European Review for Medical and Pharmacological Sciences 2022; 26: 6300-6309

What is the effect of subepithelial lesions of the esophagus on esophageal motility?

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Abstract. – OBJECTIVE: Esophageal motility is regulated both by coordinated stimulation and inhibition of the circular and longitudinal muscle layers of the esophagus. Although there are many diseases known to have an effect on esophageal motility, the effect of subepithelial lesions (SELs) of the esophagus on esophageal motility, which is often detected incidentally, remains still unclear. The aim of this study is to reveal the effect of SELs of the esophagus on esophageal motility evaluating it by high-resolution manometry (HRM).

PATIENTS AND METHODS: A total of 32 patients with SELs in the esophagus and 12 healthy individuals were included. All patients and controls included in the study underwent HRM using a Unisensor UniTip High Resolution catheter (Laborie, Amsterdam, Netherlands) and endosonographic examination.

RESULTS: The mean age was 52.60±15.56 years (range: 23-79) and the average body mass index (BMI) was 26.63±4.71 kg/m^2. Gender, height, weight, and BMI measurements, smoking status, alcohol use, and DM status did not statistically differ significantly between the groups (p>0.05). Of 32 patients with SELs, 65.6% (n=21) had lesions originating in the muscularis propria, while 34.4% had lesions originating in the submucosa. The rate of abnormal motility both in the supine and in upright positions of patients with SELs was found to be significantly higher than in the control group (p=0.001, p<0.01, respectively). In patients with SELs, the incidence of infective motility was higher than the normal group (p=0.001, p<0.01, respectively). As the size of the lesion increases (>2 cm), the probability of abnormal HRM results increased.

CONCLUSIONS: SELs of the esophagus have pathological effects on esophageal motility, mainly ineffective esophageal motility disorder.

Key Words:
Esophageal subepithelial lesions, HRM, Esophageal manometry, Chicago 4, Ineffective esophageal motility.

Introduction

Subepithelial esophageal lesions (SELs) are rare and frequently detected incidental lesions in the esophagus[1]. Investigations involving endoscopic ultrasonography, cytology, immunohistochemistry, and flow cytometry can characterize such masses by identifying the layer where the lesion originated and guiding biopsy retrieval[2]. Subtypes of SELs can be classified as leiomyomas, gastrointestinal stromal tumors, granular cell tumors, and leiomyosarcomas. Leiomyomas, which account for more than two-thirds of all subepithelial lesions, are benign and rarely symptomatic[3]. 10% of all gastrointestinal leiomyomas occur in the esophagus. They are located mainly in the middle and distal thirds of the esophagus but are uncommon in the upper third of the esophagus, where the muscular layer is predominately skeletal in origin[4]. Other subepithelial lesions include gastrointestinal stromal tumors (GISTS), granular cell tumors, and leiomyosarcomas. Granular cell tumors are the secondary common cause of non-epithelial tumors in the esophagus[5]. They are often benign in nature and originate from the submucosal area, but they have the potential to become malignant. GISTs, which are another subtype of SELs, are mesenchymal tumors that arise from the interstitial cells of Cajal, and they are characterized by expression of the CD117 (C-KIT) and CD34 antigens. All GISTs have malignancy potential, and the revised National Institutes of Health consensus criteria, incorporating lesion size and mitotic rate, have been used to gauge prognostication and the need for resection[6]. Leiomyosarcomas are a rare type of malignant subepithelial lesion of the esophagus, arising from the muscularis propria and characterized

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by significant cellular atypia compared to their benign leiomyoma counterpart. They may disrupt tissue planes, appear heterogeneous, and have associated lymphadenopathy[4].

Subepithelial lesions of the esophagus are usually incidentally detected in patients who undergo endoscopy with another indication. The symptoms of dysphagia often appear in lesions >3 cm[3,7]. Although clinical practice varies, most patients with histologically confirmed SELs will undergo surveillance endoscopic ultrasonography (EUS) at regular intervals, closely mirroring American Gastroenterology Association guidelines[8] on the management of gastric subepithelial lesions. In the guidelines, resection is often recommended for symptomatic lesions over 3 cm. However, due to the significant mortality and morbidity risks associated with surgery, tunneling endoscopic submucosal dissection (ESD) techniques have been used more frequently in recent years[9,10].

