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A small intestine neuroendocrine tumor: case report

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ABSTRACT

Introduction

Small intestinal neuroendocrine tumors (SI-NETs) are the most common small bowel tumors, they are recognized for their ability to produce hormones causing mesenteric fibrosis and carcinoid syndrome. They tend to have better surgical rate than adenocarcinomas.this work was made as an update on one of the most aggressive small intestine tumors.

Presentation of case

We discuss here the case of a sixth years old female woman admitted and operated for a small intestine neuroendocrine tumor with peritoneal carcinosis

Discussion

Neuroendocrine tumors are secreting tumors, locating mainly in the small intestine with a high malignancy risk. At the time of the diagnosis, lymph node, liver metastasis and peritoneal carcinosis are very common. Patients may be asymptomatic or consult for abdominal pain, rarely bowel obstruction, diagnosis is radiologically made and confirmed indeed histologically. Treatment involves surgery, chemotherapy, immunotherapy and radiotherapy and surveillance is assured by biomarkers, endoscopy and Octreoscan when metastatic.

Conclusion

The SI-NETs are rare but their incidence and prevalence have been increasing. Histologically, diagnosis is confirmed by positive immunohistochemical staining. Treatment and prognosis depend on the grade and stage of the tumor. Immunotherapy will serve as a future treatment modality.

Key Words: Neuroendocrine tumors, Small bowel neoplasms, Small intestinal tract surgery, Metastatic neuroendocrine tumors, Jejuno-ileal tumors

INTRODUCTION

Small intestinal neuroendocrine tumors (SI-NETs) are the most common small bowel tumors. The annual incidence of SI-NETs has increased lasting recent decades and was in 2003 around 1/100,000 [1]. They are recognized for their ability to produce histamin, serotonin and bradykinins; which may cause mesenteric fibrosis and the carcinoid syndrome, consisting of flush, frequent diarrhea, and, in advanced cases, right-sided heart failure and tricuspid valvulopathy [2]. In contrast to small bowel adenocarcinoma, SI-NETs are also known for their advantageous survival, with 5- 10- and 15-year overall survival rates of 80%, 54%, and 36%, respectively [3].

AIM OF THE ARTICLE:

To provide an update on one of the most aggressive small intestine tumors, to affirm the importance of early management and especially surveillance.

PRESENTATION OF CASE :

We report the case of a 64-year-old female patient, operated 03 years previously for a gallbladder lithiasis, who has been presenting periumbilical abdominal pain for 04 months in the form of cramps, without diarrhea or stigmata of occlusive syndrom, without flushing or hemorrhage, and which reports the notion of weight loss estimated at 15 kgs in 06 months.The physical examination found a patient in fairly good general condition, PS at 0, BMI at 16.5 kg/m². The abdominal examination found a soft abdomen, no palpable mass, no hepatomegaly or dullness of the flanks, pelvic examinations were unremarkable.

The patient underwent an abdominal CT scan which revealed at the height of the umbilicus, an intraperitoneal mass at the expense of an ileal grelic loop. It is well limited, with endo and exoluminal development, with lobulated contours, fairly evenly enhanced after injection of PDC, measuring approximately 47x22 mm, extended over 46 mm in height. (Figure 1) Tumor markers were also normal.

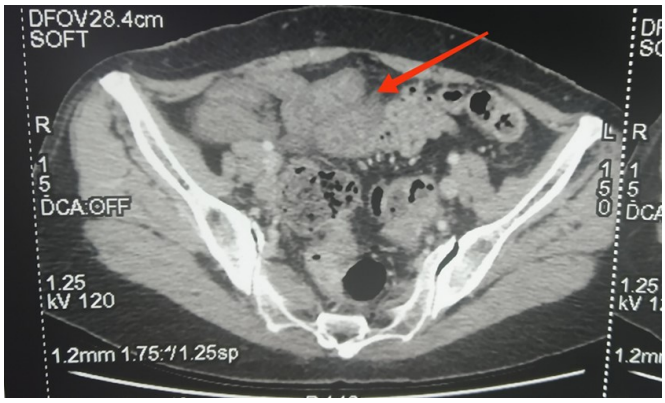

Figure 1: a CT scan slide showing the grelic mass (arrow)

The patient underwent surgery, at open laparotomy the exploration found the presence of a substenosing small bowel tumor 4cm long with long bowel distension, which invades the mesentery next to the upper mesenteric pedicle, the presence of 0.5 cm whitish nodules in the mesentery (biopsies), and low-abundance peritoneal effusion (taken). No hepatic metastasis nor latero uterine mass were stated.

