



# Acute Intestinal Obstruction Revealing Metachronous Gastrointestinal Adenocarcinoma in a Small Bowel Neuroendocrine Tumor: A Case Report

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## Abstract

Neuroendocrine tumors are cancers that develop in the diffuse neuroendocrine system. The small intestine is one of the most common sites where gastrointestinal neuroendocrine cancers develop and the most common histological types of malignant tumors of the small intestine. In the literature the relationship between neuroendocrine tumors and the development of secondary primary malignancies, whether synchronous or metachronous, is well described. Usually, these involve the colorectal, the gastro urinary tract and the bronco pulmonary system, while the localization in the small intestine is uncommon. We describe here the case of a patient followed-up for an ileal resection, which occurred in emergency for intestinal obstruction; the latter was due to a jejunal adenocarcinoma linked to a neuroendocrine tumor. This report illustrates the rare association of small intestinal neuroendocrine tumor with secondary small bowel malignancies.

## Introduction

Carcinoid tumor was coined by Oberndorfer 1907 [1] to describe a small neoplasia arising from neuroendocrine cells and characterized by a propensity to produce peptides, neuroamines and other vasoactive substances. The literature has expanded the concept of carcinoid, later replaced by the term Neuro Endocrine Tumor (NET) [2]. NETs that originate from the cells of the diffuse neuroendocrine system of the gastrointestinal tract (GI-NET) are considered rare [3]; they are the second most common neoplasia of the small intestine (Si-NET) [4]. The localisation of the tumor in jejunum/ileum tract is the third most common primary site, after lung and rectum [5]. The incidence rates have increased in the more recent years: Si-NETs are 0.67-0.81/100,000/years [6]. The mean age at diagnosis is between 60 and 65 years [6], and male to female ratio is 1.4/1.0 [5].

NET association with secondary primary malignancies (SPM) is an increasing phenomenon [7]. The occurrence of other malignancies is estimated to range up to 55% [8]; they can have a synchronous or metachronous presentation [9]. The majority of cases are localized in the colorectal tract and genitourinary tract [10,11].

We report here the case of a patient who first underwent an ileal resection for neuroendocrine carcinoma, and who after 8 months had an emergency exploratory laparotomy for jejunum occlusion.

## Case Report

A 65-year-old man was referred with generalised abdominal pain, vomiting and obstipation of 6 months duration. His medical history was hyperuricemia, dyslipidemia, implant of right hip for algodystrophy, laparoscopic sigmoidectomy for diverticula, appendectomy, resection of Meckel's diverticulum and bilateral inguinal hernia. MRI enterography revealed a mass in the right iliac fossa with dilatation of the upstream. The tumour markers were normal (CA 19.9 20; CEA 0.9; Chromogranina A 55). A contrast-enhanced CT scan of the abdomen confirmed the presence of an ileal mass without secondary localisation. The patient underwent an ileal resection in September 2015. The laparotomy showed a tumor restricted to the ileum terminal (27 cm) without hepatic metastasis, but suspected dissemination in the pelvic peritoneum.

The histopathological examination concluded for Si-NET (mitotic index 1, Ki 67 was 2%; Immunohistochemistry positivity of Chromogranina and Synaptophysin). 4 lymph nodes out of 12 were metastatic (mitotic index 5 and Ki 67 3%). The presence of 2 metastatic nodules of the pelvic

