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Characterization of genome-wide copy number aberrations in colonic mixed adenoneuroendocrine carcinoma and neuroendocrine carcinoma reveals recurrent amplification of *PTGER4* and *MYC* genes☆,☆☆

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Summary Colonic mixed adenoneuroendocrine carcinoma (MANEC) is an aggressive neoplasm with worse prognosis compared with adenocarcinoma. To gain a better understanding of the molecular features of colonic MANEC, we characterized the genome-wide copy number aberrations of 14 MANECs and 5 neuroendocrine carcinomas using the OncoScan FFPE (Affymetrix, Santa Clara, CA) assay. Compared with 269 colonic adenocarcinomas, 19 of 42 chromosomal arms of MANEC exhibited a similar frequency of major aberrant events as adenocarcinomas, and 13 chromosomal arms exhibited a higher frequency of copy number gains. Among them, the most significant chromosomal arms were 5p (77% versus 13%, $P = .000012$) and 8q (85% versus 33%, $P = .0018$). The Genomic Identification of Significant Targets in Cancers algorithm identified 7 peaks that drive the tumorgenesis of MANEC. For all except 5p13.1, the peaks largely overlapped with those of adenocarcinoma. Two tumors exhibited *MYC* amplification localized in 8q24.21, and 2 tumors exhibited *PTGER4* amplification localized in 5p13.1. A total of 8 tumors exhibited high copy number gain of *PTGER4* and/or *MYC*. Whereas the frequency of *MYC* amplification was similar to adenocarcinoma (10.5% versus 4%, $P = .2$), the frequency of *PTGER4* amplification was higher than adenocarcinoma (10.5% versus 0.3%, $P = .01$). Our study demonstrates similar, but also distinct, copy number aberrations in MANEC compared with adenocarcinoma and suggests an important role for the MYC pathway of colonic carcinoma with neuroendocrine differentiation. The discovery of recurrent *PTGER4* amplification implies a potential of exploring targeting therapy to the prostaglandin synthesis pathways in a subset of these tumors.

1. Introduction

Colonic mixed adenoneuroendocrine carcinoma (MANEC) is a rare but aggressive neoplasm [1]. Histologically, as the name suggests, it is composed of 2 malignant

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epithelial components: adenocarcinoma and neuroendocrine carcinoma (NEC). In the 2010 World Health Organization *Classification of Tumours of the Digestive System*, MANEC is classified as a subtype of NEC and is defined as each component comprising at least 30% of the tumor [2]. The 2 components can be distinct where NEC and adenocarcinoma components occur in separate areas of the same tumor (composite MANEC), or the same tumor cells demonstrate both exocrine and neuroendocrine differentiation (amphicrine MANEC) [1]. Recently, given that the term *MANEC* does not adequately convey the morphological and biological heterogeneity of gastrointestinal mixed tumors, the term *mixed neuroendocrine-nonneuroendocrine neoplasms* was proposed [3]. Regardless, it is important to recognize MANEC, as most patients have a decreased survival rate [4].

Clinical, pathological, and molecular features of colonic MANEC have been compared with high-grade NEC in several studies [5-7]. It appears as though there is no difference in patient survival between MANEC and NEC, and both entities frequently exhibit *BRAF* V600E mutation [7]. A study of a cohort of 87 high-grade gastrointestinal NECs from Shia et al suggests that the separation of non–small cell NEC into large cell and mixed subtypes (MANEC) may not be necessary, as both entities share similar clinical and pathological features [6]. However, it remains unclear to medical oncologists if a tumor with both exocrine and endocrine differentiation should be treated based on protocols for conventional adenocarcinoma or NEC.

