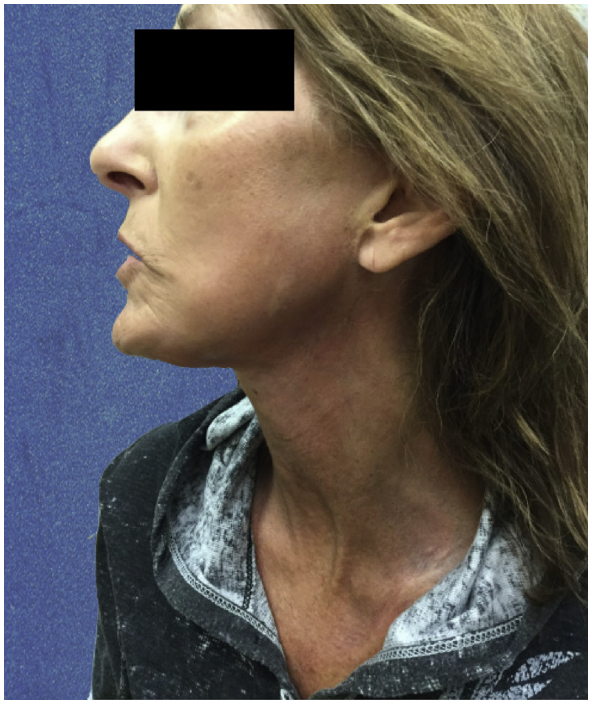

Fig 1. Pretreatment image of the patient's morphea-induced microstomia. There is marked functional impairment as well as perioral wrinkling.

neck, and face, which extended bilaterally over her temporomandibular joints (Fig 1). She was referred to oral and maxillofacial surgery for evaluation of the jaw spasms and found to have spastic dyskinesia secondary to morphea involvement of the masticatory and cervical muscles. Their recommendation was for chemical denervation of these muscles via neurotoxin and physical therapy. She expressed hesitation regarding the use of neurotoxin; thus, an off-label trial of intralesional hyaluronidase injections in her jaw was attempted with the goal of softening the sclerosis and contracture while alleviating her symptoms.

The patient received 4 treatments of intralesional hyaluronidase along her jawline (Table I). A 150-U vial of hyaluronidase was reconstituted with 1 mL of bacteriostatic saline. The injections were performed intradermally where the induration was felt to be the most clinically noticeable. Small aliquots (0.05-0.1 mL) of injections were spaced approximately 5 mm apart from each other to cover the entire surface area of each plaque. Although she noticed symptomatic improvement 1 to 2 weeks after the first injection, there was significant improvement days after the second injection, which was performed 2 weeks after the first. The sclerotic bands almost completely resolved, and she was able to open her mouth fully for the first time in years. She also experienced resolution of the jaw muscle spasms. Two additional injections were given to achieve complete plaque softening. She reported no adverse effects other than mild discomfort with the injections.

Table I. Description of the hyaluronidase injection series

Date of injection	Area	Units injected
11/12/2018	Right jawline	80
	Left jawline	35
	Chin	35
11/26/2018	Right jawline	80
	Left jawline	35
	Chin	35
12/10/2018	Right jawline	50
	Left jawline	50
	Chin	20
12/20/2018	Left jawline	15

Her vertical oral aperture improved from 2 cm before treatment to 5 cm (Fig 2). She was able to chew without discomfort and reported a 20-pound weight gain over 6 months. There was no clinical evidence of disease recurrence 6 months after her last injection. Although she remained on systemic therapies like methotrexate, her improvement with the hyaluronidase injections was almost instantaneous; thus, the rapid response was attributed to the injections, not the other therapies.

