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SUBMUCOSAL FIBROTIC CHANGES IN PATIENTS WITH ESOPHAGEAL ACHALASIA

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The OBJECTIVE of the study was to evaluate the severity of submucosal fibrosis in patients with esophageal achalasia, its influence on technical and clinical success of peroral endoscopic myotomies (POEM), and their results.

METHODS AND MATERIALS. The study included 116 patients with esophageal achalasia who underwent POEM in the Clinic of the Pavlov First Saint Petersburg State Medical University from June 2015 to March 2019. The mean age of patients was 50 years. It included 42 men and 74 women. This research was based on the retrospective analysis of video recordings of 116 POEM that were performed on patients with esophageal achalasia at the Endoscopy Department at the Pavlov First Saint Petersburg State Medical University.

RESULTS. The mean operation time was 89.6 minutes. During the operation, changes in the esophageal mucosa were recorded in all patients, which were classified according to the esophageal mucosa in achalasia (EMIA), and during creating the tunnel, the severity of submucosal fibrosis (SMF) was evaluated according to the three-stage classification (SMF from 0 to 3 stage). We found out that SMF-1 occurred in 20 patients, SMF-2 occurred in 44 patients and SMF-3 occurred in 48 patients; we identified a new group of severe submucosal fibrosis – 3b that accompanied in our study by the highest 25 % frequency of mucosal perforation during surgery.

CONCLUSION. The submucosal fibrosis of various SMF grades was determined intraoperatively in the majority of the patients and affected the POEM duration and complications.

Keywords: *esophageal achalasia, dysphagia, peroral endoscopic myotomy, submucosal fibrosis, sigmoid esophagus*

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Introduction. The major symptoms of achalasia are dysphagia, regurgitation, chest pain, and weight loss [1]. The etiology of the disease remains unknown, and its available treatments are palliative and aim at improving the passage of food through the esophagus to the stomach. The main diagnostic method for achalasia is high-resolution manometry (HRM), the procedure that became a basis for the Chicago Classification of Esophageal Motility Disorders in its current third version [2]. The pharmacological treatment of achalasia is of limited efficiency, and cannot be recognized as definitive. During the last decades, a number of operative methods, such as Balloon Dilatation and Laparoscopic Heller's Myotomy, came to be considered golden standards of achalasia treatment [3, 4]. Balloon dilatation shows high efficiency in treating achalasia symptoms, yet it often causes dysphagia relapse, which requires repeated treatment [5]. It should also be noted that balloon dilatation can cause esophagus perforation in 2–3 % of all cases on an average, with some researchers claiming that number to be as high as 21 % [6, 7].

During the last six years, a new minimally invasive operative method for treating achalasia was researched – the Peroral Endoscopic Myotomy (POEM) [8]. The main principle of this method is to create a submucosal tunnel between the esophagus and the stomach, and then to perform the dissection of the circular muscle layer in the lumen of the tunnel [9]. The initial results of POEM procedures were reassuring, since the method allowed to safely achieve very good control of the length of the muscle layer dissection [10].

