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Running title: Secondary esophageal motility disorders

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Abstract

Background: Esophageal motility disorders are most often of primary origin but may be secondary to an occult malignancy or another etiology. High-resolution esophageal manometry cannot differentiate between secondary or primary origin. This study aimed at discussing the usefulness of a morphological assessment in the diagnosis of specific esophageal motility disorders, and to establish the predictive factors of a potential secondary origin.

Methods: In this retrospective study, patients with suspected esophageal motility disorders who underwent an esophageal manometry were included. High-resolution manometry results were interpreted according to the Chicago Classification, 3rd version. The results of endoscopic ultrasound and computed tomography, assessed by a panel of experts, allowed to diagnose a secondary origin.

Key Results: Out of 2138 patients undergoing manometry, 502 patients had a esophageal motility disorder suspect to be from secondary origin; among them 182 patients underwent tomography or endoscopic ultrasound. According to experts, 16 patients (8.8%) had a secondary esophageal motility disorder: esophagogastric junction outflow obstruction (n=7), jackhammer disorder (n=4), achalasia (n=3) and localized pressurization (n=2). The etiology was malignant in 8 patients. Predictive factors suggesting potential secondary esophageal motility disorders were smoking, age ≥ 58 years and an Integrated Relaxation Pressure higher than 10 mmHg for water swallows.

Conclusion and Inferences: Esophageal motility disorders with organic origin are not uncommon. A morphological assessment using endoscopic ultrasonography and/or computed tomography may be of use to diagnose a secondary origin, especially in the elderly and smokers.

Keywords: Esophageal motility disorders, Achalasia, Tomography, Endosonography, Manometry, Etiology.

Introduction

Esophageal motility disorders (EMD) are a rare pathology resulting from complex mechanisms, involving motor or sensory abnormalities of peripheral or central origin[1]. EMD are classified as primary (e.g., achalasia) or secondary (e.g., pseudoachalasia).. Achalasia is the most prominent entity, with an overall incidence of 0.18 to 8.7 per 100.000 person-years[2]. It is typically revealed by dysphagia and/or symptoms of reflux, or retrosternal pain that may eventually lead to a deterioration of nutritional status[3].

High-resolution manometry (HRM) is considered the gold standard for diagnosing EMD[4]. Based on this method, the Chicago classification v3.0 of 2015 developed an updated analysis scheme for clinical esophageal HRM recordings[5]. The particularity of this method consists in its capacity to distinguish non-specific from specific EMD, i.e. achalasia, esophagogastric junction (EGJ) outflow obstruction, distal esophageal spasm, jackhammer esophagus and absent contractility[4,6].

The common form is primary EMD. Secondary forms are less common and have been little studied[7,8]. At yet, pseudoachalasia or "secondary achalasia" is the most studied secondary EMD. It is characterized by achalasia-like symptoms caused by secondary etiologies, malignancy in 70% cases.[9] Conventional diagnoses using manometry and barium esophagogram cannot distinguish between primary and secondary achalasia[9,10]. Endoscopic ultrasound (EUS) and computed tomography are relevant imaging investigations that proved their usefulness in differentiating primary and secondary achalasia[10–13]. Dancygier et al.[11]were the first to conclude that EUS should be applied early in the work-up of patients with dysphagia to identify small intra- and extramural esophageal lesions and carcinoma. Krishnan et al.[14] identified clinically significant lesions using EUS in 9/62 patients (15%) with dysphagia and altered the management of their disease. In two of these patients, submucosal carcinoma was identified as a cause of pseudoachalasia. In complicated cases with achalasia, computed tomography(CT-scan) may be invaluable in confirming the diagnosis or in detecting atypical features such as benign or malignant processes[13, 15]. In their retrospective series of 333 patients with achalasia, Ponds et al. diagnosed 18 patients (5.4%) with malignant pseudoachalasia, and identified a certain number of risk factors[10].To date, studies are limited only in patients with confirmed achalasia, but no study adressed the frequency of secondary EMD in a cohort of patients with HRM-confirmed EMD.

The purpose of this study was therefore to investigate the usefulness of morphological assessments, computed tomography (CT-scan) and EUS, in all patients suffering from EMD, and to identify demographic, clinical or manometric risk factors of secondary EMD.

Patients and Methods

Patients

In French hospital settings, patients are informed that their data can be used for research purposes if they have no objection. The data used in this study are derived from de-identified files, and thus, this study was exempt from Ethics Committee approval.

