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A case report and review of the literature

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Antonino Buffone*, Dario Cavallaro*, Salvatore Lo Bianco*, Lidia Puzzo**, Pietro Caglià***, Matteo Angelo Cannizzaro*

Università degli studi di Catania, Dipartimento di Scienze Mediche, Chirurgiche e tecnologie Avanzate, "G.F. Ingrassia"
**Section of Endocrine Surgery, University of Catania, Policlinico-Vittorio Emanuele Hospital, Catania, Italy*
***Section of Pathological Anatomy, University of Catania, Policlinico-Vittorio Emanuele Hospital, Catania, Italy*
****Section of Surgery, University of Catania, Policlinico-Vittorio Emanuele Hospital, Catania, Italy*

Synchronous ileal neuroendocrine tumor: diagnosis and treatment. A case report and review of the literature

INTRODUCTION: *The majority of neuroendocrine tumors (NET) are located in the gastrointestinal tract (67.5%) and in the bronchopulmonary (25.3%).*
CASE REPORT: *CA, female, 42 years old, profuse diarrhea about two months, cramping for increased peristalsis, vomiting and weight loss. The patient, diagnosed with ileal neuroendocrine tumor, by colonoscopy with biopsy of lesion, therefore came in our unit to be subjected to surgical therapy. Plasma assay Chromogranin A was performed: 160 ng / ml (nv: 15-100 ng / ml). The patient underwent surgery of right hemicolectomy.*
DISCUSSION: *Neuroendocrine tumors although are rare diseases, have an increasing impact, probably by virtue of improved diagnostic methods. In case of profuse diarrhea should be suspected a neuroendocrine tumor. Certainly the diagnosis of certainty is given by histological examination (biopsy or resected nodule).*
CONCLUSION: *After surgical excision is necessary to perform the follow-up of chromogranin A, and, if not executed, perform nuclear medicine examinations such as Octreoscan and PET.*

KEY-WORDS: Chromogranin A, Neuroendocrine tumor, Octreoscan

Introduction

Neuroendocrine tumors are a rare group of cancers that originate from cells of the diffuse neuroendocrine system in the organism, (0.49% of all malignancies).

Their incidence, however, appears to be increasing. [1,2,3] In the USA the incidence is 2-5 cases / year per 100,000 inhabitants, while in Europe is 8-9 cases / 100,000. [4]
The majority of neuroendocrine tumors (NET) are located in the gastrointestinal tract (67.5%) and in the bronchopulmonary (25.3%). In rare cases neuroendocrine tumors may arise to the breast. [5]
In the gastrointestinal tract the most common location is represented by the small intestine (41.8%), followed by rectum (27.4%), stomach (8.7%), colon and appendix (4.8%). [2]
The observation of a case of synchronous ileal neuroendocrine tumor motivated us to describe the clinical picture and to make a review of the literature.

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Correspondence to: Antonino Buffone, Via Santa Sofia 78, 95124, Catania, Italy, (e-mail: a.buffone@unict.it)

