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**Esophageal subepithelial lesion diagnosed as malignant gastrointestinal neuroectodermal tumor**

Kim SB *et al*. Esophageal malignant gastrointestinal neuroectodermal tumor

Sung Bum Kim, Si Hyung Lee, Mi Jin Gu

**Sung Bum Kim, Si Hyung Lee,** Department of Internal Medicine, Yeungnam University Hospital, Daegu 705-802, South Korea

**Mi Jin Gu,** Department of Pathology, Yeungnam University Hospital, Daegu 705-802, South Korea

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**Correspondence to:** **Si Hyung Lee, MD,** Department of Internal Medicine, Yeungnam University Hospital, 170 Hyeonchung-ro, Nam-gu, Daegu 705-802, South Korea. dr9696@nate.com

**Telephone:** +82-53-6203830

**Fax:** +82-53-6548386

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**Abstract**

A 21-year-old male visited our hospital with a complaint of aggravating dysphagia and odynophagia for a few days. Esophagogastroduodenoscopy showed huge bulging mucosa with intact surface causing luminal narrowing at 35cm from incisor teeth. Endoscopic ultrasonography showed about 35 mm sized irregular margined in-homogenous hypoechoic lesion with obscure layer of origin. Endoscopic ultrasonography fine needle aspiration revealed spindle cells proliferation without immunoreactivity for CD117, SMA and cytokeratin. The patient underwent excision of subepithelinal lesion at distal esophagus. On pathologic examination of specimen, tumor was composed of short fascicles of oval to spindle cells with eosinophilic and clear cytoplasm and vesicular nuclei. The tumor cells were positive for S-100 and SOX10 and negative for CD117, SMA, HMB-45, Melan A, cytokeratin and CD99. The split-apart signal was detected in EWSR1 on FISH suggesting malignant gastrointestinal neuroectodermal tumor. Patient is now on radiation therapy at operated site of esophagus and doing well without recurrence for three months. Malignant gastrointestinal neuroectodermal tumor is a rare gastrointestinal tumor with features of clear cell sarcoma and without melanocytic differentiation and shows poor prognosis. This is the first to report a case of malignant gastrointestinal neuroectodermal tumor arising as subepithelial lesion in esophagus.

**Key words:** Subepithelial lesion; Esophagus; Malignant gastrointestinal neuroectodermal tumor; Ewing sarcoma break point region 1 gene; Fluorescence *in situ* hybridization

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**Core tip:** This is the first report of malignant gastrointestinal neuroectodermal tumor arising in esophagus. Malignant gastrointestinal neuroectodermal tumor is a tumor with similar morphology, immunophenotype, molecular genetic features of clear cell sarcoma of tendons and aponeurosis lacking melanocytic differentiation arising in the gastrointestinal tract. The malignant gastrointestinal neuroectodermal tumor shows aggressive disease behavior with poor prognosis.

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**Introduction**

Subepithelial lesion (SEL) of the gastrointestinal tract is defined as any bulging covered with intact mucosa and represents either intraluminal lesions arising from any layers of the gastrointestinal wall or external compression caused by neighboring organs[[1](#_ENREF_1)]. Most SELs are found incidentally during esophagogastroduodenoscopy and in some cases, SEL may cause symptoms. Endoscopic ultrasonography and/or fine needle aspiration is useful in making differential diagnosis of SEL and average accuracy of fine needle aspiration reaches 80%[[2](#_ENREF_2)]. Differential diagnosis of esophageal SEL includes leiomyoma, granular cell tumor, glomus tumor, gastrointestinal stromal tumor, lipoma, cyst, varices, submucosal cancer or metastasis, or external compression by adjacent structures. The majority of mesenchymal tumors of the gastrointestinal tract are gastrointestinal stromal tumor and leiomyoma and diagnosis of malignant gastrointestinal neuroectodermal tumor (MGINET) has been reported in rare cases[[3](#_ENREF_3)].