This retrospective study was conducted in the Physiology department of Rouen University Hospital. All adult patients (≥18-year-old) (including esophageal biopsies), who underwent an esophageal HRM between the first January2011 and the 20th September 2016 for suspected EMD, were eligible. All patients underwent an upper gastro-intestinal endoscopy before HRM that showed no structural explanation for symptoms. Patients with diagnosis of EMD suspected to originate from a secondary cause, i.e. achalasia, esophagogastric junction (EGJ) outflow obstruction, distal esophageal spasm, and Jackhammer esophagus made by HRM were considered for final analysis. Patients with absent contractility, rolling hiatus hernia that may simulate extrinsic compression on HRM, history of esophageal surgery, history of esophageal dilation, eosinophilic esophagitis, incomplete manometric exploration not allowing to use the Chicago classification, and aged< 18 years were not analyzed.

Data collection

Medical records of eligible patients were reviewed. The following data were collected retrospectively: HRM indication, i.e. dysphagia, regurgitation, gastroesophageal reflux, retrosternal pain, deterioration of the health status, preoperative check-up; patient history, specifically smoking, chronic alcoholism, diabetes, cervicothoracic radiotherapy and cancer; findings of EUS and CT-scan carried out in the 3 months preceding or the year following the esophageal HRM.

As there no standard criteria, including timing, nature of the lesion or HRM pattern, to specifically address the imputability of structural lesion to HRM findings, a panel of 5 gastroenterology experts, being expert either in EMD and/or in EUS, assessed whether the manometric anomaly could be due to scan or EUS abnormalities. This assessment was carried out independently and blindly by each expert and an agreement by at least 3 experts was necessary to take a result into account.

Patients were then classified into three groups: those with morphological abnormalities on EUS and/or CT-scan probably causing the manometric anomaly were classified "Positive";patients without morphological abnormalities on EUS and/or CT-scan, or whose detected abnormality was assessed independent of the EMD were classified "Negative";patients without CT-scan and/or EUS were classified "Unexplored". Only “Positive” and “Negative” groups were compared to identify predictive factors of secondary EMD.

High-resolution manometry (HRM) system

HRM (Medical Measurement System, Enschede, The Netherlands) was performed in patients after 6 fasting hours. An electronic catheter probe (Unisensor, Attinkon, Switzerland) was placed transnasally to record pressures from the hypopharynx to the stomach with 1 cm intervals over 36 cm. For patients with a history of esophageal diverticulum, the probe was placed under videoscopic control.

Data collection was carried out over approximately 20 min. Patients were in supine position and swallowed 10 water boluses of 5 ml with an interval of 30 s (water manometry). This was followed by 10 chicken solid swallows:

Basal lower esophageal sphincter (LES) pressure, LES relaxation pressure, the mean integrated relaxation pressure (IRP) over 4 seconds, the mean distal contraction integral (DCI) and the mean distal latency (LD) were collected for water and perprandial manometries. Standard analysis of the motor pattern was performed for liquid and solid swallows using the of Chicago classification version 3.0 (CC v3.0)[5].Distal, as well as compartmentalized pressurizations revealed by the manometric plot were also analyzed[5]. Because of the lack of validated international standards for solid swallows, we performed a separated analysis for liquid et solid swallows using Chicago classification version 3.0 metrics.

Statistical analysis

Quantitative data were described by mean and standard error of the mean (SEM) and compared between groups by a Student t-test. Qualitative variables were described as absolute numbers and percentage and compared between groups usingChi² tests. A P value <0.05 was considered statistically significant.

Results

Study population

From January 2011 to September 2016, 2138 patients underwent an HRM. From this cohort, 1636 patients (76.5%) were excluded mainly for having normal HRM (993 patients) or non-specific EMD/absent contractility (288 patients) (**Figure 1**). The remaining 502 patients (23.5%) were diagnosed with specific EMD and considered as being potentially secondary to structural disease; from them, 182 patients (36.2%) had a morphological assessment by CT-scan and/or EUS. The 320 patients without morphological assessment were included in the "Unexplored" group.

According to the expert panel, in 16 of the 182 explored patients (8.8%) there was a correlation between the manometric diagnosis, and the morphological abnormality revealed by the CT-scan and/or the EUS. They were considered to have secondary EMD and were included in the "Positive" group. The remaining 166 patients (normal CT-scan and/or EUS for 132 patients and lack of correlation between morphological abnormalities and manometric diagnosis for 34 patients) were considered to have primary EMD and were included in the "Negative" group (**Figure 1**).

Characteristics of population with suspected secondary EMD

Suspected secondary EMD population included 502 patients with a mean age of 61.2 ± 0.7 years and 61.2% were women. HRM was indicated for dysphagia, gastroesophageal reflux, retrosternal pain, regurgitation, deterioration of the health status and preoperative check-up (**Table 1**).

Secondary origins of the EMD

According to the expert panel, CT-scan and EUS allowed to identify 16 patients (8.8% of the explored patients) with secondary EMD ("Positive" group). Eight patients (50%) were diagnosed with a malignant secondary origin proven histologically, five (31.2%) were diagnosed with benign secondary origin and three (18.7%) with doubtful secondary origin(no histological proof of malignancy) (**Table 2**).

