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Case Report
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Aggressive Esophageal Carcinoma with Multilineage Differentiation by Immunohistochemistry

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Abstract

Adenocarcinoma is the most common type of esophageal cancer in the United States. We present a rare report of an esophageal cancer with adenocarcinoma, neuroendocrine and squamous cell differentiation, arising from goblet cell metaplasia. The patient was a 58 year-old man with a remote history of orthotopic heart transplantation for ischemic cardiomyopathy who presented with intractable nausea, vomiting, abdominal pain and watery diarrhea. A computed tomography scan revealed a solitary lung nodule, lymphadenopathy and multiple hypoattenuated liver lesions. Upper endoscopy identified a large ulcerated gastroesophageal junction mass with extension into the gastric cardia. Biopsies of the liver and gastroesophageal lesions revealed a poorly differentiated neoplasm with patchy myxoid stroma and dyskeratosis. The overlying esophageal epithelium showed goblet cell metaplasia, seen in Barrett esophagus. By immunohistochemistry, the neoplastic cells were variable expression of MOC-31 and p63, and strongly positive for synaptophysin, consistent with multidirectional differentiation. Clinical laboratory tests found elevated Chromogranin A (811 ng/mL). The patient rapidly deteriorated within weeks of the diagnosis with progressive somnolence and confusion. Here we present an exceptionally rare case of an aggressive esophageal carcinoma with multilineage differentiation, arising in a background of goblet cell metaplasia, a precursor lesion of esophageal adenocarcinoma.

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Introduction

In 2020, there are 18,440 estimated new cases of esophageal carcinoma in the United States with an increased prevalence in males. Cancers arising from the esophagus are very aggressive with 5-year relative survival rate of only 20% and estimated deaths of 16,170 in 2020 [1]. In histologic evaluation the pathologist renders a specific diagnosis of squamous cell carcinoma or adenocarcinoma when possible for staging and treatment purposes. In cases of mixed adenosquamous carcinoma and carcinoma not otherwise classified, the lesions are staged using the squamous cell carcinoma [2].

In rare instances esophageal tumors with two or more distinct histologic types are seen, which are classified as composite or collision tumors. Composite tumors arise from one neoplastic clone which diverges into two different cell lineages. While collision tumors consist of two independent neoplasms growing in close proximity and lack the cellular intermingling seen in composite tumors [3,4]. Here we present a composite tumor with three lines of differentiation, in a background of goblet cell metaplasia consistent with Barrett esophagus.

Case Presentation

The patient is a 58 year-old male with past medical history significant for orthotopic heart transplantation in 2009 secondary to ischemic cardiomyopathy, diabetes mellitus type 2, and post-transplant hypertension and stage 3 chronic kidney diseases. The patient presented with one-month history of abdominal pain, dry heaves, bloating, vomiting and diarrhea. Diarrhea was attributed to recent *Norovirus* infection. In the work up, the computed tomography scan revealed a 1.2 cm right lowers lobe lung nodule, enlarged gastrohepatic lymph nodes and multiple hypo-attenuated lesions in the liver.

A liver biopsy was performed which was consistent for poorly differentiated carcinoma with neuroendocrine differentiation. Immunohistochemical stains for pancytokeratin, CAM5.2, CDX2 and synaptophysin were positive, with negative NKX3.1, SOX10, arginase-1 and TTF-1. The pathological differential diagnosis for the site of origin was favored to be pancreatobiliary and gastrointestinal origin.

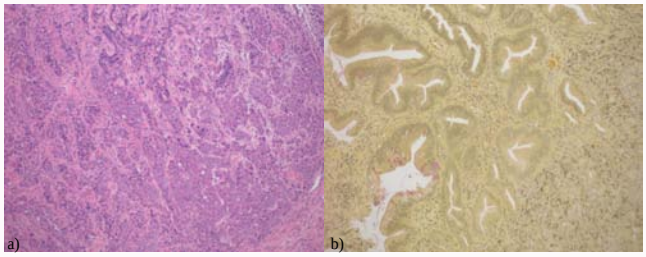

Figure 1: a) Sheets of neoplastic cells with high nuclear to cytoplasmic ratio and prominent nucleoli in a background of patchy myxoid stroma (hematoxylin-eosin, original magnifications at 100x; b) Overlying mucosa with areas of goblet cell metaplasia with mucin (mucicarmine histochemical stain, original magnifications at 100x.

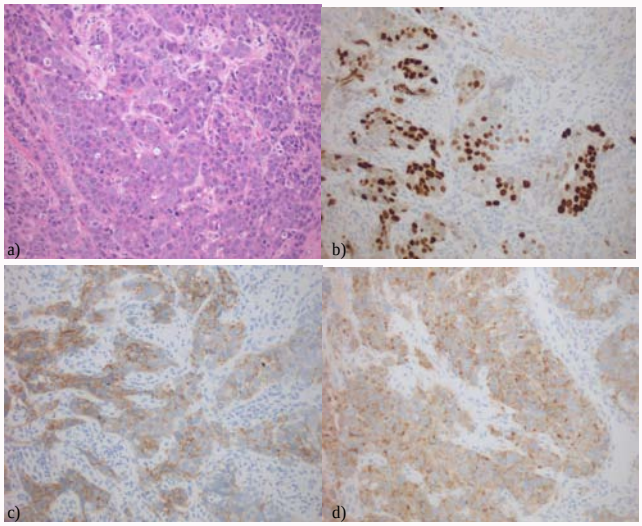

Figure 2: a) High power showing neoplastic cells with dyskeratosis and possible lumen formation; b-d) Immunohistochemistry with p63 expression showing squamous component b), MOC-31 supporting glandular differentiation c) and diffusely positive for synaptophysin consistent with neuroendocrine differentiation d) (hematoxylin-eosin and immunohistochemistry, original magnifications at 200x.

