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Case Report

Combined squamous and small cell carcinoma of the esophagus: a case report

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Abstract: The composite tumor of the esophagus is extremely rare. Here, we report an unusual case of combined squamous and small cell carcinoma of the esophagus. A 56-year-old woman was admitted to our hospital with dysphagia and chest pain. Endoscopic examination showed a semi-annular mass in the middle esophagus. Because the lesion was limited, curative esophagectomy was then performed. In the resection specimen, the tumor revealed a mixture of squamous and small cell carcinoma. Pathologically, the squamous cell carcinoma component which showed focal keratinization and pearl formation was positive for CK5/6 and P40. While the small cell carcinoma component which was characterized by high nuclear-cytoplasmic ratio, hyperchromatic nuclei, scanty cytoplasm and absent nucleoli strongly expressed CD56, Syn, NSE, CgA. Both components were negative for TTF-1, Vimentin, LCA, CD99. A brief discussion of the clinical symptoms, etio-pathogenesis, histopathological features and treatment of this rare neoplasm is presented.

Keywords: Esophagus, combined carcinoma, small cell carcinoma, squamous cell carcinoma

Introduction

Esophageal carcinoma is one of the most common malignancies worldwide. Of these esophageal carcinomas, approximately 90% or more are esophageal squamous cell carcinomas (SqCC) [1]. Primary small cell carcinoma of the esophagus (SCCE) is a relatively rare tumor, accounting for only 1% to 2.8% of all esophageal malignancies [2-4]. Combined squamous and small cell carcinoma of the esophagus, the so-called composite tumor of the esophagus, is even rarer. Here we report a case of squamous and small cell carcinoma of esophagus and a review of the literature.

Case report

A 56-year-old woman was admitted to our hospital with increasing dysphagia and chest pain for two months. Physical examination and routine laboratory test were within normal limits. Endoscopic examination showed a semi-annular mass in the middle esophagus. Histologic examination of a biopsy specimen obtained from the lesion revealed a small cell carcinoma with hyperplasia of esophageal squamous epithelium, but no invasive squamous cell carcinoma was found. The computed tomography demonstrated abnormal thickening of the middle esophageal wall, but no typical evidence of metastatic disease in the mediastinal lymph node or in distant organs. Because the lesion was limited, curative esophagectomy with lymph node dissection was then performed followed by adjuvant chemotherapy with etoposide and cisplatin (EP) for 4 cycles. However the patient eventually died of systemic carcinomatosis 21 months after the surgery.

In the resection specimen, the tumor revealed a mixture of squamous and small cell carcinoma (**Figure 1A**). The SCCE component was characterized by high nuclear-cytoplasmic ratio, hyperchromatic nuclei, scanty cytoplasm and absent nucleoli (**Figure 1B**). The SqCC component showed focal keratinization and pearl formation (**Figure 1C**).

