

# Neuroendocrine-non-neuroendocrine neoplasia of the colon (MiNEN): Unifying concepts

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## ABSTRACT

Neuroendocrine tumors represent 1% of all malignant neoplasms of the digestive system, of which 14-20% correspond to the colon and only 1-3% to the rectum. Eighty-five percent of colon neoplasms are poorly differentiated neuroendocrine carcinomas that contain a non-neuroendocrine component in 25-40% of cases.

An unusual clinical case with difficult preoperative diagnosis, in a 71-year-old female patient is presented. She consulted due to change in bowel habits and abdominal pain in the left lower quadrant. CT scan reported a 10 cm solid mass in the rectosigmoid colon, with multiple liver lesions compatible with metastases. Left hemicolectomy with left salpingo-oophorectomy was performed. A brief summary of the different names and classifications of this entity that have occurred in recent years is presented.

**Keywords:** MiNEN, adenoneuroendocrine carcinoma, colorectal neoplasia.

## INTRODUCTION

The coexistence of neuroendocrine (NE) and non-neuroendocrine (NNE) components in the same neoplasm, or mixed NE and NNE neoplasm (MiNEN), is a well-known but rare phenomenon. Cordier in 1924, first described the gastrointestinal tumors containing epithelial and NE components. Various terms have subsequently been used to describe this hybrid tumor.<sup>1</sup> Due to its dual histopathological features, the clinical behavior of MiNEN differs from that of NE carcinoma and classic adenocarcinoma.

NE neoplasms represent 1% of all malignant neoplasms of the digestive system. According to a multicenter study by the Japanese Colon and Rectal Cancer Society that analyzed the distribution of digestive NE neoplasms, of a total of 760 patients, only 1.3% corresponded to MiNEN.<sup>2</sup>

NE neoplasms of the colon represent 14 to 20%, while those of the rectum only 1 to 3%.<sup>3</sup> Most NE neoplasms of the colon (85%) are poorly differentiated and contain a NNE component in 25-40% of cases, which can be an adenocarcinoma (45-65%), an adenoma (30-35%) or a squamous cell carcinoma (5%). The NNE component arises from the mucosa, while the NE component develops from a deeper layer, which may be missed when a deep biopsy or radical resection is not performed.

We present a rare clinical case with difficult preoperative diagnosis, along with a brief summary of the different

names and classifications of this entity that have been presented in recent years.

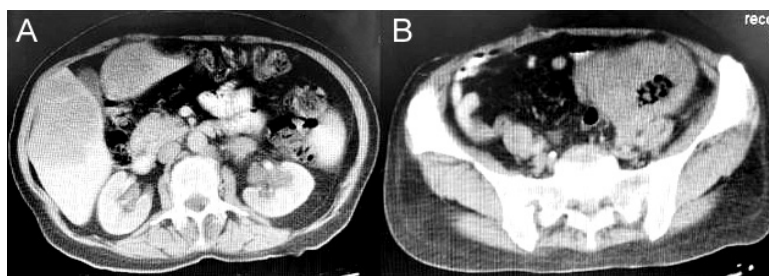
## CASE

A 71-year-old female patient, with a history of hypertension and appendectomy, consulted due to a change in bowel habits, associated with pain in the left lower quadrant that was relieved with defecation. On physical examination, she had a soft abdomen, painful on deep palpation in the flank and left iliac fossa, where a voluminous, hard stone mass was evident, which appeared adhered to deep planes, measuring approximately 7 x 5 cm. The proctological examination was normal.

Ca 19-9: 2.36 U/ml; CEA: 2.5ng/ml. Three colonoscopies were performed, all of which showed a punctate stricture in the sigmoid colon that prevented progression of the endoscope. The biopsy showed colonic mucosa with atypical cells, without a specific histological diagnosis.

Abdominopelvic CT scan showed a 1.4 cm nodule at the base of the right lung and focal hypodense hepatic lesions with heterogeneous enhancement, the largest (8 cm) in the right liver lobe, consistent with metastasis. In the left iliac fossa, an irregular solid mass measuring approximately 10 cm was observed, compatible with an atypical lesion of the entire colon wall (Fig. 1). Enlarged lymph nodes were seen in the retroperitoneum, with the largest conglomerate (3.8 cm) in the left prerenal paravertebral region.