The gold standard method for evaluating esophagus motility disorders is high-resolution manometry (HRM)[11]. However, the correlation between the manometric patterns and clinical characteristics of esophageal subepithelial lesions has been insufficiently studied and has not been examined using HRM. We aimed at evaluating esophageal motility disorders with HRM in patients with esophageal subepithelial lesions who are whether asymptomatic or symptomatic.

Patients and Methods

Patients with esophageal subepithelial lesions were enrolled in the study in Gastrointestinal Endoscopy Unit of Istanbul Medical Faculty at Istanbul University. A total of 32 patients with subepithelial lesions in the esophagus were included in the study. 12 of these patients were in the group of patients with known subepithelial lesions, and the remaining 20 patients, who were either symptomatic (dysphagia) or asymptomatic, were referred from other centers for EUS between January 2021 and October 2021.

Patients with esophageal subepithelial lesions were retrospectively identified from the computer recording system, and the patients who were selected for follow-up, and so did not undergo any surgical or endoscopic interventions, were included in the study by phone call.

Healthy individuals with no chronic illness in their medical history or active complaints who presented to our Internal Medicine clinic for routine check-ups were included in the control group. Patients with drug use affecting esophageal motility were not included in the study.

Verbal and written informed consent were obtained from all subjects. Data including demographic characteristics, comorbidities, medical history, medications, height, weight, smoking, and alcohol use were obtained for all subjects using a data collection form created by the researchers. Physical examinations were performed and the height, weight and BMI [weight (kg)/height^2 (m^2)] of all patients were recorded. Subjects were questioned about symptoms that might indicate esophageal dysmotility (dysphagia, heartburn, chest pain, regurgitation, etc.).

All patients and control subjects included in the study underwent HRM using a Unisensor UniTip High Resolution catheter (Laborie, Amsterdam, Netherlands, Chicago 4 software). Patients fasted for at least 4-6 hours before the procedure. The catheter was held in warm water for at least 10 minutes for calibration. Then, after waiting at least 60 seconds, the catheter was placed. The manometry protocol included basal recording and 10 swallows of 5 ml water in the supine position. The delay between wet swallows was at least 30 seconds to avoid effects of deglutitive inhibition. Patients' position was then changed to the upright position. Following this position change, a minimum of 60 seconds was allowed for adaptation and to determine the best anatomic landmarks. Next, wet swallows of at least five 5 ml were performed. Data obtained through HRM were analyzed using the Solar GI HRM system. The upper and lower esophageal sphincters, peristaltic waves, and the presence of hiatal hernia were evaluated using integrated relaxation pressure (IRP), distal contractile integral (DCI), distal latency (DL), contractile deceleration point (CDP), pressure inversion point (PIP), peristaltic breaks, and intrabolus pressure pattern. Findings were classified using Chicago classification version 4. All patients underwent esophagogastroduodenoscopy. The findings including the presence of hiatal hernia and esophagitis were recorded.

After the gastroscopic procedure, all patients also underwent radial endosonography to detect the layer of the subepithelial lesions of esophagus. All endoscopic and HRM procedures were also performed on patients who were previously found to have a subepithelial lesion and who had been called by phone. None of the patients were using medications that affected esophageal motil-

ity before the procedure. Approval was obtained from the local ethics committee prior to the start of the study.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio), including the Shapiro-Wilk test for normally distributed variables, as well as box plot graphs, were used. The Mann-Whitney U test was used to compare parameters that did not show a normal distribution between the groups. Pearson's Chi-Square test, Fisher's Exact test, and the Fisher-Freeman Halton test were used to compare the qualitative data. A p-value <0.05 was considered to be statistically significant.

