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First Reported Case of Localized Extra-pulmonary Small Cell Carcinoma (EPSC) of the Esophagus Treated With Triple Therapy

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Abstract. *Background/Aim: Early stage extra-pulmonary small cell carcinoma (EPSC) of the esophagus is very rare and is usually treated with chemo-radiation or surgical resection. Case Report: A case of early stage small cell carcinoma of the esophagus that was treated with all three current modalities of chemotherapy, radiation, and surgery. To our best knowledge this is the first case treated with triple therapy. The patient is a 64-year-old male with increasing gastroesophageal reflux disease (GERD) symptoms. EGD biopsy of the mass showed small cell carcinoma. Metastatic work up was negative. Patient was treated with 6 cycles of a platinum-based agents and Etoposide along with radiation. Patient underwent distal esophagectomy. Patient is alive without evidence of recurrent disease at 20 months follow up. Conclusion: Currently there are no definite treatment recommendations, but we present a possible future option with good outcomes in patients who can tolerate triple therapy.*

Extra-pulmonary small cell or high-grade neuro-endocrine tumors located in the esophagus are exceedingly rare. They represent around 2.5% of all small cell carcinomas identified and around 0.1-0.4% of all cancers identified in the United States (1, 2). Due to the low prevalence of this disease, no large clinical studies have been conducted to identify optimal treatment modalities for this disease (3). Current treatment options are based on guidelines for pulmonary small cell carcinoma involving a combination of chemotherapy, radiation, and surgical resection. We here present the case of a 64-year-old Caucasian male who was diagnosed with a localized small-cell cancer of the esophagus and treated with multimodality therapy with complete response, the first known patient to be treated with all of the available modalities. We also provide a review of the literature related to the present case and their outcomes.

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Case Report

The patient is a 64-year-old male with a past medical history of hypertension, hypothyroidism, gastroesophageal reflux disease (GERD), coronary artery disease status post cardiac stent, who presented with complaints of dysphagia, dizziness, and melena for one month. His history of GERD was treated with Protonix for over twenty years. His family history was only pertinent for a brother who developed colon cancer in his 30s. He denied any history of smoking and was a weekend social drinker. A month prior to this admission he was experiencing similar symptoms of worsening acid reflex that was refractory to medical therapy. An esophagogastroduodenoscopy (EGD) at an outside facility at that time showed a fungating mass involving the 2/3rd of the circumference of the lower third of the esophagus that when biopsied showed necrotic tissue with numerous candida species, but no evidence of any malignancy (Figure 1). He was treated with 2 weeks of fluconazole with no relief of symptoms. A CT scan at that time showed a large circumferential mass in the distal and mid esophagus without pathologically enlarged lymph nodes (Figure 2). Thereafter, the patient continued to have dysphagia with solids and a reported weight loss of around 21 pounds, a repeat EGD with biopsy was performed at our institution showing an almost completely obstructing and partially circumferential mass (Figure 3). Biopsies taken at this time stained positive for CAM 5.2, TTF-1, synaptophysin, chromogranin and CD56, but negative for CK7, CK20, CDX-2 and p40. The Ki-67 was high at approximately 80%. Histology is shown in Figure 4. CT scan of the chest, abdomen, pelvis, nuclear medicine (NM) bone scan and MRI of the brain

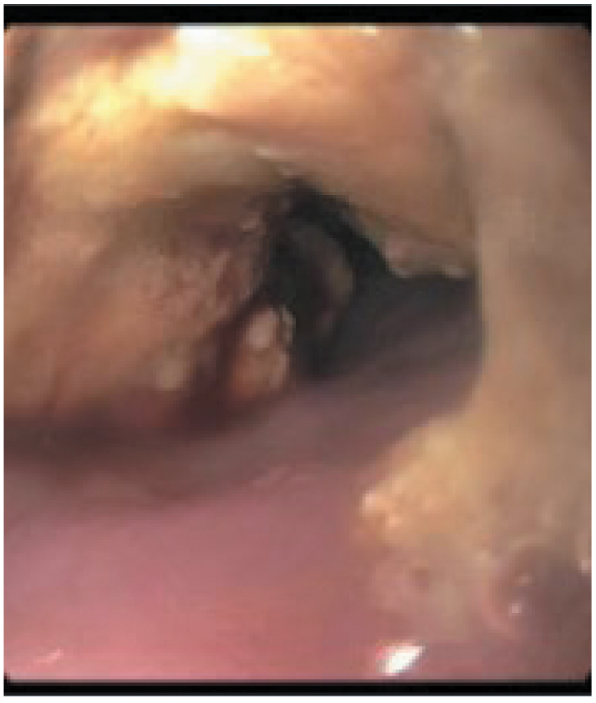

Figure 1. *Initial EGD showing the fungating mass surrounding 2/3 of the distal esophagus. Biopsies showed candida species but no evidence of malignancy.*

