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A case report and review of literature

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Luca Napolitano*, Valentina D'Alessandro*, Domenico Risio*, Camilla Marinelli**, Roberta Cianci***, Paolo Innocenti*

*Unit of General and Laparoscopic Surgery, "G. d'Annunzio" University, Chieti, Italy

**Unit of Pathology, "G. d'Annunzio" University, Chieti, Italy

***Department of Neurosciences and Imaging, Section of Radiological Imaging, "G. d'Annunzio" University, Chieti, Italy

Association between neuroendocrine tumor of the ileum and two colonic primary malignancies. A case report and review of literature.

BACKGROUND: *A high rate of association between neuroendocrine tumors (NETs) and secondary primary malignancy (SPM) has been described in literature and this association can occur either in a synchronous or a metachronous presentation. A wide range of hypothesis has been postulated to explain the high rate of association between NETs and SPM, without definitive conclusions.*

CASE PRESENTATION: *We report a case of an ileal neuroendocrine tumor found incidentally at the histologic examination of the surgical specimen in a 72 years old male underwent to right hemi colectomy for two colic adenomatous polyps with high grade dysplasia.*

CONCLUSION: *Large multicentric epidemiological studies should be considered to assess the association between NETs and SPM.*

KEY WORDS: Neuroendocrine tumors (NETs), Progression-Free Survival (PFS), Secondary primary malignancy (SPM)

Introduction

Neuroendocrine tumors (NETs), previously called "Carcinoids", are rare neoplasms arising from neuroendocrine cells part of Amine Precursor and Decarboxilation (APUD) system. These endocrine cells can be found also in lung and ovary and are largely represented in the gastrointestinal tract ¹.

NETs tumors can show a malignant behavior and so they can often metastasize. A high rate of association between NETs and secondary primary malignancy (SPM) was described, either in a synchronous or a metachronous presentation. We describe a case of an ileal NET found incidentally at the histologic examination of the surgical specimen of a right hemi colectomy performed for two colic adenomatous polyps with high grade dysplasia.

Case Presentation

A 72 years old male referred to our unit after a colonoscopy performed for the regional colorectal cancer screening program. Past medical history was characterized by chronic obstructive pulmonary disease with mainly emphysematous component, for which he had

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Correspondence to: Domenico Risio, MD, PhD., Unit of General and Laparoscopic Surgery, "G. d'Annunzio" University, Via dei Vestini 31, 66100 Chieti, Italy (e-mail address: domenicorisio@virgilio.it)

Abbreviations

Neuroendocrine tumors (NETs)
secondary primary malignancy (SPM)
Amine Precursor and Decarboxilation (APUD) system

been taking bronchodilating medications for 7 years. A large sessile polyp was found during the colonoscopy, and a biopsy was performed; the size of the polyp didn't allow an endoscopic complete removal. The histological diagnosis revealed a high-grade dysplasia tubulovillous adenoma. Physical exam was normal, the abdomen was soft and without tenderness.

A CT scan was performed staging the disease, and a polyp of the cecal region was found (Fig. 1). Blood tests were all within normal limits except for slightly elevated CA 19-9 53.1 U/ml (reference range 0,0-37,0 U/ml). A decision for surgery was made and the patient underwent a laparoscopic assisted right hemicolectomy with side-to-side hand sewn anastomosis.

The post operative course was regular and without remarkable complications. The patient was discharged home 6 days after his operation.

The histopatological diagnosis showed the synchronous presence of two high-grade dysplasia tubulovillous adenomas in the right colon segment (diameter 0.8 x 0.7 x 0.3 cm and 0.5 x 0.5 x 0.2 cm) and of a well differentiated neuroendocrine tumor (NET) of the ileum spreading into mucosa and submucosa (Fig. 2). Immunohistochemistry for CDX2, Chromogranin, CD56 and synaptophysin were highly positive. According to TNM staging, the NET was classified as a T1 N1 with