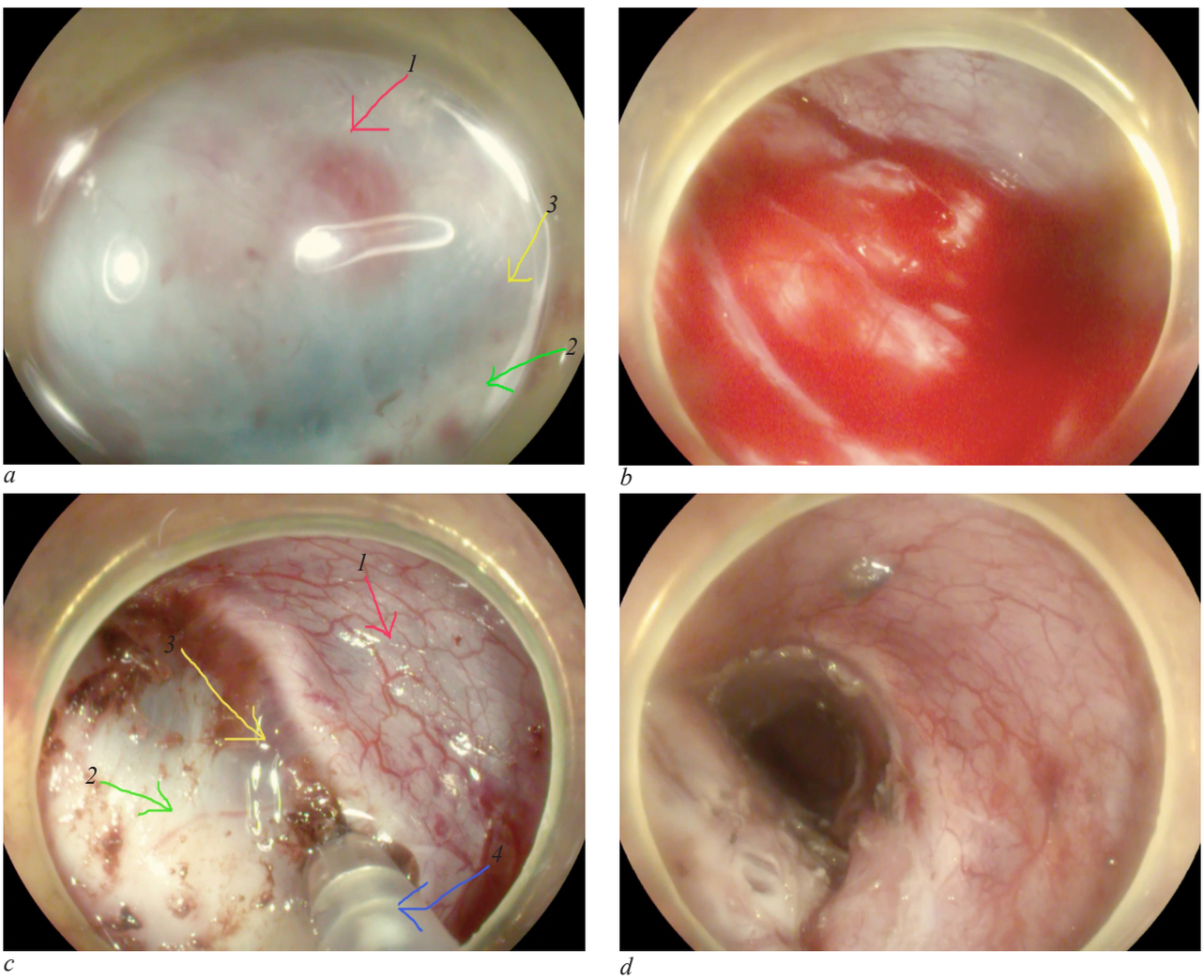

Fig. 1. Surgery images: a – the severe fibrosis, SMF-3 (arrow 1 – mucosa, arrow 2 – muscle layer, arrow 3 – the fibrotic submucosal layer after the hydropreparation); b – diffuse bleeding of the cavities' lining; c – the stage of the submucosal layer finding below the cavity and continuing performing the tunnel (arrow 1 – the cavity wall which is lining the mucosal layer, arrow 2 – the cavity wall which is lining the muscle layer, arrow 3 – the fibrotic submucosal layer, arrow 4 – injection needle); d – the view from the cavity which is proceed to the formed tunnel below

More than 5000 POEMs had been performed around the world up to this moment, and the procedure has proven to be safe and effective in treating achalasia of all types as well as other esophageal motility disorders, such as the Distal Esophageal Spasm (DES) and «Jackhammer» Esophagus [11].

Prior to performing myotomy, it is necessary to separate the mucosa from the muscle layer of the esophagus by creating a tunnel in the submucosal layer. Any changes within that layer affect the complexity of the procedure and the frequency of further complications [12]. Some researches describe POEM procedures that were aborted due to severe fibrosis of the submucosal layer [13]. Z. Nabi et al. analyzed causes of intraoperative complications and named submucosal fibrosis as one of the risk factors for mucosal perforation [14]. Y. Li et al., when faced with severe fibrosis, were not able to locate the submucosal layer distally and performed myotomy without creating a tunnel in the cardiac zone [15]. X. Feng et al. proposed the original classification of submucosal fibrosis during achalasia, which groups those changes into three degrees and allows to make a prognosis of their severity pre-surgery according to their correlation with the inflammation of the submucosal layer. This allows to make assumptions regarding the difficulty of the operation [16]. Results of the research published by Z. Nabi et al., who performed POEM on 408 patients with esophageal achalasia, specify that they could not complete the procedure in 12 cases and that in 9 of those cases, it was because of the excessive submucosal fibrosis [17]. Zhang et al. evaluated results of their five-year-long research and described the level of inflammatory changes of the mucous layer as one of the predictors of complications. Not only were former associated with expressed bleedings during initial cuts, but also with severe submucosal fibrosis, which resulted in 13 cases of aborted procedures [18].

