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The Effect of Intralesional Hyaluronidase Injections on Refractory Esophageal Stricture

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1. Abstract

A 35-year-old woman was treated for complete dysphagia resulting from a chemical burn of the esophagus. Between 2012 and 2019, numerous interventional gastroscopies (4–16 per year) were performed to alleviate her sympoms. Starting in 2017, based on our prior experience with hypertrophic skin scars, we introduced intralesional injections of hyaluronidase (10 ml of a 1500 U solution, SRS, Spain) Into the esophageal scar following each endoscopic procedure. The average number of hospitalizations per year decreased from 12.2 ± 2.12 (range: 10–16) in 2013–2016 and to 7.33 ± 2.49 (range: 4–10) in 2017–2019. A positive correlation was observed between hyaluronidase use and increased stricture, alongside a significant reduction in the number of mechanical dilations required. Post-dilation, the patient maintained a mashed diet, corresponding to a dysphagia score of 2 on a five-grade scale (grade 0 indicating no difficulty eating a normal diet. Intralesional hyaluronidase injections proved to be a safe and effective adjunctive treatment for this longstanding and complex esophageal stricture, facilitating improved outcomes compared to dilation alone. We propose that hyaluronidase may hold potential as a first-line treatment for certain types of strictures in the future.

2. Introduction

Numerous clinical circumstances, including chemical burns, scars after extensive mucosectomy and surgical interventions such as esophageal anastomosis on the neck, may lead to fibrous stenosis refractory to endoscopic dilations. Alkali ingestions involve the entire thickness of the wall and sometimes also surrounding tissues, and they belong to extensive injuries of the esophagus because they are of neutral taste and can be swallowed easily [1,2]. Esophageal dilations, steroid applications and stenting are, so far, the only alternatives to surgery [1,3,4].

3. Procedures

A 35-year-old woman was admitted to the Department of Gastrointestinal and General Surgery in March 2012 because of severe dysphagia, being able to swallow liquids only. The cause was an alkali burn of the esophagus in a suicide attempt 3 months earlier. Gastroscopy revealed a considerable stricture located 22 cm from the incisor teeth, approximately 20 mm long, allowing an endoscope with a 0.99 cm external lumen (Olympus) to be forced through the stenosis.One- or two-step endoscopic mechanical dilatations utilizing wire-guided flexible bougies of 1 mm and 15 mm (Savary-Gilliard, Wilson-Cook Medical Inc.) were performed monthly for a year, with a Roux-en-Y bypass for complete pyloric occlusion performed in September 2013. Twice, in 2014 and 2015, a biodegradable stent (Stella, Czech Republic) was inserted, but it did not reduce the number of endoscopic interventions per year. The average number of hospitalizations per year was 12.2 ± 2.12 (10–16) between 2013 and 2016 (Figure 1) and 7.33 ± 2.49 (4–10)

between 2017 and 2019. Upon admission, she usually complained of severe dysphagia, being able to swallow liquids only. We evaluated the patient's dysphagia using a four-grade Mellow-Pinkas dysphagia score: 0 = able to eat a normal diet (= no dysphagia), 1 = able to swallow some solids, 2 = able to eat semiliquids, and 3 = able to swallow liquids only. After dilations, she managed to maintain a mashed diet, corresponding to a dysphagia score of 2. In 2017, she was diagnosed with a small sliding hernia. Before 2017, the stricture did not allow the endoscope to pass into the distal esophagus without dilation during every gastroscopy. Fig. 2A shows the esophagogram made in January 2017 before hyaluronidase treatment, revealing a diverticulum above the circumferential stricture with a diameter of 7 mm ath the level of the clavicles.In our opinion, the diverticulum reflects the fibrous nature of the stricture and the difficulty of food passage through it. The small sliding hernia was also a consequence of the scr, which shortened the length of the esophagus. In March 2017, after obtaining informed consent from the patient and approval from the Ethics Committee, we started injecting the esophageal scar with 10 ml of hyaluronidase solution (SRS, Spain; 1500 U) diluted in 0.9% NaCl during every endoscopy, following dilation. After eight such interventions, we were able to pass the narrowing withour prior dilation. In January 2018, endoscopy revealed a 12 mm stricture of 5 mm length at the level of the clavicle, 21cm from the teeth(Figure 2B). The number of interventions decreased to 10 in 2018 and 4 in 2019 primarily limited to hyaluronidase injections, with only two wire-guided dilations per year using a 16-18 mm balloon (Boston Scientific). She reached a score of 1 on the dysphagia scale, with dilations performed only when she regressed to a score of 2. Figure 2C.A small sliding hiatal hernia was visible on endoscopy. The small diverticulum did not change. During every endoscopy, the stricture length and diameter were measured relative to the 0.99 cm diameter of the endoscope and its scale.Figures 3 and 4 show the relationship betwen repeated hyaluronidase injections and stricture diameter (a positive correlation, $r = 0.75408$, $P = 0.03$), as well as the relationship between the number of dilations and time (a negative correlation, $r = -0.84$, $P = 0.003$).