Results

A total of 32 patients with SELs in the esophagus and 12 healthy individuals were included. The mean age was 52.60±15.56 years (range: 23-79), the mean height was 165.81±7.88 (range: 150-185 cm), and the mean weight was 73.77±12.51 (range: 52-105 kg). 58.1% of the patients (n=25) was composed by women. BMI measurements of the study participants ranged from 19 to 40 kg/m^2, with an average BMI of 26.63±4.71 kg/m^2. The gender, height, weight, and BMI measurements, smoking status, alcohol use, and the presence of DM did not statistically differ significantly between groups (p>0.05). The ages of patients with subepithelial lesions were found to be statistically significantly higher than those in the control group (p=0.003). In addition, the rate of drug use in patients with subepithelial lesions was found to be statistically significantly higher than in the control group (p=0.043; p<0.05) There was no statistically significant difference between the rates of hiatal hernia in cases between the groups (p>0.05) (Table I). Thirty-two of the cases with subepithelial lesions (65.6%, n=21) had lesions originating in the muscularis propria, while the remaining lesions originated in the submucosa 34.4% (n=11). When the localization of subepithelial lesions was examined, it was found that 18.8% (n=6) were in the upper esophagus, 40.6% (n=13) were in the middle esophagus, and 40.6% (n=13) were in the distal esophagus. In 40.6% (n=13) of the patients, the size of the lesions under EUS examination was <1 cm, in 37.5% (n=12) it was 1-2 cm, and in 21.9% (n=7) it was

Table I. Evaluation of descriptive characteristics by each group.

		Group		
		Control (n = 11)	Subepithelial lesion (n = 32)	p
Gender	Male	3 (27.3%)	15 (46.9%)	[a]0.309
	Female	8 (72.7%)	17 (53.1%)	
Age (years)	Mean ± SD	39.36 ± 16.47	57.16 ± 12.53	[d]0.003**
	Median (Min-Max)	31 (23-69)	57.5 (26-79)	
Height (cm)	Mean ± SD	165.73 ± 6.31	165.84 ± 8.45	[d]0.644
	Median (Min-Max)	165 (155-175)	165 (150-185)	
Weight (kg)	Mean ± SD	71.18 ± 5.10	74.66 ± 14.16	[d]1.000
	Median (Min-Max)	70 (65-80)	70.5 (52-105)	
BMI (kg/m^2)	Mean ± SD	26.00 ± 2.53	26.84 ± 5.27	[d]0.865
	Median (Min-Max)	25 (24-33)	25 (19-40)	
Smoking	(-)	9 (81.8%)	26 (81.3%)	[b]0.650
	(+)	2 (18.2%)	3 (9.4%)	
	Ex-smoker	0 (0)	3 (9.4%)	
Alcohol	(-)	10 (90.9%)	30 (93.8%)	[a]1.000
	(+)	1 (9.1%)	2 (6.3%)	
Drug	(-)	8 (72.7%)	12 (37.5%)	[c]0.043*
	(+)	3 (27.3%)	20 (62.5%)	
Diabetes Mellitus	(-)	10 (90.9%)	26 (81.2%)	[a]0.656
	(+)	1 (9.1%)	6 (18.8%)	
Hiatal hernia	(-)	10 (90.9%)	26 (96.3%)	[a]0.501
	(+)	1 (9.1%)	1 (3.7%)	

[a]Fisher's Exact Test; [b]Pearson Chi-Square Test; [c]Fisher-Freeman Halton Test; [d]Mann-Whitney U Test *p < 0.05;**p < 0.01.

2 cm and above (two cases were 4 cm, one case was 4.5 cm) (Table II). In terms of the presence of symptoms (dysphagia), 8 (25%) patients with subepithelial lesions were symptomatic, while 24 (75%) patients were asymptomatic. Typical reflux symptom was present in 4 (12.5%) patients in the subepithelial lesion group.

EUS Results

There were 32 patients with subepithelial lesions, 12 of whom we had previously followed up on, with lesions originating in the muscularis propria, and for whom follow-up decisions were made. The mean follow-up period of these patients was 38.2±22.3 months (range 12-84 months) from initial identification of the SEL. The size and endosonographic characterization of the lesions did not change during the follow-up period. The mean diameter of the lesions was 2.18±1.28 cm (range:1-4.5). Twelve of the SELs compatible with GIST and the others with leiomyomas originated in the muscularis propria. No increase was observed in the size of the lesions in patients with GIST (4.5 cm) during the seven-year follow-up period. Of these 12 patients, eight received at least two surveillance scans (i.e., at least two follow-up EUS scans after the initial diagnostic examination). The median number of surveillance EUS scans performed was 2 (range 1-5). No esophageal leiomyoma growth was seen in the follow-up period, and no malignant transformation was seen.

