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Case Report

A Rare Case of Colliding Cancer of the Esophagus with Small Cell Neuroendocrine, Squamous, and Adenocarcinoma Components

Jiun-I Lai^{1,2,3,4}, Yi-Chen Yeh^{5,6}, Ming-Huang Chen^{2,3,5}*

¹Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan ²Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan ³Center for Immuno-Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan ⁴Division of Hematology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan ⁵School of Medicine, National Yang-Ming University, Taipei, Taiwan ⁶Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Abstract

Esophageal cancer is one of the top ten prevalent cancers in the world with a poor prognosis, especially in advanced stages. The prevalent cell type is different according to the location: squamous cell carcinoma is the prevalent subtype in the proximal (upper) esophagus, while adenocarcinoma is more prevalent in lower/distal esophagus. Primary small cell carcinoma of the esophagus is rare in prevalence and only limited cases have been reported. We report a 62 year old female patient who was newly diagnosed of esophageal cancer and subsequently received surgical resection. Interestingly, the pathology from the resected esophageal lesion revealed a mixed histology type with small cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Currently in the literature, a triple combined histology type cancer is rarely reported. The etiology is unclear, one possibility being multi-focal primary cancers, another being a collision of distinct primary cancers. This patient was started on postoperative CCRT and currently treatment is still ongoing. Our case presents with an interesting finding of triple cancer of the esophagus which contributes to medical knowledge and is valuable for oncologists encountering this rare scenario.

Keywords: Afatinib, esophageal squamous cell carcinoma, immunotherapy

INTRODUCTION

Esophageal cancer is one of the top ten most prevalent cancers in the world, and it is associated with poor prognosis, especially in advanced stages.^[1] The prevalent cell type differs according

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to the location: squamous cell carcinoma is more prevalent in the proximal (upper) esophagus, while adenocarcinoma

Address for correspondence: Dr. Ming-Huang Chen, Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Rd., Taipei 112, Taiwan. E-mail: mhchen9@vghtpe.gov.tw

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is more prevalent in the lower/distal esophagus. Primary small cell carcinoma of the esophagus is rare, and only a few cases have been reported.^[2] Herein, we report a case of a patient diagnosed with esophageal cancer of small cell origin combined with adenocarcinoma and squamous cell histology in the same tumor lesion. To the best of our knowledge, this is the first case presentation of a triple cell type cooccurring in esophageal cancer.

CASE REPORT

A 62-year-old female patient visited our hospital with an initial presentation of epigastric pain and dysphagia for weeks. A series of workups including chest computed tomography (CT), upper gastrointestinal endoscopy, and other studies revealed a tentative diagnosis of an esophageal mass at the middle-third section of the esophagus, favoring esophageal cancer [Figure 1]. The staging for esophageal cancer was T2N0M0 according to the CT scan and confirmed by whole-body positron emission tomography, which did not reveal any metastatic lesions. Endoscopic ultrasound staging



Figure 1: Chest computed tomographic image showing esophageal cancer in the mid-third section of the esophagus

was T1N0. A biopsy from upper gastrointestinal endoscopy revealed a mixture of small cell carcinoma and adenocarcinoma. Since the clinical diagnosis was node-negative disease, the treatment plan was direct surgical resection of the tumor. She received robotic minimally invasive esophagectomy, gastric tube reconstruction, cervical esophagogastrostomy, and feeding jejunostomy for postoperative care.

Interestingly, the pathology from the resected esophageal lesion revealed a mixed histological type with small cell carcinoma (evidenced by insulinoma-associated 1 and CD56), squamous cell carcinoma (evidenced by p40), and adenocarcinoma [Figure 2a-e]. Small cell carcinoma component was p40-negative in immunohistochemical staining. There was nodal involvement in the pericardial lymph nodes, with four positive lymph nodes out of six being dissected, all of which were confirmed to be small cell carcinoma histology. Most of the tumor mass was composed of a small cell component and possessed a poorly differentiated histology (G3). The final pathological staging was pT1bN2M0 postesophagectomy and reconstruction. A multidisciplinary team concluded that postsurgical concurrent chemoradiation therapy (CCRT) was suitable for her current status since her most advanced tumor stage was of small cell origin. She started postoperative CCRT with etoposide and cisplatin approximately 1 month after surgery, and currently, the treatment is still ongoing.