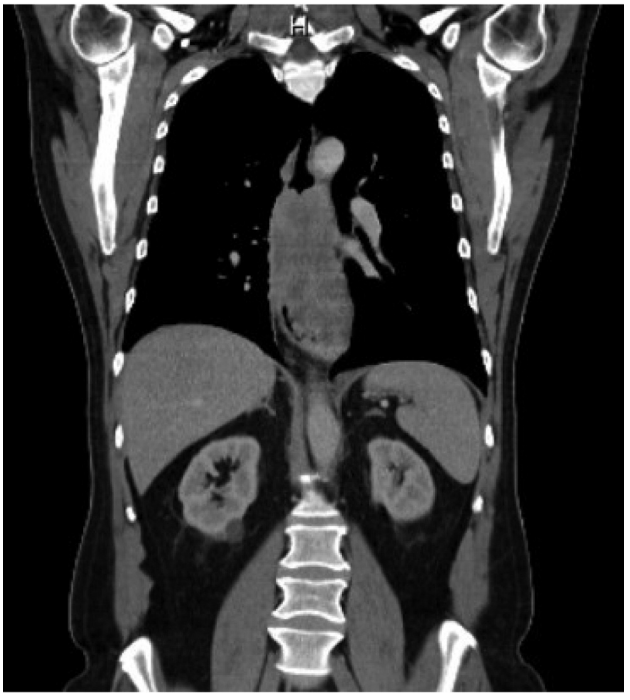

Figure 2. *Computed tomography scan with contrast showing a pathologically enlarged mid and distal esophagus concerning for malignancy, without pathologically enlarged lymph nodes or evidence of metastatic disease.*

failed to show any other site of possible primary site and evidence of metastasis. Therefore, he was diagnosed with TxN0M0 localized extrapulmonary small cell carcinoma (EPSC) of the esophagus. Based on the multidisciplinary thoracic oncology conference recommendations, patient was initiated on treatment with a total of 6 rounds of chemotherapy with cisplatin 75 mg/m^2 and etoposide at 100 mg/m^2. After one round of chemotherapy, he developed an acute kidney injury from tumor lysis syndrome in combination with cisplatin-related kidney injury and was transitioned to carboplatin with area under the ROC curve (AUC) of 5 instead. Treatment course was also complicated by deep vein thrombosis (DVT) requiring anticoagulation. He was transitioned back to cisplatin 60 mg/m^2 and etoposide 100 mg/m^2 to be given along with intensity-modulated radiation therapy (IMRT) during his third cycle of therapy, after renal recovery. His overall treatment was complicated with episodes of pancytopenia requiring dose adjustments, and AKI requiring transition again to carboplatin. He completed 6 cycles of platinum-based chemotherapy with concurrent radiation treatment of 5040 cGYs with cycles 2 and 3 and tolerated it well. A repeat positron emission tomography (PET) scan at the completion of therapy showed stable disease without any evidence of metastatic lesions. Prophylactic cranial radiation was discussed by radiation oncology but not administered at the time, given data that extra pulmonary small cell cancer does not metastasize to the brain at the same rates as pulmonary small cell lung cancer (4). His case was discussed again at the multi-disciplinary thoracic tumor board and given

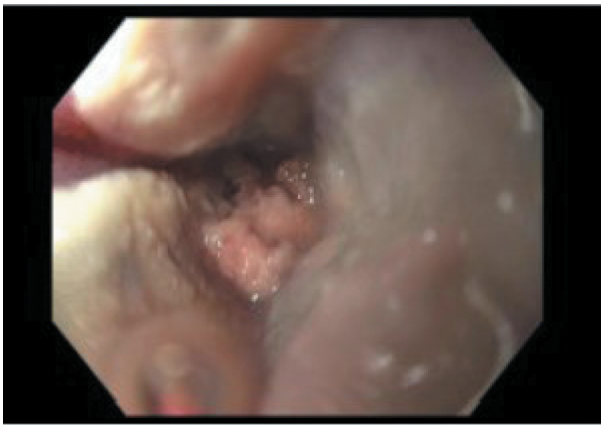

Figure 3. *Repeat esophagogastroduodenoscopy one month later showing a nearly occlusive mass of the esophagus. Biopsies corresponded with small cell carcinoma.*