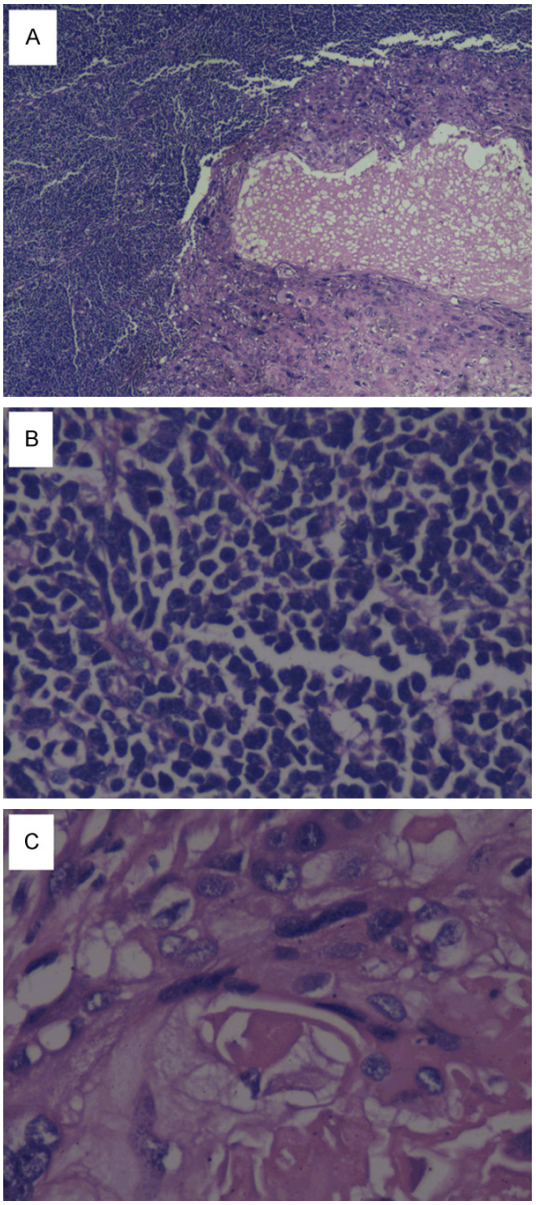

Figure 1. Hematoxylin-eosin staining findings. The tumor consists of two distinct components: SCCE on left and SqCC on right in low-power view (A, ×40). SCCE component (B, ×400). SqCC component (C, ×400).

An immunohistochemical study was performed with the use of Dako Envision method as described previously [5]. The SCCE component was positive for synaptophysin (syn, **Figure 2A**, **2D**), chromogranin A (CgA, **Figure 2B**, **2E**), neuron-specific enolase (NSE), CD56, Ki67 (80%, **Figure 2C**, **2F**), while being negative for P40 and cytokeratin 5/6 (CK5/6). Whereas the SqCC component strongly expressed P40 (**Figure 3A**, **3C**) and CK5/6 (**Figure 3B**, **3D**), but it was negative for neuroendocrine markers. Both components were negative for LCA, thyroid transcription factor (TTF-1), CD99, vimentin.

Discussion

The major risk factors and clinical symptoms of combined carcinoma of the esophagus are identical to other more common neoplasm of the esophagus. The patients had a significant history of poor nutritional status, low intake of fruits and vegetables, the use of tobacco or alcohol, and drinking beverages at high temperatures [1, 6, 7]. The presenting symptoms included rapidly progressive dysphagia, retrosternal pain and weight loss.

At present, there are two viewpoints on the etio-pathogenesis of combined small carcinoma of the esophagus. One is that the combined carcinomas are basically small cell carcinomas with squamous or adenocarcinomatous differentiation. And it is believed that the amine precursor uptake and decarboxylase (APUD) cells of the submucosal gland or stratum basal is the histogenetic precursor of small cell carcinoma of the esophagus [8-10]. As APUD cells most commonly exist in the distal esophagus, the primary lesions were often found in the middle and lower third of esophagus [3, 8-10]. The other is that biphasic neoplasm originates from pluripotential stem cells of the endoderm that can be partially differentiated into squamous cell, neuroendocrine cell or glandular cell because of the stimulation of different carcinogenic agent [11]. In the present case, the close merges between the squamous and small cell carcinoma elements histologically lend support to this hypothesis.

In this case, the biopsy specimen showed a small cell carcinoma with hyperplasia of the surface epithelium. Otherwise, the combined carcinoma was demonstrated through multiple sampling of the tumor and the normal junction in the resection specimen. Therefore, more tissues and multipoint biopsies should be performed under an endoscope to establish a correct diagnosis. To make the diagnosis of combined esophageal carcinoma, it is crucial to ensure that the small cell carcinoma component is not a metastasis from either a bronchogenic or gastrointestinal origin through clinical workup. Sometimes it is difficult to differentiate

