



Clinical, endoscopic and histopathological observation of a rare case of esophageal submucosal gland duct adenoma: A case report

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Abstract

BACKGROUND

Esophageal submucosal gland duct adenoma (ESGDA) is very rare, and easily diagnosed as adenocarcinoma.

CASE SUMMARY

A 70-year-old man presented with abdominal discomfort and intermittent dull pain during swallowing for 10 days. Digestive endoscopy revealed a polypoid bulge at the esophago-gastric junction, which was resected by endoscopic submucosal dissection (ESD). Routine pathological examination showed intestinal metaplasia of the glandular epithelium on the mucosal surface, with serous tumor-like complex glands in the submucosa which showing significant hyperplasia. This initially diagnosis was early gastric adenocarcinoma. However, we still observed a few points that did not meet the criteria for cancer such as lack of malignant features. Following multidisciplinary discussion and consultation with the experienced specialist pathologists, we finally diagnosed the lesion as a rare ESGDA by further immunohistochemistry. The follow-up examination results for the patient were satisfactory, with no evidence of tumor recurrence. And we summarize the ESGDAs reported in the literature, aiming to enhance understanding of this tumor type.

CONCLUSION

ESGDA is a benign tumor that can be cured by ESD. Accurate diagnosis can prevent unnecessary extensive therapeutic interventions.

Key Words: Esophagus; Submucosal gland; Duct; Adenoma; Case report

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Core Tip: We present an exceedingly rare case of esophageal submucosal gland duct adenoma and conduct a comprehensive literature review to elucidate the origin, pathogenesis, clinical features, endoscopic and pathological characteristics, as well as potential genetic alterations of this tumor, thereby enhancing our understanding and preventing misdiagnosis.

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INTRODUCTION

It is well known that the submucosal glands of the normal esophagus are composed of lobules and extrolobular ducts. Each submucosal glandular lobule comprises multiple acini and intralobular ducts that converge to form an external lobule duct, which opens into the esophageal cavity. The submucosal glands and ducts are distinctive features of the esophagus and absent in the stomach. The acinus can be mucinous or mucous and serous mixed parotid acinus, which produce mucin and bicarbonate to neutralize gastric acid and growth factors, which are secreted through the extrolobular ducts to the surface of the esophageal mucosa to protect the esophagus[1]. They differ from the gastric cardia-type mucinous glands that are distributed in the lamina propria at the upper and lower end of the esophagus. Intralobular and extralobular ducts have no mucous cells[2]. Esophageal submucosal gland duct adenoma (ESGDA), a benign tumor originating from the esophageal submucosal gland, is extremely rare. Due to the lack of knowledge of clinical pathologists, it is easy to be diagnosed as adenocarcinoma. We encountered an extremely rare case that was initially misdiagnosed as early stage gastric adenocarcinoma by our pathologists. After following multidisciplinary discussion, carefully the available literature reviews, and consultations with the experienced specialist pathologists, we finally diagnosed the condition as ESGDA. Here we report this ESGDA and review the literature with the intent to enhance the understanding of this lesion.

CASE PRESENTATION

Chief complaints

A 70-year-old patient presented to our hospital with a 10-day history of upper abdominal discomfort and intermittent dull pain during swallowing. He reported no significant changes in mental status, appetite, or sleep patterns, no food reflux or acid reflux, no nausea, vomiting, abdominal distension, palpitations, chest tightness, chills fever or weight loss.

History of present illness

The patient underwent upper gastrointestinal endoscopy at our hospital. Conventional endoscopy revealed a hemispherical bulge which had superficial erosion of the surface mucosa and a soft touch within the dentate line of the esophago-gastric junction (Figure 1A). Ultrasound endoscopy indicated that the bulge was located in the submucosal layer, with clear boundaries and smooth edges. It exhibited an anechoic mass and had relatively normal blood flow signals (Figure 1B). Magnifying narrow-band imaging endoscopy revealed the mass had a borderless mucosal surface with a mucosal microstructure and regular microvessels (Figure 1C).