Case report

CA, female, 42 years old, admitted to a Department of Medicine for profuse diarrhea about two months (treated at home with oral contact antibiotics and loperamide), cramping for increased peristalsis, vomiting and weight loss (about 7 Kg).
The patient was suffering from diabetes for about 7 years, HBV-related hepatitis, anxious depressive syndrome, obstructive pulmonary disease, allergy to metoclopramide. Home therapy practiced: Insulin Humalog (5 IU morning, 8 IU lunch, 8 IU evening), Insulin Lantus (5 IU evening), mirtazapine (30 mg 1 tablet / day), Trazodone hydrochloride (75 mg 1 tablet / day). Umbilical hernia repair surgery at age 13.
In the Department of Medicine, on the basis of clinical findings, was implemented symptomatic therapy: NPT (1800 calories a day), antibiotics, Loperamide and proton pump inhibitors (pantoprazole 40mg daily). The general symptoms had directed to a diagnosis of "irritable bowel" and on this basis was performed a colonoscopy that showed on the ileocecal valve and iuxtavalvolare area, presence of polypoid lesions plurilobate that were biopsied. Histopathological examination of biopsies ended with the diagnosis of a neuroendocrine tumor, with immunophenotype chromogranin A positive.
Was also performed esophagogastroduodenoscopy with negative results for diseases.
The patient, diagnosed with ileal neuroendocrine tumor, therefore came in our unit to be subjected to surgical therapy. At the entrance to the local examination of the abdomen showed a "boat abdomen" and absence of pain at the superficial and deep palpation on all quadrants.
Auscultation normal bowel sounds were heard. Increased peristalsis with cramping before of diarrhea and pain ceased with the emission of liquid stools. Laboratory tests were: Haemochrome (RBCs 4.73X10^6/µl, Hb 13.5 g/dl Ht 38.9%,WBC 10.14X10^3/µl), blood glucose (166 mg / dl), blood urea nitrogen (45 mg / dl) creatinine (1,25 mg/ dl), transaminases (AST 60 U / l, ALT 45 U / l), bilirubin (total 0,38 mg / dl, direct 0,13 mg / dl), serum albumin (3.4 g / dl), blood electrolytes (sodium 142 mmol / l , potassium 3.3 mmol / l, Calcium 9.7 mg / dl, Magnesium 1.84 mg / dl), C-reactive protein (2 mg / l). Plasma assay Chromogranin A was performed: 160 ng / ml (nv: 15-100 ng / ml) and dosage urinary 5-hydroxyindoleacetic acid (5-HIAA): 25 mg / 24h (nv <10 mg / 24h). A CT scan of the chest and abdomen was performed, with and without contrast medium, showed that presence of an area of enhancement to the last stretch of the wall of the ileum until the ileocecal valve and another hyperdensity area in the lumen of ileal loop located upstream of the previous with non-unique interpretation (Fig. 1). Liver increased in volume and with the presence of small cysts in the parenchyma. On site chest had "multiple micro nodular formations with aspect of tree in bloom to report to bronchiolitis and bilaterally multiple bronchial ectasia".

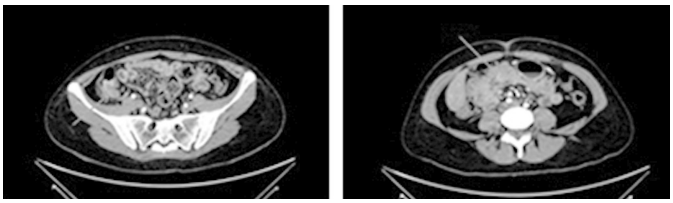

Fig. 1: CT hyperdensity area in the lumen.

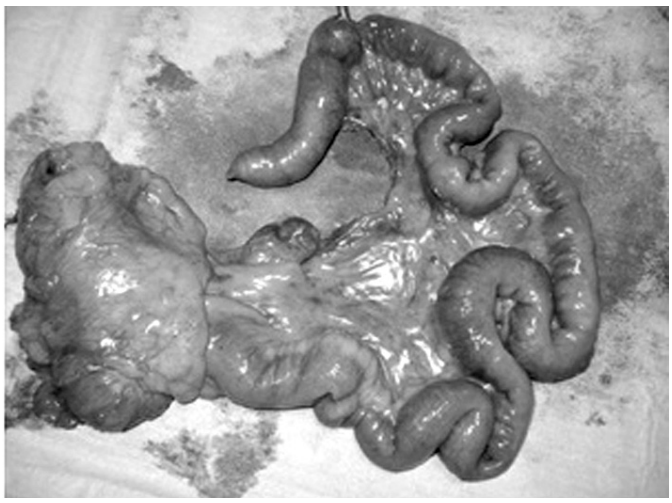

Fig. 2: Ileum and right colon.

Fig. 3: Surgical specimen.

Completed the previously mentioned diagnostic procedure the patient underwent surgery of right hemicolectomy with wide resection of the distal ileum and restoration of intestinal continuity by ileo-transverse laterolateral anastomosis with Surgical staple. At macroscopic examination, the ablated was represented by a section of ileum 42 cm in length, a 6 cm segment of the right colon with adjoining 6 cm cecal appendix (Fig. 2).