The intervention was a segmental small intestine resection carrying a ileal tumor 3m from the angle of Treitz with end-to-end small intestine anastomosis.(figure 2)

Extemporaneous examination of the whitish lesions in the mesentery showed the presence of cells suspected of malignancy.

The follow-up was unremarked, the patient was declared discharged after 05 post-operative days.

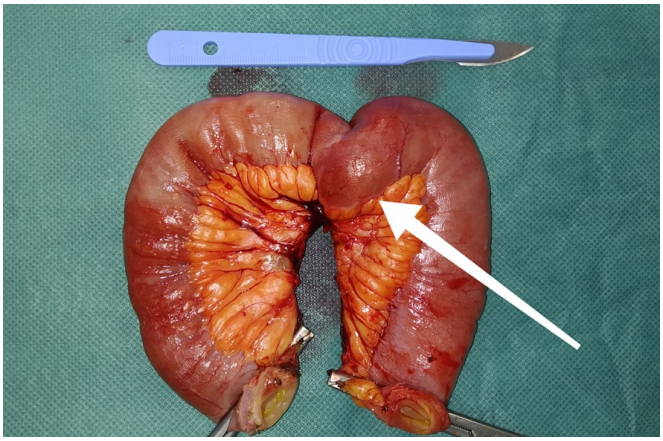

Figure 2: post-operative specimen (arrow= the tumor)

Histopathology showed a morphological and immunohistochemical appearance of a well-differentiated neuroendocrine tumor measuring 2cm long axis; This tumoral proliferation infiltrates the graft wall as far as the serosa. TNM stage: pT4N0M1b.

The patient was put under chemotherapy afterwards.

One year follow up later, showed a patient in a well general condition with no signs of recurrence.

DISCUSSION:

Neuroendocrine tumors (NETs) arise from the diffuse system of neuroendocrine cells with features of both nerve cells (which can receive message from the nervous system) and endocrine cells (which have the ability to synthesize and secrete monoamines, peptides and hormones)[5]. Neuroendocrine cells do not have any axons or nerve terminals. The electrical signals from the nervous system can be converted into hormonal signals with production of hormones, peptides and amines.

As neuroendocrine cells are ubiquitous in our body, NETs can form in different organs including the gastrointestinal tract (GI) (55%) The small intestine counting for 24,75% , pancreas, lungs, gallbladder, thymus, thyroid gland, testes, ovaries and skin. [6].

As we treat SI-NETs in our case report, Their incidence has surpassed that of small bowel adenocarcinomas. Currently the most common primary small bowel malignancy accounting for 25% of all GI-NETs[5],

The majority of patients with SI-NETs present with distant metastases, and the third most common path of dissemination after lymph node and liver metastases is peritoneal carcinomatosis (PC), which is reported in 19–33% of patients with SI-NET at specialized centers.It has been assumed that NET patients with PC practically always also exhibit liver metastases, but 25% of all patients with PC had no signs of liver metastases at presentation.

NETs are a heterogenous group of benign or malignant tumors with various morphologies and functions. The incidence and prevalence of NETs have been increasing over the last few decades[7].

SI-NETs arise from enterochromaffin cells located at the base of the intestinal crypts in the submucosa. The incidence of SI-NET has increased probably due to increased diagnostic modalities. As per SEER registry, the age-adjusted annual incidence of jejunal and ileal NETs is 0.67 per 100000 population in the United States[10]. SI-NETs are indolent, often multifocal and have a distal predilection. More than two thirds of SI-NETs are in the terminal ileum within 60 cm of ileocecal valve. The approximate distribution of SI-NET is duodenum–2%, jejunum-7% and ileum-89%[11]. Patients with SI-NETs frequently experience clinical symptoms.

About 40% NETs are hormone secreting. Most NETs are slow growing with a small percentage of NETs being rapidly growing[8].

About 20% of NETs are associated with hereditary genetic syndromes like multiple endocrine neoplasia type 1 (MEN1) and neurofibromatosis type 1 (NF-1)[9].

In 2017, the World Health Organization (WHO) updated the classification of NET. The histologic grading is based on mitotic index and Ki-67 index which are recorded in hot spots of the tumor. During cell division, Ki-67 protein is found in the cell nucleus. The proportion of Ki-67 – positive tumor cells (Ki-67 index) correlates with cellular proliferation, clinical course and its prognosis. Higher grade is considered if there is any discrepancy between mitotic index and Ki-67 index.

SI-NETs metastasize to distant locations more often than other types of NETs[12]. Duodenal and jejuno-ileal NETs are biologically and clinically distinct[13].

