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Necrotizing Sialometaplasia-Like Change of the Esophageal Submucosal Glands is Associated with Barrett's Esophagus

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Abstract

The esophageal submucosal glands (SMG) protect the squamous epithelium from insults such as gastroesophageal reflux disease by secreting mucins and bicarbonate. We have observed metaplastic changes within the SMG acini that we have termed oncocytic glandular metaplasia (OGM), and necrotizing sialometaplasia-like change (NSMLC). The aim of this study is to evaluate the associated clinicopathological parameters of, and to phenotypically characterize the SMG metaplasias. Esophagectomy specimens were retrospectively assessed on hematoxylin and eosin sections and assigned to either a Barrett's esophagus (BE) or non-BE control group. Clinicopathologic data was collected, and univariate analysis and multivariate logistic regression models were performed to assess the adjusted associations with NSMLC and OGM. Selected cases of SMG metaplasia were characterized. SMG were present in 82 esophagi that met inclusion criteria. On univariate analysis, NSMLC was associated with BE ($p=0.002$). There was no relationship between NSMLC and patient age, sex, tumor size, or treatment history. OGM was associated with BE ($p=0.031$). No relationship was found between OGM and patient age, sex, or tumor size. On multivariate analysis, BE was independently associated with NSMLC (odds ratio [OR] 4.95, $p=0.003$). Treatment history was also independently associated with OGM ($p=0.029$), but not NSMLC. Both NSMLC and OGM were non-mucinous ductal type epithelia retaining a p63-smooth muscle actin co-positive myoepithelial cell layer. NSMLC and OGM were present in endoscopic mucosal resection specimens. Our study suggests that SMG metaplasia is primarily a reflux-induced pathology. NSMLC may pose diagnostic dilemmas in resection specimens or when only partially represented in mucosal biopsies or endoscopic resection specimens.

Keywords

Gastroesophageal reflux disease; Barrett's esophagus; esophageal submucosal glands; necrotizing sialometaplasia; oncocytic metaplasia

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DISCLOSURES

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common chronic condition where the gastric contents repeatedly enter into the esophageal lumen [1–6]. Noteworthy complications from GERD include reflux esophagitis, mucosal erosions and ulcerations, stricture formation, and Barrett's esophagus (BE) [7–9,2,10,6,11]. The contributing factors that lead to progressive development of GERD complications are controversial and poorly defined [12–15,2,16–21].

The esophageal submucosal glands (SMG) are tubuloacinar glands that are distributed throughout the length of the esophagus and cluster around the upper and lower esophageal sphincters [22,23]. The SMG secrete a complex fluid that is rich in mucins and bicarbonate ions, and also contains transforming growth factor alpha, prostaglandin E2, and epidermal growth factor, which together function in luminal clearance and provide a pre-epithelial defense mechanism from insults such as GERD [23–25]. The basal rate of bicarbonate ion secretion in human SMG increases 3 fold to 32 fold in response to luminal acidification [26–28]. Likewise, mucin secretion increases after exposure of the esophageal mucosa to acid and pepsin [29,28]. This dynamic change in secretion of mucins and bicarbonate is evidence of the robust secretory capacity of the native esophageal mucosa and of the important role these secretions play in pre-epithelial defenses. Failure of these defenses are well documented in GERD patients and correspond to the progressive development of GERD complications [30,23,24,29,31,32,25]. The mechanism and histopathological correlate to this failure in pre-epithelial defenses are yet to be defined.

The minor salivary glands of the oral cavity and upper respiratory tract, which are histologically similar to the esophageal SMG, may undergo necrotizing sialometaplasia (NSM) [33–39]. In this process, the acini of the glands are infarcted and replaced by a squamous epithelium. In the oral cavity, the etiology of NSM is typically attributable to ischemia or traumatic vascular compromise [33,34]. In animal models, ligation of the major salivary gland arterial supply produces infarction with subsequent squamous metaplasia of the acini that is histologically identical to NSM [40,41]. In similar experiments, ligation of the excretory duct fails to produce the classic NSM pattern and indicates that duct obstruction is an unlikely cause of salivary gland NSM [41].

We have observed metaplastic changes within the esophageal SMG acini that we have termed oncocytic glandular metaplasia (OGM), and necrotizing sialometaplasia-like change (NSMLC). We hypothesize that these metaplasias arise in association with reflux-induced pathology such as BE. The aim of this study is to evaluate the clinicopathological associations of metaplasia occurring in the esophageal SMG and to phenotypically characterize the metaplastic epithelia.

MATERIALS AND METHODS

Specimen selection and case review

Institutional review board approval was obtained prior to initiating the study. A retrospective case-control design was employed to study all esophagectomy cases performed between 2003 and 2011 that were retrievable from the pathology archives. Cases that did not have

SMG apparent upon review were excluded from the study. Clinical-pathologic parameters were recorded such as age and gender, clinical history of GERD, tumor size in cm, and TNM staging parameters. History of pre-esophagectomy treatment was tabulated as either chemotherapy and/or radiation therapy; surgical treatment/other treatment (i.e. endoscopic mucosal resection, Barrett's segment ablation, fundoplication, myotomy, or partial surgical resection); or untreated. Cases that received a combination of chemo/radiation and surgery were grouped with chemo/radiation/combined.