At the ileocecal valve was evident a polypoid lesion (1,7x1,5x1 cm) located at 6 cm from the edge of cholic resection and 41 cm from the edge of ileal resection (Fig. 3), apparently infiltrating the visceral wall; 5cm from the edge of ileal resection, polypoid lesion was detected (1,2x1x0,8 cm) consisting of hard, yellowish color, apparently infiltrating the muscle wall. Twentyfour isolated mesenteric lymph nodes at headquarters.
The diagnosis supposed to differentiated multifocal synchronous neuroendocrine carcinoma, polypoid, solid-insular type.
Neoplastic proliferation infiltrates the entire thickness of the bowel wall until the subserosal, without perforate it. Absence of necrosis; neoplastic lymphatic invasion.
Mitotic index 4M/10HPF. Proliferative index (Ki 67) 5%. Distance from the margins of resection of the tumor in cecum respectively 6 cm, cholic side, and 41 cm, ileal side. Distance from the margins of resection of the synchronous tumor in the ileum respectively 4 cm (ileal side) and 40 cm (side cholic). Metastases to lymph nodes examined 5/24. Appendix and surgical resection margins free of cancer. Stadiation PT3(m) N1 G2. In the postoperative period is signaled reduction in blood glucose levels, below normal values, much to suspend insulin therapy. The patient was discharged with home pharmacological therapy (Pantoprazolo 40 mg 1 cpr, Loperamide 1 cpr x 2) and was scheduled for oncology consulting follow-up. One month after surgery was performed scintigraphy with 111-In-Octreoscan with whole body method that did not demonstrate focal areas of pathological accumulation of the receptorial tracer suggestive for repetitive injury (Fig. 3).
In January 2014, the patient has performed TC thoraco-abdominal control with negative results for recurrent disease and dosage of plasma chromogranin A: 128,2 ng/ml (nv 15-100 ng/ml).
In March 2014 was made a new dosage of chromogranin A: 42,4 ng/ml.
At additional control, performed in November 2014, the thoraco-abdominal CT scan revealed no disease recurrence and dosage of chromogranin A was in the normal range (39.1 ng / ml).

Discussion

In most cases, neuroendocrine tumors are asymptomatic and diagnosed incidentally [6]; These tumors can occur in the form of nodules or polyps, size of 1-2 cm., whitish or yellowish or grey [7,8]. Only in 20% of cases they produce hormones or vasoactive substances, serotonin and other mediators, which cause signs and symptoms of carcinoid syndrome. The not functioning forms come to clinical attention in advanced stage with symptoms mainly due to obstruction or compression of adjacent anatomical structures or metastases to the liver.[9] The symptoms in functional forms are represented by: flushing skin (serotonin), diabetes mellitus (glucagon, somatostatin, VIP), diarrhea and steatorrhea (gastrin, serotonin, glucagon, somatostatin, VIP), hypoglycemia (insulin). [10,11] The substance that is most frequently secreted by intestinal functioning forms is serotonin: its excessive production determines the context of the carcinoid syndrome, characterized by cutaneous flushing, diarrhea, bronchoconstriction and right heart failure [12-14]. In most of cases occur sporadically, however can rarely be part of inherited syndromes such as MEN 1, Von Hipple Lindau disease, the Neurofibromatosis type 1. Principal location of these cancers is the small intestine, in which they have synchronous or metachronous lesions in 15-30% of cases [15]. The ileal neuroendocrine tumors can also be accompanied by non-endocrine tumors in 15% of cases, this association percentage appears to be greater than the neuroendocrine tumors located in other parts of the digestive tract [15]. The classification of these cancers in the ileum was for many years under discussion, the last W.H.O. classification drafted in 2010 by Bosman et al focuses on histopathological and proliferative activity of the tumor expressed as grading [16]. In particular identifies three levels of malignancy, based on HPF mitotic index (number of mitosis in 10 fields at high magnification) and Ki67 immunohistochemical parameter.
Microscopically, we have: G1-NET: the mucosa, overlying the nodule or polyp, appears intact or moderately ulcerated; G2-NET: ulceration affecting the mucosa and submucosa; G3-NEC (neuroendocrine carcinoma), large ulcerated mass as carcinomas. Microscopically the G1NET and G2NET have rounded or oval nucleuses with cytoplasm containing granules, chromatin and eosinophils; G3NEC small or large cell carcinoma.
In relation to mitosis: G1-NET: < 2 per mm2 e/o <- 2% index Ki67: G2-NET 2-10 per mm2 e/o 3-20% index Ki67: G3-NET >20 per mm2 e/o 20% index Ki67 [14]. Chromogranin A is considered the most important marker for these tumors, can be used regardless of secreting activity of tumor; is located in secretory granules of neuroendocrine cells [17]. It should not be used as a screening test for the high frequency of false positives, but it is essential for the follow-up in patients with documented diagnosis [18,19]. The conditions most frequently responsible for false positives are kidney failure, chronic atrophic gastritis and therapy with proton pump inhibitors [20]. Another utilized marker is synaptophysin which is present in the membrane of the presynaptic vesicles; is present on high grade NET. [8] In the serotonin secreting forms is useful urinary dosage of the acid-5-hydroxyindoleacetic which has a sensitivity of 100% and a specificity of 90% [21]. Today, in gastrointestinal forms, the digestive endoscopy has considerable importance for diagnosis, which allows, for explored locations, both the location that a targeted biopsy, which, by means of histology and immunohistochemistry, direct you to the correct diagnosis and appropriate therapeutic treatment[22]; as has happened for our case report. CT and MRI are