Subsequently the esophagogastroduodenoscopy with endoscopic ultrasound demonstrated a 4 cm hemi-circumferential fungating ulcerated mass at the gastroesophageal junction, extending to the gastric cardia. The ultrasound showed full-thickness extension of the tumor with involvement of the outer aspect of the muscularis propria. Biopsy of the mass demonstrated ulcerated squamocolumnar mucosa with poorly differentiated carcinoma with morphology was similar to the neoplasm identified on liver biopsy. The histology showed sheets of neoplastic cells in the lamina propria with high nuclear to cytoplasmic ratio and prominent nucleoli, in addition the overlying epithelium showed areas of goblet cell metaplasia, supported by mucicarmine stain (Figure 1a, 1b). On high power, the neoplastic cells have areas of dyskeratosis and focal lumen formation (Figure 2a). By immunohistochemistry, the neoplastic cells expressed synaptophysin (diffuse), CD15 (variable), p63 (variable), p40 (variable), CDX2 (focal), CD56 (focal) and MOC-31 (variable) (Figures 2b-2d). The neoplastic cells were negative for chromogranin and HER2. The overall morphologic and immunohistochemical findings supported a diagnosis of poorly differentiated carcinoma with neuroendocrine, squamous differentiation and glandular differentiation in a background of goblet cell metaplasia.

Patient was evaluated by oncology and was recommended a chemotherapy regimen with folinic acid, fluorouracil (5FU) and oxaliplatin (FOLFOX). However after the port placement the patient had increasing confusion and somnolence. Patient had worsening kidney and hepatic dysfunction with hyperkalemia, hyperammonemia, and hyperbilirubinemia. With the ECOG performance status of 4, the decision was made to transition the patient to palliative comfort care measures. The patient died approximately one month after the initial diagnosis.

Discussion

In the abdomen, collision and composite tumors are estimated at less than 1% of tumor incidence [4]. While the data on these lesions are sparse, it appears that collision tumors are more prevalent than composite tumors, based on the number of case reports in the literature [3,5]. The exact oncogenic pathophysiology of composite tumors is still unclear, it is speculated that multidirectional potential of cancer stem cell in the esophageal endoderm could undergo malignant transformation independently and synchronously.

From literature review, there is a previously reported case of composite tumor with tripartite differentiation of squamous, adenocarcinoma and high-grade neuroendocrine carcinoma, where the patient underwent esophagectomy with no follow up data [6]. In addition, there is a reported case of a 1.5 cm polyp with composite esophageal carcinoma with squamous, glandular, neuroendocrine and sarcomatous differentiation, exhibiting superficial extension and mild clinical behavior [7]. Our case is unique because the background mucosa show goblet cell metaplasia which is seen in Barrett esophagus, a precursor lesion for esophageal adenocarcinoma [8].

The histologic features of the gastrointestinal tract and specifically esophagus, with multiple lineage components including glands, squamous epithelium, neuroendocrine cells and stromal elements make the theoretical approach of single progenitor cells that differentiate and that can digress into multiple different morphological neoplasms that can cohabit [9]. However, on a practical stand point, multi lineage differentiation of esophageal neoplasms is an extremely rare occurrence. Few cases are reported in literature, interestingly has variable clinical behavior [6,7]. Given the scarcity of cases, the treatment is not clearly defined for these patients, and empiric regimens or treating of the predominant histologic cell line is the only available approach.

Neuroendocrine component of these tumors are the most important determinant of mortality. The prevalence of esophageal high-grade neuroendocrine carcinoma varies geographically, accounting for 0.5% to 5.9% of Chinese population, 0.8% to 2.8% in Japan, and 1% to 2.8% in western population [10]. There are very rare reported cases of composite tumors with neuroendocrine and squamous components [5]. It is very important to precisely diagnose the neuroendocrine component, because the treatment modality is completely different from that of esophageal squamous cell carcinoma and adenocarcinoma. Esophageal composite tumors, especially those with a neuroendocrine component have poor prognosis with advanced disease at diagnosis [11,12].

Due to the rare instances of composite tumors the treatment is not well-established and usually determined on a case-by-case basis. Surgical resection is the preferred treatment for local disease with no metastasis [13]. Also treatment of the more aggressive component such as then neuroendocrine component is prioritized in order to

reduce the risk of distant metastasis [12]. With rare reported cases; there is little guidance on treatment protocols.

In summary, we report a rare case of composite esophageal cancer with background goblet cell metaplasia. Although carcinoma not otherwise classified in the esophagus are currently staged using the squamous cell carcinoma, it is essential to delineate histologic type by immunohistochemistry and ancillary studies. The immunohistochemistry profile is essential for complete characterization of these lesions, which in turn will help guide therapy in multilineage neoplasms.

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