Small Cell Esophageal Carcinoma; A rare diagnosis, Cases reports and review of the literature

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Definition

Primary small cell carcinoma (SCC) of the esophagus is a relatively rare malignancy, accounting for 0.05 – 4% of all esophageal malignancies. It is a highly aggressive tumor associated with a poor prognosis, similar to SCC that arises in the lung and other extra pulmonary organs, including breast, ovary, uterine cervix, liver, salivary gland, stomach, colon, prostate, urinary bladder, and kidney. Histologically, SCC is characterized by neuroendocrine-like architectural patterns, including nested and trabecular growth with common features including peripheral palisading and rosette formation in the tumors. Some SCC cases include carcinomas such as squamous cell carcinoma and adenocarcinoma (approx. 90–95% of all esophageal cancer worldwide) and adenocarcinoma (approx. 50–80% of all esophageal cancer in the United States)[1]
A general rule of thumb is that a cancer in the upper two-thirds is a squamous cell carcinoma and one in the lower one-third is an adenocarcinoma[2]
Primary small cell esophageal carcinoma (SCEC) is a rare and aggressive disease for which there is no recommended standard treatment at this time.

Prevalence and risk factors

Cancers arising from the esophagus and gastro esophageal junction are relatively uncommon in the United States; there were approximately 38780 new cases and 25610 deaths in 2012[2]. Worldwide, however, esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death[3]. The epidemiology of esophageal cancer has changed dramatically during the latter half of the 20th century. Although 40 years ago SCC accounted for more than 90% of all esophageal tumors in the United States, diagnoses of esophageal AC have significantly increased and is becoming endemic, especially in developing world. However, SCC remains the most common worldwide. The mean age at diagnosis is 67 years, and men are affected more frequently than women, particularly among patients with AC.
Tobacco and alcohol are major risk factors for esophageal cancers. Obesity and high body mass index are also strong risk factors. Significant changes have been observed in histology and location of upper GI tumor in UA as well as in Europe. Small cell carcinoma was first described by McKeown in 1952. Histologically it is not different from lung small cell cancer. They both originate from Kulchitsky"s or amine precursor uptake and decarboxylation cells of neuroectodermal origin. The staging of small cell esophagus is similar to small cell carcinoma of lung staging. Small cell carcinoma of esophagus is a rare disease with poor prognosis and high rate of metastases. In small cell carcinoma patients present with extensive metastasis to the liver, adrenal gland, lymph nodes, and other organs[4-5]
Osugi et al. reported that the overall survival after esophagectomy was significantly lower in patients with Small cell carcinoma as compare to squamous cell carcinoma[5]
For definitive diagnosis of this tumor, biopsy is necessary, although exact biopsy of the tumor is difficult because the tumor surface is covered with normal epithelium. Mitani et al reported that the tumor was confined to the sub mucosal layer in all long-term survivors[6]
In some cases, it is sometimes impossible to diagnose the tumor by means of endoscopy or endoscopic biopsy. For this reason, PET-CT seems to be very useful. Because esophageal cancer often spreads to the lymph nodes or other adjacent organs, CT imaging has been commonly used to diagnose the presence of metastases. The advantage of FDG-PET is that it can be used to diagnose the original lesion and the presence of metastases in the lymph nodes and adjacent organs. Regarding the use of FDG-PET in the diagnosis of esophageal cancer; Yeung et al. compared FDG to CT in the detection of primary lesions in 109 patients with esophageal cancer. They reported that sensitivity was 80% for PET and 68% for CT, specificity was 95% for PET and 81% for CT, and accuracy was 86% for PET and 73% for CT[7]

Case No. 1

59 years old male, with Diabetic Mellitus, Hypertension, hepatitis C positive, and CVA in 2008 presented in December 2011 with a 2 months history of dysphagia to solid foods, loss of appetite and weight loss of about 10 kilograms. Physical examination at the time was otherwise completely unremarkable. There were no palpable lymph nodes.
Upon first visit in Tawam Hospital several investigations were done including Endoscopy (EGD) which showed ulcerated polypoidal lesion that started from 32 cm and extending up to 41cm of esophagus and erosive duodenitis, a biopsy

taken showed Tumor cells expressing CK, EMA, Synaptophysin, chromogranin and TTF-1 strongly;Mib labeling index is 30 to 40% The Ki-67 index is 80%. Positive Stain for Helicobacter pylori is. The features were consistent with Small cell carcinoma. All blood workup including tumor markers were within normal limits. A CT scan chest/Abdomen showed; a circumferential mass lesion in the distal 9 to 10 cm of esophagus up to the GE junction.with Three large paraesophageal lymph nodes adherent to the esophageal mass with the largest one measuring 4.6 to 5.1cm; The mass partially encased the celiac axis origin.

