

Small Cell Carcinoma: an Unusual Location in a Young Healthy Female

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Abstract

Small cell carcinoma (SCC) is most commonly found in the lung but is occasionally found in the gastrointestinal tract and other extrapulmonary sites. Incidences of SCC in the esophagus and stomach are rare and have been reported almost exclusively in older individuals. The following case presents the discovery of small cell carcinoma of the stomach and esophagus in a 35 year old woman, which is the youngest reported incidence of this to date. Additionally, her course reflects the importance of early diagnostic endoscopy with biopsy and adequate sampling with appropriate immunohistochemical staining when malignancy is in the differential diagnosis, regardless of age or risk factors.

Key words

Small cell carcinoma – gastrointestinal malignancies – esophagus – stomach – immunohistochemical staining – oat cell carcinoma.

Introduction

Small cell carcinoma (SCC) is most commonly found in the lung but is occasionally found in the gastrointestinal tract, salivary glands, prostate, cervix, thymus, skin, larynx, and pancreas [1, 2]. Incidences of SCC in the esophagus and stomach have been reported, almost exclusively in older individuals and carrying a very poor prognosis [2]. The following case presents the discovery of small cell carcinoma of the stomach and esophagus in a 35 year old woman, which, to our knowledge, is the youngest reported incidence of this to date.

Case Report

A 35 year old Caucasian female presented to her gastroenterologist complaining of dysphagia for solid foods and lower sternal and epigastric discomfort for 8 months. Prior to that time period, she was without any gastrointestinal symptoms. She denied any associated weight loss, nausea, vomiting, diarrhea, or constipation. She also denied experiencing any fevers, chills, jaundice, hematemesis, melena, or hematochezia. She had previously been started by her general practitioner on cimetidine with intermittent esomeprazole, which provided minimal relief of her symptoms. At presentation, her only medication was cimetidine. The patient had no significant past medical history or surgery. Additionally, she did not have any family history of colon carcinoma, polyps, or any upper gastrointestinal disorders. Her social history was significant for smoking one and a half packs of cigarettes daily for twenty years. She denied any history of alcohol or intravenous drug use.

Physical examination was significant for mild tenderness to deep palpation in the epigastric area. Her abdomen was otherwise soft, mildly obese, and without rebound, guarding, or hepatosplenomegaly. The remainder of her physical examination was benign. Laboratory blood analysis after the initial office visit was significant for mildly low albumin, but was otherwise unremarkable.

The patient had underwent a swallowing study two weeks prior to her office visit. The study revealed a concentric, irregular, persistent area of narrowing measuring 3 cm in the distal esophagus with abrupt transition and shouldering. Findings were consistent with a possible esophageal neoplasm; however, a benign peptic stricture was also in the differential.

Two weeks following the patient's office visit, an esophagogastroduodenoscopy (EGD) was performed for further evaluation. A circumferential friable mass 35 cm from the incisors was visualized and is shown in Fig. 1. When the scope passed, somewhat snugly, through this area, the lesion was noted to extend into the cardia where an ulcerated, friable, large gastric cardia mass was evident (Fig. 2). The distal stomach, antrum, pylorus and duodenum were normal. Biopsies of both the distal esophageal mass as well as the gastric cardia mass were obtained. Given the location of the

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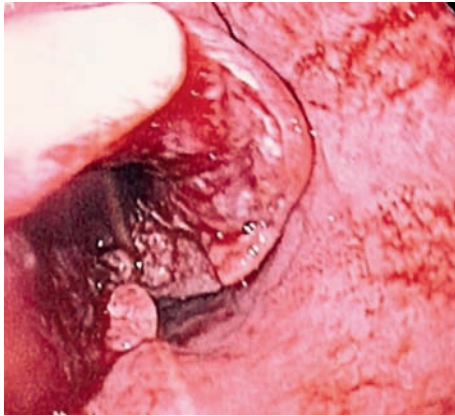


Fig 1. Circumferential lesion visualized in the esophagus.