DISCUSSION

Small cell carcinoma of the esophagus is a rare disease, with a reported prevalence of <4% of all esophageal cancers.^[2] Due to its low prevalence, most reports in the literature are case reports or small case series.^[2-5] Treatment guidelines based on large-scale phase III randomized clinical trial data are currently lacking. The treatment rationale generally follows established guidelines for small cell lung cancer and neuroendocrine tumors (NETs), especially NETs of gastrointestinal origin. Surgical resection is the mainstay of treatment for limited-stage cancers,^[2,4] and advanced cancers are treated with extensive



Figure 2: Pathology of the resected tumor revealed histological types of small cell carcinoma (a), with insulinoma-associated 1 gene (b) and CD56 (c) positive staining; and the presence of adenocarcinoma (d) and squamous cell carcinoma (e)

chemotherapy. A recent retrospective cohort study reviewed the clinical features and treatment outcomes of 152 patients with primary small cell esophageal cancer.^[6] The authors concluded that stage I/II should be treated with surgery alone and that neoadjuvant chemotherapy followed by surgery would result in the best outcome for stage III patients. This study includes one of the largest cohorts with primary esophageal small cell carcinoma, highlighting a low incidence of this disease and lack of randomized controlled trials. Esophageal squamous cell carcinoma and esophageal adenocarcinoma are the two most common cell types in esophageal cancer. Neoadjuvant CCRT followed by surgical resection is currently regarded to be the standard of care.^[7] Postoperative CCRT following esophagectomy currently lacks phase III prospective trials to evaluate its efficacy, although a recent large-scale retrospective study (4893 patients) found improved overall survival in patients with node-positive disease or residual cancer (R1, R2 resection) who received postoperative CCRT.^[8] Currently, the National Comprehensive Cancer Network recommends postoperative chemoradiation for node-positive cancers and residual cancer after surgery, as well as pT3-4 disease that is node-negative. Therefore, we selected this approach for our patient considering the high recurrence potential of small cell disease^[9] and the proven benefit of postoperative CCRT in squamous and adenocarcinoma esophageal cancers.

Our patient had the unique feature of the coexistence of squamous adenocarcinoma with small cell components. This is a rare presentation, with only a few similar case reports in the literature.^[10,11] A recent study searched the literature for cases of coexisting secondary primary cancers in the presence of a primary neuroendocrine neoplasm, and of 78 cases reported, 49.4% of the secondary neoplasms were adenocarcinoma and 4.5% were of squamous cell type.^[12] The authors included secondary tumors that occurred in different sites of the body; however, a high percentage of the tumors (68.4%) occurred in the same segment of the gastrointestinal tract. Our case is unique in that different histological subtypes occurred in the same tumor lesion. This has been proposed to be "colliding tumors,"[13] in which tumors of different origin arise simultaneously and grow toward each other until they collide, resulting in a mixed histological type.^[14] Anatomically, this was a possible scenario in our patient. A more in-depth analysis of the risk factors and clinical characteristics of colliding cancers is difficult, mainly due to the low prevalence of this scenario. In the aforementioned case series,^[13,14] the authors all concluded that further analyses are precluded by the low incidence of colliding cancers, especially for those with a small cell (or neuroendocrine) component. NETs of the esophagus are a rare entity, comprising only 0.04%-4.6% of all gastrointestinal NETs.^[15] Interestingly, in most of the cases of colliding cancers, as well as in our case, the staging of cancers was relatively early and was usually nonmetastatic. This observation needs further confirmation with more cases, although we can speculate that tumors with a tendency to migrate may

present with different cancer biology to cancers prone to early metastasis. A possible explanation is Notch signaling, which plays an important role in NETs,^[16] and may play a role in the biological behavior of colliding tumors with a neuroendocrine component. However, further studies are needed to clarify this speculation and observation. Although not performed in this case, genomic profiling such as next-generation sequencing for major oncogenes or even whole-exon profiling may yield important information, regarding cancer biology, and may be considered for future similar cases. In previous case reports of either synchronous or colliding tumors that contain small cell neuroendocrine histology, the small cell component is usually the major constituent.^[12,13] This is similar to our case as the small cell component was the largest part and was also the cell type found in the lymph node lesions.

CONCLUSION

We report a patient with esophageal cancer with a unique mixed triple cell type, including small cell, squamous, and adenocarcinoma. The patient received surgical resection followed by CCRT. This rare case presentation supports other case reports that demonstrated small cell cancer occurring with nonsmall cell histology and expands the clinical knowledge of small cell esophageal cancer.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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