Figure 1: Radiograph showing a 2 cm esophageal stenosis with prestenotic dilation and a small diverticulum on the left side after a three-year follow-up period. Image taken before the administration of hyaluronidase. The patient is positioned anteroposteriorly.

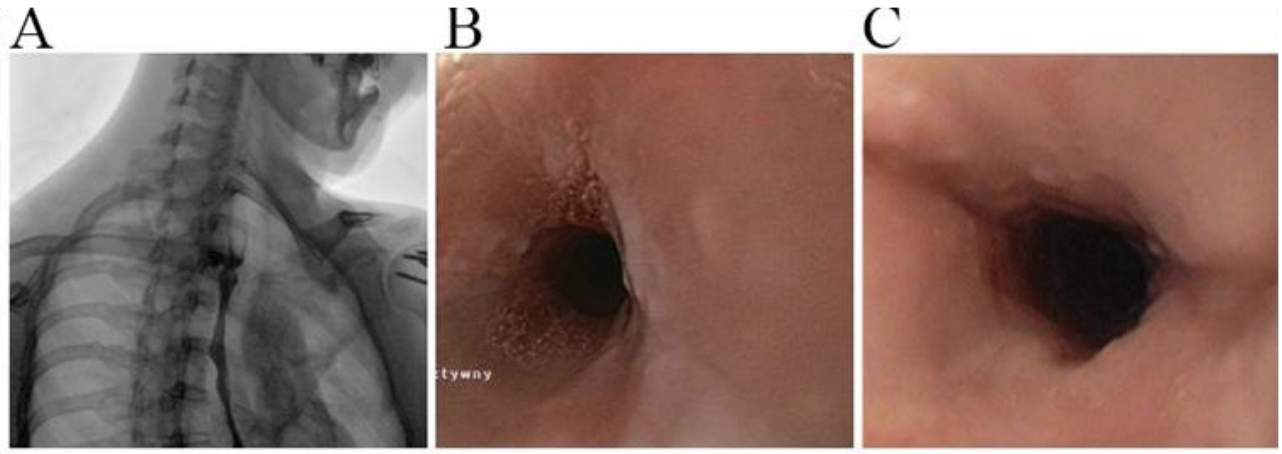

Figure 2: Annular esophageal stricture with a diameter of 0.5 cm after a series of four hyaluronidase injections without additional dilations (A); endoscopic view of the same stenosis (B); endoscopic view of the stenosis after eight hyaluronidase injections, showing an increased diameter of 0.9 cm. The small diverticulum persists (C).