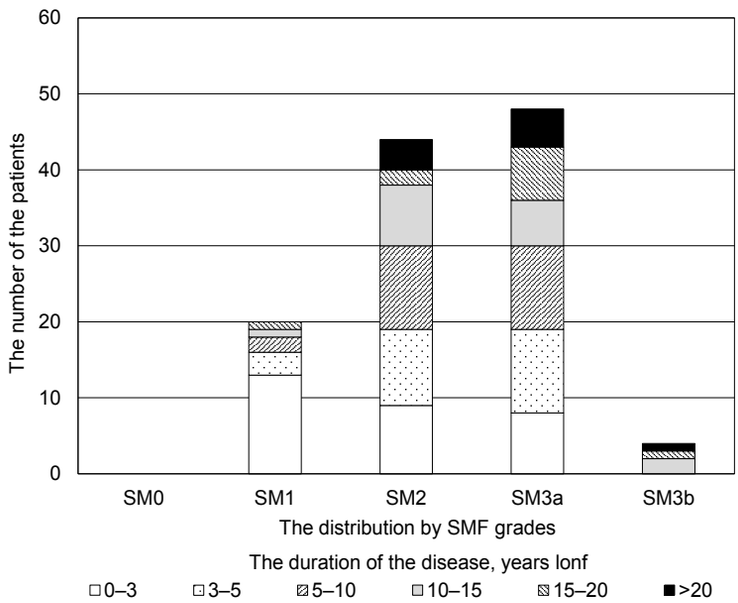

Fig. 2. Patient distribution by the grades of the submucosal fibrotic changes (SMF classification) depending on the duration of achalasia

H. Inoue et al. published data on the performed POEM on 90 patients who previously underwent Heller's Myotomy, and could not complete the procedure in 2 cases due to the severe submucosal fibrosis precluding submucosal tunneling [19]. To sum up, it could be claimed that POEM is undoubtedly a safe and effective procedure for treating esophageal achalasia. The cases with complications are few; most of those are mild (I–IIIa according to the Clavien – Dindo classification) and could be eliminated conservatively or through endoscopic intervention.

Methods and materials. This research included 116 patients (42 men and 74 women) diagnosed with esophageal achalasia who underwent POEM procedures in the Clinic of the Pavlov First State Medical University during the period from June 2015 to March 2019. In one of those cases, the POEM was aborted due to the severe fibrosis, and Balloon Dilatation was performed instead. The main criterion for including a case into the research was the availability of a complete video recording of the procedure that would allow conducting a retrospective analysis of its details. The mean age of patients was 50 years. It included 42 men and 74 women. The mean time of the procedure was 89.6 min. 77 patients underwent the HRM examination before the POEM and had their achalasia type determined according to the Chicago Classification of Esophageal Motility Disorders v. 3.0. 39 patients did not have an HRM examination due to the lack of equipment at the time of their examination.

POEM procedures were performed on patients positioned on their backs. During the surgery, the following instruments were used: the flexible high-resolution video gastroscope with 3.2 mm instrument channel and forward water jet; the electrosurgical unit set to the ENDO CUT I cutting mode (voltage 40W, effect 3, cutting duration 2, cutting interval 3) and a Q-type knife were used for creating the submucosal tunnel and myotomy; endoclips were used to close the surgical gap. Carbon dioxide that was used for insufflation was supplied through the insufflator. The sterile normal saline solution (NaCl 0.9%) with a little volume of a 0.4% solution of indigo carmine was used for submucosal lifting.