Malignant origins were adenocarcinoma of the cardia (n=3), esophageal squamous-cell carcinoma (n=2), gastric signet ring cell carcinoma (n=1), gastric adenocarcinoma (n = 1) and pancreatic adenocarcinoma with metastatic cardial lymphnodes (n=1). Leiomyoma (n=3) and lymphadenopathy (n=2) were the most benign and doubtful causes of secondary EMD, respectively.

Most of the patients with a secondary origin were diagnosed with EGJ outflow obstruction (n=7), followed by jackhammer disorder (n=4), achalasia (n=3) and localized pressurization (n=2).

Seven abnormalities with a malignant or doubtful origin were discarded by the experts: 1 pancreas head cancer, 4 mediastinal lymphadenopathies including one melanoma metastasis, and 2 pleural mesotheliomas.

Water and solid swallows efficiently in diagnosis of malignancy associated EMD

Among the 8 patients with malignant secondary origin, 5 (62.5%) were successfully diagnosed using HMR with water swallows: one patient (with gastric signet ring cell carcinoma) diagnosed with achalasia type II and 4 patients (2 with adenocarcinoma of the cardia, 2 with esophageal squamous-cell carcinoma) were diagnosed with EGJ outflow obstruction confirmed by HRM with solid swallows. The remaining 3 patients (37.5%), had a normal exam using HRM with water swallows. The disorder was successfully diagnosed only when they underwent HRM with solid swallows: 2 patients with jackhammer disorder (gastric adenocarcinoma, pancreatic adenocarcinoma) and 1 patient with EGJ outflow obstruction in (adenocarcinoma of the cardia). Noteworthy, all patients had a normal endoscopy at the time of the HRM, the diagnosis of malignancy being confirmed on CT and/or EUS or even on subsequent endoscopies.

Risk factors associated with secondary EMD: Comparison of the "Positive" and "Negative" groups

As shown in **Table 3**, there was no significant difference in gender, mean age, alcohol history, diabetes, radiotherapy, or a history of other cancers between the "Positive" and "Negative" groups. The two factors that appeared significantly different between "Positive" and "Negative" groups were the rate of smokers (P = 0.03) and the rate of patients at least 58-year-old (93.8% *vs* 65.7%, P = 0.02). There was no significant difference in the symptoms leading to a manometric indication between the two groups.

Of note, characteristics of explored patients were not different from unexplored patients, except for dysphagia that was more prevalent in the explored group.

As shown in **Table 4**, there was no significant difference between the two groups for the LES relaxation pressure, the IRP or the DCI recorded by HRM either with water or solid swallows. However, 100% of patients in the "Positive" group had an IRP greater than 10 mmHg for water swallows, whereas they were only 58.4% in the "Negative" group (P = 0.0006). This last criteria remains significant once achalasia patients have been excluded (P = 0.0002).There was no significant difference in HRM diagnosis between the two groups.

Discussion

The present study highlighted the advantages of carrying out a morphological assessment during the diagnosis of suspected secondary EMD with esophageal HRM. In our series, a conventional diagnosis with HRM was not enough to detect an organic origin of the motility disorder, hence the interest of additional imaging investigations such as EUS or CT-scan. We also found that smoking, an age $\geq$ 58-years and IRP for water swallows higher than 10mmHg are risk factors for a potential suspected secondary EMD.

After an EMD diagnosis using HRM, 182 out of 502 patients with suspected secondary EMD underwent EUS and/or CT-scan to identify a possible secondary origin of their EMD. Characteristics of patients were not different between the explored and non explored groups, except for dysphagia that was more prevalent in the explored group. This is however unlikely to explain by itself why patients where explored or not as the difference, although significant, is only 10% between the two groups.

According to the analysis performed by the panel expert, 16 patients (8.8%) were considered to have specific motility disorders with secondary origin. These findings are in contrast with recent findings suggesting that EUS have limited contribution in achalasia or other EMD diagnosis[16]. However, our findings are consistent with the majority of imaging investigations used to identify a secondary origin of achalasia [10–14, 17].EUS was useful to rule out a pseudoachalasia in doubtful cases; when a thickened circular muscle layer is observed, infiltrating tumor is rejected , therefore providing supportive evidence of achalasia[10, 12]. For these reason, the American College of Gastroenterology advises an endoscopic assessment of the EGJ and gastric cardia if pseudoachalasia is suspected[17].However in patients with negative EUS but suspected pseudoachalasia, CT or other cross-sectional imaging is necessary. CT-scan is useful in differentiating primary and secondary achalasia[13].