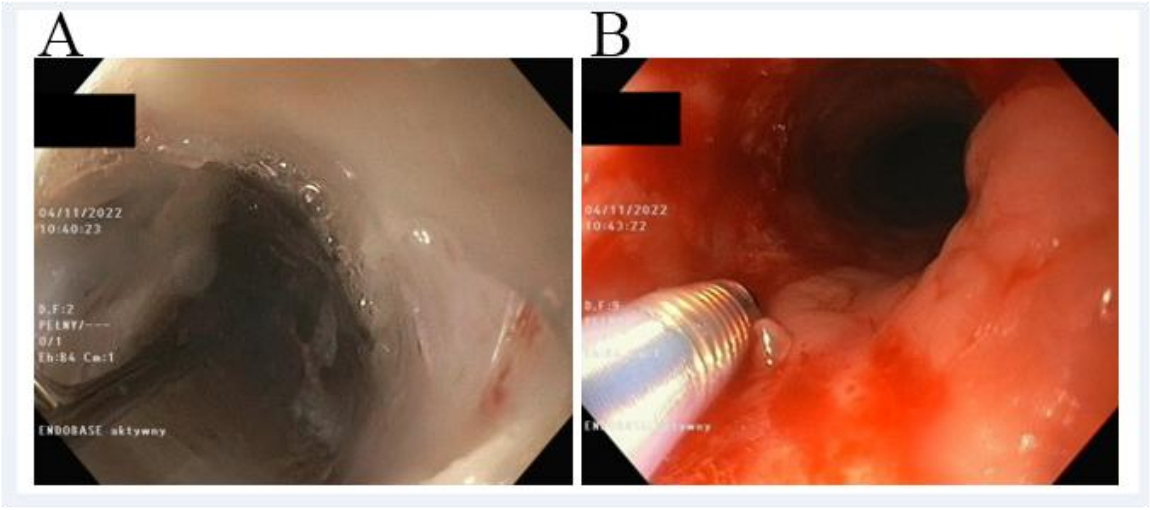

Figure 3: Endoscopic view of the stenosis after 18 months of hyaluronidase treatment. The endoscope passes through the stricture without requiring dilation (A). Visible erosions caused by a recent balloon dilation. The stricture diameter consistently ranges from 1.0 to 1.3 cm between endoscopic evaluation (B).

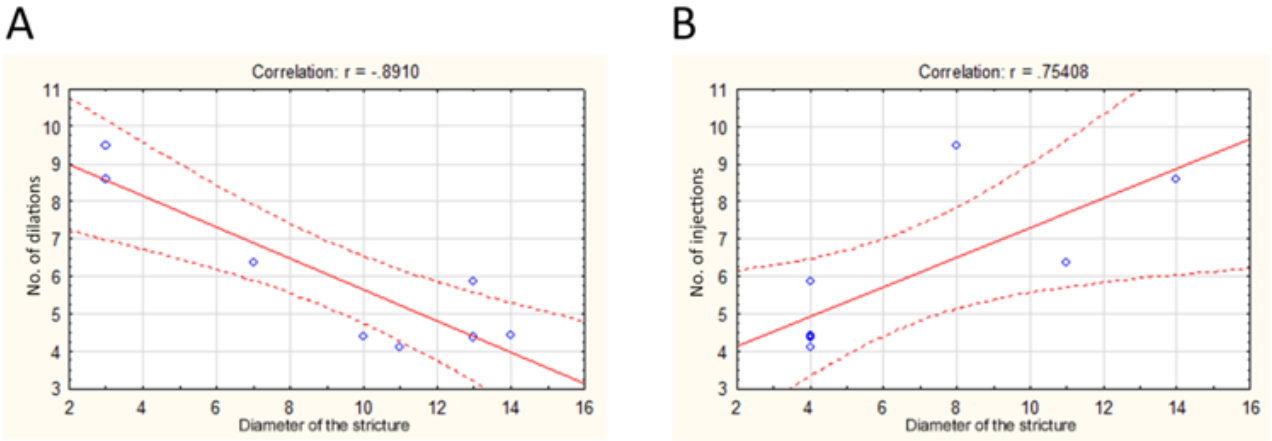

Figure 4: Graph illustrating the relationship between the number of dilations and repeated hyaluronidase injections in relation to changes in stricture diameter. Negative correlation between the number of dilations and stricture diameter, with a Pearson correlation coefficient (r) and p-value ($p = 0.003$) indicated in the upper part of the plot (A). Positive correlation between the number of hyaluronidase injections and stricture diameter, with corresponding Pearson correlation coefficient (r) and p-value ($p = 0.0307$) shown in the upper part of the plot.