According to endoscopic video recordings, all patients had mucosal changes; they were evaluated according to the EMIA classification. During the tunnel creation, the stage of submucosal fibrosis was determined by using the three-stage SMF classification (SMF from 0 to 3 stage). 20, 44, and 48 patients had SMF-1, SMF-2, and SMF-3 respectively. In four cases, the research detected changes in the submucosal layer characterized by emerging cavities of different number and size and the background of extremely severe fibrosis (SMF-3) (*fig. 1, a*). In those cases, total procedure time was more than 100 minutes, and one of the distinct challenges was to create the tunnel in spite of the cavities.

The first stage involved opening up the cavity and entering it from the cranial side through the tunnel opening, which was always accompanied by the expressed bleeding of the cavity lining and required thorough coagulation (*fig. 1, b*). Secondly, it was necessary to find the submucosal layer distally of the cavity and cut it in a specific way that would allow to continue the tunnel (*fig. 1, c, d*). All the patients in this group had visibly thin mucosal layer above the cavities. Taking into consideration additional technical complications described above, we suggest to introduce changes to the SMF classification and divide SMF 3 stage, into two subgroups, 3a and 3b. 3a will include cases with severe fibrosis, and 3b will include cases with severe fibrosis accompanied by cavities in the submucosal layer.

Results. *Analysis of Fibrotic Changes.* We estimated the intensity of fibrotic changes in the submucosal layer depending on the duration of the disease, according to which all patients were classified by the appropriate SMF grade from 0 to 3 stage (*fig. 2*).

The SMF-1 group included 20 patients, 13 of whom did not undergo the HRM examination to determine their type of esophageal motility disorder. 13 of the patients in this group (65 %) had been suffering from achalasia from three to five years. None of the patients had it for more than 20 years (*fig. 4*). 65 % of the patients did not have any mucosal changes, and only one had sigmoid esophagus (*fig. 3, 5*).

The SMF-2 group had its 44 patients distributed uniformly across the duration criterion: 9 of them had

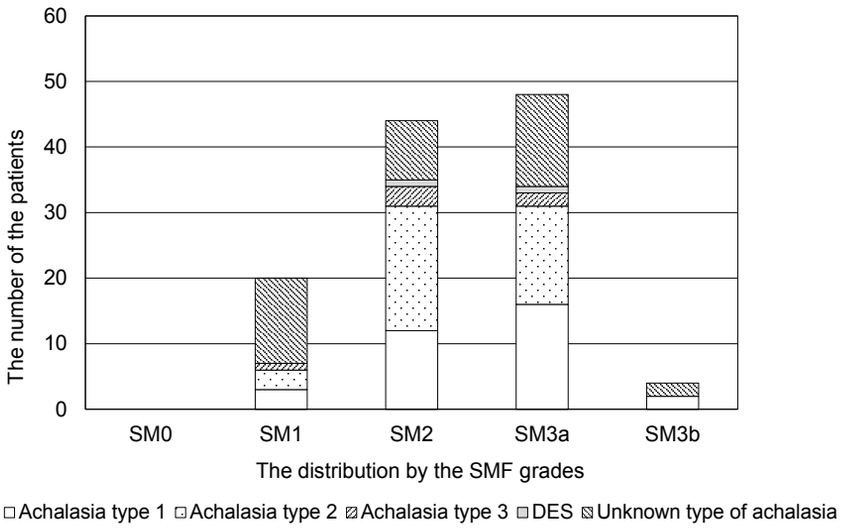

Fig. 3. Patient distribution by the grades of the submucosal fibrotic changes (SMF classification) depending on the type of diagnosis

