CLINICAL CASE

SMALL INTESTINE NEUROENDOCRINE ADENOCARCINOMA WITH MULTIPLE LIVER METASTASES AND ECTOPIC BENIGN PANCREATIC TUMOR IN A 24-YEAR-OLD WOMAN

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Abstract

Neuroendocrine tumors represent a varied group of neoplasms which have the potential to produce and secrete a wide range of hormones along with other vasoactive substances. The care of these patients involves several specialties including: surgery, oncology, radiotherapy, interventional radiology and nuclear oncology. Despite this large number of options there is currently no consensus on the optimal sequence of these treatment resources for metastatic patients. We present the case of a 24 year women who was diagnosed with a gastric tumor (could not be biopsied) by imagistics and liver metastasis. A Pean resection with metastasectomy was done. The histopathology study revealed that the gastric tumor was benign ectopic pancreas tissue and the metastases were actually of neuroendocrine origin. A somatostatin receptor scintigraphy (OctreoScan) was done which revealed the primary tumor in the ileal mesentery which was resected in a secondary intervention. The patient was started on long acting sandostatin with no recurrence.

Keywords*: neuroendocrine tumors, differential diagnosis, multidisciplinary team*

Introduction

Neuroendocrine tumors (NET's) represent a varied group of neoplasms characterized by low growth rate, which have the potential to produce and secrete a wide range of hormones along with other vasoactive substances giving birth to a variety of clinical syndromes. NET's tumors may develop either in a sporadic form or have an inherited component which can lead to a phenotypic expression such as Von Hippel Lindau syndrome, multiple endocrine neoplasms or NEM and type 1 neurofibromatosis [1, 2]. The gastrointestinal tract is the most common location of NET's where they occur in approximately 70% of cases, and represent 2% of all gastrointestinal tract tumors [3]. If such a tumor is identified, one should strive to identify associated lesions/tumors. Modlin et al. by analyzing over 13.000 carcinoid tumors localized in the small intestine identified that up to 29% of individuals developed non-carcinogenic metachronous neoplasms in other locations [4]. This association may be due to the production of trophic substances by carcinoid tumors that may have a potentially mitogenic effect on other cell types [4].

In 2010, the World Health Organization classified neuroendocrine tumors in three

categories (G1, G2, G3) based on the degree of histopathological differentiation, on the proliferation index (Ki-67), on neuroendocrine markers (such as chromogranin A and synaptophysin) on hormonal behavior, on tumor size and on direct invasion and distant metastases [5]. These classifications are useful in predicting postoperative prognosis as well as postoperative relapse [6]. Resections with curative intent should be the elective treatment for these tumors that grow slow and postoperative monitoring should be extended to a period of up to 10 years [7, 8, 9].

Liver metastases can develop in 50-95% of cases and 80% of patients with severe hepatic impairment die within 5 years of diagnosis [10, 11]. Surgical resection is supported by good long-term evolution and large retrospective studies but this option remains valid for a small number of metastatic patients - 10% [12, 13]. Cytoreductive surgery for liver metastases is indicated to reduce the level of circulating hormones and to improve clinical symptoms and prognosis. Due to the indolent evolution of these tumors, they are frequently diagnosed in advanced stages when the metastases become the only clinical manifestation. These advanced stages involve a number of clinical challenges in which few physicians have experience. A recent epidemiological study on the diagnosis and treatment of NET's which included approximately 20,000 patients indicated that approximately 11% - 14% of subjects were diagnosed with metastatic liver disease without being able to identify the primary tumor location [14]. Care of patients with NET's and liver metastases remains a problem that is still debated. It involves multidisciplinary teams comprised of: surgery, oncology, radiotherapy, interventional radiology and nuclear oncology. Despite this large number of options, there is currently no consensus on the optimal sequence of these treatments/investigations for metastatic patients.

The present paper intents to highlight the challenges of diagnosis and the treatment options available in a metastatic neuroendocrine carcinoma of the small intestine.

Case report

We present the case of a 24 years old female who presented to our clinic for left quadrant pain with irradiation to the epigastrium and weight loss with no relevant past medical history. Physical examinations showed stable vital signs, no superficial lymph nodes were palpable throughout the body, no significant abnormalities at cardiopulmonary auscultation, soft abdomen without tenderness, no palpable liver or spleen below ribs, normal bowel sounds, and negative digital rectal examination findings. The laboratory evaluations, routine blood test, blood biochemistry, coagulation functions including liver tests and blood levels of tumor markers such as alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were negative. Hepatitis indices were negative, liver and renal functions were normal. An upper gastrointestinal endoscopy was done which showed a gastric mass located on the posterior wall with central blood supply at Doppler endoscopic ultrasonography which was covered by normal mucosa. Do to the depth of the lesion a fine needle biopsy could not be retrieved.