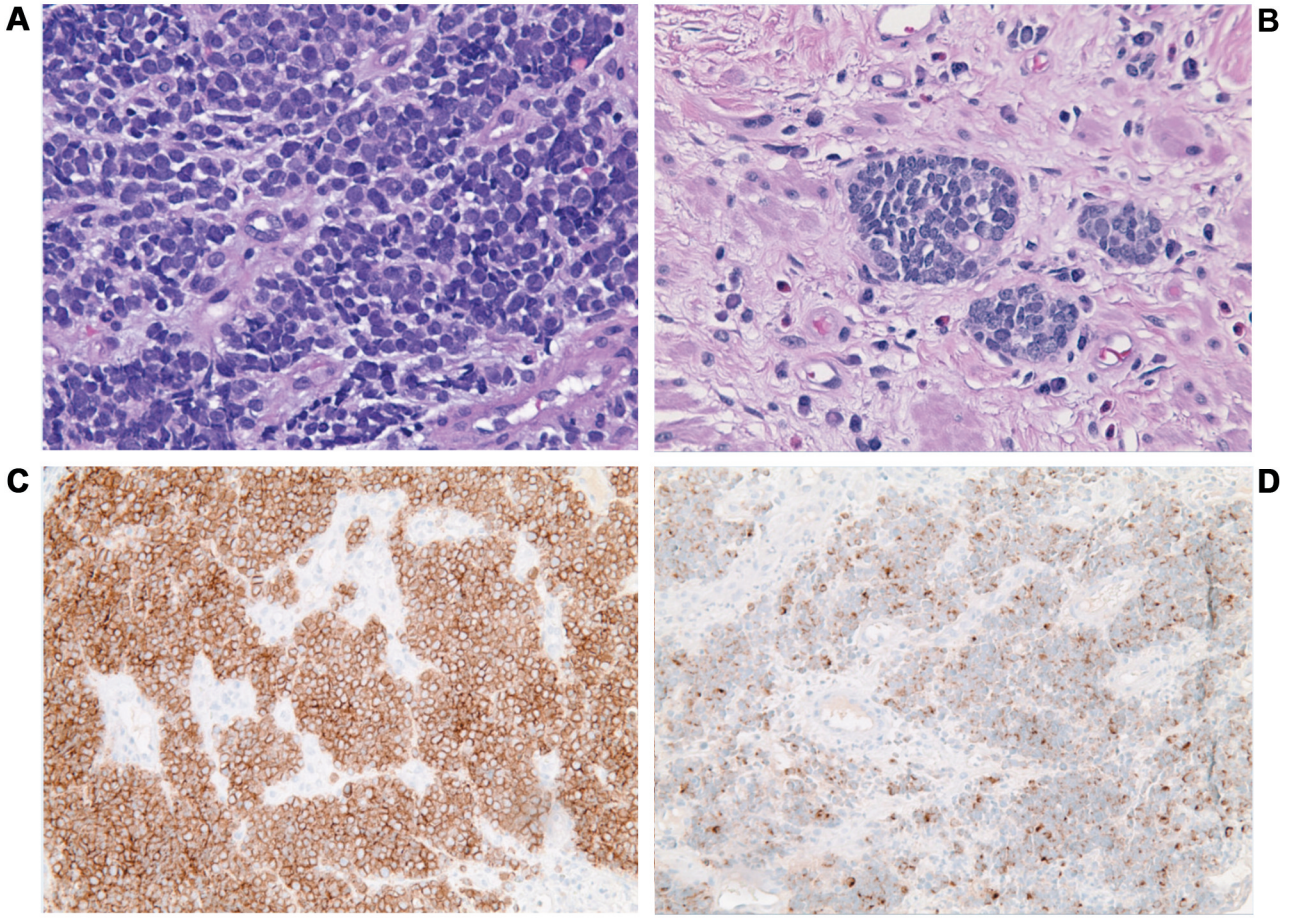

Figure 4. *Microscopic examination of mass biopsy. A. High power view of small cell carcinoma of the esophagus taken at the second biopsy. B. High power view of the residual disease after chemotherapy and radiation treatment. C. CD56 staining of tumor tissue. D. Chromogranin staining of tumor tissue.*

his overall well tolerance of the current therapy he was referred to thoracic surgery to discuss the options for possible esophagectomy. However, on the following restaging CT, he was found to have a new pulmonary nodule and underwent a wedge resection that came back negative for malignancy.