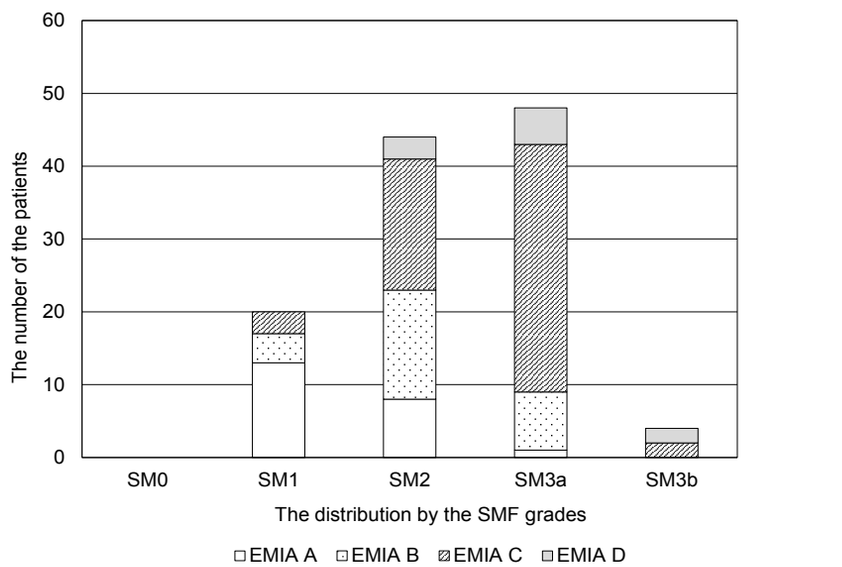

Fig. 4. Patient distribution by the grades of the submucosal fibrotic changes (SMF classification) depending on the mucosal changes according to the EMIA classification

achalasia from 0 to 3 years, 10 had it from 3 to 5 years, 11 had it from 5 to 10 years, and 8 had achalasia from 10 to 15 years. Two patients suffered from achalasia from 15 to 20 years, and 4 patients had it for more than 20 years (*fig. 2*). In this group, 12 patients were diagnosed with achalasia type 1 and 19 with achalasia type 2. 9 patients did not have the HRM examination performed (*fig. 3*). 5 patients had sigmoid esophagus according to the results of x-ray examinations. Mucosal changes predominantly fell at the B and C grades of the EMIA classification and were detected in 34 and 41 % of the patients respectively (*fig. 4; 5*). The mucosal perforation was diagnosed in 8.3% of cases (4 patients) during the operation (*table 2*).

The SMF-3a group was the largest and included 48 patients. The number of patients was distributed evenly across the duration criterion, but the percentage of those who'd had achalasia for a long time increased to 25 % compared with the SMF-2 group, where that number was at 13.6 %. 15 patients (31 %) had sigmoid esophagus, and 34 patients (71 %) had mucosal changes defined as C-grade according to the EMIA classification (*fig. 3; 5*). The mucosal perforation was diagnosed in 10.4% of cases (5 patients) during the operation (*table 2*).

The SMF-3b group included 4 patients who had been suffering from achalasia for more than 10 years (*fig. 2*). Three patients had sigmoid esophagus, and all patients had mucosal changes defined as C and D grades according to the EMIA classification (*fig. 3; 5*). Two patients did not have HRM examinations. In these 4 cases, the time of each surgery exceeded 100 minutes, and the mean surgery time was 136.25 minutes (*table 1*). This number is significantly higher than the

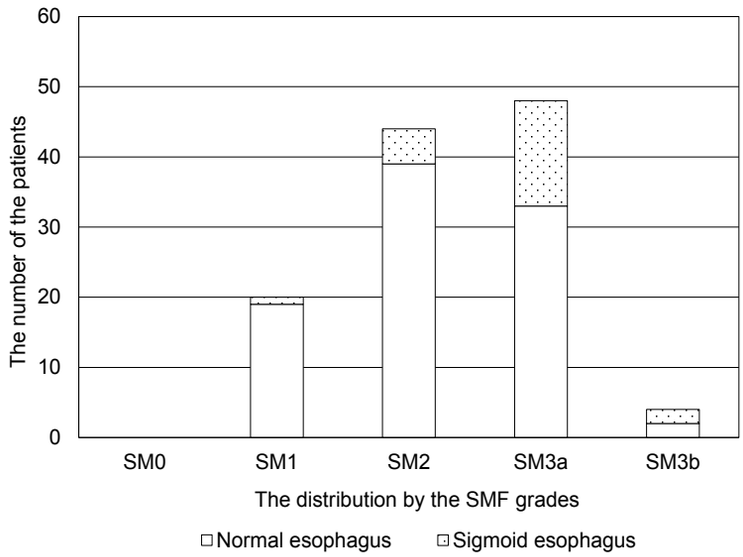

Fig. 5. Patient distribution by the grades of the submucosal fibrotic changes (SMF classification) depending on the shape of the esophagus