A computer tomography with contrast was done which confirmed the presence of a gastric mass that measured 5/4 cm and an intrahepatic heterogeneous lesion of 1/2cm which exhibited significant contrast enhancement during the arterial and portal phases and contrast washout with peripheral enhancement during the delayed phases localized in the 5-th liver segment.

The decision to operate was undertaken. A Pean resection was done with preservation of the pylorus for what was thought to be the primary lesion. During the intraoperative ultrasonography evaluation, a secondary liver metastases was identified in the 4-th segment which measured 1/2 cm so metastasectomy was decided upon with resection of both lesions (Figure 1, Figure 2).

The postoperative evolution was uneventful and the patient was discharged on day 5. The final histopathology study and immunohistochemistry confirmed the diagnosis of benign ectopic pancreas tissue in the stomach while the liver metastases were of intestinal

neuroendocrine origin. Margins of the resected liver metastases were reported as positive (R1). Immunohistochemistry confirmed the following: CD-X2 - diffuse positive in the tumoral cells, glucagon = negative in the tumor, gastrin = negative in the tumor, somatostatin = negative in the tumor, TIF1 = negative in the tumor, SATB2 = positive focal, Cadherin 17 = negative. The proliferation marker Ki-67 was 10%. The WHO classification was as G2 grade (Figure 3).

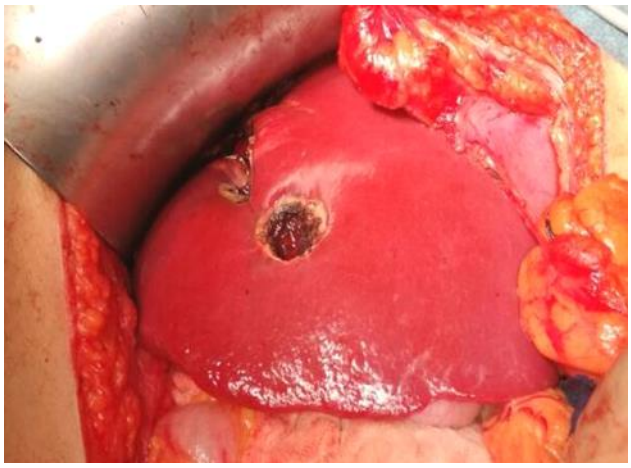

Figure 1 – Intraoperative aspect of the liver after the resection of the two metastases

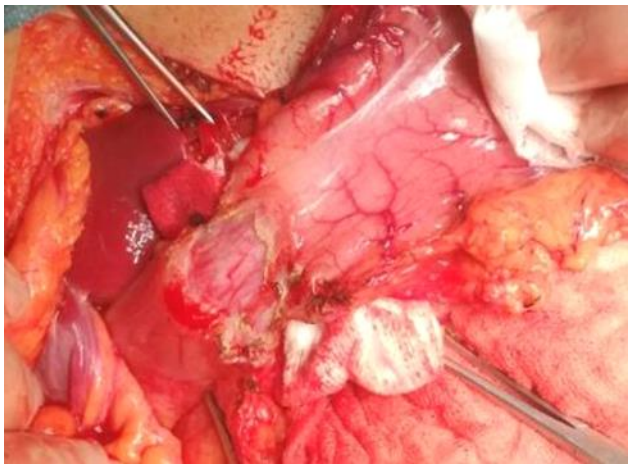

Figure 2 – Intraoperative aspect of the stomach during the Pean resection

Figure 3 – Histopathology, 4x magnification which shows Ki-67 at 10%

We tested chromogranin A (CgA) blood levels which were elevated (177 ng/ml; normal range up to 100ng/ml). The 5-hydroxyindoleacetic acid urine test was within normal value ranges. No clinical signs of carcinoid syndrome were reported.

A video-endoscopy capsule was administered to try to determine the location of the tumor in the small intestine but it could not pass through the recent gastric anastomosis. A whole body OCTREO-SCAN (99mTc-TEKTROTYD) with computer tomography hybrid imaging was obtained which confirmed the existence of a tumor located at the level of the small intestine that measured 2/3 cm and no other lesions (Figure 4).