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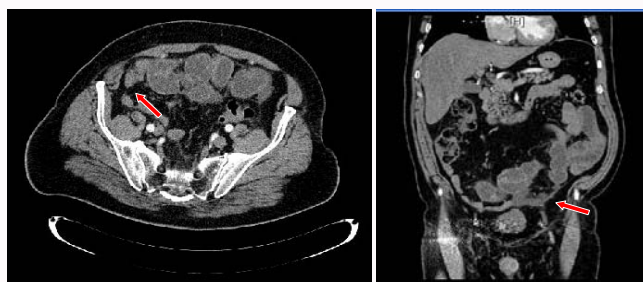
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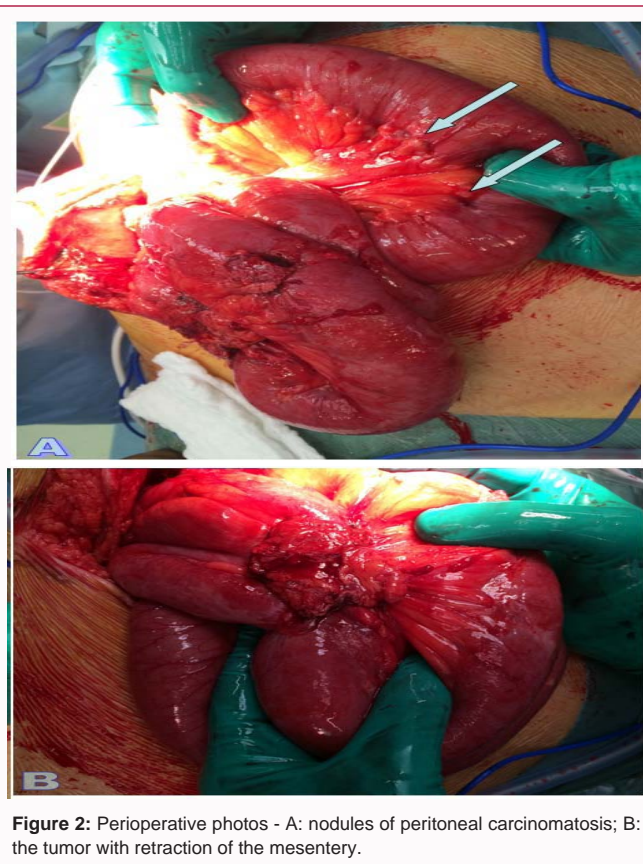
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**Figure 1:** CT showing a disparity in caliber between distended proximal small bowel loops and collapsed distal small bowel loops.



**Figure 2:** Perioperative photos - A: nodules of peritoneal carcinomatosis; B: the tumor with retraction of the mesentery.

peritoneum was noted. The global tumor stage was pT3 (m) (2) N1 (4N+/12N) L1 V1 Pn1 M1 R0. In conclusion, it was a Si-NET stage IV [12,13] and grading G2 [12,13]. The patient had a good postoperative recuperation, and the hospital discharge was on day7. A treatment with analogues of somatostatina was required. After 4 months, an abdominal hepatic MRI showed hypervascular lesion of the spleen, suspecting relapse without liver metastasis or abdominal localisation. Progressively the patient developed abdominal pain, associated with obstipation and nausea.

Due to the continuity of symptoms, a CT-scan was performed in April 2016. A small bowel obstruction at the jejunum-ileum junction in the area of the surgical intervention was detected, probably caused by adhesions, but without signs of ischemic distress (Figure 1).

After 15 days the patient required urgent hospital admission with worsening of panic symptomatology: severe bloating and abdominal cramps, nausea, vomiting and constipation. The patient underwent an emergency exploratory laparotomy that revealed a hard mass in the mid-jejunum encasing the jejunal loops and mesentery associated

with a peritoneal carcinosis (Figure 2).

In a histopathological examination peritoneal carcinomatosis was diagnosed with parietal, focal and diffuse infiltration of the ileal wall with a well differentiated adenocarcinoma. The latter morphological and immunophenotypic appearance (CK7+, CDX2+, CK20-) supported a primary intestinal origin. There was no residue of the neuro-endocrine tumour previously diagnosed.

## Discussion

Several study have investigated and provided evidence of SPM incidence in patients with NET. In 1944, Pearson and Fitzgerald described the high incidence (23%) of SPM in patients with carcinoid tumors at autopsy [8]. The association between NET and other malignancies is an increasingly appreciated phenomenon. In a retrospective review of 69 patients with GI-NET, Gerstle et al. showed that 29 (42%) had synchronous tumors and 3 (4%) had metachronous tumors. In their study, Kamp et al demonstrated that the occurrence of synchronous secondary primary intestinal malignancies is greater in GI-NET patients compared with the general population. In another French study of 270 patients with GI-NET 21 (12.8%) of them also had a synchronous tumor [13].

The incidence of SPM in patients with GI-NET ranges from 12% to 46% with an average of 17% [11]. The most common site of SPM is the gastrointestinal tract (32-62%), followed by the genitourinary tract (9-27%), breast (14-17%) and the lung system (9-13%) [1]. In about one third of the cases a small bowel carcinoid tumor may be associated to SPM, whether synchronous (22%) or metachronous (9%) [9].

