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Gastric mixed adenoneuroendocrine carcinoma: correlation of histologic characteristics with prognosis☆

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ABSTRACT

Gastric mixed adenoneuroendocrine carcinomas (MANECs) are rare, with both the exocrine and neuroendocrine components exceeding 30% volume. Several classifications for MANECs have been proposed, yet they have not been clinically evaluated. The aim of this study was to evaluate the correlation between tumor grade, histologic characteristics, and prognosis of gastric MANECs. We collected eligible 14 cases in our series and 31 cases in the literature and compared the prognostic difference among gastric MANECs with different histologic characteristics. Gastric MANECs could be divided into subgroups according to tumor grade of the neuroendocrine component and adenocarcinoma types. The high grade and large proportion of neuroendocrine component correlated with aggressive behavior and a tendency of poor clinical outcome. Gastric MANECs with a poorly differentiated adenocarcinoma showed a significant lower survival rate than did MANECs with a differentiated adenocarcinoma or mucin-producing carcinoma ($P = .0008$). Gastric MANECs were a heterogeneous group with different tumor grades, histologic subtypes, combination patterns, and patient outcomes. Previous classifications were evaluated. This study proves that histologic characteristics correlate with clinical outcomes. Our findings are complements to the latest prognostic classification.

1. Introduction

Gastrointestinal mixed epithelial tumor with an exocrine and a neuroendocrine component has been described using many terms, such as composite carcinoid, argentaffin cell adenocarcinoma (AC), goblet cell carcinoid, adenocarcinoid, glandular-endocrine cell carcinoma, and mixed endocrine-exocrine carcinoma [1]. The spectrum of these tumors with mixed divergent differentiation along exocrine and neuroendocrine lineages displays a variable extension of the 2 components, ranging from adenomas to ACs with divergent differentiation and neuroendocrine tumors (NETs; G1/G2) to neuroendocrine carcinomas (NECs; G3) [2,3]. Moreover, different combinations were depicted ranging from the single neuroendocrine cell scattered in conventional AC to classical NEC, and the reverse condition, for example, focal AC in almost pure NEC. The diversity of histology gave rise to considerable confusion among surgeons, gastroenterologists, and pathologists. Apparently, these tumors need detailed definition and subdivision.

The term, *mixed exocrine-endocrine tumor*, was introduced in the 2000 World Health Organization (WHO) classification of endocrine tumors, with each component representing at least 30% of the lesion [4]. In the 2010 WHO classification of tumors of the digestive system, mixed carcinomas containing an exocrine and a neuroendocrine component, with one component exceeding 30%, are designated as mixed adenoneuroendocrine carcinomas (MANECs) [5]. Although several classifications for MANECs have been proposed, yet they have not been clinically evaluated [1]. So far, less than 100 cases of gastric MANEC have been reported. They are commonly described in case reports or the minor subject in series studies [6-8]. Hence, limited agreements have been reached on histogenesis, diagnostic criteria, prognosis, and reporting of gastric MANECs. The correlation between tumor grade, histologic characteristics, and prognosis also remains uncertain.

In the present study, we evaluated the histologic and immunohistochemical features and clinical outcomes of 14 cases and eligible literature cases so as to reveal the correlation between histologic characteristics and clinical outcomes of gastric MANECs.

2. Materials and methods

2.1. Case selection

The pathology records between 2003 and 2014 were searched; 10 cases in Drum Tower Hospital and 4 cases in the First Affiliated Hospital

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of Nanjing Medical University were retrieved among surgically resected gastric cancers. All cases meet the current diagnostic criteria of gastric MANEC as defined by the 2010 WHO classification. The histologic, immunohistochemical, and clinical features were reassessed. The stage was defined according to the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* for carcinoma of the stomach, seventh edition [9]. The curability of the surgical procedure was evaluated using the residual tumor classification: R0, no residual tumor; R1, microscopic residual tumor; and R2, macroscopic residual tumor. The median follow-up period was 17 months (range, 9-46 months) in the present study. The matched group was patients with gastric NEC treated at the Drum Tower Hospital between 2003 and 2014.

2.2. Histologic and immunohistochemical analysis

For each case, all slides were reviewed for the following parameters: proportion and combination pattern of the 2 components, histologic subtypes of the AC component, number of mitoses per 10 high-power fields (HPFs) of the neuroendocrine component, the number and content of metastasis, muscularis propria (MP) invasion, and staging. The AC component of different histologic subtypes was divided into 3 subgroups: differentiated AC (DA; including papillary AC and tubular AC), mucin-producing carcinoma (MPC; including mucinous AC and signet-ring cell carcinoma), and poorly DA (PDA; including solid type AC and poorly cohesive carcinoma other than signet-ring cell carcinoma). Adenocarcinoma with mixed components was categorized into the most malignant subgroup, and the sequence of malignancy was that PDA > MPC > DA. Special subtypes in the AC component, if any, was evaluated and categorized into the subgroup with similar grade of malignancy.