Among the 16/182 (8.8%) patients with secondary motility disorders, eight patients (4.4%) were diagnosed with secondary malignant origin. These proportion are comparable with previous studies reported rates of pseudoachalasia between 4% and 12.5%[10, 12, 18, 19].

However, these studies were performed only with patients with secondary achalasia and did not include other motility disorders. In our study, we identified only 3 cases with secondary achalasia; among them only one case had malignant secondary origin (gastric signet ring cell carcinoma) and the two other patients had benign secondary origin (lipoma and leiomyoma). Most of motility disorders in patients with secondary EMD were EGJ outflow obstruction (n = 7), and jackhammer disorder (n = 4). Beyond specific EMD, we also found 2 patients diagnosed with localized pressurization secondary to benign and doubtful mediastinal lymphadenopathy origin. These findings highlight the importance of the morphological assessment of all EMD phenotypes. Surprisingly, EGD negative (including systematic biopsies) preceding the HRM were all negative in the two patients further diagnosed with cardia adenocarcinoma. Whether the strategy to perform a second endoscopy instead of a combined second endoscopy associated with an EUS remains to be evaluated in a larger population study.

In order to avoid anesthesia risks and to reduce the examinations costs, it seemed important to target the population for which a morphological assessment is most relevant. We found that 100% of our “Positive” group patients had an IPR higher than 10mmHg for water swallows, 93.5% were aged of 58 years or older (one patient was 29-year-old and had a cardiac adenocarcinoma) and half of them had a smoking history. Our findings are consistent with 8 reports studying 28 cases of pseudoachalasia. After exclusion of 9 cases with unavailable detailed information, 84% of patients were ≥ 60-year-old at the time of diagnosis[20–27]. Ponds et al.[10] suggested that an age≥55 year-old was a the factor for potential malignancy associated pseudoachalasia. In another series including five patients with pseudoachalasia, four (80%) were 54-year-old or older (only one patient was 28-year-old had a leiomyomatosis of the gastric cardia) and four (80%) had a IRP higher than 13 mmHg (one patient had non available data)[28]. Comparably, Our study suggest that smoking, age of 58-year-old or older and an IRP higher than 10mmHg for water swallows are risk factors that indicate potential secondary EMD.

Use of HRM has improved the accuracy and diagnostic yield of clinical investigation in patients with suspected EMD[6].However, our results showed that HRM findings based on water swallows alone failed to detect motility disorders in 4 out of 16 (25%) cases with secondary origin (3 of them had malignant secondary origin). Their disorders were diagnosed only when HRM with solid swallows was performed. This is in favor of additional examination. The performance of a esophageal HRM is generally carried out on 10 water swallows, but this approach may not be clinically relevant for the diagnosis of disorders with symptoms occurring only during the ingestion of solid foods. HRM measurements with solid swallows are more sensitive to clinically relevant dysfunction, to identify the cause of symptoms and guide effective management[29, 30].In the present study, multiple rapid swallows or rapid drink challenge tests data are unfortunately lacking although recent studies suggest these may be of use in such patients [31]. Further studies are warranted to evaluate if these parameters may also be predictive of secondary EMD.

In our study, there was a lack of distinction between EUS and Computed Tomography. The EUS allows precise information of the esophageal wall but has a low sensitivity in the detection of off-site injuries whereas the CT-scan allows a good analysis of injuries far from the esophagus but is not very sensitive in the detection of esophageal wall intrinsic anomalies. This is in favor of the complementarities of these two exams.

Our study presents some limitations. First, it is a retrospective study where available data, especially clinical, are collected from medical files of patients, which can lead to an information bias. Second, a majority of patients in our cohort were not explored. This did not mean however, that these patients had no secondary EMD. Our study provides even clues to speculate they may have similar rates of secondary EMD. Indeed, patients of explored and non explored group were comparable in term of age, gender, symptoms, and HRM metrics. We can therefore speculate that these parameters did not guided clinicians to perform additional exploration. However, weight loss or co-morbidities were note systematically recorded in our cohort due to the retrospective nature of the study. These parameters may nevertheless have participated in clinician's choice. Other aspects may have also taken part in clinician's choice. These include the anticipation of a low detection rate, which was however unknown until our study was conducted. In addition, the unavailability of the exploration, in particular EUS, at different center may have also influence the performance of additional tests. The different rate of additional exploration in our study varied from 13.6% to 62.5% across centers, which may reflect limited access in a region (Normandy) where inequity in the access to healthcare providers has already been pointed out [32].