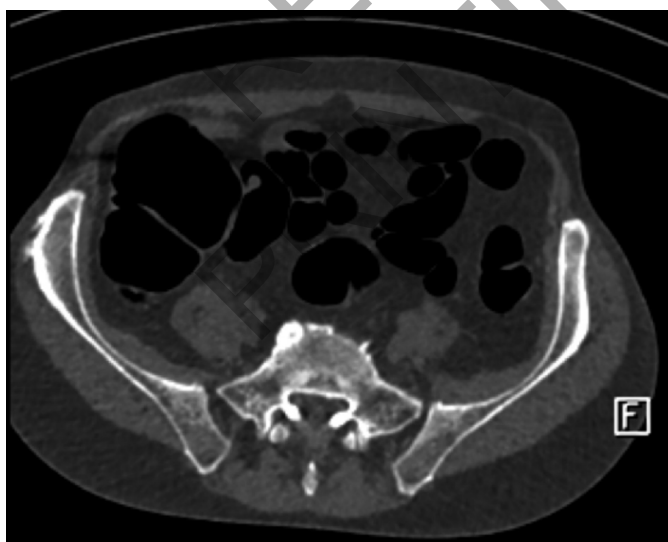


Fig 1: Identification of colonic tumor by CT scan
CT scan showing polypoid lesion (arrow) of the cecum

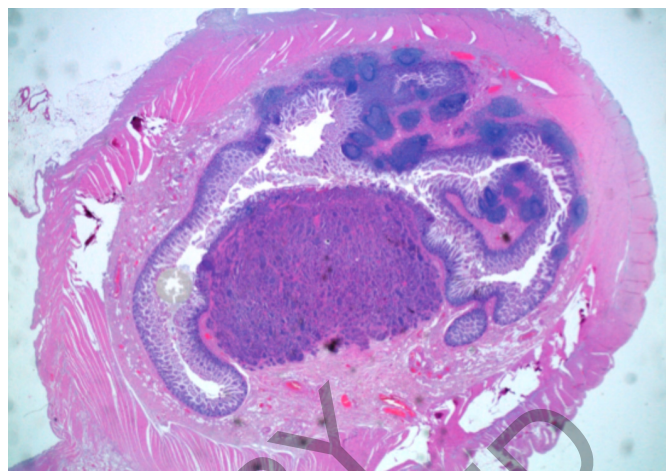


Fig 2: Microscopic findings of the neuroendocrine tumor (NET) of the ileum. The cross section shows a 0,7 cm nodule within the ileal wall. The tumor expands the submucosa and bulges into the mucosa. (Hematoxylin-eosin staining. Original magnification 10x).

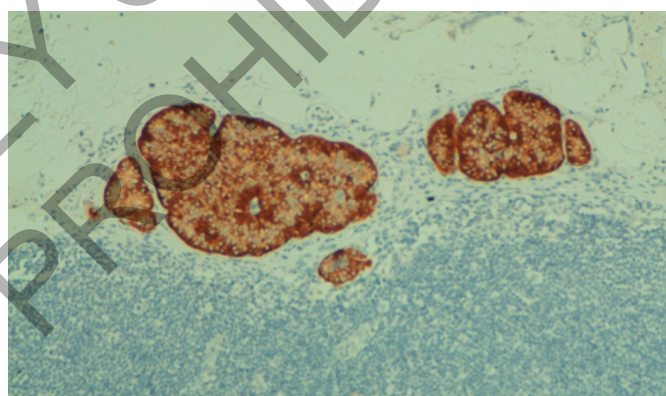


Fig 3: Immunohistochemical staining for Synaptophysin. Tumoral cells with neuroendocrine differentiation were observed. Synaptophysin was highly positive (Original magnification 100x).

grading G1-G2. Lymphnodal metastasis from NET were found in 2 out of 7 lymph nodes examined (Fig. 3).

Octreoscan and chromogranin dosage were performed after one month from surgery and showed no sign of active disease. For this reason a strict 3 months follow up with CT scans, octreoscans and repeated blood tests for chromogranin was proposed to the patient.

Conclusion

The most common site of NETs is the appendix, as the incidence of about 2.8 per million seems to show. Nevertheless, Moertel et al. have reported an incidence of the NETs of the small bowel around 25%, with a prevalence of 0.65 %³.