essential not only for the location of the primary tumor but also for any distant metastasis and / or regional lymph nodes, monitoring post-treatment; these investigations have a sensitivity of 80% [2]. Scintigraphy with 111 In-pentetreotide (OctreoScan), appears to be more useful to evaluate the extent of disease [22], to search of enlarged lymph nodes and monitoring of the disease (progression or regression after treatment) [22,11]. The Octreoscan has a sensitivity of 80-90% [4,22]. As pointed out by Salyers many neuroendocrine tumors are clinically silent and may occur in advanced stage with symptoms of intestinal obstruction or hypersecretion: typical carcinoid syndrome characterized by skin flushing and diarrhea occurs in patients who already have liver metastases [22].
The 5-year survival is 60% of the cases, falling to 18% in the presence of liver metastases [2].

Conclusion

Neuroendocrine tumors although are rare diseases, have an increasing impact, probably by virtue of improved diagnostic methods. Despite this, there are no characteristic symptoms especially in early and therefore early diagnosis is often difficult, prompting a misdiagnosis such as "irritable bowel" but, as is also evident from the clinical case described by us, with persistently diarrhea should occur the suspicion of a NET. Certainly the diagnosis of certainty is given by histological examination (biopsy or resected nodule). After surgical excision is necessary to perform the follow-up of chromogranin A, and, if not executed, perform nuclear medicine examinations such as Octreoscan and PET. In our opinion it is essential, to avoid a delay in diagnosis, which can lead to a deterioration of prognosis, proper integration among Specialists and Doctors working in the territory thus guiding the patient towards a proper therapeutic diagnostic process.

Riassunto

INTRODUZIONE: la maggior parte dei tumori neuroendocrini (NET) si trova nel tratto gastrointestinale (67,5%) e broncopolmonare (25,3%).
CASO CLINICO: CA, femmina, 42 anni, diarrea profusa da circa due mesi, crampi per aumentata peristalsi, vomito e perdita di peso. Alla paziente, viene diagnosticato un tumore neuroendocrino ileale mediante colonscopia con biopsia, e quindi viene nella nostra unità per essere sottoposto a terapia chirurgica. Viene effettuato il dosaggio della Cromogranina A plasmatica: 160 ng / ml (NV: 15-100 ng / ml). La paziente viene sottoposto ad intervento chirurgico di emicolectomia destra.
DISCUSSIONE: i tumori neuroendocrini, anche se sono delle malattie rare, hanno un impatto crescente, probabilmente in virtù dell'avanzamento dei metodi diagnostici. In caso di diarrea profusa dovrebbe essere sospettato un tumore neuroendocrino. Certamente la diagnosi di certezza è data dall'esame istologico (biopsia o un nodulo asportato).
CONCLUSIONE: dopo l'asportazione chirurgica del tumore è necessario eseguire il follow-up tramite il dosaggio della Cromogranina A, e, se non sono stati eseguiti, eseguire gli esami di medicina nucleare, come Octreoscan e PET.

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