The major series before 1975 in English literature are reported in Table 1. The percentage of involvement of the small intestine as SPM ranges from 0% to 17%, whereas that of Godwin' series combines into one group ileum and cecum. Then, this sustains that the jejunum-ileum SPM is really uncommon [14].

In an epidemiological study about Si-NET and adenocarcinoma Zar et al. [15] have found that SPM are generally diagnosed within the first years after diagnosis of a first tumor and that metachronous tumor is defined according to the lesion diagnosed > 6 months [16]. In our case, the diagnosis of jejunum adenocarcinoma was 8 months after the first tumor; so, it is a metachronous tumor.

Amin et al. [17] have considered the risk of metachronous cancers in patients with SI-NET. Between 1973 and 2007 the authors identified 8331 patients with SI-NET thanks to the Surveillance, Epidemiology, and END Results database (SEER). They observed that 33% had developed a metachronous primary tumor. They also estimated that only 3% of SPM were localized in the small bowel. Besides, metachronous malignancy may be associated to a genetic predisposition, behavioural risk factors or common environmental exposures. Exogenous mitotic effects of secretory products from a primary tumor can also generate neoplastic transformation, even a combination of all these factors [18]. Several studies have tried to establish the relationship between NET and the development of SPM. Some consider the secretion of biologically active compounds by the neuroendocrine cells. Zuncker et al. [19] proposed that many of the secreted peptides have growth factor properties and that non carcinoid tumor cells can over express receptors for these regulatory peptides. However, other authors have considered the role played by non-neuroendocrine peptides in carcinogenesis.

**Table 1:** NET: NeuroEndocrine Tumors; GI-NET: Gastrointestinal Neuroendocrine Tumors; SPM: Secondary Primary Malignancies; S: Synchronous; M: Metachronous; GI: Gastrointestinal; - data not available; \*value that considers two series together; the separate cases that return a value of 17% and 18%; also, small intestine and cecum are treated in the same group.

Study	NET n°	GI NET %	SPM %	Time of SPM		Site SPM				
				S	M	Small Bowel	Colorectal	Breast	Genitourinary tract	Lung/Bronchus
Godwin et al. [21]	2837	86	12	62%	38%	32% *	25%	-	-	5%
Kothari et al. [24]	96	100	24	59%	41%	-	48% (GI)	-	30%	9%
Gerstle et al. [8]	69	100	46	88%	12%	-	48% (GI)	-	23%	10%
Prommegger et al. [22]	96	93	14.6	36%	57%	0%	22%	14%	14%	0%
Amin et al. [17]	8331	100	29	-	33%	3%	9%	14%	32%	6%
Kamp et al. [16]	459	100	13.7	2.80%	6.30%	3%	12%	15%	13%	6%
Reina et al. [25]	111	81	18.9	36%	64%	9%	24%	5%	9%	19%
Clift et al. [23]	169	88	17	28%	7%	0%	21%	17%	31%	3%

Regarding diagnosis, Zar et al. [15] stressed the importance of an accurate research of synchronous primary malignancies in presence of Si-NET. In our case, the diagnosis of Si-NET was incidental and histological. However, even if during the first surgery the abdominal cavity was explored no tumor was identified.

Therefore, an intensive follow up of patients is warmly recommended for the prevention of late-stage diagnosis to monitor the possible development of metachronous tumor. Habal et al. [11] asserted that the overall prognosis depends primarily on the more aggressive SPM. The authors [15] evaluated the cause of death in patients who had been diagnosed SI-NET; they observed that 32% of those patients had died within 30 days from diagnosis of SPM. In our experience the patient had peritoneal carcinomatosis at diagnosis of SPM. He developed an advanced malignant tumor in 8 months, although he was under intensive follow-up. During this period, the instrumental investigations had not revealed anything that could identify SPM. The only relevant fact was signs of obstruction syndrome, which is presumably falsely interpreted as postoperative adhesion. The importance of an intensive follow-up was confirmed in the Consensus guidelines for the management of patients with digestive NET (ENETS 2016). For patients with G2 NET a check-up every 3-6 months recommends a life-long follow-up [5], considering that after 25 years only approximately 20% of all patients are free of disease [20]. In our case, which was discussed in a multidisciplinary meeting with endocrinologists and oncologists, the follow-up was set at 3 months, taking into consideration the peritoneal localisation. Unfortunately, the diagnosis of an advanced cancer was made.

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