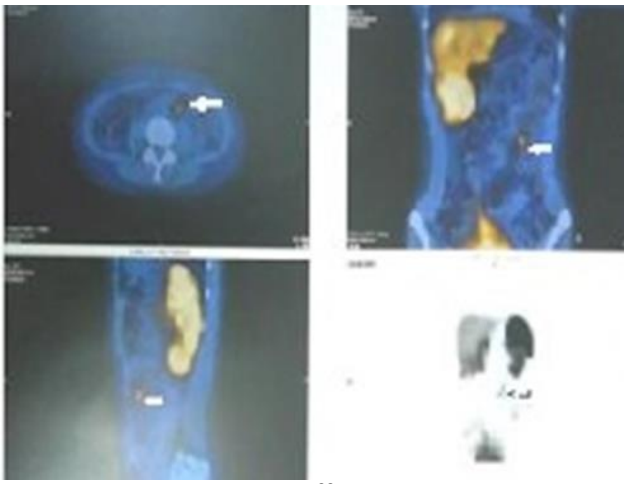

Figure 4 – Octreo-Scan (^{99}mTc-Tektrotyd) which shows the primary NET at the level of the mesentery (arrow)

The patient underwent a second intervention, intraoperative exploration identified the primary lesion at the level of the ileum on the mesenteric

side with retraction on the neighboring tissue (sized about 2 × 3 cm) and several adenopathies (sized about 0.5 – 1 cm) were palpable in the surrounding mesentery (Figure 5). A segmental enterectomy with a termino-terminal anastomosis was done (Figure 6).

The postoperative evolution was uneventful. The final histopathology report with the accompanied immunohistochemistry confirmed this was the primary tumor site with the following TNM staging: pT3N2M1HEP, R0, intravascular and perineural invasion were observed. The immunohistochemical findings were: CD-X2 - diffuse positive in the tumoral cells, glucagon - negative in the tumor, gastrin - negative in the tumor, somatostatin -negative in the tumor, TIF1 negative in the tumor, SATB2 - positive focal, Cadherin 17 - negative, Ki-67 = 10%.

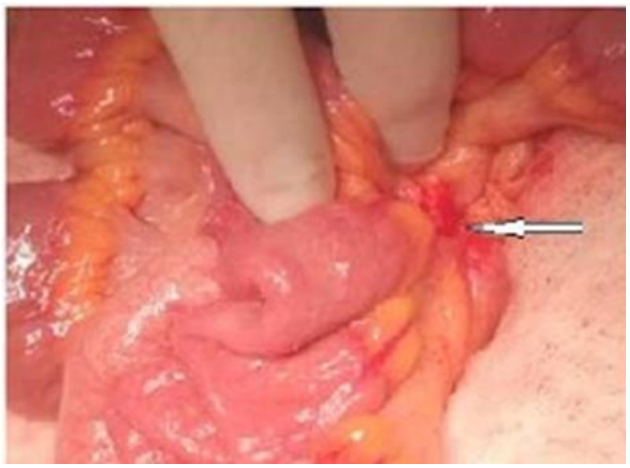

Figure 5 – Intraoperative aspect of the primary NET located in the mesentery with surrounding tissue retraction (arrow)

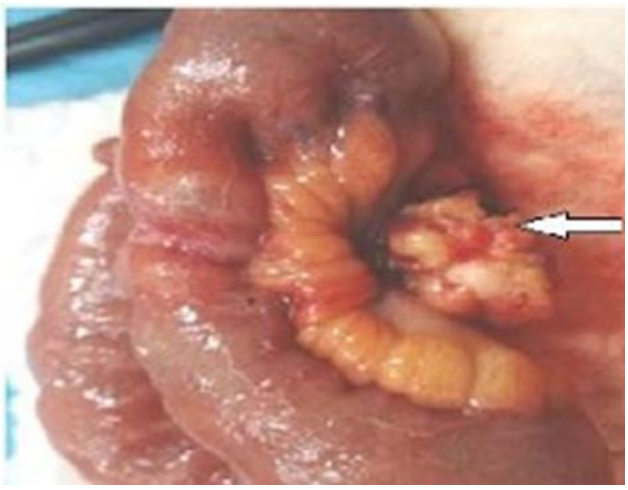

Figure 6 – Postoperative aspect of the resected specimen and tumor (arrow)

The patient was started on long acting octreotide and at 1 year revaluation was disease free.