To gain a better understanding of the heterogeneous nature of colonic MANEC and to search for robust biomarkers, a comprehensive molecular profiling of MANEC is essential. Although recent studies using next-generation sequencing techniques and focusing on hotspot mutations have suggested that colonic MANEC is genetically similar to conventional adenocarcinoma, unique genomic features characteristic of colonic MANEC have not yet been fully characterized [8-10]. Furthermore, comprehensive genomic data on structural alterations, such as genome-wide copy number aberration (CNA) of MANEC, remain missing. Here, we sought to identify unique chromosomal alterations of MANEC and NEC by comparing their genome-wide CNAs to those of 269 conventional adenocarcinomas [11].

2. Materials and methods

2.1. Tumor tissue samples

The study was approved by our institutional research ethics board. All colonic tumors with a previous diagnosis of

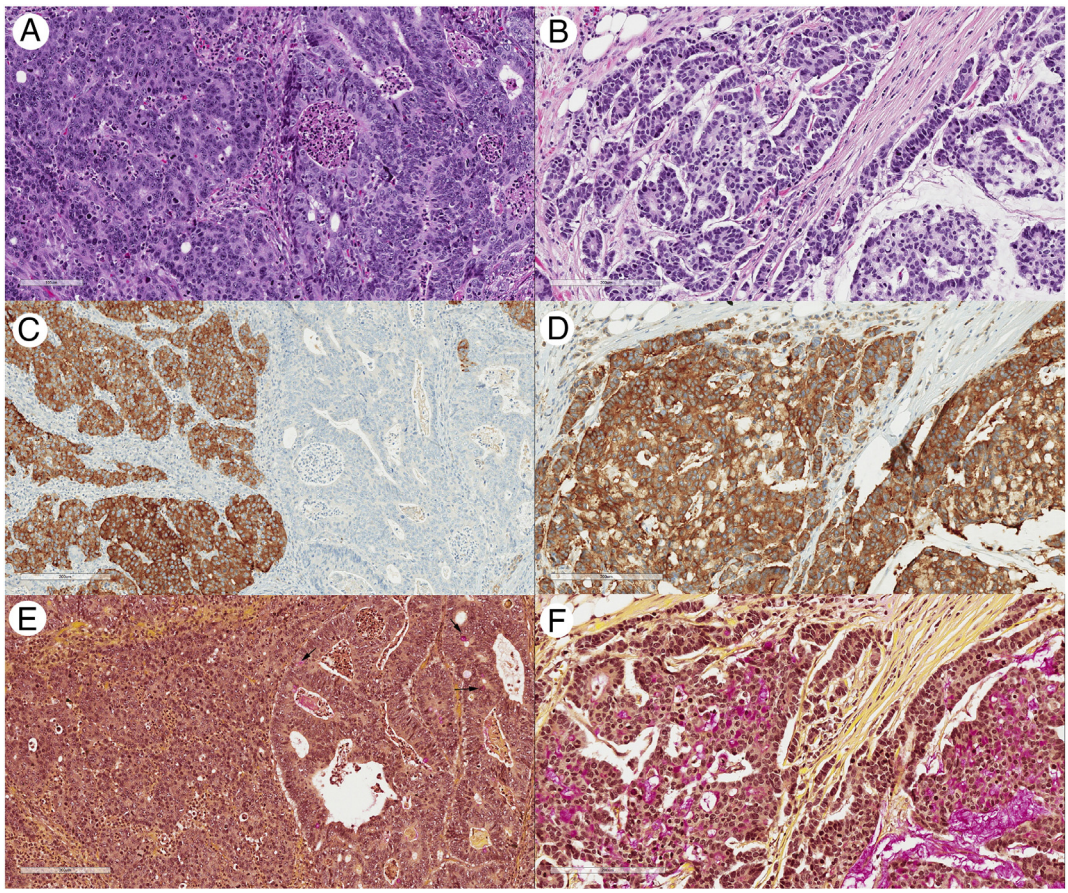

Fig. 1 Colonic MANEC with composite features (A, C, E) and a MANEC with biphenotypical features (B, D, F). A and B, Hematoxylin and eosin; C and D, IHC of synaptophysin; E and F, Mucicarmine stain. E, Arrows indicate mucin droplets in the adenocarcinoma component.