High Resolution Manometry Results

HRM was performed in all patients and control subjects. Eight members of the patient group (25.4%) had normal motility in the supine position, while 24 (74.6%) had pathological findings. In the upright position, normal HRM results were found in six patients (18.7%) with subepithelial lesions. In the control group, 11 subjects (100%) had normal HRM results in the supine position, but in the upright position three patients had abnormal HRM results. The rate of pathological manometry results in both the supine and upright position of patients with subepithelial lesions was found to be significantly higher than in the control group (p=0.001, p<0.01, respectively). In patients with subepithelial lesions, the incidence of infective motility in the supine position was higher, while in the control group the normality of their diagnosis was higher (p=0.001, p<0.01, respectively). The distribution of motility diseases in patients with subepitelial lesions in the supine position was as follows: ineffective esophageal motility, 59.4%; EJG outlet obstruction, 3.1%; absent contractility, 6.3%; and distal esophageal spasm 6.3%. In the upright position, the distribution was as follows: Ineffective esophageal motility 43.8%; absent contractility, 28.1%; distal esophageal spasm, 6.2%; achalasia type 2, 3.1% (Table III).

HRM metrics, including mean IRP, DCI, DL, were similar across groups (p>0.05 for each comparison). In the upright position, the mean IBP values were significantly higher for patients with subepithelial lesions (30.57±21.04 mmHg) compared to the control group (15.56±5.54 mmHg) (p<0.005). In the supine position, higher mean IBP values were recorded for patients with subepithelial lesions (30.12±18.85 mmHg) compared with the control group (17.51±4.69 mmHg, p<0.05), but the difference did not reach statistical significance (p<0.05) There were significantly more large mucosal breaks in the patient group than in the control group (p=0.048; p<0.05). (Table IV). A statistically significant difference was found between the diagnoses based on manometry results in the supine position according to lesion diameter in EUS (p=0.010; p<0.05). As the size of the lesion increased (>2 cm), the probability of abnormal HRM results also increased in the supine position (Table V). Patients were also evaluated according to the

Table II. Distribution of patients' group characteristics according to their subepithelial lesion.

		N (%)
Originating layer in EUS	Muscularis propria	21 (65.6%)
	Submucosal	11 (34.4%)
Localization of lesion in EUS	Upper esophagus	6 (18.8%)
	Mid esophagus	13 (40.6%)
	Distal esophagus	13 (40.6%)
Size	< 1 cm	13 (40.6%)
	1-2 cm	12 (37.5%)
	≥ 2 cm	7 (21.9%)

Table III. Evaluation of HRM diagnosis by groups according to Chicago 4 HRM classification.

	Group		
	Control (n = 11)	Subepithelial lesion (n = 32)	p
Manometry			
Normal	11 (100%)	8 (25.4%)	[a]0.001**
Pathological	0 (0)	24 (74.6%)	
HRM in supine position diagnoses			
Normal	11 (100%)	8 (25.0%)	[c]0.001**
Disorders of EGJ outflow	0 (0)	1 (3.1%)	
Disorders of peristalsis	0 (0)	23 (71.8%)	
HRM in upright position diagnoses			
Normal	8 (72.7%)	6 (18.7%)	[c]0.001**
Disorders of EGJ outflow	1 (9.1%)	1(3.1%)	
Disorders of peristalsis	2 (18.2%)	25 (78.1%)	
HRM in supine position diagnoses			
Normal	11 (100%)	8 (25.0%)	[c]0.001**
Ineffective esophageal motility	0 (0)	19 (59.4%)	
EGJ outflow obstruction	0 (0)	1 (3.1%)	
Absent contractility	0 (0)	2 (6.3%)	
Distal esophageal spasm	0 (0)	2 (6.3%)	
HRM in upright position diagnoses			
Normal	8 (72.7%)	6 (18.8%)	[c]0.001**
Ineffective esophageal motility	1 (9.1%)	14 (43.8%)	
EGJ outflow obstruction	1 (9.1%)	0 (0)	
Absent contractility	0 (0)	9 (28.1%)	
Distal esophageal spasm	1 (9.1%)	2 (6.2%)	
Type II achalasia	0 (0)	1 (3.1%)	

[a]Fisher's Exact Test; [b]Pearson Chi-Square Test; [c]Fisher-Freeman Halton Test; **p <0.01.

symptom of dysphagia. There was no correlation between the size of the esophageal subepithelial lesion, the layer of the lesion where it originated, and the presence of a motility disorder according to this symptom (Table VI). No correlation was found between the typical reflux symptom and presence of motility disease in patients with typical reflux symptoms.