Lastly, the size of the present cohort may be viewed as small. However, when compared with the existing literature, the number of patients analyzed is comparable and even superior to the majority of studies on secondary esophageal motor disorders. Indeed, they reciprocally included 62 [31], 333 [10], 28 [13], and 69 patients [16].The small number of secondary EMD of our series limits the statistical interpretation and the possibility of highlighting differences between "positive" and "negative" patterns. The causal link between the morphological abnormalities and MHR data was validated by a committee of independent experts who discardedseven abnormalities of malignant or doubtful origin. However, several reports presented cases of pseudoachalasia secondary to pleural mesothelioma[33]–[38], pancreatic[39] or hepatobiliary [40, 41], pulmonary[21, 23, 26, 42], or lymphnode metastases[43]. Furthermore, other 23 morphological abnormalities with no malignant origin were not retained by the panel of experts. This shows the difficulties encountered to judge the accountability between morphological abnormalities and manometric diagnosis.

In order to limit these biases, prospective multicenter studies should be performed to confirm these results and to determine more precisely the incidence of secondary esophageal motility disorders in the French population.

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References

[1] Galmiche JP, Clouse RE, Bálint A, Cook IJ, Kahrilas PJ, Paterson WG, et al. Functional Esophageal Disorders. Gastroenterology 2006:130;1459-65. doi: 10.1053/j.gastro.2005.08.060.

[2] Marlais M, Fishman JR, Fell JME,. Haddad MJ, Rawat DJ UK incidence of achalasia: an 11-year national epidemiological study . Archives of Disease in Childhood, 2011:96; 192-194. doi: 10.1136/adc.2009.171975.

[3] Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: Prevalence, severity, and response to proton pump inhibitor treatment. Clinical Gastroenterology and Hepatology 2004:2; 665-668. doi: 10.1016/S1542-3565(04)00289-7.

[4] Rohof WO, Bredenoord AJ. Chicago Classification of Esophageal Motility Disorders: Lessons Learned . Curr Gastroenterol Rep 2017:19;37. doi: 10.1007/s11894-017-0576-7.

[5] Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ et al. « The Chicago Classification of esophageal motility disorders, v3.0 ». Neurogastroenterol. Motil. 2015:27;160-174. doi: 10.1111/nmo.12477.

[6] Ivashkin VT, Maev IV, Trukhmanov AS, Storonova OA, Kucheryavyi YA, Barkalova EV et al. High resolution manometry and new classification of esophageal motility disorders. Ter. Arkh.2018:90;93-100 doi: 10.26442/terarkh201890593-100.

[7] Park JH, Park DI, Kim HJ, Cho YK, Sohn CI, Jeon WK et al. An Unusual Case of Submucosal Invasion of Esophageal Squamous Cell Carcinoma Mistaken as Primary Achalasia. J Neurogastroenterol Motil 2010:16;194-198. doi: 10.5056/jnm.2010.16.2.194.

[8] Segal J,Lagundoye A, Carter M. Achalasia leading to diagnosis of adenocarcinoma of the oesophagus . BMJ Case Reports 2017:bcr-2017-219386. doi: 10.1136/bcr-2017-219386.

[9] Abubakar U, Bashir M et Kesieme E. Pseudoachalasia: A review . Niger J Clin Pract 2016:19,303. doi: 10.4103/1119-3077.179275.

[10] Ponds FA ,van Raath MI, Mohamed SM,. Smout AJ Bredenoord AJ. Diagnostic features of malignancy-associated pseudoachalasia . Aliment Pharmacol Ther, 2017:45;1449-1458. doi: 10.1111/apt.14057.

[11] Dancygier H , Classen M. Endoscopic ultrasonography in esophageal diseases . Gastrointestinal Endoscopy, 1989:35;220-225. doi: 10.1016/S0016-5107(89)72762-0.

[12] Ziegler K, Sanft C, Friedrich M, Gregor M, Riecken EO. Endosonographic appearance of the esophagus in achalasia. Endoscopy 1990:22;1-4. doi: 10.1055/s-2007-1012776.

[13] Licurse MY, Levine MS, Torigian DA, Barbosa EM. Utility of chest CT for differentiating primary and secondary achalasia. Clinical Radiology 204:69;1019-1026. doi: 10.1016/j.crad.2014.05.005.

[14] Krishnan K, Lin CY. Keswani R, Pandolfino JE, Kahrilas PJ, Komanduri S. Endoscopic ultrasound as an adjunctive evaluation in patients with esophageal motor disorders subtyped by high-resolution manometry. Neurogastroenterol Motil.2014:26;1172-1178. doi: 10.1111/nmo.12379.

[15] Rabushka LS, Fishman EK, Kuhlman JE. CT Evaluation of Achalasia . Journal of Computer Assisted Tomography1991:15;434-439. doi: 10.1097/00004728-199105000-00016.

[16] Oumrani S, Barret M, Roseau G, Brieau B, Leblanc S, Coriat R,et al. Do we need endoscopic ultrasonography for the workup of patients with esophageal motility disorder? . Clinics and Research in Hepatology and Gastroenterology. 2019:43; 608-613. doi: 10.1016/j.clinre.2019.02.005.