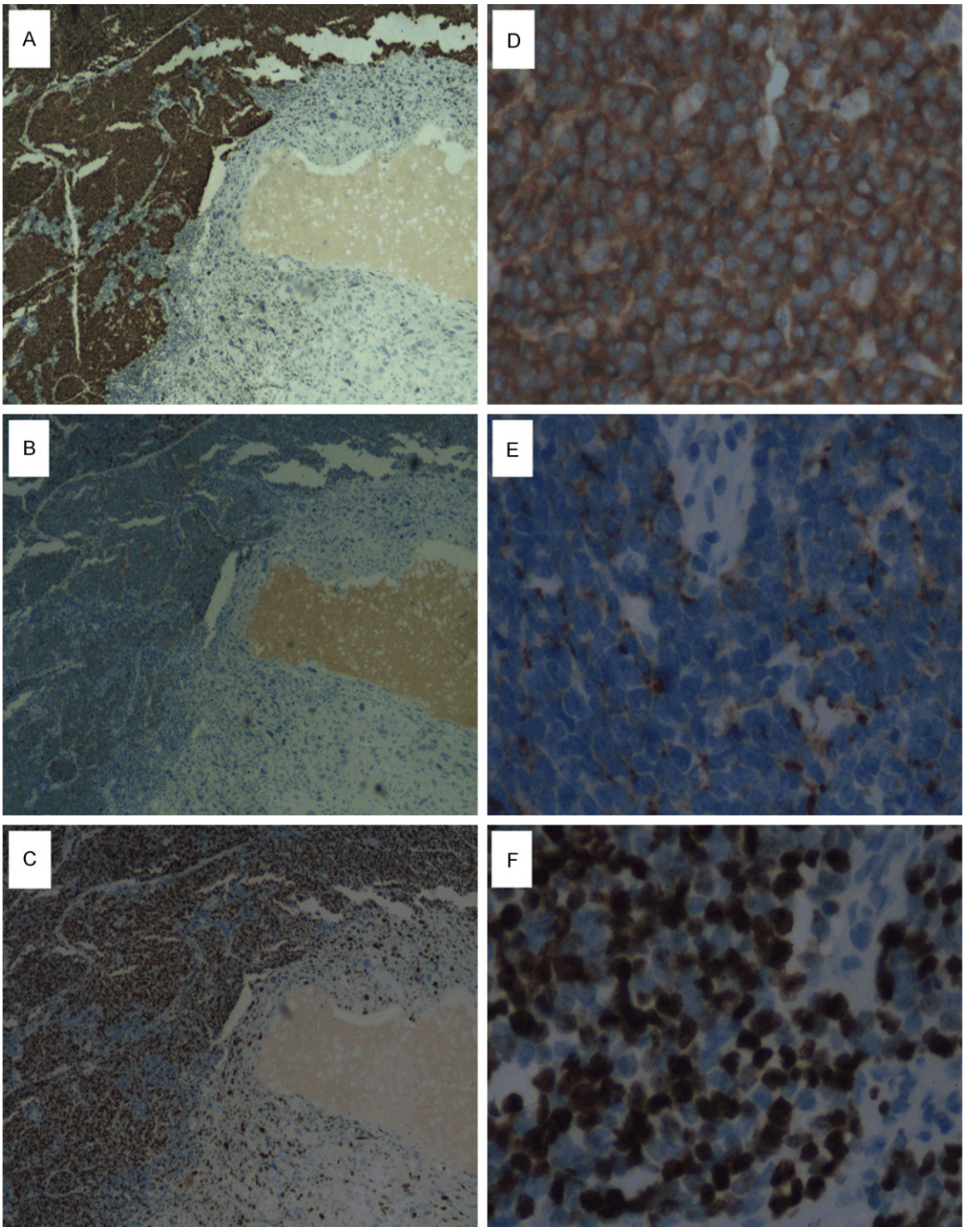

Figure 2. Immunoreactivity in SCCE component. Positive for syn and CgA indicate SCCE component (A, B, ×40). Strong positive for ki-67 (C, ×40). Magnifying views of (A-C) (D-F, ×400).

SCCE from poorly differentiated SqCC, malignant lymphoma, chronic inflammation and malignant melanoma. In this setting, a panel of appropriate immunohistochemical stains will help for diagnosis. The expression of cytokeratin demonstrates that the tumor is a carcinoma. About 90% of SCCE has neuroendocrine features, so the most useful neuroendocrine