We report on a case of a subepithelial lesion of the esophagus diagnosed as MGINET, which is the first to be reported in esophagus. We also provided a short review of literature on MGINET.

**Case report**

A 21-year-old male visited our hospital with a complaint of aggravating dysphagia for a few days. The patient had experienced intermittent dysphagia after overeating for a year. He had no significant past medical or familial history. He was a non-smoker and a social alcohol drinker. On physical examination, he had relatively well-being appearance with alert mentality and soft, non-tender abdomen with no palpable mass. Initial vital signs included blood pressure 140/90 mmHg, heart rate 97 beats/min, respiration rate 20 breaths/min, and body temperature 36.9 °C, respectively. The initial laboratory findings were as follows; white blood cell 9820 cells/μL, hemoglobin 16.5 g/dL, platelet 2.09 x 105 cells/ μL, total bilirubin 0.67 mg/dL, total protein 7.18 g/dL, albumin 4.18 g/dL, aspartate aminotransferase 13 IU/L, alanine aminotransferase 24 IU/L, alkaline phosphatase 263 IU/L, γ-glutamyl transpeptidase 166 IU/L, lactate dehydrogenase 301 IU/L, prothrombin time 12.0 s, blood urea nitrogen 7.5 mg/dL, creatinine 1.01 mg/dL, Na+ 134 mEq/L, K+ 4 mEq/L and Cl- 97 mEq/L. Esophagogastroduodenoscopy showed huge bulging mucosa with intact surface causing luminal narrowing at 35 cm from incisor teeth (Figure 1). On endoscopic ultrasonography (EUS), an irregular margined in-homogenous hypoechoic lesion measuring approximately 35 mm in size with obscure layer of origin was observed (Figure 2). EUS guided fine needle aspiration was performed and on microscopic view, spindle cell proliferation without immunoreactivity for CD117, CD34. DOG-1, smooth muscle actin and cytokeratin were observed. Abdominal computed tomography scan showed a well defined round mass measuring approximately 3.5 cm in size in distal esophagus (Figure 3). The patient underwent excision of the subepithelial lesion at the distal esophagus. Gross finding showed a mass measuring 3.5 cm x 3.5 cm in size and the cut surface showed heterogeneous white grayish appearance with focal hemorrhage. On microscopic examination of the specimen, the tumor was composed of short fascicles of oval to spindle cells with eosinophilic and clear cytoplasm and vesicular nuclei (Figure 4). Mitosis was seen frequently with mitotic count of 55/50 high power field. The tumor cells were positive for S-100, SOX10 (Figure 5a, b) and vimentin and negative for CD117, CD34, Dog-1, smooth muscle actin, desmin, HMB-45, Melan A, cytokeratin (AE1/AE3) and CD99. The split-apart signal was detected in Ewing sarcoma break point region 1 gene *(EWSR1)* on Fluorescence *In Situ* Hybridization. Further evaluation with positron emission tomography showed no evidence of regional or distant metastasis. The patient is now on radiation therapy at the operated site of the esophagus and doing well without recurrence for 5 mo.