[17] Vaezi MF, Pandolfino JE, Vela MF. ACG Clinical Guideline: Diagnosis and Management of Achalasia . American Journal of Gastroenterology 2013:108;1238-1249. doi: 10.1038/ajg.2013.196.

[18] . Campo SMA, Zullo A, Scandavini CM, Frezza B, Cerro P, Balducci G. Pseudoachalasia: A peculiar case report and review of the literature. World J Gastrointest Endosc 2013:5;450-454. doi: 10.4253/wjge.v5.i9.450.

[19] Barthet M, Mambrini P, Audibert P, Boustière C, Helbert T, Bertolino JG et al. Relationships between endosonographic appearance and clinical or manometric features in patients with achalasia. Eur J Gastroenterol Hepatol 1998:10;559-564. doi: 10.1097/00042737-199807000-00006.

[20] Hassan WA, Darwish K, Shalan IM, Elbaki LA, Elmohsen EA, Sayed WH. Aetiologic mechanisms of dysphagia in lung cancer: A case series. Egyptian Journal of Chest Diseases and Tuberculosis 2014:63;435-442. doi: 10.1016/j.ejcdt.2013.10.017.

[21] Can B, Balli F, Korkmaz U, Yilmaz H, Can FI, Celebi A. Achalasia secondary to lung adenocarcinoma . Korean J Intern Med 2015:30;250. doi: 10.3904/kjim.2015.30.2.250.

[22] Lee HR, Lennon VA, Camilleri M, Prather CM. Paraneoplastic gastrointestinal motor dysfunction: clinical and laboratory characteristics . Am J Gastroenterol 2001:96;373-379. doi: 10.1111/j.1572-0241.2001.03454.x.

[23] Anaizi A, Rizvi-Toner A, Valestin J, Schey R. Large cell neuroendocrine carcinoma of the lung presenting as pseudoachalasia: a case report., J Med Case Reports 2015:9;56. doi: 10.1186/s13256-015-0514-y.

[24] Rozman RW , Achkar E. Features distinguishing secondary achalasia from primary achalasia . Am J Gastroenterol.1990:85;1327-1330.

[25] Liu W, Fackler W, Rice TW, Richter JE, Achkar E, Goldblum JR. The pathogenesis of pseudoachalasia: a clinicopathologic study of 13 cases of a rare entity . Am. J. Surg. Pathol. 2002:26;784-788. doi: 10.1097/00000478-200206000-00013.

[26] Hirano T, Miyauchi E, Inoue A, Igusa R, Chiba S, Sakamoto K et al. Two cases of pseudo-achalasia with lung cancer: Case report and short literature review . Respiratory Investigation 2016:54;494-499. doi: 10.1016/j.resinv.2016.04.006.

[27] Katzka DA, Farrugia G, Arora AS. Achalasia secondary to neoplasia: a disease with a changing differential diagnosis. Dis. Esophagus 2012:25;331-336. doi: 10.1111/j.1442-2050.2011.01266.x.

[28] Gockel I, Eckardt VF, Schmitt T, Junginger T. Pseudoachalasia: a case series and analysis of the literature. Scand J Gastroenterol.2005:40;378-385. doi: 10.1080/00365520510012118.

[29] Sweis R, Anggiansah A, Wong T, Brady G, Fox M. Assessment of esophageal dysfunction and symptoms during and after a standardized test meal: development and clinical validation of a new methodology utilizing high-resolution manometry . Neurogastroenterol. Motil.2014:26;215-228. doi: 10.1111/nmo.12252.

[30] Ang D, Misselwitz B, Hollenstein M, Knowles K, Wright J, Tucker E et al. Diagnostic yield of high-resolution manometry with a solid test meal for clinically relevant, symptomatic oesophageal

motility disorders: serial diagnostic study. The Lancet Gastroenterology & Hepatology 2017:2;654-661. doi: 10.1016/S2468-1253(17)30148-6.

[31] Carlson DA , Roman S. Esophageal provocation tests: Are they useful to improve diagnostic yield of high resolution manometry? NeurogastroenterolMotil 2018:30;e13321 doi: 10.1111/nmo.13321.

[32] Dejardin O, Bouvier AM, Faivre J, Boutreux S, De Pouvourville G, Launoy G. Access to care, socioeconomic deprivation and colon cancer survival. Aliment Pharmacol Ther 2008:27;940-949. doi: 10.1111/j.1365-2036.2008.03673.x.

[33] Branchi F, Tenca A, Bareggi C, Mensi C, Mauro A, Conte D et al. A Case of Pseudoachalasia Hiding a Malignant Pleural Mesothelioma. Tumori Journal 2016:102;S50-S53. doi: 10.5301/tj.5000521.