History of past illness

The patient has a 20-year history of hypertension and diabetes. He takes oral Amlodipine daily and receives insulin injections subcutaneously with good control of blood sugar levels. His highest recorded blood pressure was 170/100 mmHg. He underwent a 'left inguinal hernia repair' three years ago. No history of other diseases and no food or drug allergies.

Personal and family history

The patient denied any family history of hereditary diseases or tumors.

Physical examination

The dimension of the resected tissue measured 3.5 cm × 2.6 cm × 0.2 cm, with a hemispherical polypoid mass measuring 0.7 cm protruding from the mucosal surface (Figure 1D). It was vertically sectioned into strips of tissue, each 2 mm width.

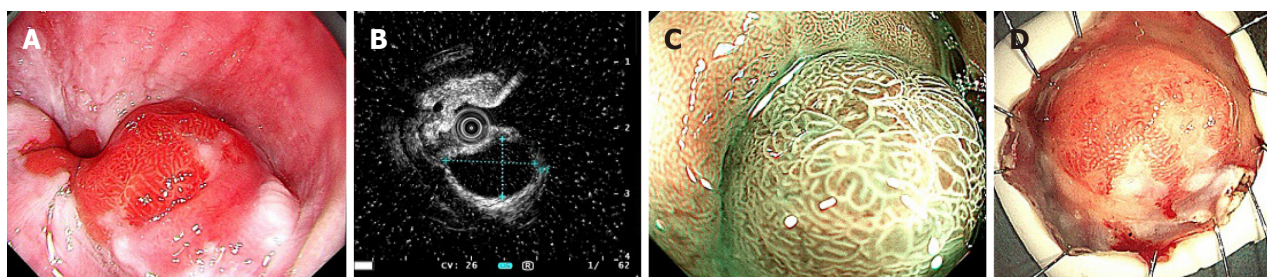


Figure 1 Endoscopic images of esophageal submucosal gland duct adenoma. A: The hemispherical polyp was located at the gastro-esophageal junction with superficial erosion of the surface mucosa; B: Ultrasound endoscopy showed an anechoic lesion located in the submucosa with a clear and smooth boundary; C: Magnifying narrow-band imaging endoscopy revealed a mass with borderless mucosal surface along with a slightly irregular microstructure, twisted and thickened glands, but regular microvessels; D: Gross observation showed a hemispherical bulge on the surface of the specimen removed by endoscopic submucosal dissection, and the surface mucosa was smooth.

Based on the incision profile, the mass was situated beneath the mucous membrane, which appeared largely normal on its surface. The mass exhibited a grayish-white coloration, had a medium consistency, and was distinctly demarcated from adjacent tissue.

Laboratory examinations

Histologic studies: All tissue strips were cut into slices by the conventional methods, and stained with H&E. The lesion was 0.5 cm × 0.5 cm in size and was located on the submucosal layer without any envelope wrapping (Figure 2A). It was composed of several ducts or cysts with papillary and tubular structures; moreover, lymphocyte clusters were observed in its interstitia along with germinal centers (Figure 2B and C). Furthermore, these ducts or cysts had an inner luminal duct cell layer and an outer myoepithelial cell layer. Both these layers had oncocytic differentiation with granular and eosinophilic cytoplasm. The luminal cells had micropapillary and microglandular hyperplasia in the glandular cavity. There were few nuclear atypicals, lack of mitotic figures, necrosis and mucin production (Figure 2D).

Immunohistochemical studies: Immunohistochemical assay was carried out in strict accordance with the kit instructions. We used EDTA heat antigen repairing methods, with a DAB chromogen. Antibodies used in the immunohistochemistry included: CK7 (OV-TL 12/30; Dako), CK20 (KS20.8; Dako), P63(4A4; Dako), CDX2 (EPR2764Y, Dako), MUC1 (MRQ; Dako), MUC2 (Ccp58; Dako), MUC6 (MRQ-20; Dako), MUC5AC(45M1; Dako), MDM2 (SPM14; Dako), P53 (BP-53-12; Dako), and Ki-67 (Mib1; Dako).