In addition, no relationship was found between the layer of origin of the subepithelial lesion and the motility disease. The findings of the study are summarized in Figure 1.

Discussion

Although subepithelial lesions in the esophagus are often detected incidentally, their effect on the motility of the esophagus is unknown, even if they are asymptomatic[3]. Our study is the first to evaluate the effect of subepithelial lesions on motility.

In this study, we aimed at evaluating the effect of esophageal subepithelial lesions on esophageal motility in patients, regardless of whether they were asymptomatic or symptomatic, in comparison with a healthy control group. We found that esophageal dysmotility was significantly higher in patients with esophageal subepithelial lesions than in healthy controls. Ineffective esophageal motility (IEM) was found to be the most common motility disorder in patients with subepithelial lesions. Ineffective esophageal motility (IEM) is identified by a well-defined set of manometric criteria, but its etiology is poorly understood[12-14]. Vagal hyper-reactivity, advanced age, or damage to the enteric nervous system or smooth muscle are some possible etiologies that have been defined in the literature[15-17]. Kim et al[18] reported that esophageal smooth muscle of patients with IEM frequently exhibited fibrosis, myolysis, and widened intercellular spaces, suggesting the possibility of a myopathic process. In addition, more neuronal nitric oxide synthase (nNOS) immunoreactivity was seen in the circular muscle layer of patients with IEM[18,19]. Thus, excessive nitric oxide (NO) production, with consecutive diminished amplitude of esophageal peristalsis, is one plausible mechanism of IEM[19]. The esophageal tissues revealed histopathologic changes in my-

Table IV. Evaluation of IRP, UES, LES, DCI, CFV, DL, CFV, IBP, mucosal break values according to each Group.

		Group		
		Control (n = 11)	Subepithelial lesion (n = 32)	p
Median IRP mmHg (supine)	Mean ± SD	7.31 ± 2.97	9.22 ± 6.96	[d]0.412
	Median (Min-Max)	7.6 (1.8-12.1)	9.3 (0-33.2)	
Median IRP mmHg (upright)	Mean ± SD	7.82 ± 6.12	15.72 ± 34.33	[d]0.271
	Median (Min-Max)	7 (0.1-22.1)	8.8 (0.2-200)	
UES resting P mean (supine)	Mean ± SD	147.62 ± 117.72	113.02 ± 64.04	[d]0.664
	Median (Min-Max)	105.5 (61.9-372.2)	102.4 (35-302)	
LES resting pressure	Mean ± SD	16.00 ± 17.73	19.25 ± 22.46	[d]0.617
	Median (Min-Max)	9.5 (1-38)	15 (-23-76)	
LES resting pressure	Normal	3 (50.0)	14 (56.0)	[c]0.552
	Hypotensive	3 (50.0)	7 (28.0)	
	Hypertensive	0 (0)	4 (16.0)	
LES median IRP4 (supine)	Mean ± SD	7.79 ± 2.5	9.23 ± 6.96	[d]0.565
	Median (Min-Max)	7.7 (4.4-12.1)	9.3 (0-33.2)	
LES median IRP4 (upright)	Mean ± SD	9.17 ± 6.22	9.4 ± 7.21	[d]0.883
	Median (Min-Max)	8 (0.1-22.1)	8.3 (0.2-30.6)	
DCI mmHg•s•cm (supine)	Mean ± SD	1729.64 ± 1164.23	2625.84 ± 1945.78	[d]0.360
	Median (Min-Max)	1191 (577-3835)	2588 (0-6484)	
DCI mmHg•s•cm (upright)	Mean ± SD	1700.64 ± 1394.74	2358.28 ± 1868.29	[d]0.481
	Median (Min-Max)	1146 (358-4600)	2004 (0-4871)	
CFV (supine)	Mean ± SD	4.61 ± 1.66	13.92 ± 27.36	[d]0.494
	Median (Min-Max)	4.3 (3-7)	3.8 (0-100)	
CFV (upright)	Mean ± SD	4.24 ± 2.07	12.53 ± 28.43	[d]0.898
	Median (Min-Max)	3.2 (2-7)	3.3 (0-100)	
Distal latency (ms) (supine)	Mean ± SD	6.77 ± 0.81	6.64 ± 2.70	[d]0.772
	Median (Min-Max)	6.7 (5.3-8.3)	6.9 (0-13.4)	
Distal latency (ms) (upright)	Mean ± SD	7.03 ± 1.17	7.21 ± 2.50	d0.337
	Median (Min-Max)	7.3 (5-9)	7.5 (0-10.6)	
IBP (mmHg)(supine)	Mean ± SD	17.51 ± 4.69	30.12 ± 18.85	d0.046
	Median (Min-Max)	18.1 (10-23.9)	29.2 (5.9-68.8)	
IBP (mmHg) (upright)	Mean ± SD	15.56 ± 5.54	30.57 ± 21.04	[d]0.005**
	Median (Min-Max)	17 (7-21.8)	30.7 (4.4-65.6)	
	20 (0-100)	20 (0-100)	100 (0-100)	
Mucosal break (supine)	Absent-small	11	27 (77.1%)	[c]0.048*
	Large	0 (0)	4 (12.9%)	
Mucosal break (upright)	Absent-small	11	28 (77.5%)	[c]0.542
	Large	0 (0)	4 (12.5%)	