**Discussion**

Clear cell sarcoma of tendons and aponeurosis is a malignant melanoma arising in soft parts with characteristic features of melanocytic differentiation and chromosomal translocation of EWSR1-ATF1 t(11;22)(q13;q12). Tumors with similar morphology, immunophenotype, molecular genetic features of clear cell sarcoma of tendons and aponeurosis lacking melanocytic differentiation arising in the gastrointestinal tract have been reported. Zambrano first designated these tumors as clear cell sarcoma like tumor of the gastrointestinal tract in 2003[[4](#_ENREF_4)]. Further studies have demonstrated that clear cell sarcoma like tumor of the gastrointestinal tract arises from the autonomic nervous system and Stockman *et al*[[3](#_ENREF_3)] re-designated clear cell sarcoma like tumor of the gastrointestinal tract as MGINET in 2012. Immunohistochemical staining of MGINET characteristically shows positive results for vimentin, S100 and SOX10 and negative results for human melanoma black (HMB) 45, melan A, tyrosinase, CD 117, CD 34, DOG-1, CD 99, α-smooth muscle actin, desmin and glial fibrillary acidic protein. Conflicting immunohistochemical staining results for CD 56, synaptophysin, NB 84, non-specific enolase and neurofilament protein have been reported. Consistent with previous reports[[3](#_ENREF_3),[5-11](#_ENREF_5)], our case showed positive immunohistochemical staining results for S-100 protein, SOX 10 and vimentin and negative results for HMB 45 and melan A. Differential diagnosis with GIST was made by negative immunohistochemical staining results for CD 117, CD 34 and DOG-1. In our case, final diagnosis of MGINET was confirmed by split-apart signal detected in Ewing sarcoma break point region 1 gene *(EWSR1)* on Fluorescence *In Situ* Hybridization.

Review of the case reports written in English searched through PubMed and Google Scholar® found 39 cases of MGINET and we reviewed 40 cases of MGINET, including our case[[3-16](#_ENREF_3)]. Median age of the 40 patients diagnosed as MGINET was 35 years (range: 10-81) and 25 (62.5%) patients were diagnosed at age below 40. Male to female ratio was equal. The most common affected site of MGINET was small intestine with 28 patients (70%), followed by stomach in 8 (20%) cases, colon in 3 (7.5%) cases and esophagus in 1 (2.5%) case. Mean size of the primary tumor was 4.86 cm. Among 33 patients with information on lymph node status, 23 (69.7%) patients had lymph node metastasis at initial diagnosis and among 36 patients with information on local or distant metastasis, 14 (38.9%) patients had local or distant metastasis at initial diagnosis. The most common site of metastasis in MGINET was liver with 16 cases (40%), followed by peritoneum, mesentery, omentum, pelvis, and lung. Among 13 patients with information on tumor invasion depth, 11 (84.6%) patients had transluminal involvement. Stockman *et al*[[3](#_ENREF_3)] reported clinical follow up data of 12 patients with MGINET; six patients died with tumor, four patients were alive with regional or distant metastasis and only two patients were alive without recurrence. MGINET showed aggressive clinical feature with high rate of recurrence even after complete resection and high mortality rate. Among 12 patients with both initial and follow up clinical information, even patients with small tumor size of 3.5 cm developed liver metastasis at 12 mo. Among two patients with intact serosa, one patient developed liver metastasis at 24 mo and one had no metastasis at 24 mo. Among five patients with positive lymph node metastasis, three patients developed or died from metastasis and among four patients without lymph node metastasis, two patients developed or died from metastasis. Four patients were free of disease at last follow up, however long term data were not available. As one patient developed metastasis at 60 mo from initial diagnosis, further follow up may increase the incidence of metastasis or death from tumor in these patients. Involved site, tumor, size, presence of trans-mural involvement and lymph node involvement at initial diagnosis do not appear to affect prognosis of MGINET. More cases and further follow up data are needed in order to understand behavior of MGINET. In our case, the patient had localized disease resected with negative margin and had no evidence of regional or distant metastasis on imaging studies, including computed tomography and PET, and early detection of the esophageal lesion due to symptoms caused by narrowing of esophageal lumen might have led to better prognosis in our patients, however further clinical follow up data are needed. We report on a case of subepithelial lesion diagnosed as malignant gastrointestinal neuroectodermal tumor, which is the first report found in esophagus.

**COMMENTS**

***Case characteristics***

A 21-year-old male presented with aggravating dysphagia for a few days.

***Clinical diagnosis***

Physical examination on the abdomen revealed unremarkable findings.

***Differential diagnosis***

Leiomyoma, granular cell tumor, glomus tumor, gastrointestinal stromal tumor, lipoma, cyst, varices, submucosal cancer or metastasis, or external compression by adjacent structures.

