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PRACTICAL APPLICATION

# Clinical and histopathological improvement of scleromyxedema-induced microstomia after hyaluronidase injection

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## Abstract

**Introduction:** Scleromyxedema is a rare primary cutaneous mucinosis characterized by numerous firm, waxy, confluent papules. Recently, intravenous immunoglobulin (IVIG) is accepted by many authors as the first-line treatment option for severe cases. We report a 69-year-old male patient who has been suffering from scleromyxedema, with reduced mouth opening. He has been on a high-dose IVIG regime for 5 years.

**Methods:** The patient stated that he had difficulty in wearing and removing his dentures because of reduced mouth opening lately. Before considering to add any other immunosuppressants to his regime, we injected 1500 IU of hyaluronidase in total in one session periorally. The patient has been told open his mouth maximum and photographs have been taken before injections and after one month. We used a photo measurement application when evaluating microstomia to increase accuracy. We also took punch biopsies in order to evaluate effect of hyaluronidase histopathologically before and one month after injections.

**Results:** One month later, he was able to reattach and remove his dentures without adding any adjuvant immunosuppressants other than hyaluronidase. Mouth opening was increased in measurements and histopathologically, mucin deposition, fibroblastic proliferation, and perivascular lymphocytic infiltration were decreased.

**Conclusions:** We think hyaluronidase is a safe, easily accessible, and effective treatment option for microstomia caused by scleromyxedema.

KEYWORDS
hyaluronidase, microstomia, papular mucinosis, scleromyxedema

## 1 | INTRODUCTION

Scleromyxedema or papular mucinosis is a rare primary cutaneous mucinosis characterized by numerous firm confluent papules and areas of induration caused by papillary dermal mucin deposition and increased dermal collagen.[1,2] The disease commonly affects middle-aged adults, and there is usually a co-occurrence of monoclonal gammopathy. If sclerosis involves the face, that may cause microstomia leading to mastication, phonation, and oral hygiene difficulties.[3]

## 2 | CASE

We report a 69-year-old male patient with scleromyxedema involving the face, neck, and extremities. Physical examination showed flesh-colored papules arranged linearly on the hands and face and coarse skin evident on the glabella (Figure 1A,B). Diagnosis of scleromyxedema was confirmed by histopathologic examination, and the patient was prescribed high-dose intravenous immunoglobulin (IVIG) therapy from April 2016, after unsuccessful therapies with UVA1 phototherapy and para-aminobenzoic acid potassium (POTABA).

  

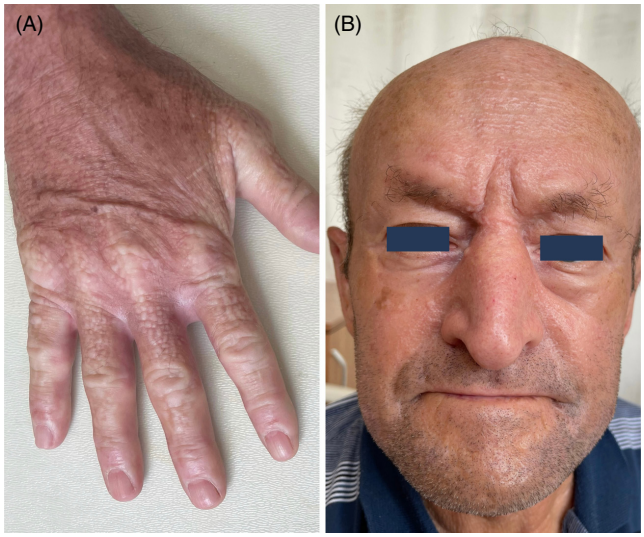


FIGURE 1 Clinical appearance of the patient. (A) Small white papules on the dorsal side of fingers and hand. (B) Course appearance of the glabella, linear arrangement of white papules on the forehead, inverted lips, and radial lines on the perioral area

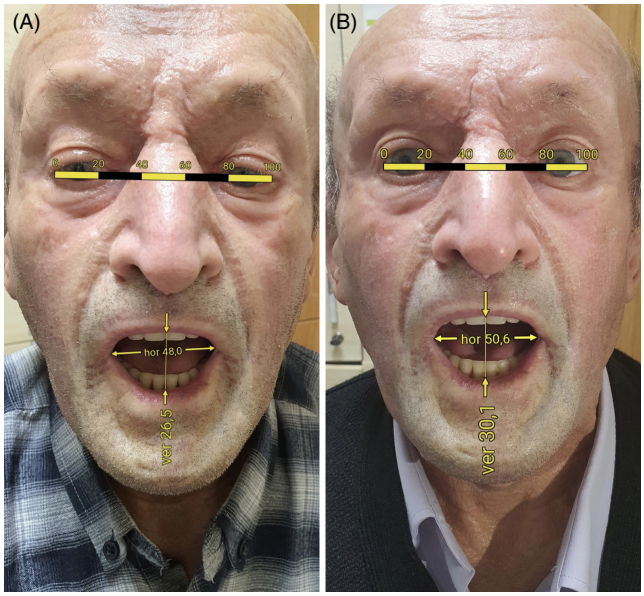


FIGURE 2 ImageMeter measurements. (A) Before treatment, when the outer canthal distance was accepted as 100 units, the horizontal opening was 48,0 units, and the vertical opening was 26,5 units proportionally. (B) After treatment, when the outer canthal distance was accepted as 100 units, the horizontal opening was 50,6 units, and the vertical opening was 30,1 units proportionally

The patient was screened for adverse effects from the beginning of the therapy, and plasma cell dyscrasia was not observed during this period. The skin lesions had regressed, but he found wearing and removing his dentures difficult due to a reduced ability to open his mouth.