The incidence of small intestine NETs is increasing from 1,09 per 100.000 in 1973 to 5,25 per 100.000 in 2001⁴. This could be explained by more efficient diagnostic tools (such as routine endoscopy for colorectal cancer screening) and in part by an improvement of oncological classification of those tumors.

NETs present a variable degree of malignancy and account for less than 1% of all malignant tumors of gastrointestinal tract⁵.

Only 8-20% of patients affected by NETs present the "carcinoid syndrome" characterized by watery diarrhea, flushing and abdominal pain caused by the release of serotonin by the tumor^{6,28,29}.

Sometimes, people with gastrointestinal NET, could not have signs and symptoms of carcinoid syndrome. Napolitano et al. presented 9 cases of gastro-enteropancreatic neuro-endocrine biologically inactive tumors³⁰. The malignant potential of these neoplasm varies according to dimensions^{7,8}, to the site of onset^{8,9}, female gender, multiplicity, mitotic index¹⁰ and cell differentiation¹¹.

Carcinoids of appendix have better 5 year survival prognosis (>95%) than those arisen from small intestine (70-80%)¹².

Gastrointestinal NETs can be classified, according to pathologic criteria of malignancy of the World Health Organization, in four types: well-differentiated endocrine tumors, well-differentiated endocrine carcinoma, mixed endocrine-exocrine carcinomas, and poorly differentiated endocrine carcinomas.

Well-differentiated endocrine tumors (previously called "Carcinoids") are composed of small-medium sized cells with no or minimal atypia. These tumors are limited to mucosa and submucosa. Usually the clinical course is benign.

Well-differentiated endocrine carcinoma (former definition: "Malignant carcinoids") are composed of cells with mild or moderate atypia. These tumors can show angioinvasion and/or neural invasion; they can spread to muscularis propria and beyond and they can metastasize. The clinical course of those neoplasms can be malignant. Mixed endocrine-exocrine carcinomas (previously known as "Adenocarcinoid") are composed of epithelial and endocrine cells, with a prevalence of the mucinous component. This malignant tumors spread in the muscularis propria and/or beyond it and show capability of metastasization. This tumor can demonstrate moderate or high malignancy clinical course.

Poorly differentiated endocrine carcinomas (former defined as "Small cell carcinoma") are composed of atypical small sized cells with high nucleocytoplasmic ratio. Usually these malignancies show metastatic disease at presentation demonstrating a very high malignant clinical behavior¹³.

In 2010 WHO introduced a new classification of neuroendocrine neoplasms of the digestive system based on proliferation rates: these parameters used for this scoring are the mitotic index MI (assessed with the number of

mitosis in 10 High power Fields HPF) and the Ki-67 index (as the percentage of cells showing nuclear immunoreactivity) which is known as an important predictor of progression-free survival (PFS) in ileal NET¹⁴. In case of malignancy of the NETs the prognosis is heavily influenced by the T stage, which is site specific, the lymph-nodal involvement and/or distant metastases¹⁵. Besides these characteristics influencing the harmful potential of these neoplasms, others aspects regarding NETs have to be considered. Pearson et al. reported for the first time a high incidence of carcinoid tumors with second primary malignancy (SPM) in an autopsy series². Many reports described an high incidence of association between NETs and second primary malignancy (SPM). SPM have been reported to occur in 10-55% of patients^{11,16,18}. Micheletto et al. describes a similar case in which a 73-year-old male with an adenomatous colonic polyp, not suitable of endoscopic treatment, and a synchronous carcinoid of small intestine discovered during surgical procedure³¹.

The majority of second tumors is located in the gastrointestinal tract, which accounts for 32-62% of all SPM^{1,17}, but tumors in the other sites are described as well^{18,19}. Genitourinary tract is involved in 9-22% of cases and lung/bronchial system in 9-13%¹. Most of these SPM are synchronous with NETs (59-87%)¹, but there also some reports regarding metachronous cases¹¹.

In literature the rate of association between NETs and metachronous SPM varies from 3,6 % to 9,6 %¹⁶.