[c]Fisher-Freeman Halton Test; [d]Mann-Whitney U Test *$p < 0.05$. IRP: integrated relaxation pressure; UES: Upper esophageal sphinter; LES: Lower Esophageal Sphincter; DCI: distal contractile integral (DCI); CFV: Contraction front velocity; DL: distal latency; IBP: Intra bolus pressure.

Table V. Evaluation of manometry diagnoses according to lesion sizes.

	EUS			
	< 1 cm (n = 13)	1-2 cm (n = 12)	≥ 2 cm (n = 7)	p
HRM in supine position diagnoses				
Normal	6 (46.15%)	0	2 (28.57%)	[c]0.013*
Disorders of EGJ outflow	0	0	1 (14.28%)	
Disorders of peristalsis	7 (53.85%)	12	4 (51.15%)	
HRM in upright position diagnoses				
Normal	4 (30.76%)	1 (8.34%)	1 (14.28%)	[c]0.12*
Disorders of EGJ outflow	0	0	1 (14.28%)	
Disorders of peristalsis	9 (69.25%)	11 (91.66%)	5 (71.42%)	

[c]Fisher-Freeman Halton Test. *$p < 0.05$.

Table VI. Evaluations by presence of symptoms in patients with subepithal lesion (n=32).

		Dysphagia		
		(-) (n = 24)	(+) (n = 8)	*p*
Presence of motility disease (supine)	(-)	7 (28.2%)	1 (12.5%)	[a]0.422
	(+)	17 (70.8%)	7 (87.5%)	
Presence of motility disease (upright)	(-)	4 (16.66%)	2 (25%)	[a]0.35
	(+)	20 (73.34%)	6 (75%)	
Lesion's size in EUS	0-1 cm	10 (41.6%)	3 (37.5%)	[c]0.432
	1-2 cm	8 (33.3%)	4 (50%)	
	≥ 2 cm	6 (25%)	1 (12.5%)	
The layer of origin of the lesion in EUS	M.propria	16 (66.6%)	5 (62.5%)	[a]0.575
	Submucosal	8 (33.4%)	3 (37.5%)	

[a]Fisher's Exact Test; [c]Fisher-Freeman Halton Test.

opathy, whereas the myenteric plexus appeared morphologically normal, so the myopathic process may contribute more to the pathogenesis of IEM[19]. Although the etiology of the ineffective motility disorder of the patient with subepithelial lesions cannot be clearly explained, the accompanying reflux and hiatal hernia may also contribute to IEM disorder in these patients. But in our patients' group reflux symptom frequency was not high and also no correlation between reflux symptoms and motility diseases was found. Unfortunately, we did not perform pH or pH-impedance monitoring.