Jejuno-Ileal NETs account for 23% to 28% of all GI-NETs. Most of the Jejuno-Ileal NETs (JI-NETs) are nonfunctioning. The mean age of diagnosis is 6th or 7th decade of life with no sex predilection [15]. The JI-NETs are generally > 2 cm in size, and consist of multiple tumors in up to 40% of cases [16]. At the time of diagnosis, 70% of them have invaded the muscularis propria with metastasis to the regional lymph nodes, and 50% of patients may have hepatic metastasis regardless of tumor size [17]. The hallmark of JI-NETs is desmoplastic reaction leading to mesenteric fibrosis which may manifest in about 50% of cases[18]. Fibrosis around the metastatic lymph nodes causes mesenteric contraction (or mesenteric retraction) which can kink the small bowel resulting in intestinal obstruction. Mesenteric fibrosis can also impinge on the mesenteric blood vessels giving rise to mesenteric ischemia in about 10% of affected patients [19]. Desmoplastic reaction can also involve the retroperitoneum leading to retroperitoneal fibrosis, obstructive uropathy and hydronephrosis. Clinically, patients may be completely asymptomatic or may present with abdominal pain, intestinal obstruction, gastrointestinal bleeding and decreased urination.

Radiologically, mesenteric fibrosis appears as a mesenteric mass with linear soft tissue opacities and possible calcification radiating outwards in a “wheel spoke”pattern. Mesenteric fibrosis does not depend on the NET size or Ki-67 proliferative index. It is associated with not only various comorbidities but also distant metastasis and poor prognosis[20]. Diagnostic modalities include:

- Biomarkers: Serum CgA, serum NSE and urinary 5-hydroxy indole acetic acid (as a marker of carcinoid syndrome);
- Endoscopy: Capsule endoscopy and balloon-assisted or spiral endoscopy; and
- Imaging: SRS (Octreoscan), Ga-DOTATE PET/CT or 111In-DTPA-Octreotide scan.

Treatment of JI-NET includes surgical resection of primary NET with regional lymphadenectomy even in the presence of hepatic metastasis. There is no role of chemotherapy in well- differentiated JI-NET. Combination chemotherapy-capecitabine and temozolomide for metastatic poorly differentiated JI-NET[21], and combination of cisplatin or carboplatin and etoposide for JI-NET[84] have been found to be helpful. Hepatic metastasis can be treated by octreotide therapy, transarterial emboli-

zation with microparticles (bland embolization), TACE, radiotherapy (peptide receptor radionucleotide therapy) with yttrium 90-DOTA-lanreotide or 177-lutetium-DOTA-lanreotide, and radiofrequency ablation.

Cytoreduction surgery(CRS) may be used with/without total peritoneal resection and chemotherapy in SI-NETs with peritoneal carcinosis, therefore the results don't vary significantly. [37]

In about 20%-30% of cases of JI-NETs when they metastatize to the liver, patient experience the carcinoid syndrome, it occurs when bioactive amines and peptides (about 40 different types) produced by the NETs enter the systemic circulation. 90% of carcinoid syndrome have metastatic NETs to the liver except bronchopulmonary NETs, ovarian NETs and GI-NETs with extensive retroperitoneal lymph node metastasis as they can release their bioactive amines directly into the systemic circulation and do not need to be metastatic to the liver to produce carcinoid syndrome. Clinically, the syndrome is characterized by chronic flushing (occurring in 94% of patients), and/or diarrhea (occurring in 80% of patients). Other manifestations include wheezing (occurring in 10%-20% of patients) due to bronchospasm, pellagra due to niacin deficiency and carcinoid heart disease (occurring in 40%-50% of patients). Flushing is due to excessive release of tachykinins (substance P, neurokinin A, neuropeptide K) and histamine. Diarrhea is mainly due to excessive secretion of serotonin which increases gastrointestinal motility and secretion[23]. Bronchospasm is histamine-induced but carcinoid wheezing should not be confused with bronchial asthma as administration of beta-2 agonist may cause severe and prolonged vasodilation. As most of the dietary tryptophan (70% instead of only 1% normally) is converted to serotonin by the NETs leading to deficiency of tryptophan necessary for niacin synthesis, niacin deficiency occurs. Carcinoid heart disease is due to histamineinduced plaque-like deposit of fibrous tissue on the endocardium and valves of right heart leading to restrictive cardiomyopathy, and tricuspid and pulmonary regurgitation with or without coexistent stenosis and ultimately right heart failure [24].

