

Mixed Adenoneuroendocrine Carcinoma in the Transverse Colon: An Infrequent Neoplasm in an Unusual Location

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Abstract

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumor of the gastrointestinal tract that consists of a dual adenocarcinomatous and neuroendocrine differentiation. Frequently only one component is identified, leading to incomplete diagnosis and suboptimal treatment. This kind of tumors therefore constitutes a diagnostic challenge. They represent a minority of gastrointestinal neoplasms, being more frequent in the stomach, gallbladder and pancreas. Only a hundred cases have been described in the colon, and specifically only 6 cases in the transverse colon have been published in the English literature.

Introduction

High grade neuroendocrine tumours of the colon are rare, but they also can be associated with adenocarcinoma, classified as "mixed adenoneuroendocrine carcinoma (MANEC)". It is a neoplasm with dual differentiation, and its diagnosis is mainly based on the tumor histology and immune histochemical findings.

Case Report

We present the case of a 67 year old man who consults for abdominal pain. After blood analysis, thoracoabdominal computed tomography (CT) and colonoscopy; a tumor of 5 cm was evidenced in the splenic angle of the transverse colon, with locoregional lymph nodes and multiple unresectable synchronous liver metastases [1-3]. The biopsy was labelled as a low grade colorectal adenocarcinoma. Only CEA marker (11, 0-6.3) was elevated. KRAS mutation was positive. Palliative chemotherapy with FOLFOX-Bevacizumab was started, but intestinal perforation at tumor site took place after the third cycle. Hemicolectomy and lymphadenectomy was performed. Histological analysis of the surgical specimen revealed a high-grade (G3) MANEC with vascular, lymphatic and perineural invasion, and no local response to the treatment. 30% of the tumor was well differentiated conventional infiltrating adenocarcinoma, and the remaining 70% was a poorly differentiated small cell neuroendocrine carcinoma with positive pancytokeratin AE1/AE3 and synaptophysin, and negative chromogranin. The proliferative index (Ki67) was 50-60%.

Reviewing abdominal CT scan at the moment of the perforation, liver lesions had decreased. A study with positron emission tomography (PET-CT) F-DOPA showed deposits only in two liver metastases, and no new information was obtained using Somato-SCAN. Tumor markers became normal after surgery. We continued FOLFOX-Bevacizumab obtaining a partial response of the liver lesions after 4 cycles. We start maintenance therapy with 5FUBevacizumab after that, and a new response was observed in the TAC revaluation after three months [4].

Discussion

Although the first case was described in 1924, the term of MANEC was introduced by the World Health Organization in 2010. We differentiate 3 degrees (G1, G2, G3) [5] according to the mitotic count or Ki-67 index, then our case was G3 (Ki67>20%). Although there may be clusters of neuroendocrine phenotype in many colorectal adenocarcinomas, this tumor met the definition [6] of MANEC due to each component represents at least a 30%.

Positivity for synaptophysin helped to confirm the diagnosis, taking into account that neuroendocrine cells have variable immunoreactivity for their specific markers [7]: chromogranin (60-70%), synaptophysin (75%-90%) and CD56 (50%). We completed the extension study taking into account the demonstrated efficacy in F-DOPA8 uptake [8] (Figure 1).



Figure 1: In the left half of the image, the adenocarcinoma component is predominant. In the right half of the image we can see large cell neuroendocrine cells: large cells with abundant eosinophilic cytoplasm and nuclei with dispersed chromatin showing evident nucleoli.

The origin of these tumors is unclear [9], but they must have genetic correlations. A recent study of 12 cases [10] showed that KRAS mutations at the identical locus in both components were present in

57%. They are usually aggressive tumors, with a high risk of hepatic, ganglionic, and less frequently peritoneal metastases [11]. Surgery is the only curative treatment in early stages and resectable cases, adding adjuvant chemotherapy or radiotherapy because of the high rate of recurrence.

However, management in metastatic tumors is unclear. The evolution seems to be conditioned by the neuroendocrine face [12], although each component may have a degree of differentiation that marks the prognosis. The main therapeutic guidelines [13,14] recommend chemotherapy regimens for TNE, especially when it is poorly differentiated. In our case, this component predominated in the resected sample, being a minority in the distant hepatic metastasis [15]. Given that we obtained a good response with the chemotherapy administered and the known response of this type of tumor to platinum and anti-angiogenic therapies (specifically with FOLFOX16 and Bevacizumab), as we can see in at least two Asiatic studies [16,17], we decided to maintain the same regimen, actually obtaining a maintained response. This situation has also been observed in other reports [18] (Figure 2).



Figure 2: On the left side: the neuroendocrine component is immunoreactive for synaptophysin. On the right side: Ki 67 expression <50%.

Conclusion

We conclude that the coexistence of neuroendocrine tumors with adenocarcinomas is rare, even more in the colon. The diagnosis is not simple and its incidence is probably underestimated. The worst prognosis is generally attributed to the neuroendocrine component due to a more aggressive biological behaviour, but we also have to take de distant disease characteristics into account. More studies are needed to clarify the origin of these neoplasms and to establish the most appropriate treatment.

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