***Laboratory findings***

Initial laboratory findings were unremarkable.

***Imaging diagnosis***

Esophagogastroduodenoscopy revealed a huge bulging mucosa with intact surface causing luminal narrowing at 35 cm from incisor teeth, endoscopic ultrasonography showed an irregular margined inhomogeneous hypoechoic lesion measuring approximately 35 mm x 32 mm in size with obscure layer of origin, and abdominal computed tomography scan showed a well-defined mass measuring approximately 35 mm in size in the distal esophagus.

***Pathological diagnosis***

Histological examination showed spindle cells with eosinophilic and clear cytoplasm and vesicular nuclei and positive immunohistochemical staining results for S-100 protein, SOX 10, and vimentin and negative results for HMB 45 and melan and the final pathological result was confirmed as malignant gastrointestinal neuroectodermal tumor.

***Treatment***

The patient received excision of the subepithelial lesion in distal esophagus and subsequently treated with radiation therapy.

***Related reports***

Malignant gastrointestinal neuroectodermal tumor most commonly involves small intestine, followed by stomach and colon.

***Term explanation***

Malignant gastrointestinal neuroectodermal tumor is a tumor with similar morphology, immunophenotype, molecular genetic features of clear cell sarcoma of tendons and aponeurosis lacking melanocytic differentiation arising in the gastrointestinal tract

***Experiences and lessons***

This case report presents a case of malignant gastrointestinal neuroectodermal tumor arising in esophagus and most malignant gastrointestinal neuroectodermal tumor shows aggressive behavior and poor prognosis.

***Peer-review***

The case report on the esophageal subepithelial lesion diagnosed as malignant gastrointestinal neuroectodermal tumor is well written. The topic of the paper is interesting and important.