At the initiation of the study, the electronic medical records were thoroughly reviewed for a clinical or endoscopic history of BE, and previous in house and outside pathology reports were reviewed in addition to reviewing the final esophagectomy specimen before assigning the case to a study group. Cases that could not be confidently classified to a group were excluded from the study. Formalin fixed paraffin embedded tissue sections routinely stained with hematoxylin and eosin were assessed for the presence of SMG, OGM, and NSMLC (See results section for histopathological definitions). SMG involved by or adjacent to tumor were excluded from analysis to avoid tumor-induced changes of the SMG. SMG acini that had recognizable radiation-induced changes were also excluded from tabulation. To denote tumors arising outside of the anatomic esophagus and gastroesophageal junction (GE junction) as having no relevant mass effect within the esophagus a tumor size of 0, a grade and TNM stage of GX, TX, and NX were respectively assigned. Six pediatric autopsy cases that contained SMG were studied to confirm baseline histology. Additionally, endoscopic mucosal resection (EMR) specimens were evaluated for SMG metaplasia.

Statistical analysis

Student's t-test and Fisher's exact test were used to compare the study groups. The potential confounding variables assessed were age, sex, tumor size (cm), and treatment history. T stage was excluded from analysis due to the strong relationship with tumor size. The univariate association of each variable with each outcome, NSMLC and OGM, was assessed using the chi-squared test and ANOVA. Multivariate logistic regression models were run including BE, and the remaining covariates were entered subject to a backward variable selection method with an alpha=0.25 removal criteria from the model. The significance level was set as 0.05. Semiquantitative scores from the immunohistochemical and histochemical stains were compared by Student's t-test. The analysis was performed using SAS 9.3 (SAS Institute, Cary, NC).

Immunohistochemical and histochemical stains

Antibodies to CK19, p63, smooth muscle actin (SMA)[42], and Ki67 (MIB-1) were used in the dilutions shown in the Supplemental Tables. The Bond Polymer Refine Detection Kit (using a DAB chromogen; Leica Microsystems, Bannockburn, IL) was used as a secondary visualization system. All immunohistochemistry were routinely performed with defined protocols performed on the Leica Bond Maxx III automated system and counterstained with hematoxylin. For Alcian Blue-PAS staining slides were deparaffinized, stained in Alcian Blue (pH 2.5) for 30 minutes then 1% periodic acid for 5 minutes, and followed by Schiff reagent for 15 minutes at room temperature. The slides were counter stained with Nuclear Fast Red (Sigma-Aldrich, St. Louis, MO). The immunohistochemical and histochemical

stains were qualitatively analyzed due to the focal nature of the SMG. Semiquantitative scoring of the histochemical and immunohistochemical stains were undertaken on a per foci basis utilizing the following scoring system: 0- no staining/negative, 1 – weak/focal staining, 2 – strong focal/patchy staining, 3 – strong diffuse staining.

RESULTS

Definition and distribution of metaplastic changes occurring within the esophageal submucosal glands

Upon evaluation of the 6 pediatric autopsy cases, appreciable metaplastic changes within the SMG were not present. Normal glands were those composed of mucinous acinar cells arranged in lobules with a centrally to eccentrically located excretory duct (Figure 1A, B). This was similar to the normal adult SMG morphology that has previously been defined [23,22].

Two types of metaplastic change were repeatedly identified in the SMG. Necrotizing sialometaplasia-like change (NSMLC) was defined as the replacement of acini with duct-like structures composed of a single layer of flat to cuboidal epithelium that displays dilation/ectasia. True stratified squamous epithelium was rare but was identified on occasion. Cytologically, the nuclei were condensed, round to oval, and basally located. The change replaced the majority of acini or prominently occupied a lobule. The metaplastic ductal structures were accompanied by an increase in chronic inflammatory cells, and reactive lymphoid follicles could occasionally be found. The basement membranes were often thickened. The SMG stroma exhibited fibrosis and sometimes desmoplasia-like changes. An acute necrotizing phase, an organizing phase, and the stable NSMLC phase could be recognized (Figure 1; D–F). In the necrotizing phase, the acini are destroyed and an acute inflammatory reaction is found along with reactive stratified ductules. Organization can be recognized by a predominant histiocytic mononuclear cell infiltrate surrounding the ectatic ductules (not shown). The stable phase is characterized by the ectatic ductules that have replaced either a portion of or the entire SMG lobule accompanied by varying degrees of chronic inflammation and stromal fibrosis. NSMLC was observed underlying the gastroesophageal junction, normal squamous epithelium, areas of erosive esophagitis, ulcerations, and segments of intestinal metaplasia (IM) (Figure 2; A–D). Most cases exhibited focal NSMLC but many demonstrated extensive NSMLC throughout the sampled tissue.

