Esophageal subepithelial lesion diagnosed as malignant gastrointestinal neuroectodermal tumor

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Endoscopic ultrasonography showed an about 35 mm sized irregular margined in-homogenous hypoechoic lesion with an obscure layer of origin. Endoscopic ultrasonography fine needle aspiration revealed spindle cell proliferation without immunoreactivity for CD117, SMA, and cytokeratin. The patient underwent excision of the subepithelial lesion at the distal esophagus. On pathologic examination of the specimen, the 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 a malignant gastrointestinal neuroectodermal tumor. At the time of writing, the patient is on radiation therapy at the operated site of esophagus and doing well, with no recurrence for three months. Malignant gastrointestinal neuroectodermal tumor is a rare gastrointestinal tumor with features of clear cell sarcoma, without melanocytic differentiation, and shows a poor prognosis. This is the first reported case of malignant gastrointestinal neuroectodermal tumor arising as subepithelial lesion in the 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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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 an intact surface causing luminal narrowing at 35 cm from the incisor teeth.
301 IU/L lactate dehydrogenase, 12.0 s prothrombin time, 7.5 mg/dL blood urea nitrogen, 1.01 mg/dL creatinine, 134 mEq/L Na+, 4 mEq/L K+, and 97 mEq/L Cl-. Esophagogastroduodenoscopy showed a huge bulging mucosa with an intact surface causing luminal narrowing at 35 cm from the incisor teeth (Figure 1). On EUS, an irregular margined inhomogeneous hypoechoic lesion measuring approximately 35 mm × 22 mm in size with an obscure layer of origin was noted. (Figure 2). EUS guided fine needle aspiration was performed and, on microscopic view, spindle cell proliferation without immunoreactivity for CD117 and CD34. DOG-1, smooth muscle actin, and cytokeratin were observed. An abdominal computed tomography scan showed a well-defined round mass measuring approximately 3.5 cm in size in the 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 × 3.5 cm in size with the cut surface showing a 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 tumors show aggressive disease behavior with a poor prognosis.

**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]. Most SELs are found incidentally during esophagogastroduodenoscopy and, in some cases, may cause symptoms. Endoscopic ultrasonography (EUS) and/or fine needle aspiration is useful in making differential diagnoses of SEL, with the average accuracy of fine needle aspiration reaching 80%[2]. Differential diagnosis of esophageal SEL includes leiomyoma, granular cell tumor, glomus tumor, gastrointestinal stromal tumor, lipoma, cyst, varices, submucosal cancer/metastasis, or external compression by adjacent structures. The majority of mesenchymal tumors of the gastrointestinal tract are gastrointestinal stromal tumor or leiomyoma, with the diagnosis of malignant gastrointestinal neuroectodermal tumor (MGINET) being reported in rare cases[3].

We report on a case of a SEL of the esophagus diagnosed as MGINET, which is the first to be reported in the esophagus. We also provide a short review of the 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 over-eating for a year. He had no significant past medical or familial history, and was a non-smoker and a social alcohol drinker. On physical examination, he had the appearance of relative well-being, with an alert mentality and a soft, non-tender abdomen with no palpable mass. Initial vital signs included 140/90 mmHg blood pressure, 97 beats/min heart rate, 20 breaths/min respiration rate, and 36.9 °C body temperature. The initial laboratory findings were as follows: 9820 cells/μL white blood cells, 16.5 g/dL hemoglobin, 2.09 × 10⁵ cells/μL platelets, 0.67 mg/dL total bilirubin, 7.18 g/dL total protein, 4.18 g/dL albumin, 13 IU/L aspartate aminotransferase, 12 IU/L alanine aminotransferase, 263 IU/L alkaline phosphatase, 166 IU/L γ-glutamyl transpeptidase,
nuclei (Figure 4). Mitosis was seen frequently, with a mitotic count of 55/50 under a high power field. The tumor cells were positive for S-100, SOX10 (Figure 5), 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 the 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. At the time of writing, the patient is on radiation therapy at the operated site of the esophagus and is doing well, with no recurrence for 5 mo.

DISCUSSION

Clear cell sarcoma of tendons and aponeurosis is a malignant melanoma arising in soft tissue, 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 to clear cell sarcoma of tendons and aponeurosis lacking melanocytic differentiation arising in the gastrointestinal tract have been previously reported. Zambrano first designated these tumors as clear cell sarcoma-like tumor of the gastrointestinal tract in 2003[14]. 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] 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, CD117, CD34, DOG-1, CD99, α-smooth muscle actin, desmin, and glial fibrillary acidic protein. Conflicting immunohistochemical staining results for CD56, synaptophysin, NB 84, non-specific enolase, and neurofilament protein have been reported. Consistent with previous reports[3,5-11], 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 gastrointestinal stromal tumor was made by negative immunohistochemical staining results for CD117, CD34, and DOG-1. In our case, final diagnosis of MGINET was confirmed by split-apart signal detected in the EWSR1 on fluorescence in situ hybridization.

For our review of English language case reports on the subject, we included 40 cases of MGINET (39 from a search of PubMed and Google Scholar® in addition to our own case[3-16]). Median age of the 40 patients diagnosed as MGINET was 35 years (range: 10-81), with 25 (62.5%) patients being diagnosed at younger
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 an intact surface causing luminal narrowing at 35 cm from the incisor teeth. Endoscopic ultrasonography showed an irregular margined inhomogeneous hypoechoic lesion measuring approximately 35 mm × 32 mm in size with an obscure layer of origin. An 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. Immunohistochemical staining results were positive for S-100 protein, SOX 10, and vimentin and negative for HMB 45 and melan. The final pathological result was confirmed as a malignant gastrointestinal neuroectodermal tumor.
Treatment
The patient received excision of the subepithelial lesion in the distal esophagus and was subsequently treated with radiation therapy.
Related reports
Malignant gastrointestinal neuroectodermal tumor most commonly involves the small intestine, with the stomach and colon being the next most common sites, respectively.
Term explanation
Malignant gastrointestinal neuroectodermal tumor: a tumor with a similar morphology, immunophenotype, and molecular genetic features to 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 the esophagus. The most malignant gastrointestinal neuroectodermal tumors show aggressive behavior and a poor prognosis.
Peer-review
The case report on an 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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