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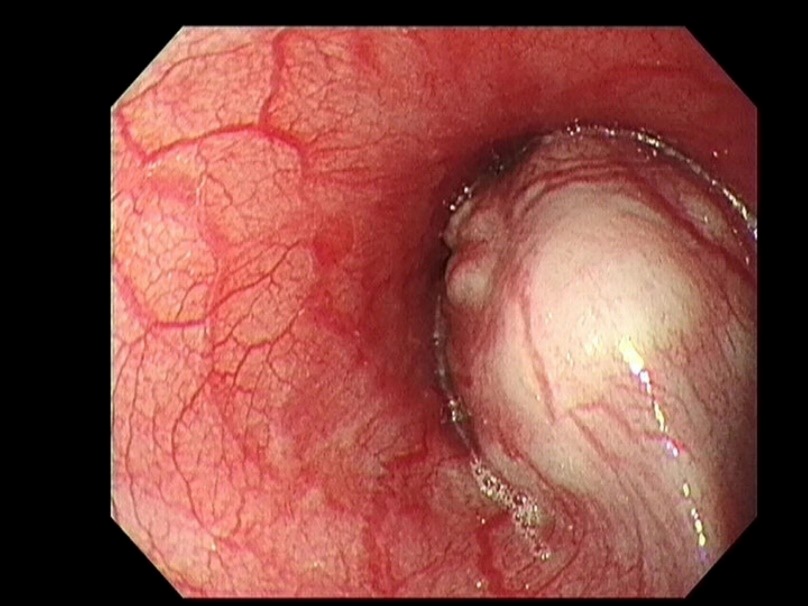
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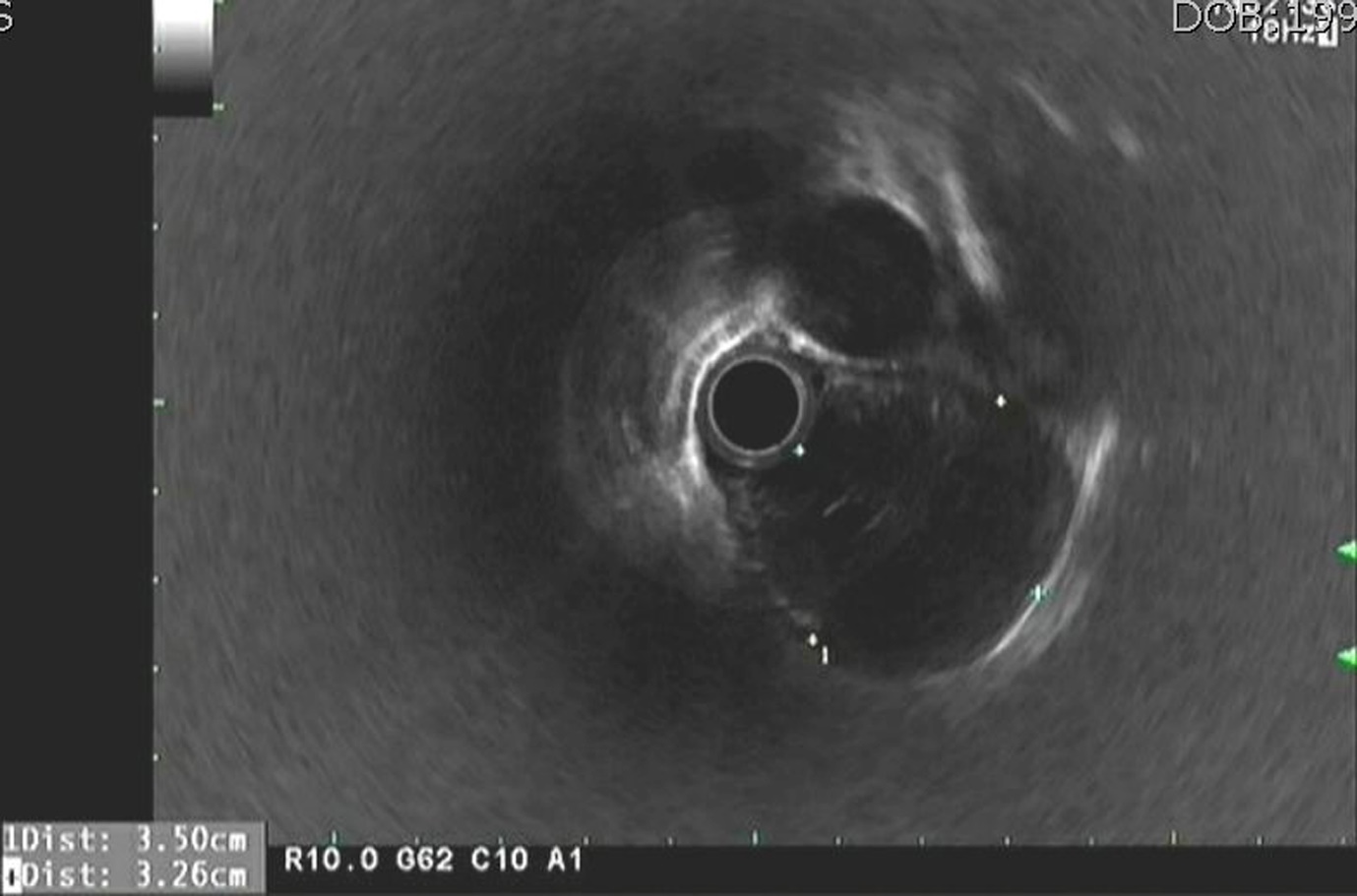
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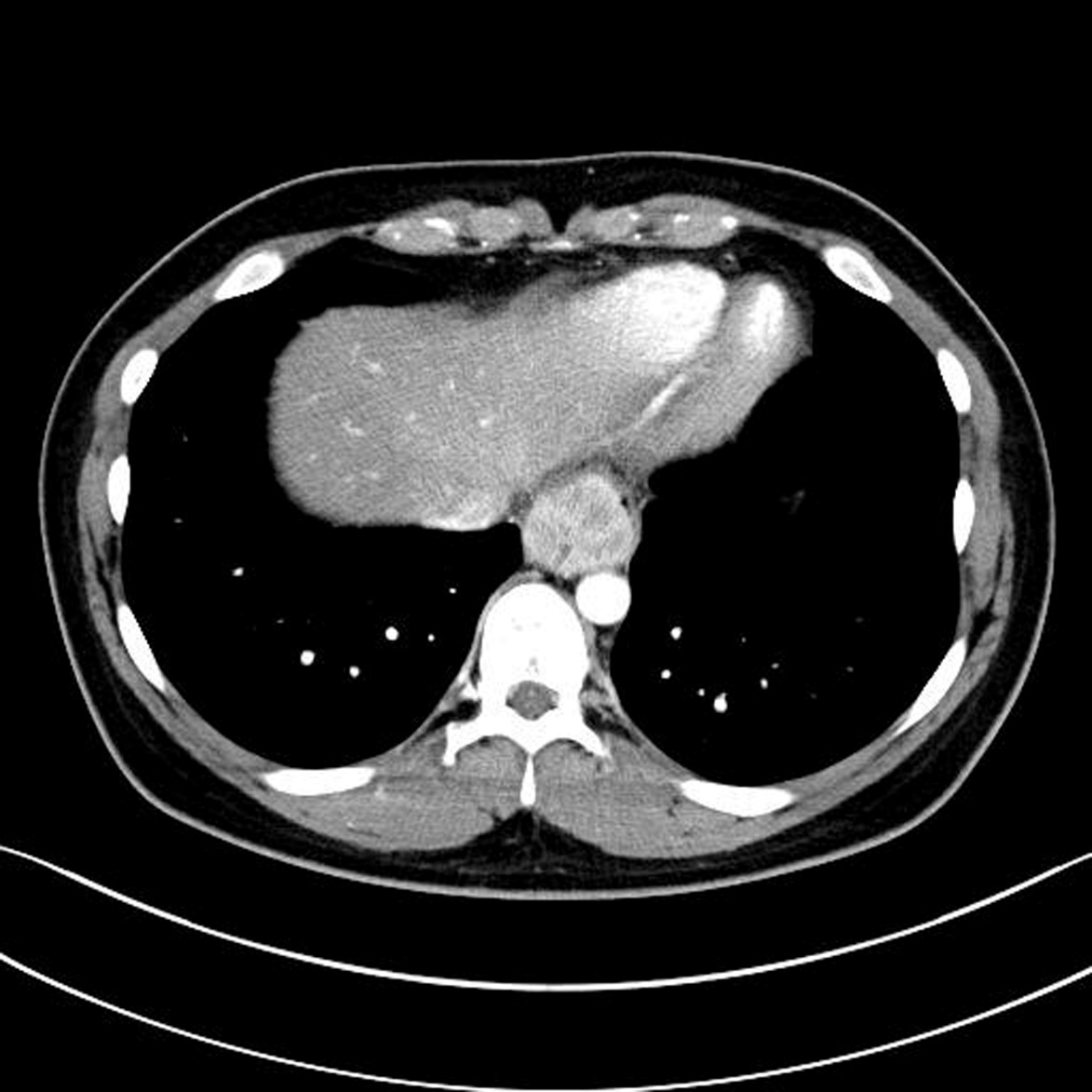