Second, oncocytic glandular metaplasia (OGM) has previously been described in relation to intramural pseudodiverticulosis [43]. We have defined OGM as replacement of the SMG acini by oncocytes, cells having abundant granular eosinophilic cytoplasm and a condensed round centrally to apically located nucleus (Figure 1C). OGM was focal or extensive, occurring under intact squamous or intestinalized epithelium and an associated chronic inflammatory infiltrate sometimes accompanied OGM.

Clinicopathological characteristics of the esophagectomy study group

An initial group of 115 esophagectomy cases were reviewed. Of the 115 cases, 84 cases had SMG present and 31 cases were excluded due to no SMG being present for evaluation. Of the 84 cases with SMG present, 82 could be confidently assigned to a study group. It was not possible to determine if the patient carried a history of BE due to a lack of clinical history in 2 cases and therefore the cases were excluded due to inadequate information to confidently assign the case to a study group (See Supplemental Figure 1). Statistical analysis was performed with 82 cases of the original 115 (71%) and the clinicopathological characteristics of these cases are displayed in Table 1 (and Supplemental Tables). There were no statistically significant differences between the non-BE control group and the BE group in preoperative treatment history or tumor size. There were statistically significant differences between the study groups for patient age and sex (See Table 1). The indications for the 82 esophagectomy cases are as follows: adenocarcinoma 43 (52%), laryngeal squamous cell carcinoma 9 (11%), esophageal squamous cell carcinoma 9 (11%), achalasia 5 (6%), high grade columnar dysplasia arising in a background of Barrett's esophagus 4 (5%), stricture 3 (4%), hiatal hernia 2 (2%), incompetent lower esophageal sphincter 1 (1%), fistula 1 (1%), gastrointestinal stromal tumor 1 (1%), melanoma 1 (1%), metastatic lung carcinoma 1 (1%), erosion 1 (1%), perforation 1 (1%). There were a total of 18 cases of adenocarcinoma or high grade columnar dysplasia occurring at the GE junction. Of these, 12 cases were assigned to the BE group and 6 were assigned to the non-BE control group.

The majority of NSMLC was found in esophagectomy cases performed for adenocarcinoma. However, NSMLC was found in two of four cases of BE related high grade columnar dysplasia and in four BE cases where the primary tumor was non-BE related (squamous cell carcinomas [n=3] and metastatic melanoma [n = 1]). The indication for esophagectomy in the non-BE control group was more heterogeneous. In the non-BE control group, NSMLC was found in eight cases; three in patients with documented clinical history of GERD and four in patients with achalasia (three of which had undergone myotomy).

Clinicopathological parameters associated with metaplasia of the submucosal glands

Univariate and multivariate analyses were performed utilizing the 82 cases that contained SMG. The characteristics of these cases are displayed in the Supplemental Tables.

NSMLC was found in 33 (40%) of total cases, 8 (22%) of the non-BE controls, and in 25 (56%) of BE cases. OGM was found in 44 (54%) of the total cases, 15 (41%) of non-BE controls, and in 29 (64%) of the BE cases. On univariate analysis (Table 2) BE was associated with both NSMLC and OGM. There was no relationship between NSMLC and patient age, sex, tumor size, or treatment history. OGM was negatively associated with a history of treatment. No relationship was found between OGM and patient age, sex, or tumor size.

On multivariate analysis (Table 3; Supplemental Tables) BE was strongly associated with NSMLC but not OGM. History of treatment was not significantly associated with NSMLC, but a history of chemo/radiation/combined (OR 0.28, $p=0.018$) and surgery/other (OR 0.27, $p=0.043$) were both negatively associated with OGM compared to no treatment.

Evaluation of endoscopic mucosal resection specimens

In addition to reviewing esophagectomy specimens for SMG metaplasia, we evaluated EMR specimens. Of the 25 EMR cases evaluated, 9 (36%) cases had SMG present (Supplemental Table 5). NSMLC was present in 5/9 (56%), and OGM was present in 6/9 (67%). These cases were not included in the detailed clinicopathological analysis.

Phenotype of the submucosal gland metaplasia

To characterize the differentiation of the metaplastic cell types, a panel of immunohistochemical and histochemical markers was performed in a subset of cases (Figure 3; Table 4). The normal SMG phenotype has previously been defined [42].

In general, the epithelia of the metaplastic SMG had statistically significant decreases in staining intensity of SMA and AB-PAS, and statistically significant increases in staining intensity of CK19 and MIB-1 (Table 4). NSMLC demonstrated strong CK19 expression with no mucin detectable by Alcian Blue-PAS staining, and consistent nuclear MIB-1 labeling. The lobules demonstrated an SMA-p63 copositive myoepithelial cell layer on immunohistochemistry. The oncocytes of OGM displayed a similar profile to NSMLC but with fewer MIB-1 positive cells (Figure 3).