The luminal duct cells were positive for CK7 (Figure 2E), whereas the myoepithelial cells were positive for P63 (Figure 2F). Both the two-layer cells were negative for CK20, CDX2, MUC1, MUC2, MUC6, and MUC5AC (Figure 2G), and there was no evidence of P53 mutation and MDM2 gene expansion. In fact, Ki-67 showed almost no expression of ductal epithelial cells and expressed in only a few myoepithelial cells (< 5%; Figure 2H).

The patient learned that the tumor was considered benign and successfully removed, he declined our suggestion to conduct relevant gene sequencing for further analysis of the tumor.

MULTIDISCIPLINARY EXPERT CONSULTATION

After the initial multidisciplinary team discussion, we performed an endoscopic submucosal dissection (ESD) for the patient's tumor. Following a preliminary pathological examination of the postoperative specimen, we reconvened a multidisciplinary expert consultation which included specialists from both within and outside our institution for the diagnosis of this patient.

FINAL DIAGNOSIS

After a thorough review of pertinent literature, we arrived at a finally diagnosis of ESGDA.

TREATMENT

Following a multidisciplinary discussion and the formulation of a comprehensive treatment plan, we proceeded with ESD on the patient. Tumor was successfully resected *en bloc* from the submucosa with an estimated blood loss of approximately 10 mL. After the surgery, the patient was placed on fasting status for the first day and received intravenous fluid resuscitation. From the second day, the patient was transitioned to a liquid or semi-liquid diet. Throughout the postoperative period, the patient remained asymptomatic and was subsequently discharged on the fifth postoperative day.

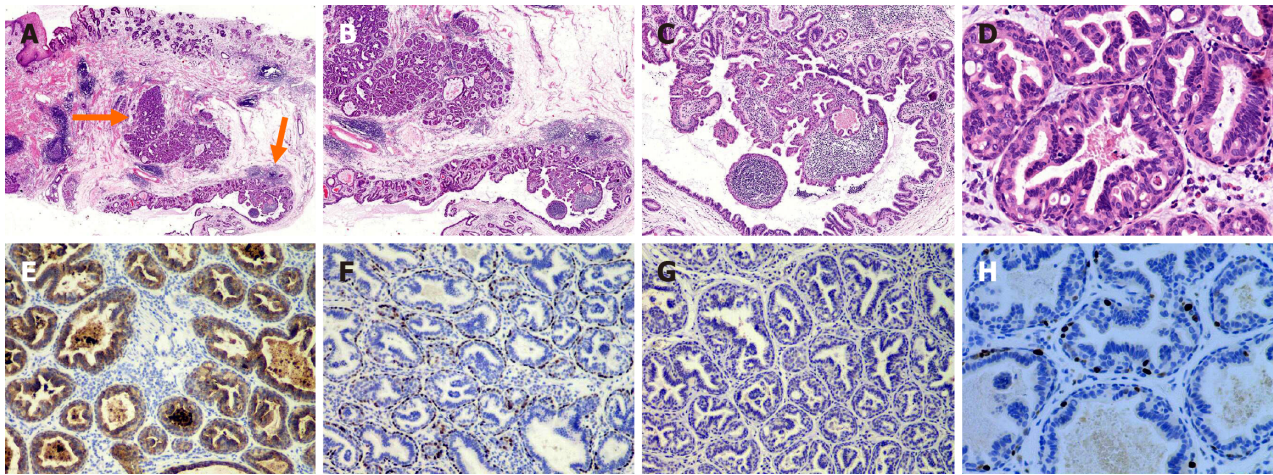


Figure 2 Pathological images of esophageal submucosal gland duct adenoma. A: The orange arrow denoted the submucosal lesion within the esophagus (original magnification $\times 40$); B and C: The lesion was composed of ducts or cysts containing papillary and tubular structures with lymphocytic infiltrates in the interstitial (B: Original magnification $\times 100$, C: Original magnification $\times 200$); D: Tumor cells were composed of moderate bilayer epithelium with no mitotic figures (original magnification $\times 400$); E: CK7 was positive in inner cells and negative in outer cells (original magnification $\times 200$); F: P63 was negative in inner cells and positive in outer cells (original magnification $\times 200$); G: All cells were negative for MUC5AC (original magnification $\times 200$); H: Ki-67 showed only expression in a few myoepithelial cells (original magnification $\times 400$).