[34] Goldschmiedt M, Peterson WL, Spielberger R, Lee EL, Kurtz SF, Feldman M. Esophageal achalasia secondary to mesothelioma . Dig Dis Sci 1989:34;1285-1289. doi: 10.1007/BF01537280.

[35] Lopez-Liuchi JV, Kraytem A, Uldry PY. Oesophageal achalasia secondary to pleural mesothelioma . J R Soc Med 1999:92;24-25. doi: 10.1177/014107689909200111.

[36] Hostein J, Gignoux C, Roget L, Théry JP, Fournet J. Achalasia of the lower esophageal sphincter caused by pleural mesothelioma. Gastroenterol. Clin. Biol.1984:8;880-881.

[37] Saino G, Bona D, Nencioni M, Rubino B, Bonavina L. Laparoscopic diagnosis of pleural mesothelioma presenting with pseudoachalasia. World J Gastro 2009:15;3569. doi: 10.3748/wjg.15.3569.

[38] Seki H, Matsumoto K, Ohmura K, Fukushi Y, Fujita T, Kiriyama H et al. Malignant Pleural Mesothelioma Presenting as Achalasia. Inter Med 1994:33;4. DOI: 10.2169/internalmedicine.33.624

[39] Kim HM, Chu JM, Kim WH, Hong SP, Hahm KB, Ko KH. Extragastroesophageal Malignancy-Associated Secondary Achalasia: A Rare Association of Pancreatic Cancer Rendering Alarm Manifestation. Clin Endosc 2015:48;328. doi: 10.5946/ce.2015.48.4.328.

[40] . Choi AD, Moles V, Fuisz A, Weissman G. Cardiac magnetic resonance in myocarditis from adult onset Still's disease successfully treated with anakinra . International Journal of Cardiology 2014:172;e225-e227.doi: 10.1016/j.ijcard.2013.12.151.

[41] García-Alonso F, Hernández Tejero M, Castanon-Deprit A. Hepatobiliary and Pancreatic: Pseudoachalasia from pancreatic cancer: Education and Imaging . J Gastroenterol Hepatol 2015:30;1336-1336. doi: 10.1111/jgh.12961.

[42] Jian H, Ming G, Shuai S, Tianyou W, Dong C. Case report of achalasia secondary to a lung carcinoma of the mediastinal type: Achalasia secondary to lung carcinoma. Dis Esophagus 2016:29;891-893. doi: 10.1111/dote.12313.

[43] Lahbabi M, Ihssane M, Sidi Adil I, Dafr Allah B. Pseudoachalasia secondary to metastatic breast carcinoma mimicking radiation stenosis. Clinics and Research in Hepatology and Gastroenterology 2012:36;e117-e121. doi: 10.1016/j.clinre.2012.05.016.

Tables

Table 1: Clinical features of patients with suspected secondary esophageal motility disorder.

	Patients (*n*=502)
Age (years) [Mean±SD]	61.2 ±16,4
Gender: n (%)	
Male	195 (38 .8%)
Female	307 (61.2%)
Symptoms	
Dysphagia	382 (76.1%)
Gastroesophageal reflux	52 (10.4%)
Retrosternal or epigastric pain	49 (9.8%)
Regurgitation	41 (8.2%)
Alteration of health status	34 (6.8%)
Preoperative check-up	19 (3.8%)

SD: Standard deviation.

Table 2.: Diagnostic features of patients with secondary esophageal motility disorder

	Malignant origin (n=8)	Benign origin (n=5)	Doubtful origin (n=3)
Achalasia n(%)	**1 (12.5%)**	**2 (40.0%)**	-
Type I	-	-	-
Type II	Gastric signet ring cell carcinoma (n=1)	-	-
Type III	-	Lipoma (n =1) Leiomyoma (n=1)	-
EGJ outflow obstruction n (%)	**5 (62.5%)** Adenocarcinoma of the cardia (n=3) Esophageal squamous-cell carcinoma (n=2)	**1 (20.0%)** Leiomyoma (n=1)	**1 (33.3%)** Esophageal compression from subcarinal lymphadenopathy (n=1)
Jackhammer disorders n (%)	**2 (25%)** Gastric adenocarcinoma (n=1) Pancreatic adenocarcinoma (n=1)	**1 (20.0%)** Leiomyoma (n=1)	**1 (33.3%)** Right upper lobe lung mass and right mediastinal and hilar lymph node (n=1)
Localized pressurization n (%)	**-** **-**	**1 (20.0%)** Substernal goiter (n=1)	**1 (33.3%)** Mediastinal lymphadenopathy (n=1)

EGJ:esophagogastric junction

Table 3. Clinical features in the three groups: Positive, Negative and Unexplored groups