DISCUSSION

The data presented here indicate that the esophageal SMG undergo metaplasia in Barrett's esophagus. Specifically, we have recognized a process resembling necrotizing sialometaplasia (NSM) of the oral cavity minor salivary glands [34], hence the term necrotizing sialometaplasia-like change. BE was strongly associated with NSMLC on univariate and multivariate regression analysis. NSMLC was mostly observed underlying normal squamous epithelium and segments of IM in patients with BE. OGM is associated with BE on univariate analysis but this association does not hold on multivariate analysis. Evaluation of EMR specimens confirmed the presence of these lesions in this specimen type at a comparable frequency to the esophagectomy specimens. Furthermore, our data did not find a statistical relationship between tumor size, patient age, or a history of pre-esophagectomy treatment and NSMLC; thus, confounding factors such as mass effect or effects from chemotherapy, radiation, or surgical manipulation are unlikely to contribute to the development of NSMLC. Interestingly, OGM was found to be negatively associated with a history of treatment.

Although we designed our inclusion and exclusion criteria so that we could accurately assign cases to a study group (Supplemental Figure 1), it is not impossible for an intestinalized segment of esophagus to have been destroyed by the invasive tumor at the GE junction and be inaccurately assigned to the non-BE control group. However, only 6 cases of adenocarcinoma occurring at the GE junction were assigned to the non-BE control group and therefore, this scenario is unlikely to introduce a significant amount error into the study. Likewise, all of the 12 BE group cases with adenocarcinoma or high grade columnar dysplasia occurring at the GE junction could be confidently assigned to this study group due

to the presence of intestinal metaplasia within the tubular esophagus or a documented history of BE.

The phenotypic characteristics of NSMLC are that of ductal epithelium with a myoepithelial cell layer (Table 4). This fact may be helpful in resection specimens where NSMLC may mimic squamous cell carcinoma or adenocarcinoma, and pose diagnostic dilemmas in assessing tumor involvement of the submucosa or at margins of resection. In these instances, NSMLC can be distinguished due to its lobular architecture or with immunohistochemistry for myoepithelial markers. NSMLC was found in several EMR specimens and may pose a diagnostic difficulty in this context as well. Another diagnostic issue may arise in mucosal biopsies or endoscopic mucosal resections in which partial sampling of the submucosa yields only the necrotizing phase of NSMLC with epithelial cells floating in extravasated mucin, a scenario mimicking mucinous adenocarcinoma. Pathologists aware of the phases of NSMLC may avoid these potential diagnostic pitfalls.

The distribution of where NSMLC occurs offers insights into its etiology. NSMLC can be observed under segments of intestinal metaplasia and normal squamous epithelium in BE patients, underlying segments of reflux esophagitis, and at the gastroesophageal junction in patients with GERD. These findings suggest that NSMLC is due to reflux and not necessarily a direct effect of Barrett's esophagus. Furthermore, an association between oral NSM and bulimia is emerging [44–47], and lends support to a relationship between acidic refluxate and tubuloacinar gland necrosis.

The physiological implications of NSMLC are clear: destroying the SMG acini would decrease the intrinsic secretory capacity of the esophagus. Hence, our findings can be regarded as a putative explanation for the impaired mucosal secretory capacity found in GERD patients. As such, we propose that GERD impairs pre-epithelial defenses via destruction of the submucosal glands, which may contribute to the progressive development of GERD complications such as BE.