OUTCOME AND FOLLOW-UP

Endoscopic examinations were conducted at 3 months and 1 year post-operation, all of which revealed complete healing of the scar in the surgical area. The patient had no discomfort. Subsequently he underwent biennial endoscopic examinations, and no evidence of tumor recurrence was observed over a period of 69 months.

DISCUSSION

Rare adenomas of the esophagus have been reported since the middle of the last century. Unfortunately, these reports lacked detailed histological descriptions and photomicrographs[3,4]. ESGDA was first comprehensively introduced by Takubo *et al*[5] in 1993 and identified as esophageal submucosal tumor. The rarity of this neoplasm has resulted in terminological ambiguity, with various designations including esophageal pleomorphic adenoma, serous cystadenoma, and sialadenoma papilliferum[6,7]. In 1995, Rouse *et al*[8] formally designated it as ESGDA and posited that it may originate from the ductal components of the submucosal glands. We reviewed the existing literature and found 23 cases in which ESGDA was adequately described in case reports. The clinical characteristics of these cases are summarized in Table 1[5-18].

The average of the 23 patients with ESGDA was 66 years (range: 45-81 years), exhibiting a male predominance (male:female = 15:8). Among them, 2 cases of ESGDA were incidentally discovered due to the presence of esophageal squamous cell carcinoma alongside gastric adenocarcinoma[5,12]; the remaining cases primarily presented with initial symptoms of abdominal discomfort, dysphagia, belching, vomiting, loss of appetite, wasting, acid reflux and abdominal pain, which occasionally posed challenges to their condition and complicated the diagnosis of gastroesophageal reflux disease. During digestive endoscopy, these lesions manifested as small hemispherical or dome-shaped submucosal protrusions. All patients had single ESGDA, which ranged in diameter from 0.3 to 3.5 cm, with an average of 1.0 cm. They were removed by ESD or endoscopic mucosal resection. All ESGDAs exhibited well-defined boundaries but lacked an envelope. Histologically, they were characterized by multiple cystic dilatations of glandular ducts, which contained two layers of epithelial cells exhibiting proliferation and papillary folds. The cytoplasm of the inner luminal ductal epithelial cells was granular and eosinophilic, featuring round to oval nuclei with minimal nuclear atypia. The outer basal cells were spindle with distinct or weak eosinophilic cytoplasm. All the tumors showed a low mitotic activity without necrosis. Diffuse or focal lymphocytic infiltration in the interstitium was commonly observed. In immunohistochemical analysis, both layers expressed epithelial markers like pan cytokeratin and epithelial membrane antigen. The inner ductal epithelial cells demonstrated low molecular weight cytokeratins such as CK7 and CK18, while the outer layer expressed basal cell markers including CK5/6, P63, S-100 among others. Markers such as CK20, CDX2, MUC1, MUC2, MUC5AC, MUC6 and P53 were all negative. The proliferations index of Ki-67 was very low (1%-5%). Few reports on the molecular genetic changes of ESGDA, only Hua *et al*[18] conducted genomic analysis on 7 cases of ESGDA, and found 5 of them exhibited a *BRAF V600E* mutation (71.4%). There were no recurrences of ESGDA, and the prognosis was highly favorable.

The glands of the esophagus are categorized into esophageal cardiac glands and submucosal glands, which are distributed in different levels. The esophageal cardiac gland is situated within the mucosal lamina propria and exhibits structural similarities to gastric glands. It comprises MUC6-positive glandular ducts, with a rare presence of parietal cells and chief cells. The epithelium of the glandular pit shows positive expression for MUC5AC, while MUC2 positivity may

Table 1 Clinicopathological characteristics of the present case of esophageal submucosal gland duct adenoma and the 23 cases in prior literature