In our patients group, a patient with symptoms of dysphagia, who had a leiomyoma 2 cm in size, was diagnosed with achalasia type II. Regarding the co-incidence of achalasia and leiomyoma, Katzka et al[20] found a pattern of achalasia type 2 in a patient with esophageal leiomyomatosis. Further, they demonstrated diffuse thickening of the muscularis propria associated with nodules proximally and extending 24 cm from the

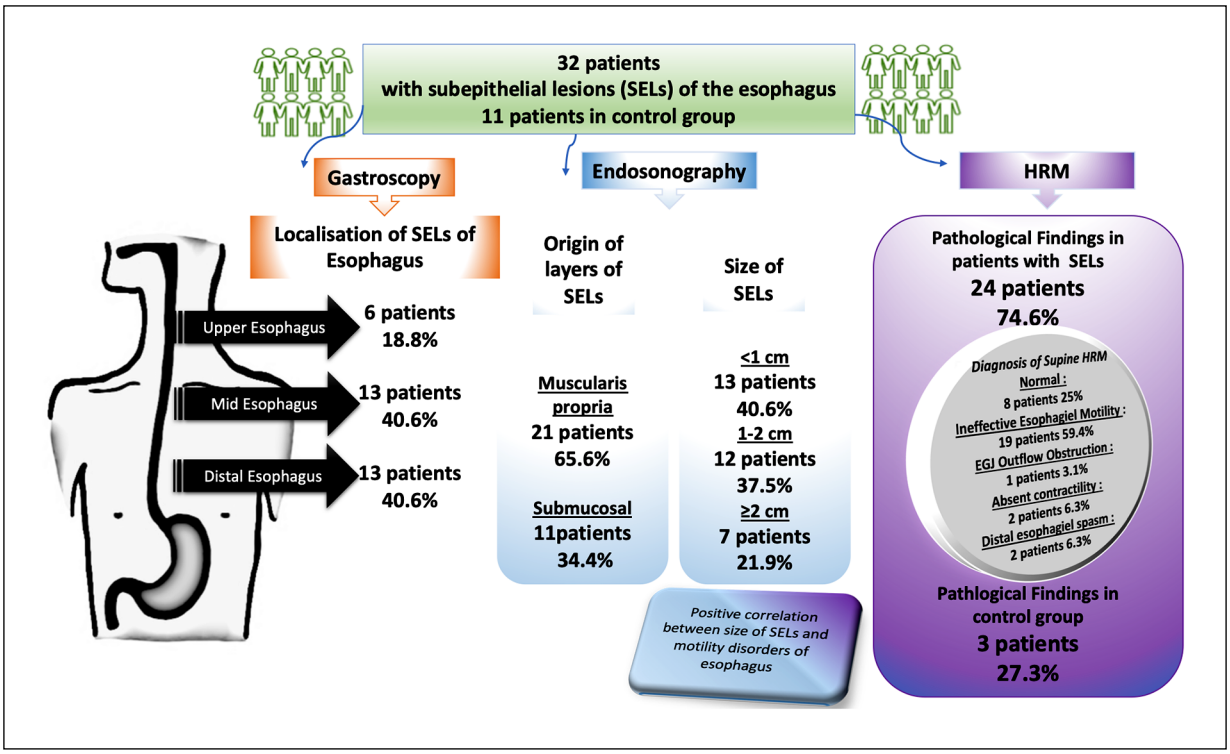

Figure 1. The findings of the study.

incisors into the cardia. The mechanism of this pattern is unclear. The authors speculated a lack of adequate neural proliferation in response to muscle hypertrophy, with a consequent lack of coordinative signaling. It was also interesting that they identified a type II pattern in the patient, with marked muscular hypertrophy in contrast to vigorous achalasia (type III). However, leiomyomatosis is a diffuse phenomenon, so it is difficult to determine how accurately we identified this pathogenesis in our case[21,22].

In the literature, case reports indicate that subepithelial lesions of the esophagus can affect motility. A case with multiple leiomyoma with motility dysfunction was reported by Wong et al[23] In this case report, the authors associated motility dysfunction with infiltration of the muscular layer. However, in our study, we found that the involvement layer, whether or not it is the propria, does not have an effect on motility. A total of 25.4% (n=8) of patients with subepithelial lesions of the esophagus were asymptomatic. No relationship was found between the presence of symptoms and the layer of involvement and the size of the lesions.