In summary, our data indicates that BE is strongly associated with NSMLC. Our study suggests that NSMLC is the result of reflux-induced pathology. NSMLC may pose diagnostic challenges in esophagectomy specimens, endoscopic mucosal resections, or mucosal biopsies that incompletely sample the submucosa.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hershcovici T, Gasiorowska A, Fass R. Advancements in the analysis of esophageal pH monitoring in GERD. *Nature reviews Gastroenterology & hepatology*. 2011; 8 (2):101–107.10.1038/nrgastro.2010.212 [PubMed: 21293510]
2. Kandulski A, Malfertheiner P. Gastroesophageal reflux disease--from reflux episodes to mucosal inflammation. *Nature reviews Gastroenterology & hepatology*. 2012; 9 (1):15–22.10.1038/nrgastro.2011.210 [PubMed: 22105108]
3. Hershcovici T, Fass R. Gastro-oesophageal reflux disease: beyond proton pump inhibitor therapy. *Drugs*. 2011; 71 (18):2381–2389.10.2165/11597300-000000000-00000 [PubMed: 22117130]
4. Kandulski A, Malfertheiner P. GERD in 2010: diagnosis, novel mechanisms of disease and promising agents. *Nature reviews Gastroenterology & hepatology*. 2011; 8 (2):73–74.10.1038/nrgastro.2010.220 [PubMed: 21293505]
5. Ang D, Sifrim D, Tack J. Mechanisms of heartburn. *Nature clinical practice Gastroenterology & hepatology*. 2008; 5 (7):383–392.10.1038/ncpgasthep1160
6. Mastracci L, Spaggiari P, Grillo F, Zentilin P, Dulbecco P, Ceppa P, Baccini P, Mansi C, Savarino V, Fiocca R. Microscopic esophagitis in gastro-esophageal reflux disease: individual lesions, biopsy sampling, and clinical correlations. *Virchows Archiv: an international journal of pathology*. 2009; 454 (1):31–39.10.1007/s00428-008-0704-8 [PubMed: 19048292]
7. Reid BJ, Li X, Galipeau PC, Vaughan TL. Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer*. 2010; 10 (2):87–101. nrc2773 [pii]. 10.1038/nrc2773 [PubMed: 20094044]
8. Winters C Jr, Spurling J, Chobanian SJ, et al. Barrett's esophagus: a prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology*. 1987; 92:118–124. [PubMed: 3781178]
9. Fiocca R, Mastracci L, Riddell R, Takubo K, Vieth M, Yerian L, Sharma P, Fernstrom P, Ruth M. Development of consensus guidelines for the histologic recognition of microscopic esophagitis in patients with gastroesophageal reflux disease: the Esohisto project. *Hum Pathol*. 2010; 41 (2):223–231.10.1016/j.humpath.2009.07.016 [PubMed: 19800099]
10. Fiocca R, Mastracci L, Engstrom C, Attwood S, Ell C, Galmiche JP, Hatlebakk J, Junghard O, Lind T, Lundell L. Long-term outcome of microscopic esophagitis in chronic GERD patients treated with esomeprazole or laparoscopic antireflux surgery in the LOTUS trial. *Am J Gastroenterol*. 2010; 105 (5):1015–1023.10.1038/ajg.2009.631 [PubMed: 19904246]
11. Chandrasoma PT, Lokuhetty DM, Demeester TR, Bremmer CG, Peters JH, Oberg S, Groshen S. Definition of histopathologic changes in gastroesophageal reflux disease. *Am J Surg Pathol*. 2000; 24 (3):344–351. [PubMed: 10716147]
12. Cameron AJ, Arora AS. Barrett's esophagus and reflux esophagitis: is there a missing link? *Am J Gastroenterol*. 2002; 97 (2):273–278.10.1111/j.1572-0241.2002.05454.x [PubMed: 11866261]
13. Lee J, Anggiansah A, Anggiansah R, Young A, Wong T, Fox M. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association*. 2007; 5 (12):1392–1398.10.1016/j.cgh.2007.08.011 [PubMed: 17936081]
14. Malfertheiner P, Nocon M, Vieth M, Stolte M, Jaspersen D, Koelz HR, Labenz J, Leodolter A, Lind T, Richter K, Willich SN. Evolution of gastro-oesophageal reflux disease over 5 years under routine medical care--the ProGERD study. *Alimentary pharmacology & therapeutics*. 2012; 35 (1):154–164.10.1111/j.1365-2036.2011.04901.x [PubMed: 22070159]
15. Pace F, Bianchi Porro G. Gastroesophageal reflux disease: a typical spectrum disease (a new conceptual framework is not needed). *Am J Gastroenterol*. 2004; 99 (5):946–949.10.1111/j.1572-0241.2004.04164.x [PubMed: 15128365]
16. Falkenback D, Oberg S, Johnsson F, Johansson J. Is the course of gastroesophageal reflux disease progressive? A 21-year follow-up. *Scandinavian journal of gastroenterology*. 2009; 44 (11):1277–1287.10.3109/00365520903314157 [PubMed: 19891578]
17. Isolauri J, Luostarinen M, Isolauri E, Reinikainen P, Viljakka M, Keyrilainen O. Natural course of gastroesophageal reflux disease: 17–22 year follow-up of 60 patients. *Am J Gastroenterol*. 1997; 92 (1):37–41. [PubMed: 8995934]