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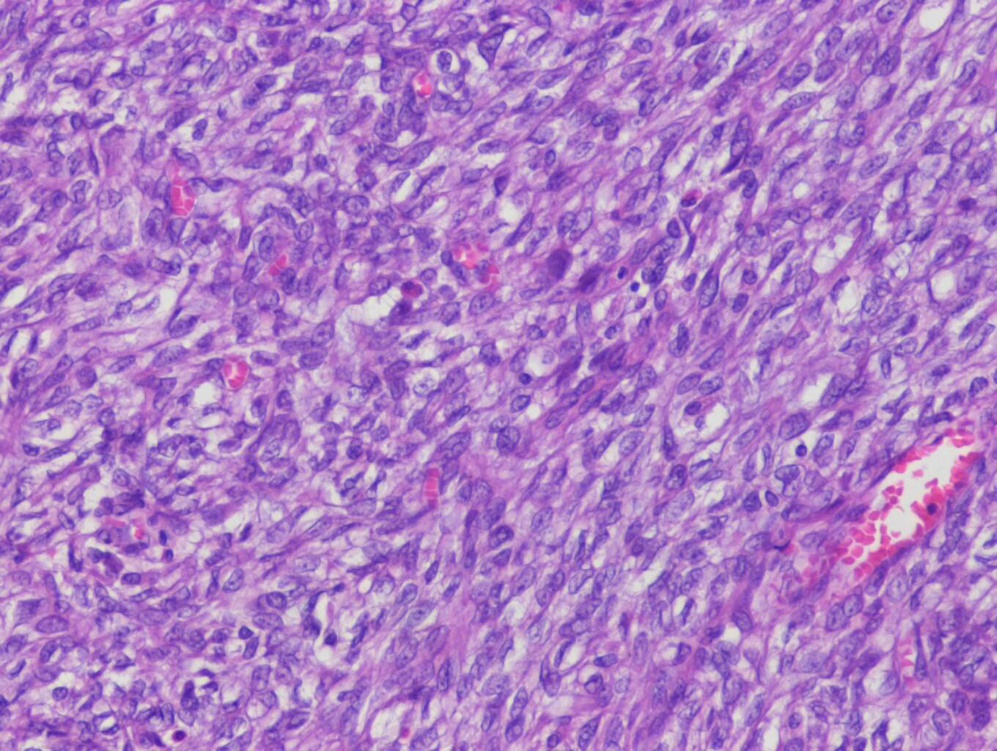
**Figure 1 Esophagogastroduodenoscopy at admission.** A huge bulging mucosa with intact surface causing luminal narrowing at 35 cm from incisor teeth was seen.