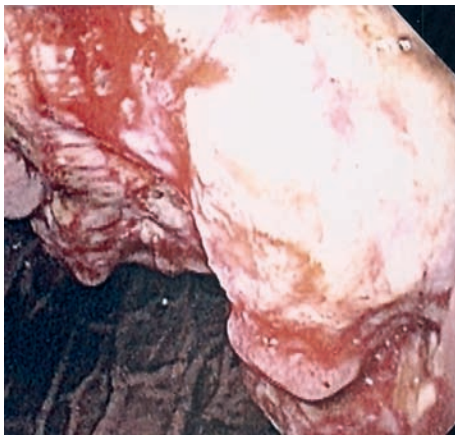


Fig 2. Large mass visualized in the gastric cardia.

mass in combination with the patient's symptoms, the lesion was considered "adenocarcinoma until proven otherwise".

Pathologic analysis of the EGD biopsies revealed predominantly necrotic and ulcerated tissue with occasional fibrin thrombi. Poorly preserved crushed cells suggestive of malignancy were present. A Giemsa stain was negative for *Helicobacter Pylori*; however, fungal hyphae and spores consistent with *Candida* species, were present. Immunohistochemical staining was initially unrevealing; as such, the pathologist requested a repeat biopsy from the periphery of the lesion, in a non-necrotic area, for flow cytometry studies. Following a repeat endoscopy with biopsy, the immunoperoxidase stains showed results consistent with a high-grade malignant tumor of neuroendocrine derivation. Final analysis was consistent with malignant small cell undifferentiated ("Oat-Cell") carcinoma. These stains are shown in Figs. 3 and 4.

The patient underwent a CT with contrast of the chest, abdomen and pelvis. Thickening of the distal esophageal wall with extension to the cardia and enlarged nodes at the root of the mesentery and along the gastrohepatic ligament were noted. There were no other abnormal abdominal masses or collections. The liver, gallbladder, spleen, pancreas, kidneys, and lungs were within normal limits.

Chemotherapy is the first line of treatment for extra-pulmonary SCC, with surgical interventions being limited to

cases in which palliative care is the goal [3,4]. Subsequently, the patient underwent 21 rounds of chemoradiation with Topotecan and Dexamethasone. After 7 years, the patient has remained in remission and has not required any further treatment. She continues to be screened by EGD every three months.

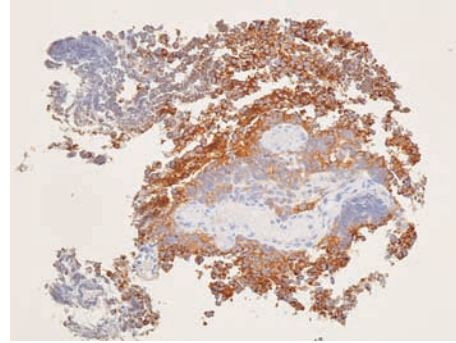


Fig 3. Immunohistochemical stain: synaptophysin showing neuroendocrine differentiation.

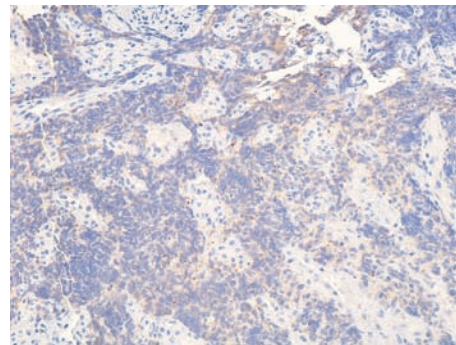


Fig 4. Immunohistochemical stain: chromogranin, granular positivity in cytoplasm showing neuroendocrine differentiation.

Discussion

Small cell carcinoma (SCC) is most commonly found in the lung, but there are several reports of SCC of the esophagus and stomach. Whether occurring in lung or in extra-pulmonary tissues, it is an aggressive tumor without a standard therapy, and is therefore associated with a poor prognosis [5]. Patients often present with widespread metastases, which may be due to its predilection for vasculo-lymphatic invasion and deep infiltration [3, 6]. Median age at diagnosis is 66, with males outnumbering females [3]. The presenting symptoms when found in the esophagus or stomach are similar to those of other types of upper gastrointestinal cancer including complaints of epigastric pain, nausea, vomiting, dysphagia, early satiety, weight loss and melena [1, 3]. Since the lesion in this patient was found in both the esophagus and stomach, it is difficult to determine where the primary tumor originated. However, CT scans suggest the tumor arose from the gastric cardia and went on to invade the distal esophagus and lymph nodes along the root of the mesentery and the gastrohepatic ligament.