When the lesions were sorted based on size, we found that 71.4% of the lesions with a diameter of 2 cm and above were associated with motility disorders. In other words, we found that the incidence of motility defects increases as the size of the lesion increases. In the literature, Takahashi et al[24] performed HRM analysis of diffuse 6-cm esophageal leiomyomatosis lesions originating in the muscular layer and found no peristalsis of the thoracic esophagus (smooth muscle area), while a dilatated esophagus and retention of the barium were observed on the proximal side of the tumor. In their report, HRM findings revealed a complete loss of peristalsis in the smooth muscle area, whereas peristalsis of the striated muscle area was preserved.

In our study, although IRP was normal in patients with subepithelial lesions, IBP was found to be high.

Our results demonstrate that elevated IBP predicts subepithelial lesions and can potentially indicate restriction in transit across the EGJ, even when a conventional measure of esophageal outflow obstruction (i.e., IRP) is within normal limits[25].

The IRP, defined as the lowest mean EGJ pressure over four contiguous or noncontiguous seconds of relaxation, evaluates deglutitive EGJ function[25]. Median IRP values above the upper normal limit indicate obstructive pathophysiology at the EGJ. Elevated IRP can lead to compartmentalization of IBP antecedent to the contractile front and upstream of the obstruction[26]. IBP elevation can also result from increases in bolus size or when esophageal or LES distensibility is impaired[27]. In most settings, the IBP needs to overcome the EGJ residual pressure for the bolus to cross the EGJ. Therefore, elevated IBP can potentially indicate restriction in transit across the EGJ, even when a conventional measure of esophageal outflow obstruction (i.e., IRP) is within normal limits[28]. In our study, although IRP was normal in patients with subepithelial lesions, IBP was found to be high regardless of the location of the lesions.

Quader et al[29] determined that IBP could be used to identify structural EGJ processes when IRP is normal. They reported that elevated IBP predicts the presence of structural EGJ findings in patients with dysphagia in the absence of esophageal outflow obstruction or major motor disorders on esophageal HRM. In the current study, we observed no significant difference between esophageal subepithelial lesions and control subjects in terms of IRP, DCI, CFV, distal latency, and LES resting pressure.

In our study, we did not detect malignant transformation or size change in 12 of the muscularis propria-induced lesions during the follow-up period. One of the patients had a diagnosis of GIST (4.5 cm) and he was followed up for seven years. Although there are no clear guidelines in the literature regarding the follow-up of these patients, it is recommended that patients who are asymptomatic and do not have malignant characteristics (below 3 cm) should be followed up. In Codipilly et al[30], 15% of patients with esophageal leiomyomas were monitored with EUS findings. The follow-up period was 4-288 months, and no significant growth or malignant transformation was detected. Our data are also consistent with the literature. However, a surveillance strategy is limited in that a non-resected presumed esophageal leiomyoma could be a GIST or leiomyosarcoma instead.

Limitations

One of the main limitations of our study is the small number of patients, especially those with large subepithelial lesions. Another limitation was in the fact that we did not perform a systematic assessment of gastro-esophageal reflux with pH or pH-impedance monitoring. On the other hand, our patient group for reflux symptom was small.

Conclusions

Subepithelial lesions of the esophagus have pathological effects on esophageal motility, mainly ineffective esophageal motility disorder, regardless of the symptoms, the layer from which it originates, and the location. Therefore, patients with SEL should be evaluated not only for the size and characterization of the lesion but also for esophageal motility disorders.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

None.

Funding

None.

Informed Consent

Informed consent was obtained from the patients before each endoscopic and manometric procedure.

Authors' Contribution

ACO, BC, FA, RA, ZI performed the research, analyzed results, contributed to scientific discussion and wrote the paper. ACO, FA, BC analyzed results and wrote the paper. AB, MK, BH performed endoscopies and contributed scientific discussion. ACO, BC, FA performed EUS, HRM. VŞ, ZI, KN contributed to scientific discussion and edited manuscript. SK, FB, KD contribute to scientific discussion and edited manuscript.

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Ethical Approval

Approval was obtained from the local ethics committee prior to the start of the study (Number: E-29624016-050.99-783469).

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