18. Pace F, Bollani S, Molteni P, Bianchi Porro G. Natural history of gastro-oesophageal reflux disease without oesophagitis (NERD)--a reappraisal 10 years on. *Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2004; 36 (2):111–115.10.1016/j.dld.2003.10.012
19. Gutschow CA, Bludau M, Vallbohmer D, Schroder W, Bollschweiler E, Holscher AH. NERD, GERD, and Barrett's esophagus: role of acid and non-acid reflux revisited with combined pH-impedance monitoring. *Digestive diseases and sciences*. 2008; 53 (12):3076–3081.10.1007/s10620-008-0270-6 [PubMed: 18438712]
20. Martinek J, Benes M, Hucl T, Drastich P, Stirand P, Spicak J. Non-erosive and erosive gastroesophageal reflux diseases: No difference with regard to reflux pattern and motility abnormalities. *Scandinavian journal of gastroenterology*. 2008; 43 (7):794–800.10.1080/00365520801908928 [PubMed: 18584517]
21. Malfertheiner P, Lind T, Willich S, Vieth M, Jaspersen D, Labenz J, Meyer-Sabellek W, Junghard O, Stolte M. Prognostic influence of Barrett's esophagus and *Helicobacter pylori* infection on healing of erosive gastro-oesophageal reflux disease (GORD) and symptom resolution in non-erosive GORD: report from the ProGORD study. *Gut*. 2005; 54 (6):746–751.10.1136/gut.2004.042143 [PubMed: 15888776]
22. DeNardi FG, Riddell RH. The normal esophagus. *Am J Surg Pathol*. 1991; 15 (3):296–309. [PubMed: 1996732]
23. Long JD, Orlando RC. Esophageal submucosal glands: structure and function. *Am J Gastroenterol*. 1999; 94 (10):2818–2824.10.1111/j.1572-0241.1999.1422_b.x [PubMed: 10520827]
24. Sarosiek J, McCallum RW. Mechanisms of oesophageal mucosal defence. *Bailliere's best practice & research. Clinical gastroenterology*. 2000; 14 (5):701–717.10.1053/bega.2000.0119 [PubMed: 11003804]
25. Niv Y, Fass R. The role of mucin in GERD and its complications. *Nature reviews Gastroenterology & hepatology*. 2012; 9 (1):55–59.10.1038/nrgastro.2011.211
26. Meyers RL, Orlando RC. In vivo bicarbonate secretion by human esophagus. *Gastroenterology*. 1992; 103 (4):1174–1178. [PubMed: 1397875]
27. Brown CM, Rees WD. Human oesophageal bicarbonate secretion: a phenomenon waiting for a role. *Gut*. 1997; 40 (5):693–694. [PubMed: 9203955]
28. Namiot Z, Sarosiek J, Rourk RM, Hetzel DP, McCallum RW. Human esophageal secretion: mucosal response to luminal acid and pepsin. *Gastroenterology*. 1994; 106 (4):973–981. [PubMed: 8144002]
29. Marcinkiewicz M, Han K, Zbroch T, Poplawski C, Gramley W, Goldin G, Sarosiek J. The potential role of the esophageal pre-epithelial barrier components in the maintenance of integrity of the esophageal mucosa in patients with endoscopically negative gastroesophageal reflux disease. *Am J Gastroenterol*. 2000; 95 (7):1652–1660.10.1111/j.1572-0241.2000.02198.x [PubMed: 10925964]
30. Brown CM, Rees WD. Review article: factors protecting the oesophagus against acid-mediated injury. *Alimentary pharmacology & therapeutics*. 1995; 9 (3):251–262. [PubMed: 7654887]
31. Rourk RM, Namiot Z, Edmunds MC, Sarosiek J, Yu Z, McCallum RW. Diminished luminal release of esophageal epidermal growth factor in patients with reflux esophagitis. *Am J Gastroenterol*. 1994; 89 (8):1177–1184. [PubMed: 8053431]
32. Namiot Z, Sarosiek J, Marcinkiewicz M, Edmunds MC, McCallum RW. Declined human esophageal mucin secretion in patients with severe reflux esophagitis. *Digestive diseases and sciences*. 1994; 39 (12):2523–2529. [PubMed: 7995174]
33. Brannon RB, Fowler CB, Hartman KS. Necrotizing sialometaplasia. A clinicopathologic study of sixty-nine cases and review of the literature. *Oral surgery, oral medicine, and oral pathology*. 1991; 72 (3):317–325.
34. Carlson DL. Necrotizing sialometaplasia: a practical approach to the diagnosis. *Archives of pathology & laboratory medicine*. 2009; 133 (5):692–698.10.1043/1543-2165-133.5.692 [PubMed: 19415943]
35. Sneige N, Batsakis JG. Necrotizing sialometaplasia. *The Annals of otology, rhinology, and laryngology*. 1992; 101 (3):282–284.