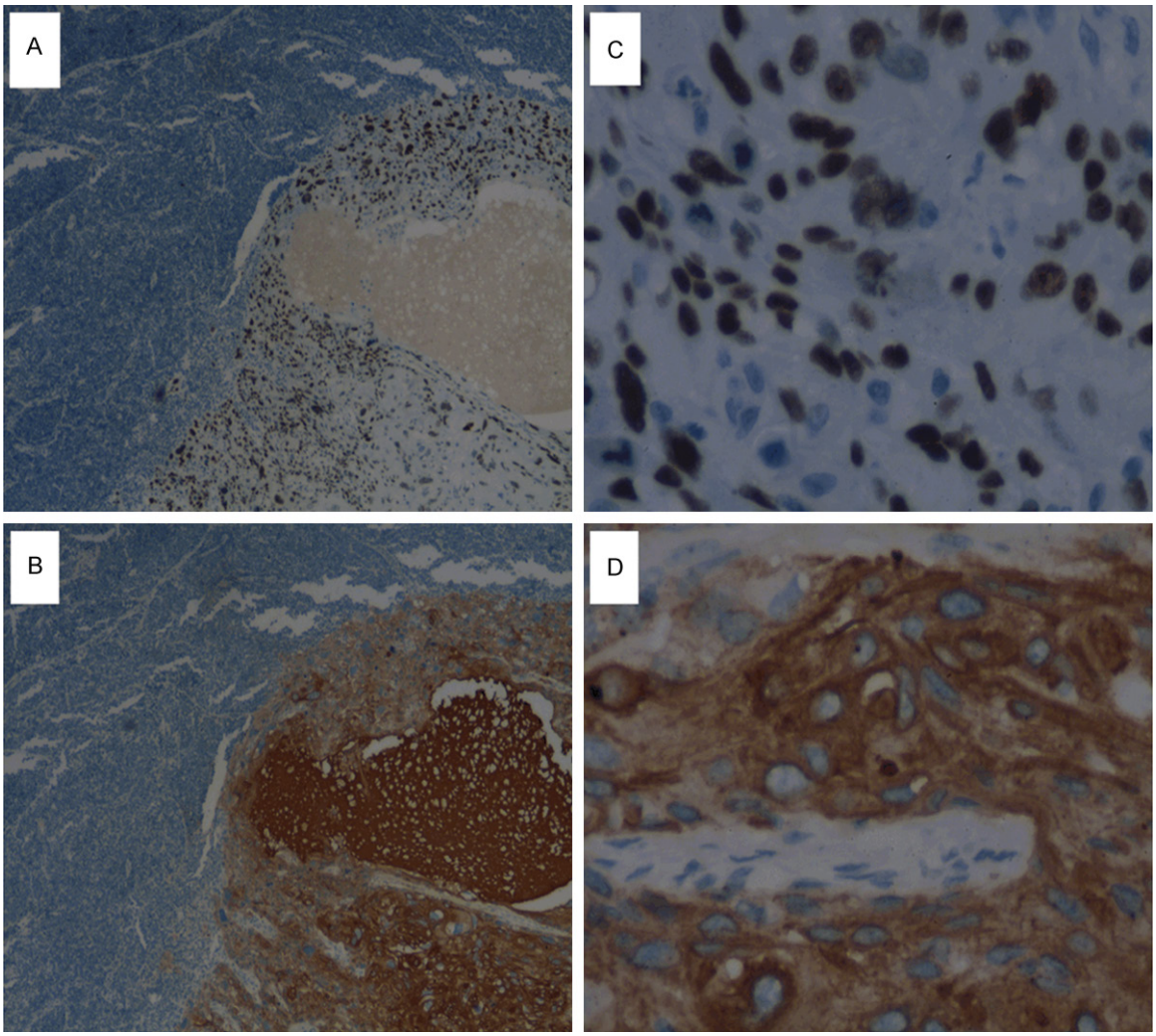

Figure 3. Immunoreactivity in SqCC component. Positivity of P40 and CK5/6 indicate SqCC component (A, B, ×40). Magnifying views of (A, B) (C, D, ×400).

antigens such as CgA, syn, NSE and CD56 are best used as a pane. Other stains such as lymphoid markers (LCA, CD3, CD20, CD45RO, PAX-5), squamous markers (CK5/6, P40, P63), melanoma markers (S100, HMB-45) and PENT marker (CD99) may be helpful in the differential diagnosis, respectively [12]. The present case showed that the small cell areas showed diffuse and intense immunoreactivity for neuroendocrine markers, while being negative for CK5/6 and P40, whereas the squamous areas were positive for squamous markers and negative for neuroendocrine markers.

The combined small cell carcinoma displays highly aggressive biologic behavior, early distant metastasis and poor prognosis. The survival rate is not clear owing to the paucity of cases. However, survival was thought to be similar to that of small cell lung carcinoma [8-11]. Nevertheless, no standard treatment of combined small cell carcinoma of the esophagus has been well defined because of only limited reports. The significance of surgery is still controversial. Some reports have emphasized that surgery should be avoided for patients with advanced disease [13, 14]. On the other hand, some authors think surgery remains the primary method in patients with locoregional disease [15, 16]. In recent reports, regimens including cisplatin and etoposide have achieved better response and radiotherapy is also effective [9]. Several cases suggested that the patients were treated with surgical resection, radiotherapy and chemotherapy in combination may result in

survival benefits [17, 18]. However, personalized treatment should be encouraged based on clinical features, pathologic diagnosis, the grading and staging classification.

Disclosure of conflict of interest

None.

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