The metachronous SPM following NETs did not have a clear pattern and did not show a preference of second cancer type or site of onset according to the primary site of NETs¹⁶. Overall, studies reported that the increased risk of second cancer after NETs may occur in a wide array of body sites. Many hypotheses have been advanced to explain the pathogenesis of association between NETs and second primary malignancy.

The field-effect theory. This hypothesis asserts that a common carcinogenic effect stimulates growth of neuroendocrine and SPM cancer cells^{1,20}.

A stem cell defect. Some gene mutations have been identified in NETs. For example gastric NETs are sometimes associated with loss of heterozygosis on 18q and 18p²¹ as well as the X chromosome²².

This theory suppose that a genetic defect can lead to the develop of concomitant NETs and SPM: only in MEN 1 syndrome, where NETs occur associated to adenomas of pituitary, pancreas and parathyroid glands, there is an evidence of heritable cause⁸.

The neuropeptides release. NETs produce and release a wide range of neuropeptides such as: Gastrin, Cholecystokinin and Bombesin. Most of these have demonstrated growth factors properties⁸. In particular Gastrin and Cholecystokinin have been previously involved in the direct regulation of the growth in colorectal carcinoma²³. Besides SPM often overexpress receptors for these compounds⁸. Moreover NETs secrete

other substances such as PDGF, FGF and TGF, which act as non-neuropeptides cell growth factors. These substances regulate angiogenesis and blood vessel ingrowth in tumors^{24,25}.

The prognosis for the patient is often heavily influenced by the malignancy of the second tumor but in our case report the NET, although found incidentally, presented high aggressiveness. Even if the size of the tumor was less than 1 cm and its grade was G1 (well differentiated), at the time of the diagnosis NET presented two lymph nodal metastases. This finding seems to be different from the data showed in the large series by Yao CJ et al, which found an high correlation between grading of the tumor and disease stage ($P < 0.01$). In this paper age at diagnosis ($P .001$), sex ($P > 0.001$), and race ($P > 0.001$) were also prognostic of survival, with women showing a better outcome than men²⁶.

The main effort for the treatment of NETs is to perform a complete surgical resection which is the only chance of cure at the present moment. Whereas the introduction of octreotide meant a dramatic improvement of the survival, especially in patients who present with a carcinoid syndrome in order to control symptoms and avoid organ failure, strong data from randomized studies are not currently available²⁷.

Conclusions

In our report a G1 ileal NET, located near to the ileocecal valve, was associated with two early stage colonic neoplasms in the right colon. The association of three primary neoplasms can reinforce the hypothesis of a carcinogenesis promoting peptide released by the NET that could cause the onset of a tumor in other sites. Moreover, we observed an aggressive behavior of the NET, which in spite of a G1 grading, presented two nodal metastases at the time of the diagnosis.

We hope that large multicentric epidemiological studies can definitively explain the role of NETs in the onset of other primary neoplasms, in order to treat properly this rare association.

Authors' contributions

LN, VD and DR performed the surgery, wrote the manuscript and have given final approval of the version to be published; VD conducted a literature search and cared the patient's follow-up; CR carried out the histological and bio-molecular studies; PI supervised the draft. All authors read and approved the final manuscript.

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Riassunto

In letteratura sono stati riportati alcuni casi di associazione tra tumori neuroendocrini (NETs) ed un secondo o più tumori primitivi (SPM). Quest'associazione può presentarsi sia in maniera sincrona che metacrona. Dal punto di vista eziopatogenetico sono state fatte molteplici ipotesi, senza alcuna conclusione definitiva. L'ipotesi più accreditata sostiene l'insorgenza di un secondo tumore in seguito al ruolo carcinogenetico svolto dai peptidi rilasciati dal tumore neuroendocrino

Noi riportiamo il caso di un tumore neuroendocrino ileale scoperto incidentalmente all'esame istologico del pezzo operatorio di un uomo di 72 anni sottoposto ad emicolectomia destra per la presenza di due polipi adenomatosi del colon destro con alto grado di displasia. Dovrebbero essere considerati ampi studi epidemiologici multicentrici per caratterizzare meglio e spiegare le cause patogenetiche dell'associazione tra NET ed SPM.

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