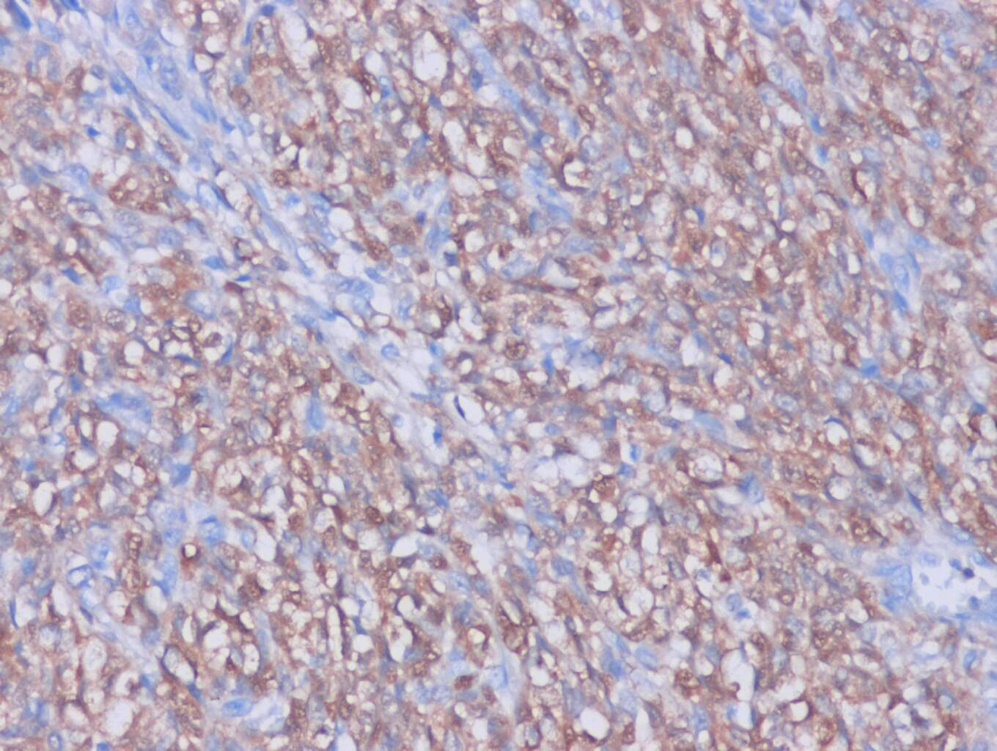
**Figure 2 Endoscopic ultrasonography at admission.** (A) Irregular margined inhomogeneous hypoechoic lesion measuring approximately 35 mm x 22 mm in size with obscure layer of origin was noted.