Ten months after the initial diagnosis of EPSC, the patient underwent a minimally invasive esophagectomy with jejunostomy tube insertion. There was only a 0.4 cm residual tumor (ypT1b) and all margins were negative, no lymphovascular invasion was identified, and all lymph nodes tested negative for metastatic disease. One month after the surgery the jejunostomy tube was removed without complications. Six months postoperative the patient continues to remain in good health. He has surveillance PET scans every 3 months as he is unable to have contrast enhanced CT scans due to his chronic kidney disease. A repeat PET scan 9 months post-surgery was initially concerning for hypermetabolic activity in the jejunum and right hepatic lobe, but a follow up MRI did not show any suspicious mass or abnormal enhancement to correlate to the areas of uptake on the PET. The patient continues to remain in good health with no complaints at this time, 20 months since diagnosis.

Discussion

Extrapulmonary small cell cancer (EPSCC) is an exceedingly rare disease that can originate in any organ system. The clinical course of the EPSCC is generally aggressive with over half of patients presenting with metastatic disease and often recurrence despite therapy (3, 5-7). The most common primary sites for this tumor have been described in the esophagus, breast and thymus, with less common sites being the pancreas, stomach, cervix, prostate, colon, parotid gland and liver (2). Of these, esophagus EPSCC seems to be the most common primary gastrointestinal site for this tumor. There may be some association between smoking and

esophageal EPSCC, but most studies are limited by retrospective design (2, 5, 8). Unfortunately, GI primary sites also carry the worst prognosis compared to other primary sites, with an overall survival time of weeks to 12 months compared to 14 months for all patients with other EPSCCs (2). The extent of disease is one of the most important prognostic factors for survival, with local disease having a median survival of 8 months compared to 3 months with systemic disease (5).

Treatment regimens for localized EPSCC are limited due to the rarity of the disease and inability to create large scale clinical trials. Most of the treatment regimens are based on the treatment recommendations for small cell lung cancer (SCLC) or retrospective studies (6). Regardless of primary site, most of these tumors are initially examined to confirm that they are EPSCC and do not represent metastatic SCLC (5). Patients with localised disease are usually treated with either surgical resection or chemo/radiation. In SCLC, those with limited disease staged T1 on the TNM staging system are indicated for surgery alone (9). Those treated with surgical resection of localised disease only have a variable course of survival ranging from rapidly recurrent disseminated disease in several weeks to disease-free survival of up to 9 years (5). Even if only localised disease is found and resected, evidence supports treatment with systemic chemotherapy due to the high probability of micrometastases in adjacent lymph nodes (7, 10). Chemotherapy is most commonly pursued due to the high incidence of metastatic disease upon diagnosis of EPSCC. Most chemotherapeutic regimens used are similar to those of SCLC, containing a platinum agent and etoposide. A large retrospective review of 199 patients with esophageal small cell carcinoma concluded that chemotherapy should be the cornerstone of treatment for both local and systemic disease with evidence to support long term remission and survival (6). Radiation therapy is most commonly used in conjunction with chemotherapy with curative intent. Evidence with small cell lung cancer suggests improved survival of the combination therapy compared to chemotherapy alone (11, 12). In a retrospective study of 25 patients, 4 patients with limited disease who were alive at the 38-month follow up received induction chemotherapy followed by chemoradiation therapy with no surgical intervention (13). A study of 127 patients showed that radiation and chemotherapy had a higher overall three-year survival compared to that of surgery and chemotherapy, 50 versus 24 percent, respectively (14). There have been some anecdotal cases of immunotherapy with EPSCC that show promise and thus, several studies are currently being conducted investigating immune check point inhibitors being added to chemotherapy regiments (15). Several other studies are looking at individualistic tumor markers with potential molecular stratification base on the primary site for specific targeted therapy (16). After a review of the literature, this is the first case treated initially with chemoradiation, followed by surgery with curative intent. A few cases of initial primary care with surgery followed by chemoradiation do exist (2). If primary treatment with a platinum-based regiment fail, even less data exists for possible second line treatments without prospective studies (17). Insufficient data exist to support the use of prophylactic cranial radiation in individuals with EPSCC (3, 12).

This case is interesting in that chemotherapy and radiation were initially used, followed by surgery with curative intent for the treatment of localized esophageal EPSCC. After the patient underwent initial disease control with chemotherapy and radiation, surgical resection of the tumor was completed. In review of case reports, it is unclear if this is the first time the combination of all three therapeutic methods was used as treatment for EPSCC. However, due to the overall positive outcome of our patient, this combination therapy could be especially useful in the future for select patients who have a good performance status. Our patient is currently 20 months since the initial diagnosis, meeting the upper limit of overall survival of GI primary EPSCC. A follow up report will be published in the future to update his disease status.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Study concept and design: AH, DP; Drafting the manuscript: All Authors; Critical revision of the manuscript for important intellectual content: All Authors; Administrative, technical, or material support: DP, DM.

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