Ref.	Age (years)/gender	Symptoms	Location	Gross morphology/size (cm)	Histological morphology	Dysplasia	Necrosis/mitotic figures	Ki-67 index	Follow-up
Tsutsumi <i>et al</i> [6], 1990	77/male	Nausea	M	Globoid polyp/1.0	Multiple microcysts and papillary proliferation with two layers of cells	Mild and moderate	None/some	NM	Well over 2 years
Takubo <i>et al</i> [5], 1993	58/male	Abdominal discomfort	M	Dome-like polyp/0.8	Papillary and tubular structures with two layers of cells	None	None/none	NM	Well over 6 months
Rouse <i>et al</i> [8], 1995	81/male	Dysphagia	GEJ	Pedunculated polyp/1.5	Tubules and cystic lumens filled with papillae by two layer of cells	None	None/rare	NM	Well over 12 months
Su <i>et al</i> [7], 1998	70/male	Abdominal fullness	L	Broad-based polypoid/1.0	Papillary glandulars with two layers of cells	Benign	None/none	NM	Well over 12 months
Agawa <i>et al</i> [9], 2003	71/male	NM	L	Sessile polypoid tumor/1.5	Dilated gland ducts containing papillary and tubular components with two layers of cells	Benign	None/ none	NM	Well over 12 months
Hayashi [10] 2004	60/female	Abdominal discomfort	M	Dome-like protruding lesion/1.1	Cysts, papillary and tubular proliferation with two layers of cells	Minimal	None/none	NM	Well over 11 years
Chinen <i>et al</i> [11], 2004	67/female	None	L	Polypoid lesion/0.6	Multiple cysts, tubules and papillae with two layers of cells	Mild	None /rare	NM	Well over 6 months
Harada <i>et al</i> [12], 2007	75/male	NM	L	Well demarcated without a capsule/0.3	Papillary and cystic structures with two layers of cells	Minimum	None/rare	1%-2%	NM
Nie <i>et al</i> [13], 2016	74/male	Retrosternal discomfort	L	Dome-like polypoid tumor/0.5	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well over 4.5 years
	54/female	Abdominal discomfort and heartburn	L	Hemispherical protruding lesion/0.3	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well over 4 years
	45/male	NM	L	Hemispherical protruding lesion/0.4	Multiple glandular cysts and papillary folds with two layers of cells,	Minimum	None/none	1%	Well
Shibata <i>et al</i> [14], 2017	66/female	None	L	Slightly protruding tumor/0.5	Dilated ducts and papillary proliferations with two layers of cells	Slight	None/none	2%	NM
Genere <i>et al</i> [15], 2019	78/female	Dysphagia	U	Submucosal mass with well-defined borders/2.0	Multiple lobulated cystic proliferations of two layers of cells	Mild	None/rare	NM	Well
Yamamoto <i>et al</i> [16], 2020	73/female	None	L	Subepithelial tumor with a central depression/0.8	Tubular and cystic pattern with two-cells	None	None/none	NM	Well

					layers				
Chen <i>et al</i> [17], 2023	58/male	Gastro-esophageal reflux symptoms	L	Hard mass with well-defined heterogeneous/3.5	Cystic pattern with two layers of cells	Benign	None/rare	NM	Well over 12 months
Hua <i>et al</i> [18], 2025	65/male	None	U	SMT/0.5	Glandular ducts, cysts and papillae, with two-cells layers	Bland	None/none	< 1%	Well over 68 months
	75/male	Loss of appetite	U	SMT/1.5					Well over 46 months
	65/male	Belching, acid reflux	M	SMT/1.5					Well over 36 months
	55/female	Discomfort during swallow	L	SMT/0.5					Well over 25 months
	51/female	Acid reflux, vomiting	L	SMT/0.8					Well over 24 months
	73/male	Abdominal pain	L	SMT/0.3					Well over 50 months
	63/male	None	GEJ	SMT/2.0					Well over 37 months
Our case	70/male	Abdominal discomfort	GEJ	Hemispherical bulge/0.5	Tubular, cysts and papillary structures with two layers of cells	Few	None/none	< 5%	Well over 69 months