Discussion

Pancreatic endocrine tumors (islets of pancreatic ectopic tissue or PET's) occur with an incidence of 0.4 - 1 in 100,000 people. PET's comprise about 1% of all pancreatic neoplasms, although the values quoted in the literature may reach 15% [15, 16]. Such tumors are commonly found in MEN-1 family syndromes characterized by the 3 P's (parathyroid, pituitary, and pancreas) which have an aggressive evolution and are frequently accompanied by metastases [17]. Clinically relevant pancreatic tumors are present in 30% - 50% of patients with MEN1 syndrome and almost all patients with MEN1 syndrome have small, non-functional, ectopic pancreatic tumors [15].

In contrast, carcinoid tumors are rare neoplasms but still comprise about 85% of all neuroendocrine gastrointestinal neoplasms [18]. Unlike neuroendocrine tumors that develop in the gastric, duodenal, or pancreatic organs, carcinoid tumors that originate in the midgut (ileal, jejunum) rarely associate themselves with syndromes such as MEN 1 or neurofibromatosis [19]. Yantiss et al. who analyzed multiple cases of ileal carcinoid tumors, observed that these tumors can associate multifocality by the presence of multiple small tumor nodules in other locations in the digestive tract. This phenotype is associated with a higher incidence in younger patients and with a worse prognosis. Tumor multifocality indicates a high aggressiveness of the disease regardless of its staging at diagnosis [19]. With each tumor that originates independently, the possibility of one of the lesions to produces genetic aberrations that favor the occurrence of an invasive phenotype increases, thus exhibiting a more aggressive biological behavior than that seen in carcinoid solitary tumors [19]. Up to 15-25% of all neuroendocrine tumors show a synchronous or metachronus association with other tumors of the digestive tract, these tumors have to be actively sought for diagnosis and treatment [20].

From these data we can observe that patients with carcinoid gastrointestinal neuroendocrine tumors associate multifocality through multiple tumor nodules in the intestinal mucosa which are of the same nature while patients with gastric / proximal or foregut tumors and rarely associate intestinal carcinoid tumors at distance. These lesions frequently associate themselves with tumors of the pancreas or duodenum. This conclusion cannot be applied or studied in the case presented because in addition to the gastric lesion (ectopic pancreatic cells) the patient associated a completely different type of tumor with different origin - an ileal carcinoid tumor with serotonin secretion. NET's tumors represent a substantial diagnostic and therapeutic challenge because clinical presentation is nonspecific and usually delayed when metastases are already evident, the mean diagnosis delay is ~ 5 years. Local manifestations - mass, bleeding, obstruction or perforation of the intestine - reflect invasion or tumor induced fibrosis that we have seen in the presented case. Although gastrointestinal neuroendocrine tumors can be anywhere located in the digestive tract, they are frequently found at the ileal level (17.1%) - as we have seen in the case presented. The prognosis and the cell type are influenced by location [21]. There are no environmental factors that may influence the occurrence of these tumors but they may occur sporadically (non-familial) or as family syndromes such as MEN, von Hippel-Lindau or neurofibromatosis. When the presence of this familial syndrome is suspected, consideration should be given to the existence of several primary tumors at the gastrointestinal tract level [22]. The clinical triad of carcinoid syndrome appears late in the evolution of the disease and consists of cutaneous erythema (90%), diarrhea (70%), abdominal pain (40%) but can also associate extradigestive manifestations such as carcinoid cardiac disease (40-50%) and bronchoconstriction (15%) [19]. The clinical manifestations may occur spontaneously or may be triggered by external factors such as food, stress, or alcohol, so in assessing a patient, the context in which these manifestations become apparent is important to establish a link to each other in order to facilitate the diagnosis [23, 24].

The choice to administer long acting octreotide in this patient was a difficult one to take. In the absence of carcinoid syndrome, it was discussed whether the anti-proliferative effect of this drug would benefit our patient. The first and most important argument for administration was the fact that the hepatic metastasis specimen had microscopic positive margins, so the whole intervention cannot be considered curative [25]. However, the somatostatin receptor scintigraphy did not identify any lesion in the liver postoperatively. The fact that the immunohistochemistry reported the ki67 value of 10% in both specimens, classifying this tumor as intermediate grade, was another pro argument for this therapy. The patient tolerated sandostatin very well, no toxicities were reported with this drug, so continuation of administering this drug seemed the best choice [26].

To sum up, there were several particularities of this case that made this worth presenting. The first one is the presence of ectopic pancreatic tissue in the gastric wall and the misinterpretation that it was the primary tumor. The second one was the difficult decision to administer long acting octreotide in this patient. The most important conclusion is that decisions in neuroendocrine tumors are often difficult and they always have to be taken in multidisciplinary team.

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