36. Walker GK, Fechner RE, Johns ME, Teja K. Necrotizing sialometaplasia of the larynx secondary to atheromatous embolization. *American journal of clinical pathology*. 1982; 77 (2):221–223. [PubMed: 7064921]
37. Wenig BM. Necrotizing sialometaplasia of the larynx. A report of two cases and a review of the literature. *American journal of clinical pathology*. 1995; 103 (5):609–613. [PubMed: 7741108]
38. Abrams AM, Melrose RJ, Howell FV. Necrotizing sialometaplasia. A disease simulating malignancy. *Cancer*. 1973; 32 (1):130–135. [PubMed: 4716764]
39. Grillon GL, Lally ET. Necrotizing sialometaplasia: literature review and presentation of five cases. *J Oral Surg*. 1981; 39 (10):747–753. [PubMed: 6944453]
40. Englander A, Cataldo E. Experimental carcinogenesis in duct-artery ligated rat submandibular gland. *Journal of dental research*. 1976; 55 (2):229–234. [PubMed: 1062421]
41. Standish SM, Shafer WG. Serial histologic effects of rat submaxillary and sublingual salivary gland duct and blood vessel ligation. *Journal of dental research*. 1957; 36 (6):866–879. [PubMed: 13481222]
42. Harada O, Ota H, Katsuyama T, Hidaka E, Ishizaka K, Nakayama J. Esophageal gland duct adenoma: immunohistochemical comparison with the normal esophageal gland and ultrastructural analysis. *Am J Surg Pathol*. 2007; 31 (3):469–475.10.1097/01.pas.0000213400.64945.9e [PubMed: 17325490]
43. Medeiros LJ, Doos WG, Balogh K. Esophageal intramural pseudodiverticulosis: a report of two cases with analysis of similar, less extensive changes in “normal” autopsy esophagi. *Hum Pathol*. 1988; 19 (8):928–931. [PubMed: 3136073]
44. Kaplan I, Alterman M, Kleinman S, Reiser V, Shuster A, Dagan Y, Shlomi B. The clinical, histologic, and treatment spectrum in necrotizing sialometaplasia. *Oral surgery, oral medicine, oral pathology and oral radiology*. 2012; 114 (5):577–585.10.1016/j.oooo.2012.02.020
45. Schoning H, Emshoff R, Kreczy A. Necrotizing sialometaplasia in two patients with bulimia and chronic vomiting. *International journal of oral and maxillofacial surgery*. 1998; 27 (6):463–465. [PubMed: 9869289]
46. Scully C, Eveson J. Sialosis and necrotising sialometaplasia in bulimia; a case report. *International journal of oral and maxillofacial surgery*. 2004; 33 (8):808–810.10.1016/j.ijom.2004.02.002 [PubMed: 15556334]
47. Solomon LW, Merzianu M, Sullivan M, Rigual NR. Necrotizing sialometaplasia associated with bulimia: case report and literature review. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*. 2007; 103 (2):e39–42.10.1016/j.tripleo.2006.08.005

Figure 1. Definition of pathological changes in the esophageal submucosal glands

A: SMG in a pediatric autopsy shows well-developed acini and duct. B: Normal adult SMG residing immediately beneath the muscularis mucosa. C: SMG demonstrating marked oncocytic metaplasia. D: NSMLC; Acute necrotizing phase shows necrosis of the SMG acini. E: NSMLC Stable phase; Ectatic ducts replace the mucous cells of the acini and are accompanied by a dense lymphoplasmacytic infiltrate. F: NSMLC Stable phase; Complete loss of the SMG acini with markedly dilated ducts and stromal desmoplasia-like changes. All H&E staining. (SMG, submucosal glands; NSMLC, necrotizing sialometaplasia-like change)

Figure 2. Distribution of NSMLC within the esophagus

A: Esophagectomy specimen showing NSMLC (arrow) underlying a segment of squamous mucosa in a patient with BE. B: Specimen from an EMR showing NSMLC (large arrow) underlying a segment of erosive esophagitis (small arrow) in a non-BE control patient with GERD. C: Esophagectomy specimen showing NSMLC underlying an intestinalized segment of esophagus in a BE patient. D: EMR specimen showing high grade columnar dysplasia overlying an SMG with NSMLC (Inset is higher power of NSMLC). All H&E staining. (EMR, Endoscopic Mucosal Resection; GERD, gastro-esophageal reflux disease; SMG, submucosal glands; NSMLC, necrotizing sialometaplasia-like change)

Figure 3. Comparison of immunohistochemical and histochemical markers in the metaplastic changes of the esophageal submucosal glands

Serial sections of a normal SMG are displayed in the first row in comparison to OGM in the second row and NSMLC in the third. (AB-PAS, Alcian-Blue Periodic Acid Schiff; SMA, Smooth muscle actin; SMG, submucosal glands; NSMLC, necrotizing sialometaplasia-like change).

Table 1

Clinicopathological Characteristics of the Esophagectomy Cases

		Group	
	Total n=82(%)	Non-BE Control n=37(%)	Barrett's Esophagus n=45(%)
Mean Age (quartiles)	61.6(53–69)	58.5 (48.5–68) /	64.0 (59–71.5) /
Sex			
Male	58 (71)	21 (57) ²	37 (82) ²
Female	24 (29)	16 (43)	8 (18)
NSMLC Present	33 (40)	8 (22) ²	25 (56) ²
OGM Present	44 (54)	15 (41) ²	29 (64) ²
Treatment History	45 (55)	24 (65)	21 (47)
Not Treated	38 (46)	14 (38)	24 (53)
Surgical/Other	16 (20)	9 (24)	7 (16)
Chemo/XRT/Combined	28 (34)	14 (38)	14 (31)
Tumor Size, cm (quartiles)	2.1 (0 - 3.5)	1.6 (0 - 3.7)	2.5 (0.85 - 3.5)
Indication for Esophagectomy			
Adenocarcinoma	43 (52)	8 (22) ²	35 (78) ²
Laryngeal Squamous Cell Carcinoma	9 (11)	7 (19)	2 (4)
Esophageal Squamous Cell Carcinoma	9 (11)	6 (16)	3 (7)
Achalasia	5 (6)	5 (14)	0 (0)
High Grade Columnar Dysplasia	4 (5)	0 (0)	4 (9)
Stricture	3 (4)	3 (8)	0 (0)
Hiatal Hernia	2 (2)	2 (5)	0 (0)
Incompetent Lower Esophageal Sphincter	1 (1)	1 (3)	0 (0)
Fistula	1 (1)	1 (3)	0 (0)
Gastrointestinal Stromal Tumor	1 (1)	1 (3)	0 (0)
Melanoma	1 (1)	0 (0)	1 (2)
Metastatic Lung Carcinoma	1 (1)	1 (3)	0 (0)
Erosion	1 (1)	1 (3)	0 (0)