Immunohistochemical staining was performed on 4-μm-thick paraffin-embedded tumor tissue sections from the 14 cases using a panel of antibodies. The antibodies used were chromogranin A (CgA; clone DAK-A3; dilution 1:500; Dako Cytomation, Glostrup, Denmark), synaptophysin (Syn, clone 27G12; dilution 1:250; Novocastra, Newcastle, United Kingdom), CD56 (clone CD564; 1:200; Novocastra), anti-p53 (clone DO-7; 1:300; Dako Cytomation), Ki67 (clone MIB-1; 1:400; Dako Cytomation), and E-cadherin (clone 4A2C7; 1:100; Invitrogen, Carlsbad, CA). For staining, we used a BenchMark XT automated immunostainer according to the vendor's protocol. EnVision+ method was used for detection. Appropriate positive and negative controls were conducted. Color was developed by using 3′-diaminobenzidine as the chromogen. The stainings located at the membrane or cytoplasm were evaluated according to the extent of positive cells as follows: <5%, −; 5% to 25%, +; >25% and <75%, ++; and ≥75%, +++. The results of nuclear staining were recorded as the percent of positive tumor cells in the hot spot (Ki67), or just to be negative or diffusely positive (anti-p53). All slides was reviewed and scored by 2 pathologists independently. The discrepancy between readers was resolved with consensus.

2.3. Literature review and statistical analysis

We conducted a literature search on PubMed using the search terms: “mixed adenoneuroendocrine carcinoma,” “glandular-endocrine cell carcinoma,” or “mixed endocrine-exocrine carcinoma.” Case reports between January 2000 and December 2015 were selected and recorded. Cases without follow-up information or detailed description of the 2 components were excluded for further statistical analysis. The concurrent and collision tumors were also excluded.

Statistical analysis of the categorical variables was performed using the χ^2 or Fisher exact test. Continuous data were analyzed using *t* test or the Mann-Whitney *U* test. The follow-up extended from the date of diagnosis to the date of death or to the last available assessment. The survival analysis was performed using the Kaplan-Meier method, and differences between survival curves were determined using log-rank tests. Results were regarded as significant if *P* is equal to or less than .05. Data were analyzed using GraphPad Prism 6.0 (GraphPad Prism Software Inc, San Diego, CA).

3. Results

3.1. Clinical characteristics

The clinical characteristics of the 14 patients with gastric MANEC are summarized in Table 1. The patients were predominantly men, with a median age of 60.5 years. A gastrectomy with lymph node dissection was performed in all included cases, and an additional partial hepatectomy was performed in 1 patient. The lesions were mainly located at the upper stomach. Eleven patients had locally advanced disease with invasion into the MP or deeper. Nodal metastasis was detected in 9 patients, among whom 1 patient had distant metastasis to the liver. Curative resection (R0) was achieved in all patients. For the prognosis, 4 patients died within 1 year and 1 patient lost to follow-up.

3.2. Histologic features

Two combination patterns of gastric MANECs were observed. The first combination pattern (CP1) was that superficial DA was located upon the deep NEC (Fig. 1a); the second combination pattern (CP2) was that the 2 components were juxtaposed (Fig. 1b) with a morphological transition (Fig. 1c), and without an up and down arrangement. CP2 was generally presented in MANECs with MPC and PDA. Lymphatic or vascular involvements were observed in 9 cases. The metastatic portion could be either or both of the 2 components. Microscopically, they metastasized alone, simultaneously or in combination. The percentage of neuroendocrine component, though not statistically significant, was more related to lymph node metastasis and deep invasion in our series.

All neuroendocrine components in the 14 gastric MANECs were NECs, large cell type. Most neuroendocrine components showed a solid growth pattern, followed by broad trabecular, tubular, and scirrhous growth patterns. Peripheral palisading and rosette formation were frequently observed. Necrosis was observed at least focally in all the cases. Mitoses were frequent with a median of 45 per 10 HPFs (range, 22-95/10 HPFs). The tumor cells were uniform round-to-oval cells with moderate amounts of eosinophilic and finely granular cytoplasm, granular or vesicular nuclei, with or without visible nucleoli. The AC components also showed a wide spectrum of histology, and the special subtype, hepatoid AC (HA), was observed in one case. Because patients with HA had poor prognosis, it was categorized into subgroup of PDA.

3.3. Immunohistochemical results

All the neuroendocrine components were positive for at least 2 of the conventional NE markers: Syn, CgA, and CD56. Synaptophysin was the most sensitive marker and positive in 100% NEC components, followed by CgA (64%) and CD56 (57%). Anti-p53 were commonly synchronous expressed in the 2 components, but it was not always in the case for E-cadherin which was less frequently expressed in neuroendocrine components (Fig. 2).

3.4. Histologic characteristics and clinical outcomes

Thirty-one patients with gastric MANEC in the literature were retrieved (Table S1) [10-34]. For the purpose of revealing the correlation of different histologic subtypes and clinical outcomes, gastric MANECs were divided into 2 groups according to tumor grade of the neuroendocrine component, which were MANECs (AC/NEC) and MANECs (AC/NET). The former was more common and further divided to MANECs (DA/NEC), MANECs (MPC/NEC), and MANECs (PDA/NEC) according to histologic subtypes of the AC component.