Groups	**« Positive » N= 16**	**« Negative» N=166**	**« Unexplored» N=320**	***P* value** Positive vs Negative	***P value*** Explored vs Non explored
Age (years) [Mean±SD]	66.9 ±13.3	62.3 ± 15,8	60.2 ±16,7	0.21	0,09
Age ≥ 58 years old n (%)	15 (93.8%)	109 (65.7%)	196 (61,3%)	0.02	0,77
Gender					
Male n (%)	10 (62.5%)	68 (41.0%)	117 (36.6%)	0.12	0,18
Female n (%)	6 (37.5%)	98 (59.0%)	203 (63.4%)		
History n (%)					
Tobacco	8 (50.0%)	39 (23.5%)	MD	0.03	
Alcohol	2 (12.5%)	11 (6.6%)	MD	0.32	
Diabetes	1 (6.3%)	13 (7.8%)	MD	1.00	
Radiotherapy	0 (0.0%)	7 (4.2%)	MD	1.00	
Other cancer	2 (12.5%)	14 (8.4%)	MD	0.64	
Symptoms n (%)					
Dysphagia	13 (81.3%)	135(81.3%)	233 (72.6%)	1.00	0,04
Vomiting/regurgitation	1 (6.3%)	14 (8.4%)	27 (8.4%)	1.00	1,00
Pain	0 (0.0%)	20 (12.0%)	29 (9.0%)	0.22	0,53
AHS	0 (0.0%)	13 (7.8%)	20 (6.2%)	0.25	0,71
GERD	1 (6.3%)	15 (9.0%)	36 (11.3%)	0.24	0,44

SD: Standard deviation. **AHS**: Alteration in Health Status. **GERD**:gastroesophageal reflux disease **MD** : missing data

Table 4.HRM characteristics in the three groups: Positive, Negative and Unexplored groups

	« Positive » N= 16	« Negative » N=166	« Unexplored » N=320	*P*-value Positive vs Negative
Manometry: Mean [mmHg ±SD]				
LES relaxation pressures	39.8 ±27,2	34.9 ±17,6	34.8 ± 17,9	0.76
Water IRP	24.8 ±22,6	14.6 ±10,4	14.6 ±11,1	0.12
Solid IRP	17.8 ±13,8	16.1±10,0	16.8 ±11,5	0.78
Water IRP> 10mmHg	16 (100%)	97 (58.4%)	198 (61,9%)	0.0006
Water DCI	2010.6 ±2058	2587.2±4403	2311.5±3489	0.68
Solid DCI	4272.9 ±4146	6376.1±8606	4706.9±6042	0.28
Water manometry: diagnosis : n (%)				
Normal	4 (25.0%)	36 (21.7%)	54 (16.9%)	0.75
EGJ obstruction	6 (31.5%)	34 (20.5%)	82 (25.6%)	0.34
Achalasia type I	0 (0.0%)	4 (2.4%)	8 (2.5%)	1.00
Achalasia type II	1 (6.2%)	25 (15.1%)	59 (18.4%)	0.48
Achalasia type III	2 (12.5%)	11 (6.6%)	11 (3.4%)	0.32
Spasm	0 (0.0%)	12 (7.2%)	13 (4.0%)	0.60
Jackhammer	1 (6.2%)	11 (6.6%)	16 (5.0%)	1.00
HLES alone	0 (0.0%)	21 (12.7%)	54 (16.9%)	0.22
Localized pressurization	2 (12.5%)	10 (6.0%)	22 (6.9%)	0.28
Perprandial manometry: diagnosisn (%)				
Normal	0 (0.0%)	2 (1.2%)	2 (0.6%)	1.00
EGJ Obstruction	5 (31.3%)	41 (24.7%)	80 (25.0%)	0.50
Achalasia type I	0 (0.0%)	2 (1.2%)	5 (1.7%)	1.00
Achalasia type II	0 (0.0%)	18 (10 .8%)	44 (13.8%)	0.30
Achalasia type III	1 (6.3%)	12 (7.3%)	13 (4.0%)	1.00
Spasm	1 (6.3%)	14 (8.4%)	18 (11.3%)	1.00
Jackhammer	5 (25.0%)	26 (15.7%)	39 (12.2%)	0.10
HLES alone	0 (0.0%)	8 (4.8%)	20 (6.3%)	1.00
Localized pressurization	1 (6.2%)	14 (8.4%)	27 (8.4%)	1.00

SD: Standard deviation**, IRP:** integrated relaxation pressure**, LES :**lower esophageal sphincter, **DCI** : Distal contractile integral**, EGJ:**esophagogastric junction, **HLES** : Hypertonia of lower esophageal sphincter.

Figure 1: Patient flow chart