Diagnosis of carcinoid syndrome is supported by elevated 24 h urinary 5 hydroxylindoleacetic acid (5-HIAA) which has a sensitivity and specificity of > 90% and elevated serum CgA which is released from well-differentiated NETs. The level of 5-HIAA reflects tumor burden and decreases with treatment response. There are various food and medications that can affect 5-HIAA level. Tryptophan rich food (like banana, plum, pineapple, kiwi, eggplant, avocado, peanut, walnut, pecan, oats, beans, lentils, seeds, tofu, cheese, eggs, fish, chicken, turkey and red meat) can yield a false positive result. Acetaminophen, nicotine, caffeine, guaifenesin, phenobarbital and methamphetamine can increase 5-HIAA levels. Alcohol, aspirin, imipramine, methyldopa, levodopa, monoamine oxidase inhibitors, corticotropin and INH can decrease 5-HIAA level. Patients should be advised to stop taking these medications 24h before and during urine collection.

Treatment options for carcinoid syndrome: (1) Long-acting somatostatin analog: Octreotide LAR 20 mg to 30 mgor lanreotide 60 mg to 120 mg intramuscularly every 4 wk[25]. Flushing and diarrhea are improved in 80% of patients by this therapy[26]. If the symptoms are not adequately controlled, Octreotide LAR or lanreotide can be given every 3 wk instead of every 4 wk; (2) Hepatic re-

section: considered in neuroendocrine liver metastasis when 90% or more of the disease bulk can be resected keeping adequate functional hepatic reserve[27]. Prophylactic octreotide therapy should be given preoperatively and intra-operatively to prevent carcinoid crisis; and (3) Hepatic artery bland embolization or chemoembolization can reduce flushing and diarrhea in carcinoid syndrome [28]. Prophylactic octreotide therapy should be given pre and postembolization to prevent carcinoid crisis.

In refractory symptomatic cases, other treatment options include: (1) Telotristat ethyl (tryptophan hydroxylase inhibitor) 250 mg by mouth 3 times day in combination with somatostatin analog therapy can control diarrhea in patients with carcinoid syndrome not responding to somatostatin analog therapy[29]; (2) Interferon-alpha: 3 to 5millions up to 3 to 5 times per week can improve the symptoms of carcinoid syndrome (flushing, diarrhea) in 40% to 50% of cases refractory to somatostatin analog therapy[30,31]. Interferon has multiple antitumor effects as it can stimulate T cells, induce cell cycle arrest and inhibit angiogenesis. But Interferon is rarely used because of its tremendous side effects; (3) Everolimus - a mammalian target of rapamycin inhibitor in combination with octreotide can improve flushing and diarrhea in patients with carcinoid syndrome refractory to octreotide therapy [32]; (4) 177-Lutetium dotatate (peptide receptor radioligand therapy): Can improve diarrhea in patients with carcinoid syndrome refractory to octreotide[33]; and (5) Anti-diarrheal agents – lomotil, loperamide and cholestyramine are good adjunctive therapies to control diarrhea.

The 5-year survival rate of JI-NET is 60% in non-metastatic disease but becomes 18% when metastatic to the liver.

In 2007, the European Neuroendocrine Tumor Society (ENETS) presented a consensus document about PC in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The document concluded that data on PC in GEP-NETs are scarce and it also proposed that the Lyon prognostic index may be used to retrospectively classify PC. [34,35,36]

The Lyon prognostic index comprises 4 stages, ranging from small, localized nodules, to larger and diffusely spread nodules in the peritoneum (Table I). The Lyon prognosis index results being put to indicate the overall survival.

Table I. Lyon prognostic index to classify the extent of PC

Stage 0	No macroscopic disease
Stage I	Localized nodules in one part of the abdomen <5 mm in size
Stage II	Diffuse nodules spread to the whole abdomen <5 mm in size
Stage III	Localized or diffuse nodules 5–20 mm in size
Stage IV	Localized or diffuse nodules or masses >20 mm in size

PC, Peritoneal carcinomatosis.

According to the Lyon prognosis, our patient was diagnosed on stage I PC, and as stated earlier, no liver metastase has been noted.

According to Das S. and al, the presence of PC at the time of the diagnosis reduces the overall survival (OS) by 4 years on average, with an 8 years OS in the presence of PC vs 12years OS in the absence of PC.

PC causes significant morbidity and mortality in SI-NET patients and as such, cytoreductive therapies such as radionuclide therapy with 177 lutetium-

dotatate and capecitabine plus temozolomide are now available for SI-NET patients.

CONCLUSION:

The SI-NETs are rare but their incidence and prevalence have been increasing. Patients tend to be asymptomatic but can sometimes present with symptoms from mechanical causes or causes fibrosis along with GI bleeding. Histologically, diagnosis is confirmed by positive immunohistochemical staining. Treatment and prognosis depend on the grade and stage of the tumor. Immunotherapy will serve as a future treatment modality. Patients should be kept under surveillance program following treatment of SI-NETs.

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