DISCUSSION

We report the use of hyaluronidase for treatment of sclerotic plaques in morphea that were persistent and disabling despite treatment with methotrexate, UVA-1 phototherapy, prednisone, and hydroxychloroquine. Hyaluronidase is an enzyme found endogenously in both humans and animals with broad applications in medicine.[5] For example, in the realm of aesthetic medicine, hyaluronidase is used frequently to treat complications and unwanted results of hyaluronic acid fillers, such as overcorrections, asymmetry, edema, or granulomatous reactions.[5] The enzyme hydrolyzes disaccharides at hexosaminidic linkages to degrade components of the extracellular matrix.[5] In sclerosing disorders involving the skin such as systemic sclerosis (SSc), increased deposition of hyaluronic acid and collagen in the extracellular matrix can lead to fibrosis and scarring, so hyaluronidase treatment is thought to work by hydrolyzing these components to improve skin tightening.[3] Although the pathogenesis of morphea is poorly understood, theories are often extrapolated from studies of SSc.[6] Thus, we postulate

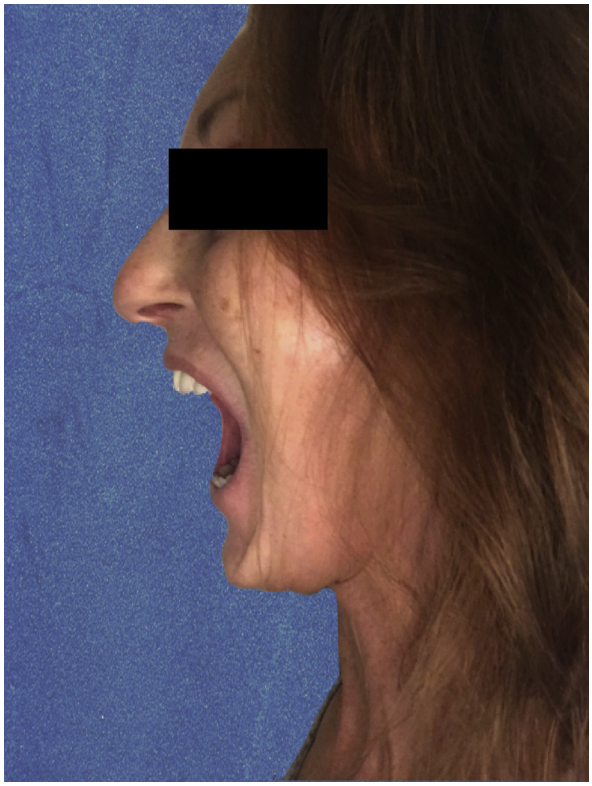

Fig 2. Posttreatment image. The patient's oral aperture is markedly imporved, with markedly reduced perioral wrinkling and tightness.

that the same mechanism of action for hyaluronidase as shown in treatment of SSc holds true for morphea. Generally, hyaluronidase is well tolerated, although mild allergic reactions have been reported.[5]

There are only limited reports of the use of hyaluronidase for morphea. One case report describes it to be mildly efficacious in treating radiation-induced morphea.[7] However, there are several reports on the use of hyaluronidase injections in another sclerosing disorder, SSc, also known as *scleroderma*.[2,8,9] Hyaluronidase injections have been used to successfully treat decreased oral aperture, or microstomia, in the context of perioral involvement of SSc.[2,8] Notably, Melvin et al[2] described hyaluronidase injections for a 53-year-old woman with limited cutaneous SSc and disabling microstomia despite treatment with mycophenolate mofetil and systemic corticosteroids. This patient, similar to ours, saw substantial improvement in her oral aperture with the injections.[2] Another report demonstrated its efficacy in generalized progressive scleroderma as well.[9]

The reports of hyaluronidase injections to treat decreased oral aperture in SSc prompted the trial of the injections in this patient with morphea, leading to complete resolution of sclerosis and dramatic improvement in her oral aperture. Given that she had persistent sclerosis despite systemic immunotherapy and UVA-1 phototherapy followed by rapid improvement after hyaluronidase injections, we believe that the results were due to hyaluronidase. These findings underscore a potential new treatment for persistent disabling sclerotic lesions in patients with morphea lesions that do not improve despite systemic treatment.

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