M: Middle esophagus; GEJ: Gastroesophageal junction; L: Lower esophagus, U: Upper esophagus; SMT: Submucosal tumor, NM: Not mentioned.

occur in cases of intestinal metaplasia. Esophageal submucosal glands reside in the submucosa and function as exocrine glands, considered an extension of the small salivary glands of the oropharynx. These glands are dispersed throughout the esophagus along its longitudinal axis but exhibit greater concentration at the junction between the lower esophagus and cardiac, where significant alterations in physical and chemical properties occur. Submucosal gland acinar secretions are collected *via* ducts that transport them to the esophageal lumen; initially covered by a single cuboidal epithelium, these ducts subsequently transition into a double-layered epithelium before traversing through various layers including the muscularis mucosa, lamina propria mucosa, and the epithelium of the esophagus[17,19].

The occurrence location of ESGDA mirrors that of esophageal submucosal glands. It resided within the submucosa where normal submucosal gland tissues frequently surrounded it. Occasionally observed transitional relationships between both structures suggested an intuitive possibility that ESGDA might originate from these submucosal glands, which was further corroborated by immunohistochemical findings. The immunophenotypic characteristics of the inner ductal epithelial cells of ESGDA were closely align with that of the normal esophageal submucosal duct epithelium. Tumor cells expressed MUC5B, CK7, CK5/6, and CK19 while showing no expression for CK20, CDX2, Villin, MUC5AC, MUC6, MUC2 or GCDFP15. All these indicated a lack of differentiation phenotype characteristic typical to digestive tract-type glandular epithelia or submucosal mucous acinoid epithelia. It is worth mentioning that Harada *et al*[12] found through immunohistochemistry of MUC5B and electron microscopy that a few ductal epithelial cells in ESGDA displayed limited mucus secretion localized to their subapical regions, implying that tumor cells may have the ability of terminal duct (intercalated duct) differentiation. And They effectively delineated microvilli on both the basement membrane and the apical surface of the luminal duct cells with Alcian blue (PH 2.5) and periodic acid-Schiff (AB-PAS) staining, corroborating the findings from MUC5B immunostaining. The basal layer cells of ESGDA expressed P40, P63, SMA, Calponin, and S-100 protein, suggesting characteristics of myoepithelial differentiation.

Current research indicates that gastroesophageal reflux not only serves as the primary etiological factor in the development of Barrett's esophagus (BE) but is also intricately linked to the progression of ESGDA[12]. Other environmental factors include long-term smoking, drinking, overheated diet and other irritants. These factors induced injury to the esophageal mucosa and promotes inflammatory cell infiltration within both the mucosal and submucosal layers. This results in a dual impact: On one hand, inflammatory cells impair myoepithelial contractile function; on the other hand, inflammatory exudates or epithelial debris obstruct the ducts of submucosal glands. The cumulative effects of these detrimental factors hinder proper secretion discharge from esophageal submucosal glands, leading to noticeable expansion or contraction of acini when these symptoms persist. Prolonged exposure to secretions and inflammatory cells stimulates precursor cells with multidirectional differentiation potential to proliferate, resulting in multilayered epithelium (some studies suggest this may represent a precursory lesion for BE) and papillary formations, which contribute

to the distinctive histological characteristics observed in ESGDA[19]. Concurrently, cyst formation within submucosal glands is regarded as a precursor for ESGDA due to their overlapping clinicopathological features and ongoing interrelationship[12,13]. No family history of ESGDA has been found in the literature. Whether genetic susceptibility and other factors may also affect the occurrence of ESGDA remains to be further studied.

Adenomas of the esophagus are infrequent and typically associated with intestinal metaplasia, specifically BE, which is a consequence of GERD. These lesions are characterized by raised polypoid mucosal formations composed of intestinal or gastric glandular epithelium exhibiting varying degrees of dysplasia. They may be not represent true adenomas in nature but precursor lesions for BE-related adenocarcinoma[20]. ESGDA discussed in this paper is a true primary submucosal adenoma which is extremely rare and located in the submucosal layer, originating from the submucosal gland duct cells. Its immunophenotypic profile indicates a closer association with tumors of salivary adenoid origin.