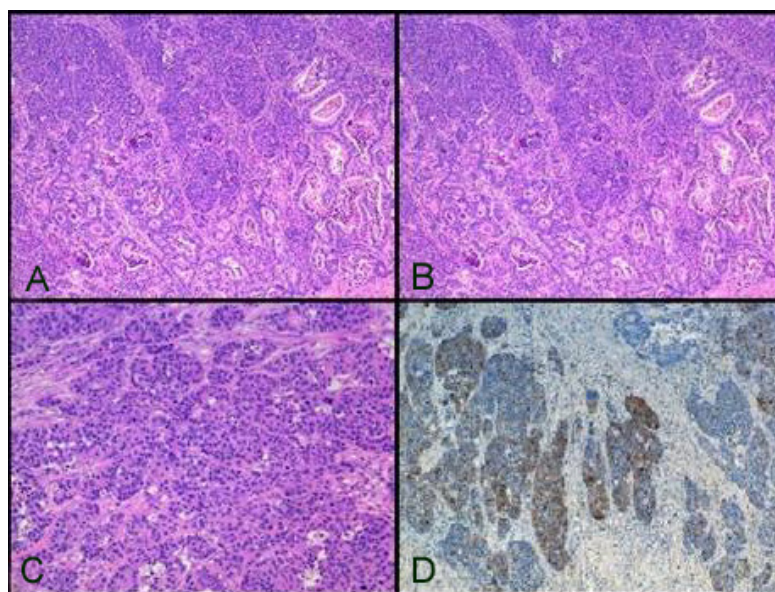
Given the progressive occlusive symptoms and the absence of a definitive histological diagnosis, surgery is indicated. The laparotomy revealed little free serous fluid and a voluminous mass in the sigmoid colon measuring 15x10 cm, attached to deep planes. Multiple metastases in both liver lobes, the largest measuring 12 cm. An en bloc left hemicolectomy with left salpingo-oophorectomy was performed. Histopathological examination informed a mixed NE and NNE neoplasia (small cell NE carcinoma with moderately differentiated adenocarcinoma) is observed invading adjacent structures (left Fallopian tube and ovary), with perineural and vascular invasion. Margins are free. Two of 12 lymph nodes have massive neoplastic infiltration. IHC: chromogranin and synaptophysin positive in NE component. CK20: positive in adenocarcinoma component. MiNEN, pT4b pN1b M1 (Fig. 2).



**Figure 1.** Computed tomography. *A.* Large hypodense lesion involving the right and left hepatic lobes. *B.* Thickening of the sigmoid colon.

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**Figure 2.** Histopathology. H&E. **A.** NNE component: adenocarcinoma. Atypical epithelial proliferation arranged in glands with different degrees of differentiation, some retain mucosecretion. **B.** MiNEN. Glandular structures and solid areas. **C.** NE component: approximation of solid nuclei, cells with a moderate amount of cytoplasm, homogeneous nuclei with salt and pepper chromatin, with different degrees of differentiation. **D.** IHC. Positive labeling for chromogranin, with arrangement in solid nests.

## DISCUSSION

The nomenclature of mixed NE and NNE neoplasms has undergone numerous successive modifications in the last 20 years.

These neoplasms contain two or more different histological components, with at least one of them of NE origin that compromises at least 30% of the tumor, given that lower percentages do not influence tumor behavior.<sup>4</sup>

The diagnosis is made with the histopathological study. Once hematoxylin-eosin staining demonstrates the presence of NE and epithelial components, confirmatory testing with immunohistochemistry should be performed. At least two of three NE markers (synaptophysin, chromogranin, and CD 56) are used.

### Historical evolution of nomenclature

#### For NE component

NE neoplasms were called “carcinoid tumors” since their first description in 1907 and remained so for at least a century. Then, in 1994, when a different behavior was observed between well-differentiated and poorly differentiated tumors, the latter were called “small cell carcinomas” leaving the term carcinoid for the well-differentiated ones.

In 2010, with the arrival of the Ki-67 index, the WHO adopted a classification based on this marker. Grade 1 and 2: Ki-67 index  $\leq 20\%$  and Grade 3: Ki67 index  $>20\%$ .<sup>5</sup> Furthermore, according to their morphology, these tumors were divided into well-differentiated or NET (NE tumor) and poorly differentiated or NEC (NE carcinoma). Any of these neoplasms, whether NET or NEC, can constitute the NE component of a MiNEN.

#### For non-NE components

In 1987, Lewin formally proposed a classification system for mixed NE neoplasms that he termed “composite glandular endocrine cell carcinomas”.<sup>6</sup>

In 2000, these neoplasms were adopted in the WHO Classification of Tumors of the Digestive System as “mixed exocrine-endocrine carcinomas” (MEEC), a terminology that was short-lived and was modified by “mixed adenoneuroendocrine carcinoma” (MANEC) in a later edition (2010). The goal was to create a comprehensive and appropriate term for mixed NE neoplasms that could be used in any organ, a difficult task due to the great variability of NE neoplasms and their different sites of origin. The term neoplasia or neoplasms, instead of carcinoma, was used to be able to include the benign NNE component and remain part of the MiNEN classification.<sup>7</sup>

The diagnosis of these rare tumors is often challenging because commonly only one component is identified. This leads to incomplete diagnosis with suboptimal treatment. Its management is recommended in multidisciplinary rounds with expert pathologists and oncologists or with special interest in NE neoplasms, which allows determining the prognosis and adapting the treatment to the most aggressive component of the tumor.

## CONCLUSION

MiNEN is not a diagnosis, it is a general term used for mixed neuroendocrine neoplasms. The interdisciplinary team must know and be updated regarding the nomenclature so that everyone speaks the same language. The challenge for pathologists is to clearly report all tumor components, so that oncologists can risk stratify and appropriately plan the management of these neoplasms.

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