Group			
Non-BE Control n=37(%)	1 (3)	1 (1)	
Barrett's Esophagus n=45(%)	0 (0)		
Perforation			

1 Statistically significant difference by Student's t test (alpha <0.05)

2 Statistically significant difference by Fisher's Exact Test (p <0.05)

BE, Barrett's esophagus; NSMLC, necrotizing sialometaplasia-like change; OGM, oncoytic glandular metaplasia.

Table 2

Univariate Associations with NSMLC and OGM

Covariate	NSMLC			OGM		
	No N=49 (%)	Yes N=33 (%)	p-value [†]	No N=38 (%)	Yes N=44 (%)	p-value [†]
BE						
No	29 (78.38)	8 (21.62)	0.002	22 (59.46)	15 (40.54)	0.031
Yes	20 (44.44)	25 (55.56)		16 (35.56)	29 (64.44)	
Age						
Mean	59.8	64.18	0.101	59.03	63.75	0.072
Median	62	64		61	63	
Sex						
F	16 (66.67)	8 (33.33)	0.412	13 (54.17)	11 (45.83)	0.361
M	33 (56.9)	25 (43.1)		25 (43.1)	33 (56.9)	
Treatment History						
Not Treated	25 (65.79)	13 (34.21)	0.576	11 (28.95)	27 (71.05)	0.013
Surgical/Other	9 (56.25)	7 (43.75)		10 (62.5)	6 (37.5)	
Chemo/XRT/Combined	15 (53.57)	13 (46.43)		17 (60.71)	11 (39.29)	
Tumor size (cm)						
0	20 (71.43)	8 (28.57)	0.107	14 (50)	14 (50)	0.523
0-3	13 (44.83)	16 (55.17)		11 (37.93)	18 (62.07)	
>3	16 (64)	9 (36)		13 (52)	12 (48)	

[†]The p-value was calculated by ANOVA for numerical covariates and Chi-Square test for categorical covariates.

Bold text = statistically significant

BE, Barrett's esophagus; NSMLC, necrotizing sialometaplasia-like change; OGM, oncocytic glandular metaplasia; XRT, radiation therapy.

Table 3

Multivariable Analysis Predicting NSMLC and OGM (n=82)

Covariate	NSMLC ¹		OGM ²	
	Odds Ratio (95% CI)	OR p-value	Odds Ratio (95% CI)	OR p-value
BE	4.95 (1.73, 14.18)	0.003	2.37 (0.93, 6.08)	0.072
Treatment History				
Chemo/XRT/Combined	2.70 (0.86, 8.50)	0.089	0.28 (0.10, 0.80)	0.018
Surgical/Other	2.53 (0.63, 10.15)	0.190	0.27 (0.08, 0.96)	0.043
Not Treated	-	-	-	-

¹The models were adjusted for age and treatment history.

²The models were adjusted for treatment history.

Bold numbers = statistically significant

BE, Barrett's esophagus; NSMLC, necrotizing sialometaplasia-like change; OGM, oncocytic glandular metaplasia; Chemo, Chemotherapy; XRT, radiation therapy.

Table 4Semiquantitative Scoring of Markers in SMG by Foci Type¹

Marker	SMG (n = 18)		OGM (n = 16)		NSMLC (n = 7)		p-value ²		
	Mean	St Dev	Mean	St Dev	Mean	St Dev	SMG vs. OGM	SMG vs. NSMLC	OGM vs. NSMLC
AB-PAS	3.0	0.0	0.06	0.25	0.0	0.0	<.0001	<.0001	0.3854
CK 19	0.33	0.49	2.4	0.63	1.9	0.69	<.0001	<.0001	0.0334
SMA	2.9	0.24	2.5	0.63	2.3	0.95	0.0292	0.0135	0.4125
p63	2.1	0.42	2.1	0.77	2.7	0.76	0.9748	0.0252	0.0292
MIB1	0.33	0.49	0.8	0.66	1.6	0.79	0.0280	<.0001	0.0092

AB-PAS, Alcian blue-periodic acid Schiff; CK 19, cytokeratin 19; SMA, smooth muscle actin; SMG, normal submucosal glands; OGM, oncoytic glandular metaplasia; NSMLC, Necrotizing sialometaplasia-like change;

¹ Scored from 0 to 3 (see materials and methods)

² p-value alpha= 0.05

Bold numbers = statistically significant