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Original contribution

Undifferentiated carcinoma of the esophagus: a clinicopathological study of 16 cases☆

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Summary Undifferentiated carcinoma of the esophagus is a rare histologic variant of esophageal carcinoma. Using criteria based on studies of undifferentiated carcinomas arising at other sites, we have collected 16 cases of resected esophageal undifferentiated carcinomas. Patients ranged in age from 39 to 84 years (mean, 65.5 years) and were predominantly male (94%). The tumors were characterized by an expansile growth pattern of neoplastic cells organized in solid sheets and without significant glandular, squamous, or neuroendocrine differentiation. The neoplastic cells had a syncytial-like appearance, little intervening stroma, and patchy tumor necrosis. In a subset of cases, the tumor cells adopted a sarcomatoid (n = 2), rhabdoid (n = 1), or minor component (<5%) of glandular morphology (n = 3). In 1 case, reactive osteoclast-like giant cells were found interspersed among the neoplastic cells. Lymphovascular invasion, perineural invasion, and lymph node metastases were identified in 88%, 56%, and 81% of cases, respectively. In 12 (75%) specimens, the background esophageal mucosa was notable for Barrett esophagus. Consistent with the epithelial nature of these neoplasms, cytokeratin positivity was identified in all cases. In addition, SALL4 expression was present in 8 (67%) of 12 cases. Follow-up information was available for 15 (94%) of 16 patients, all of whom were deceased. Survival after surgery ranged from 1 to 50 months (mean, 11.9 months). Before death, 67% patients had documented locoregional recurrence and/or distant organ metastases. In summary, esophageal undifferentiated carcinomas are aggressive neoplasms and associated with a high incidence of recurrence and/or metastases and a dismal prognosis.
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1. Introduction

Esophageal cancer is the eighth most common cancer type and the sixth most common cause of cancer-related deaths worldwide. It affects more than 450 000 patients per year, and the incidence is increasing rapidly [1-3]. The 5-year overall survival ranges from 15% to 30%, and outcomes are significantly dependent on tumor stage [4,5]. Early diagnosis of esophageal cancer is associated with a good prognosis, whereas poor outcomes are related to advanced stages of disease and the propensity for metastasis. Squamous cell carcinoma and adenocarcinoma account for greater than 90% of all esophageal cancer cases [6,7]. In addition, the World

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Health Organization recognizes other histologic variants of esophageal cancer including undifferentiated carcinomas [8].

Undifferentiated carcinomas of the esophagus are rare neoplasms and associated with a poor prognosis. Reports of these neoplasms have been limited to large epidemiological and randomized clinical trials for esophageal cancer [6,7,9-14]. However, the prevalence of undifferentiated carcinoma within these studies varies widely and ranges from 0.15% to 4.5%. This disparity in prevalence may reflect the lack of diagnostic criteria for esophageal undifferentiated carcinomas. Other than the absence of identifiable histologic differentiation beyond an epithelial phenotype, a defining set of pathologic features for undifferentiated carcinomas has not been established. Considering that undifferentiated carcinomas are aggressive neoplasms, an accurate diagnosis and appropriate classification of these neoplasms are clinically relevant. Using criteria from prior studies of undifferentiated carcinomas arising at other sites, we have collected 16 cases of esophageal undifferentiated carcinoma and described their clinical, gross, microscopic, immunophenotypic, and follow-up findings.

2. Materials and methods

2.1. Case selection

Study approval was obtained from the University of Pittsburgh Institutional Review Board. A total of 269 esophagectomy specimens from patients treated for esophageal carcinoma at the University of Pittsburgh Medical Center were reviewed. Based on prior studies of undifferentiated carcinomas arising at other sites, each case was screened for a solid, sheet-like growth of neoplastic cells with less than 5% glandular, squamous, or neuroendocrine differentiation [15-22]. In addition, specific histologic patterns including signet ring cell formation and medullary growth were excluded. Among these 269 cases, 22 esophageal carcinomas fulfilled the initial selection criteria (as reviewed by A.D.S. and R.R.S.).

A representative tumor block from each case was selected for ancillary studies. Immunohistochemical stains for cytokeratin AE1/AE3 and CAM 5.2 were done to confirm the epithelial origin of all tumors. Glandular (mucicarmine and periodic acid–Schiff diastase), squamous (p40 and CK5/6), and neuroendocrine (synaptophysin and chromogranin A) markers were also performed. Cases with more than 5% staining of the neoplastic cells with any of the aforementioned markers were excluded from this study. Overall, 16 esophageal carcinomas were categorized as an undifferentiated carcinoma. A review of the pathology reports from these 16 tumors revealed 1 diagnosed as undifferentiated carcinoma, whereas the remaining were diagnosed as poorly differentiated carcinoma (n = 8) and poorly differentiated adenocarcinoma (n = 7).

For all 16 cases, patient demographic data, history of tobacco and alcohol abuse, clinical presentation at the time of initial diagnostic workup, personal and family medical history, and whether the patient received neoadjuvant therapy were gathered from the patient's medical records. Clinical follow-up information was also obtained from patient's medical records including survival data. Gross pathology reports were reviewed to assess tumor location, size, and appearance.

All routine hematoxylin and eosin–stained slides for each undifferentiated carcinoma were analyzed for growth pattern, necrosis, perineural invasion, vascular invasion, margin assessment, and regional lymph node metastases. The background esophageal and gastric mucosa was also evaluated. Pathologic staging was determined in accordance with the guidelines of the seventh edition of the American Joint Committee on Cancer (AJCC) prognostic staging system [23].

2.2. Special stains, immunohistochemistry and in situ hybridization

Special stains and immunohistochemical labeling were performed on 4-μm unstained whole sections. Slides were deparaffinized with serial xylene treatments. Special stains (mucicarmine and periodic acid–Schiff) were performed on the BenchMark XT system (Ventana Medical Systems; Tucson, AZ) per the manufacturer's protocol. For immunohistochemical stains, antigen retrieval was done using heated citrate solution (pH 6.0). Supplementary Table 1 summarizes the antibodies, clones, and dilutions used within this study. In situ hybridizations for Epstein-Barr virus were also performed using probes targeting Epstein-Barr early RNA (EBER; Ventana Medical Systems) on the Ventana Benchmark XT system. All cases tested for EBER were also tested for integrity of total RNA using an RNA-positive control probe.

3. Results

3.1. Clinical characteristics

The main clinical findings for each patient are summarized in Table 1. Patients at diagnosis ranged in age from 39 to 84 years (mean, 65.5 years; median, 67 years) and were predominantly male (15/16, 94%). At clinical presentation, patients experienced progressive dysphagia (n = 8, 50%), gastroesophageal reflux (n = 6, 38%), weight loss (n = 4), anemia (n = 2), chest pressure (n = 1), chest pain (n = 1), abdominal pain (n = 1), hematemesis (n = 1), anemia (n = 1), and dyspnea (n = 1). Other than gastroesophageal reflux, the duration of clinical symptoms ranged from 1 week to 6 months (mean, 9 weeks; median, 5.5 weeks). In 4 cases, the tumor was identified during endoscopic surveillance for Barrett esophagus. Past medical history was significant for tobacco usage in 7 (44%) patients and alcohol intake in 2

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