He was started on first line chemotherapy with Cisplatin 50 mg/m^2 with Etoposide (VP-16) 180 mg/m^2 with all supportive treatment. And has completed 6 cycles after which he a CT scan done showed almost total resolution of lower esophageal wall thickening with Regression in size of the lesser sac mass with No sign of distant metastasis.

He was followed up until September 2012 when a repeat CT scan showed progressive disease with bone metastases; MRI of the spine was done showing soft tissue mass with pressure effect on the epidura and nerve root so he received radiotherapy to spine T2-T7 20 Gy and 4 fraction; he was also started on Topotecan as 2nd line with Zometa after 2 cycles of chemotherapy he developed a stroke and duplex scan of carotid artery showed complete occlusion of the right internal carotid artery (history of CVA) he was switched to FOLFIRI; he completed one cycle and developed febrile neutropenia and severe mucositis; his condition kept worsening until his family decided to stop all treatment and take him back to his home country as January 2013

Case No. 2

57 years male heavy smoker; history of Diabetic Mellitus, Hypertension and Dyslipidemia; underwent a coronary artery bypass graft surgery (CABG) in 2006 Patient first presented to Tawam Hospital in June 2010 with persistent dysphagia and vomiting for 3 months duration and a significant weight loss. Physical examination was otherwise completely unremarkable, no palpable lymph nodes. EGD showed thickening of the lower esophageal wall, Mild stenotic polypoid lesion starting at 28 cm from the incisors, in the lower esophagus Barrett mucosa is well definable. Endoscopy U/S showed infiltration of the wall, no adjacent organ involvement & 2 lymph nodes, staging was T3N1M0. All blood workup including tumor markers were within normal limits. A CT scan reported mild lymphadenopathy in the upper mediastinum measuring 1 cm. Lungs were clear, and thickening of the distal third wall of esophagus

Esophageal biopsy showed neuroendocrine carcinoma, poorly differentiated, with small cell components, Ulcerated Barrett esophagus pieces seen.

Surgery was performed as minimal invasive esophagectomy with chest anastomosis and Bronchoscopy.

Post operatively he was started on chemotherapy with Cisplatin 50mg/m^2 and Etoposide (VP-16) 180 mg/m^2; in January 2010 he completed 4 cycles and up to date patient was followed up with CT scan and EGD every 3 months two times without any recurrence of disease.

Discussion

Small Cell carcinoma of the esophagus is very rare and it represents about 1-2% of all esophageal cancers[8]. McKeown first described two cases after autopsy as esophageal small cell carcinoma as oat cell carcinoma in 1952[9]. It cannot be treated adequately only by esophagectomy, although it recommended only for limited cases, in many cases the metastases were found during operation. In Extended disease cases, it should be treated with chemotherapy and /or radiotherapy[10]

Levenson et al and Kelsen et al recommended chemotherapy as first line treatment. Beyer et al reported as combination chemotherapy is the best choice[9]. Recently he also reported about limited disease treated by adjuvant therapies with surgical resection and achieved longer survival time[11] they also mentioned that patient who received preoperative chemotherapy survived 33 months.

Radiotherapy is as effective as in small cell lung cancer in limited disease, but only for local control, radiation alone if not first line choice. Cisplatin is reported as better treatment for small cell of esophagus. Tanabe et al reported that five drugs (CDDP, VP-16, VCR, ADM, CPA), CDDP and VP-16 are the best choice and more effective and WBRT should be applied as prophylactic treatment[12]. They also reported patient treated with chemotherapy also died from Meta brain disease. Since pathology of both small cell carcinoma of lung and esophagus is same they both treated with same chemotherapy regimen. However, extensive metastasis to the liver, adrenal gland, lymph nodes, and other organs, is often seen at the time of diagnosis.

In summary, small cell carcinoma of esophagus is almost impossible to get complete heal, local treatment like operation and radiotherapy are not good options alone, it should be treated with multi drug regimen chemotherapy with CDDP, with or without radiotherapy as first line.

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