In terms of molecular genetics, only Hua *et al*[18] found *BRAF V600E* mutations in five of the seven ESGDAs. Given that the *BRAF V600E* mutation has been previously confirmed in sialadenoma papilliferum, this finding provides additional evidence that ESGDA is an esophageal counterpart of minor salivary gland tumors. The *BRAF V600E* mutation may promote cell proliferation by activating the MAPK signaling pathway, and its role in ESGDA and whether it may lead to malignant transformation require further investigation.

The pathological diagnostic criteria supporting the diagnosis of ESGDA include: (1) Multiple glands or cysts arranged in a lobular configuration and covered by two layers of cells, the inner luminal epithelial cells and the outer basal or myoepithelial cells; (2) The existence of multilayered epithelium and papillary structures within the glands or cysts, without necrosis and significant cytologic atypia, and nuclear mitotic figures are infrequent; (3) Lymphocytic infiltration accompanied by acinar atrophy or disappearance; and (4) Luminal lining cells exhibiting positivity for MUC5B and various cytokeratins (such as CK5/6, CK7, CK18, CK19), whereas outer cell markers P40, P63, S-100, Calponin and SMA show positive expression alongside a low Ki-67 proliferation index. AB-PAS staining reveals microvilli on the apical surface adjacent to the basement membrane along with tubular epithelial cell[21].

The most important aspect of the diagnosis was identifying the adenocarcinoma, which was always invasive, had an obvious structure and cytological atypia, and was accompanied by multiple mitotic figures and abnormal mitotic figures. The presence of ESGDA bilayer epithelium, lack of cytologic atypia, and lack of mitoses were key criteria for the identification. Similarly, another rare tumor, known as oxyntic gland polyp/adenoma or adenocarcinoma of fundic gland (chief cell-predominant type), was identified[22]. It was mainly composed of proliferation of the chief cells and oxyntic cells along with low-grade cytology and a similar low Ki-67 index as that observed for ESGDA. This tumor showed low-grade malignancy with rare occurrences of lymphatic and venous invasion[23,24].

ESGDA can be cured by ESD regardless of whether it occurs at upper or lower esophagus, and whether it is 0.3 cm or 3.5 cm in size. No recurrence or malignant transformation cases have been found in the literature. We think the incomplete resection may be the root cause of recurrence. And if the tumor has sufficient growth time in a suitable environment, the possibility of malignant transformation cannot be ruled out. Especially if the tumor suddenly increased in size in a short period of time, the possibility of malignant transformation should be vigilantly considered. When the pathological morphology shows highly anaplastic tumor cells, accompanied by significantly active pathological mitotic figures and necrosis, even invasive growth, it suggests tumor malignant transformation. We believe that long-term regular follow-up of this tumor is very necessary. As with other gastrointestinal tumors, we recommend endoscopic examination every one or two years when the patient has no digestive discomfort symptoms, and at any time once there are gastrointestinal discomforts.

CONCLUSION

To summarize, ESGDA is a benign neoplasm that can be completely resected by ESD. It occurs predominantly in the lower third of the esophagus and is more common in elderly male patients. Symptoms include abdominal discomfort or difficulty swallowing, although it may occasionally be asymptomatic. They are small hemispherical or dome-shaped polypoid submucosal polypoid lesions that can be resected endoscopically, but it is still uncertain whether they can progress from adenoma to adenocarcinoma. Extensive ductal metaplasia, hyperplasia and/or retention cyst formation are considered to be the basis or precursors of ESGDA. The histological, immunohistochemical and molecular evidence of ESGDA support that it is an esophageal counterpart of minor salivary gland tumors.

FOOTNOTES

Author contributions: Lu T and Liu JX contribute equally to this study as co-first authors; Lu T carried out experiments; Liu JX searched the literature and drafted manuscript; Xia Y aided in specimens collection; Zhao Y designed experiment methods, analyzed results, and revised manuscript; all authors had access and approved the last version of the manuscript.

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Conflict-of-interest statement: All authors report no relevant conflicts of interest for this paper.

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