To evaluate and measure the patient's microstomia, we used a photo measurement application (ImageMeter, Algorithmic Research, Stuttgart, Germany) to increase accuracy. The distance between the outer canthi was taken as the reference length. The oral commissural distance was accepted as the horizontal opening, and the vertical line passing between the upper central incisors and the upper and lower lips was accepted as the vertical opening (Figure 2). When we accept the outer canthal distance as 100 units, the horizontal opening was 48,0 units, and the vertical opening was 26,5 units, proportionally in the first evaluation (Figure 2A).

Following recent literature, we decided to inject hyaluronidase into the perioral area before considering whether to add adjuvant immunosuppressants to the IVIG treatment.[3–5] An informed consent was taken before the procedure. A 1500-IU vial of hyaluronidase (Total Corrector©, PB Serum) was reconstituted with 2 ml of physiological saline. 0.05 ml of the product was injected into the forearm intradermally, and no allergic reaction was observed after 20 min at the injection site. A −3 mm punch biopsy was taken from an indurated area on the chin before starting serial injections to investigate the histopathologic effects of the hyaluronidase on the sclerotic tissue. Then, a small amount of the product (0.1 ml in the areas with severe induration and 0.05 ml in the other areas) was injected intradermally with 5 mm intervals to the perioral area and cheeks.

After one month, the patient stated that his face was much softer, and he had no further problems wearing and removing his dentures. We evaluated the effects of the hyaluronidase on the microstomia as before; with the outer canthal distance of 100 units, the vertical opening was 30,1, and the horizontal opening was 50,6, proportionally (Figure 2B). The patient declined a second injection. A 3-mm punch biopsy was taken 1 cm laterally to the previous biopsy site. A comparison of the biopsies showed decreased fibroblastic proliferation and perivascular lymphocytic infiltration in the upper dermis. In addition, decreased mucin deposition in the upper dermis was noticed (Figure 3).

## 3 | DISCUSSION

Scleromyxedema is an uncommon, chronic disease affecting middle-aged adults. Widespread symmetric eruption of 2–3 mm, firm, waxy, closely-spaced papules, commonly locates on the face, upper trunk, and extremities.[1]

There is no unified approach to the treatment of scleromyxedema due to the lack of randomized trials and incomplete understanding of the disease's pathophysiology.[6] Recently, IVIG has gained widespread acceptance as the first-line therapy in severe cases, in patients with fast progression of skin symptoms, dermatoneuro syndrome, or a life-threatening involvement of the internal organs.[2,6]

Hyaluronidase is a naturally occurring enzyme that works by hydrolyzing glucosaminidic and glycosidic bonds within hyaluronic acid and other connective tissue mucopolysaccharides, which results in extracellular matrix (ECM) hydrolysis.[7] The use of hyaluronidase in sclerotic skin diseases began in 1953. Claesson and Lindquist first used hyaluronidase in a ten-year-old child who had