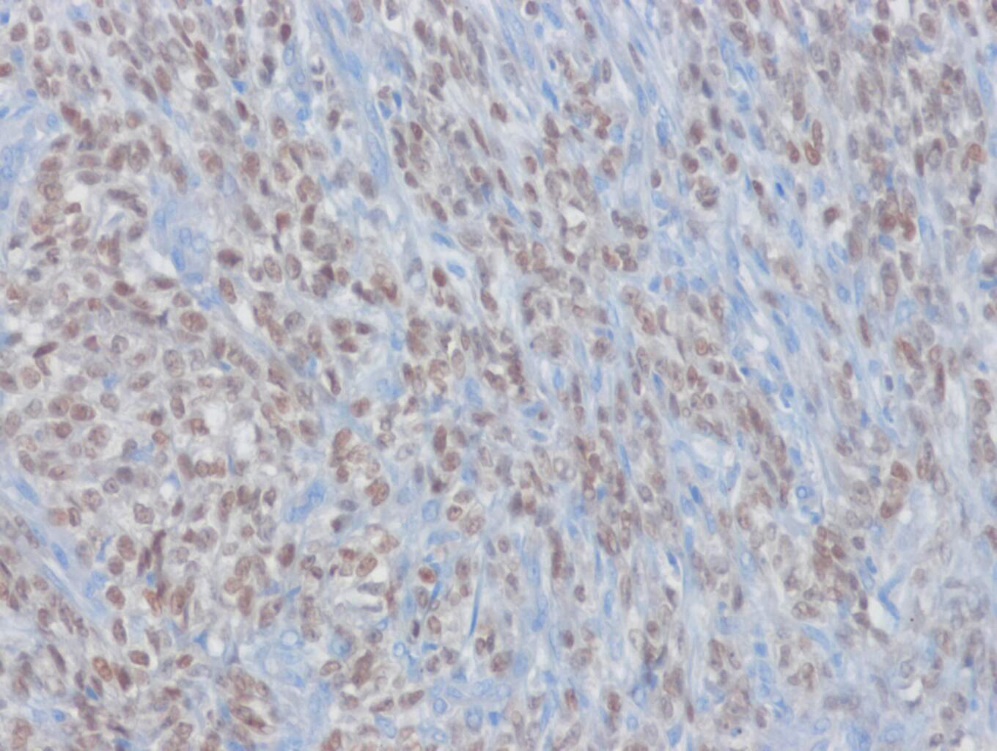
**Figure 3 Abdominal computed tomography scan at admission.** A well defined mass measuring 35 mm in size in distal esophagus was noted (arrow).



**Figure 4 Histologic examination.** Malignant gastrointestinal neuroectodermal tumor consisting of spindle cells with eosinophilic and clear cytoplasm and vesicular nuclei was noted. (HE stain, x 200).



**a**



**b**

**Figure 5 Histologic examination with immunohistochemical staining.** a positive for S-100 (A) and positive for SOX10 (B) was noted (x 200).