Small cell carcinoma represents 0.1% of all gastric carcinomas, and 0.4-7.6% of all esophageal carcinomas [6, 7]. The carcinoma has been found to be of mixed type 63% of the time, demonstrating coexisting adenocarcinomatous and squamous cell histological characteristics [7]. This characteristic initially led to speculation that esophageal and gastric SCCs derive from the mucosa with early proliferation into the submucosa [7]. Biochemical and ultrastructural analysis pointed to the cancer rising from neuroendocrine amine precursor uptake decarboxylation (APUD) cells – a collective term used to describe a diffuse spectrum of endocrine cell types scattered throughout the body [8]. These neuroendocrine cells have the ability to produce substances such as epinephrine, norepinephrine, serotonin, dopamine, and substance P [9]. Recent investigations have shown that it is more likely that SCC is derived from pluripotent basal epithelial cells located in endodermal tissues [6]. These cells are thought to be the common precursor for adenocarcinomas, squamous cell carcinomas, and SCCs, with an ability to differentiate into either mucin-producing or keratin-forming cells. This theory has provided a better explanation as to why the same lesion has the ability to contain squamous, small cell, and glandular structures [6].

Esophagogastroduodenoscopy is the most precise diagnostic tool for all esophageal and gastric carcinomas. Gastric SCC is indistinguishable from adenocarcinoma on radiologic studies [10]. When the tumor has the same or lower attenuation as the adjacent gastric wall, the enhancement pattern on CT is unable to differentiate between SCC, adenocarcinoma, or lymphoma [11]. Since management of a patient with esophageal or gastric adenocarcinoma is often through endoscopic or surgical measures, whereas SCCs are primarily treated with chemotherapy, early determination of the type of cancer using upper endoscopy with biopsies is essential [12, 14].

Immunohistochemical staining of the biopsied cells is vital to determine the precise type of carcinoma [7]. In this case, immunoperoxidase stains demonstrated positive staining for the neuroendocrine markers, synaptophysin and chromogranin A, while being negative for CD45, CK7, CD20 (lymphoma markers) and CAM5.2 (epithelial tumor marker). A stain for CD99 helped to rule out a peripheral neuro-ectodermal tumor, and supported the diagnosis of SCC. A good practice is to take multiple random biopsies of the site due to the propensity for mixed-cell type carcinomas [7]. Figures 3 and 4 show the positive stains of the biopsied cells, using both synaptophysin and chromogranin A.

As previously mentioned, the prognosis of extrapulmonary SCC tends to be extremely poor, with median survival time being 9 months [13]. Proliferative ability and angiogenesis are important determinants of the aggressive nature of any tumor. It has been postulated that a good marker of proliferative potential is the number of cells that are positive for proliferating cell nuclear antigen (PCNA). This is known as the PCNA labeling rate (LR). In immunohistochemical analyses, esophageal and gastric SCC has been shown to demonstrate higher PCNA labeling rates than other types of gastrointestinal carcinomas [14]. As for a tumor's ability to undergo angiogenesis, the expression of vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PD-ECGF) have

shown to be good indicators. The expression of these growth factors has also been shown to induce hepatic metastasis [14]. In one study of SCC, 87.5% of the tumors stained positive for VEGF, and 100% stained positive for PD-ECGF [14].

While there is currently no definitive protocol for treatment of esophageal or gastric SCC due to the paucity of cases, chemotherapy appears to be the most effective treatment. Regimens usually closely follow those for pulmonary SCC [3]. Success has been reported using combination-based treatments, such as cisplatin and etoposide, which are the first line of treatment for small cell lung cancer (SCLC) [4, 15]. Topotecan, a second line drug approved to treat relapsed SCLC, as well as advanced cervical and ovarian cancers, proved to be successful in this patient [2,4]. This is likely attributable to the lack of metastases at the time of diagnosis. Many patients demonstrate a response to the treatments but since the disease is often late-stage at the time of diagnosis, the median survival time remains low. Radical surgery is generally a palliative measure and is not considered a first line treatment [3].

Conclusion

Young patients have occasionally been described in previous reports of extrapulmonary gastrointestinal small cell carcinoma [16]; however, to our knowledge, this 35 year old patient represents the youngest case to date. Her course reflects the importance of early diagnostic endoscopy even in healthy young patients with biopsy and adequate sampling including appropriate immunohistochemical staining, when malignancy is part of the differential diagnosis.

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