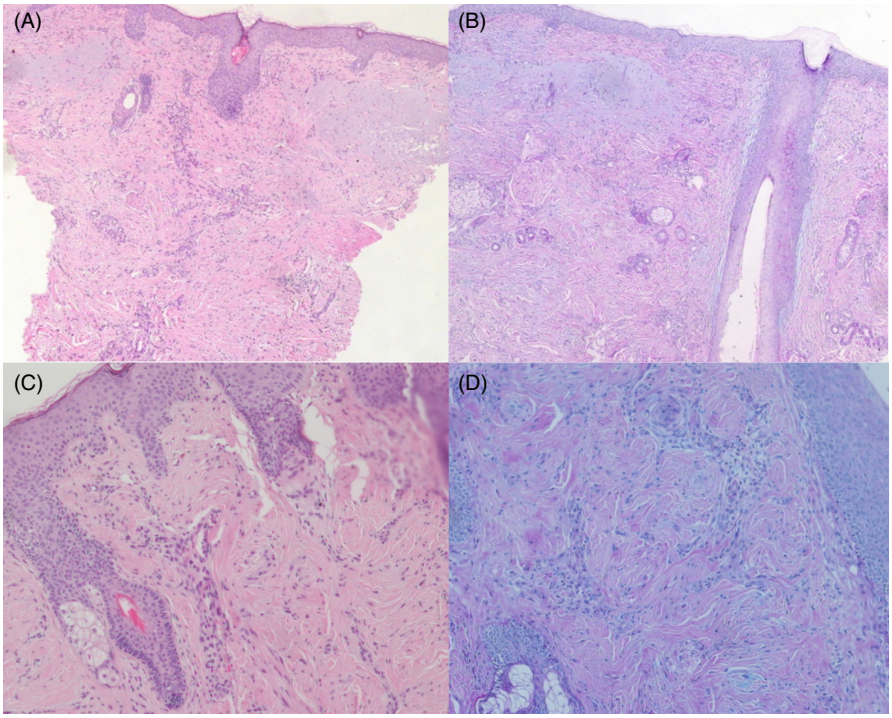


**FIGURE 3** Histopathologic evaluation before and after treatment. (A) Solar degeneration in the papillary dermis. Under this zone, apparent fibroblastic proliferation, mucin extravasation, and perivascular lymphocytic infiltrate in the upper dermis before treatment (HE 40×). (B) Mucin deposition in the upper dermis before treatment (PAS-ALCIAN BLUE 40×). Figure (C) Solar degeneration in the papillary dermis, decreased fibroblastic proliferation, and perivascular lymphocytic infiltrate in the upper dermis (HE 100×). (D) Decreased mucin deposition in the upper dermis (PAS-ALCIAN BLUE 100×)

linear scleroderma of the right arm. They saw improvement in both extremity movement limitation and skin lesions.[8] Melvin et al.[3] and Abbas et al.[4] used hyaluronidase for scleroderma-induced microstomia and both reported marked improvement. Microstomia can cause severe morbidity functionally and psychologically. Facial involvement and microstomia were patients' most significant concerns in a study of 300 systemic sclerosis patients.[9]

We evaluated the histopathological effects of hyaluronidase in scleromyxedema, and we found decreased fibroblast proliferation and mucin deposition that may have resulted from extracellular matrix (ECM) hydrolysis. Since the ECM is known to sequester certain cytokines, such as fibroblast growth factors, this hydrolyzing process may have resulted in a reduction in the amount of cytokines that promote sclerosis. Also, injection of small amounts of hyaluronidase into the tissue may act as a reserve if hyaluronidase expression is decreased in the related sclerosing skin disease. These hypotheses need further confirmations.

We injected 1500 IU in total to almost all face and neck in one session. Given the fact the hyaluronidase loses its effect and new hyaluronic acid is synthesized in 48 h it would be more reasonable to perform additional injections at weekly intervals to let the tissue expose hyaluronidase more but our patient did not want the next injections. Considering he had microstomia despite systemic IVIG therapy followed by rapid improvement after hyaluronidase injections, we believe that the results were due to hyaluronidase. Also, in histopathologic investigations there was mucin deposition and fibroblast proliferation under IVIG treatment before hyaluronidase injection. In control biopsy, which had been taken after 1 month from hyaluronidase injection, decrease of these parameters had been shown, but the histopathological change was not as prominent as clinical improvement. This may be because the patient did not want subsequent injections, and there was also solar elastosis in histopathological slides which may cause mucin accumulation itself.

There is no standard guideline hyaluronidase implementation in sclerotic skin diseases, but it appears that it can be an effective and easily applicable option for microstomia caused by sclerotic skin diseases.

## CONFLICT OF INTEREST

There is no conflict of interest in this study.

## ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received. The US National Research Council's guidelines for the Care and Use of Laboratory Animals were followed.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

1. Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol*. 2001;44(2):273-281.
2. Haber R, Bachour J, El Gemayel M. Scleromyxedema treatment: a systematic review and update. *Int J Dermatol*. 2020;59(10):1191-1201.

3. Melvin OG, Hunt KM, Jacobson ES. Hyaluronidase treatment of scleroderma-induced microstomia. *JAMA Dermatol*. 2019;155(7):857-859.
4. Abbas LF, Coias J, Jacobe HT, Nijhawan RI. Hyaluronidase injections for treatment of symptomatic pansclerotic morphea-induced microstomia. *JAAD Case Rep*. 2019;5(10):871-873.
5. Ramamurthi A, Bicknell L, McCarty M. Hyaluronidase in the treatment of papular dermal mucinosis: first case reported in North America. *J Surg Dermatol*. 2016;1(2):61-65.
6. Rey JB, Luria RB. Treatment of scleromyxedema and the dermatoneuro syndrome with intravenous immunoglobulin. *J Am Acad Dermatol*. 2009;60(6):1037-1041.
7. Lee A, Grummer SE, Kriegel D, Marmur E. Hyaluronidase. *Dermatol Surg*. 2010;36(7):1071-1077.
8. Claesson U, Lindquist B. Use of hyaluronidase in scleroderma. *Acta Paediatr*. 1953;42(3):278-281.
9. Paquette D, Falanga V. The psychosocial dimensions of scleroderma: a survey. *Arthritis Rheum*. 2000;43(9):320.

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