4. Discussion

There are various endoscopic methods for the treatment of esophageal strictures: bouginage, balloon dilation, stent insertion and scar plasty [1-3]. Some attempts at steroid use are also described in the literature, but to our knowledge, there are no reported cases of hyaluronidase injections for such a condition. We found only some evidence of a beneficial impact of hyaluronidase combined with steroid injections in the treatment of oral submucous fibrosis and keloids [5,6].Generally, esophageal strictures may form fibrosis from the submucosa to the adventitia, so they require a careful approach [1,4]. The risk of hyaluronidase treatment is related to the risk of standard gastroscopy itself. However, injecting into long segments of scar tissue might be technically difficult and not possible on the first attempt without dilation. Dilation might also be necessary to preserve oral feeding because the remodeling process takes time. Mechanical dilations result in lacerations of the mucosa, which, in turn, heal as microscars and may deteriorate the final outcome of the dilation. Hyaluronidase injections in hypertrophic, strongly fibrotic skin scars made them softer and more elastic, with long-lasting results [7]. A positive correlation between the diameter of the stricture and the number of hyaluronidase injections demonstrated the positive influence of hyaluronidase on the elasticity of the refractory fibrotic stricture in the esophagus. Hyaluronidase usage resulted in a statistically significant reduction in dilation interventions. A negative correlation between the number of hyaluronidase injections and the number of endoscopic interventions for dysphagia supports its potential as a realistic goal in a patient with recurrent strictures. We believe that such an effect – decrease in the number of intervensionshas further implications for scar remodeling. It may also be very useful as a first treatment option for long scars in the esophagus, potentially diminishing fibrosis and preventing perforation if balloon dilation is necessary. This thesis is the subject of our ongoing study, but further research is clearly required. The small diverticulum formed in the esophagus after a few years proves how refractory to treatment the scar was. Moreover, as a consequence of severe segmental fibrosis of the esophagus, a hiatal hernia occurred, with the scar shortening the length of the esophagus. Further observation may show an effect of hyaluronidase on submucosal fibrosis reduction and, we believe, on preventing further shortening of the esophagus. The mechanism of hyaluronidase interactions with connective and scar tissue remains unclear. Results of one study on lung extracellular matrix (ECM) demonstrated an anti-inflammatory effect of bovine hyaluronidse, with histopathological evidence of fibrosis reduction in the lung: decreased neutrophils counts, reduced collagen content and lower production of tumor growth factor-β (TGF-β), which is directly involved in fibrosis. Hyaluronidase administration also showed a profund increase in mononuclear cells, which had phenotypic features of mesenchymal steam cells (MSCs).8 MSCs at the site of injury exert an anti-inflammatory effect. On the other hand, the accumulation of hyaluronian fragments in the scar and increased activation of TGF-β stimulate fibrosis [8]. We presented this case to show that hyaluronidase may contribute to less invasive and more effective treatment of patients with benign esopnhageal stricture compared to balloon dilations alone, which, when repeated, may lead to further scarring and narrowing of the lumen during wound healing. Moreover, dilation alone might be ineffective and could cause perforation in longer segmental stenoses or fibrotic strictures, such as those resulting from alkali ingestion, extensive mucosectomy or refractory anastomotic strictures in the neck. Serious complications in a cachectic patient are hazardous. Hialuronidase appears to remodel old scar tissue in the esophagus. We have completed a prosepcitve study using hyluronidase for the treatment of benign esophageal strictures, and the results are promising.

5. Funding Information

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6. Ethics Statement

The study was approved by Ethics Committee of Wroclaw Medical Univeristy. Registry and the Registration No. of the study: KB-679/2017.

References

1. Hwang J. Safe and proper management of esophageal stricture using endoscopic esophageal dilatation. Clin Endosc. 2017; 50: 309-310.
2. Hanaoka N, Ishihara R, Motoori M. Endoscopic balloon dilation followed by intralesional steroid injection for anastomotic strictures after esophagectomy: a randomized controlled trial. Am J Gastroenterol. 2018; 113: 1468-1474.
3. Mizusawa T, Kobayashi M, Terai S. Radial incision and cutting for refractory benign esophageal stricture. Dig Endosc. 2019; 31: e46-e47.
4. Ten Kate CA, Vlot J, Sloots CEJ, Van den Akker E L T, Wijnen R M H The effect of intralesional steroid injections on esophageal strictures and the child as whole: A case series. J Pediatr Surg. 2020; 55: 646-650.
5. James L, Shetty A, Rishi D, Abraham M. Management of oral submucous fibrosis with injection of hyaluronidase and dexamethasone in grade III oral submucous fibrosis: a retrospective study. J Int Oral Health. 2015; 7: 82-85.
6. Cornbleet T. Treatment of keloids with hyaluronidase. J Am Med Assoc. 1954; 3: 154: 1161-1163.
7. Tabola R, Augoff K, Grabowski K Cirrochi R. Role of hyaluronidase in the treatment of hypertrophic scars. Dermatologic Surgery. 2018; 44: 1155-1157.
8. Bitencourt CS, Pereira PA, Ramos SG, Sampaio SV, Arantes EC, Aronoff DM, Faccioli LH. Hyaluronidase recruits mesenchymal-like cells to the lung and ameliorates fibrosis. Fibrogenesis Tissue Repair. 2011; 4: 3.