Table 1

The operation time in the SMF-3b group

Indicator	Patient 1	Patient 2	Patient 3	Patient 4	Mean operation time
The operation time, min	155	170	100 т	120	136,25

Table 2

The frequency of the mucosal perforations during POEM in the groups with the different SMF grades

Показатель	SMF0	SMF1	SMF2	SMF3a	SMF3b	Total number of patients
Number of patients	0	20	44	48	4	116
Mucosotomy	0	0	4	4	1	9
Linear mucosal laceration	0	0	0	1	0	1
%	0	0	8,3	10,4	25	8,6
Total number of complications	0	0	4	5	1	10

mean time for POEM procedures among all patients whose cases were part of the research, which was 89.6 minutes. In this group, one patient (25%) had an intraoperative mucosal perforation (*table 2*). All of the mucosal perforations were eliminated by using the endoscopic clips and no complications occurred during the postoperative period.

Within the SMF-1 group, visual changes of the mucosa were absent in 65 % of the cases, whereas in the SMF-2 group, they were absent in 18 % of the cases. In the SMF-3a group, only one patient (2 %) had his mucosa unchanged, and in the SMF-3b group, none of the patients had a normal mucosa (*fig. 3*). Patients with sigmoid esophagus underwent a separate classification based on submucosal fibrosis stages. In SMF-1, SMF-2, SMF-3a and SMF-3b groups, sigmoid esophagus was detected in 5.3 %, 12.8 %, 45.5 % and 50 % of the cases respectively (*fig. 5*).

Discussion. Creating a tunnel in the submucosal layer is a preparatory phase for the myotomy procedure, yet the necessity of this stage is undisputed, and complications that arise due to fibrotic changes in the submucosal layer make the surgery more difficult, and can even prevent its completion [12]. Severe submucosal fibrosis is the most frequent reason behind incomplete POEM procedures, and various complications of such cases are described in many significant clinical research papers, meta-analysis and literature reviews [20–22].

Y. Wang et al. analyzed their experience of performing 1912 POEM procedures and concluded that submucosal fibrosis is one of the predictors that increase the chance of mucosal perforation [23]. There are few research papers that analyze the occurrence and progression of submucosal fibrosis and its contributing factors [16, 24]. While X. Feng et al. suggested that submucosal fibrosis gradually intensifies together with the increase of disease duration. That conclusion was partially confirmed by our research: it was corroborated by the data in the SMF-3b group, which did include patients with duration of the disease exceeding 10 years.

It is possible that features such as severe mucosal changes according to the EMIA classification, sigmoid esophagus, and long-standing history of the disease can indirectly indicate the increased complexity of the upcoming POEM procedure due to their associations with fibrotic changes of the submucosal layer. Preoperative assessment of that data could help to assign most experienced and competent surgeons for the procedure in accordance with the Comprehensive Evaluation of the Learning Curve for POEM, which might include from 25 to 90 surgeries [25].

Conclusions. 1. In this research, severe mucosal changes graded EMIA-C and EMIA-D were coupled with severe submucosal fibrosis (SMF-3a and SMF-3b) in 63.2 and 70 % of the cases respectively.

2. The submucosal fibrosis of various SMF grades was determined intraoperatively in the majority of the patients, while severe SMF-3b submucosal fibrosis was associated with the duration of achalasia exceeding 10 years in all cases.

3. Patients with severe fibrosis who have cavities in the submucosal layer require special attention and should be allocated in a separate group within the classification because the combination of those features complicates tunnel creation.

4. The mean operation time for patients in the SMF-3b group was longer than the mean operation time among all POEM procedures studied in this research.

5. The research notes that the increase in submucosal fibrotic changes was consistent with the increase in the percentage of intraoperative mucosal perforation.

6. Features such as the sigmoid esophagus, severe mucosal changes according to the EMIA classification, long-standing history of the disease, and manometric type of achalasia enabled us to indicate fibrotic changes of the submucosal layer prior to POEM procedure in the majority of cases.

Conflict of interest

The authors declare no conflict of interest.

Compliance with ethical principles

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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