

LATE DIAGNOSIS OF AN END STAGE PANCREATIC ACTH-OMA; CASE REPORT AND LITERATURE REVIEW

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LATE DIAGNOSIS OF AN END STAGE PANCREATIC ACTH-OMA; CASE REPORT AND LITERATURE REVIEW (Abstract): Background: The management of digestive endocrine tumors is often challenging. These tumors are classified in two groups: pancreatic endocrine tumors (PEnT) and endocrine tumors from digestive tract. Methods: A 27 years old, woman was admitted in the First Surgical Clinic Iași for ectopic Cushing syndrome and unknown origin liver metastasis. A laparoscopic liver metastasectomy (for biopsy) and thermonecrosis of the other liver metastasis by overheated steam were performed. The histological and immune-histochemistry exams diagnosed metastasis from endocrine tumors. The biological exams revealed high levels of cortisol, ACTH and persistent hypokaliemia. Further imagery exams (CTscan, PETscan and Octreoscan) diagnosed the primary tumor in the pancreas (ACTH-oma) and other metastasis in ovaries. The patient was admitted again for upper GI hemorrhage and near-total dysphagia. The endoscopy and enteroscopy diagnosed multiples ulcers on the stomach, duodenum and jejunum, and peptic esophageal stenosis with reflux esophagitis. Other three surgical procedures have been performed: bilateral ovariectomy due to metastasis, bilateral adrenalectomy (to control the hypercortisol levels) and jejunostomy. The postoperative course was complicated by bone (vertebral) metastasis with paraplegia. The patient died after 18 months. Conclusions: PEnTs are rare tumors, and their management is always challenging. For these tumors it is necessary to recognize the clinical signs of the secreting tumors (inclusive carcinoid syndrome) and to carefully explore the patients. Unfortunately, Octreoscan and Positron Emission Tomography are not available in Romania. Aggressive surgical treatment - excision of the primary lesion and multimodality approach of the liver metastasis (resection, ablative techniques, chemotherapy) - is indicated for PEnTs, even in advanced stages. Liver transplant for non-resectable liver metastasis from PEnTs, it is also recommended in selected patients (after resection of the primary tumor).

KEY WORDS: PANCREATIC ENDOCRINE TUMORS, LIVER, METASTASIS, LAPAROSCOPY, THERMONECROSIS

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BACKGROUND

Neuroendocrine tumors are rare, slow-growing tumors derived from neural crest cells. Common types of neuroendocrine tumors include carcinoids, pancreatic endocrine tumors (PEnT), melanomas, pheochromocytomas and medullary thyroid carcinomas. These tumors are classically considered as part of APUD (Amine Precursor Uptake and Decarboxylation) system, defined by Capella as „a network of nerves and endocrine cells with a common phenotype characterized by simultaneous expression of general

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protein markers of neuroendocrine cells and hormonal product specific to each cell type” [1,2].

The management of PEnT is often challenging. These tumors are usually classified in functioning (e.g. insulinoma, gastrinoma etc.) and non-functioning tumors, benignant, border-line or malignant. PEnTs can be associated with other endocrine tumors in multiple endocrine syndromes: MEN, Recklinghausen disease, Hippel-Lindau disease. Usually, malignant PEnTs have a better survival prognosis than pancreatic adenocarcinoma. However, these tumors frequently metastasize to regional lymph nodes, bones and liver. In addition, neuroendocrine hepatic metastases can lead to incapacitating symptoms and can also decrease long-term survival.

CASE PRESENTATION

We present a case with synchronous liver metastasis from a PenTs.

A 27 years old woman was admitted in First Surgical Clinic Iași, for the first time, in September 2006 for pain in the right abdominal quadrant, flush, amenorrhea, Cushing syndrome. Ultrasound exam revealed multiple hypoechoogenous tumors disseminated in the liver in segments VI, VII and III with different dimensions (30-45 mm) (Fig. 1).

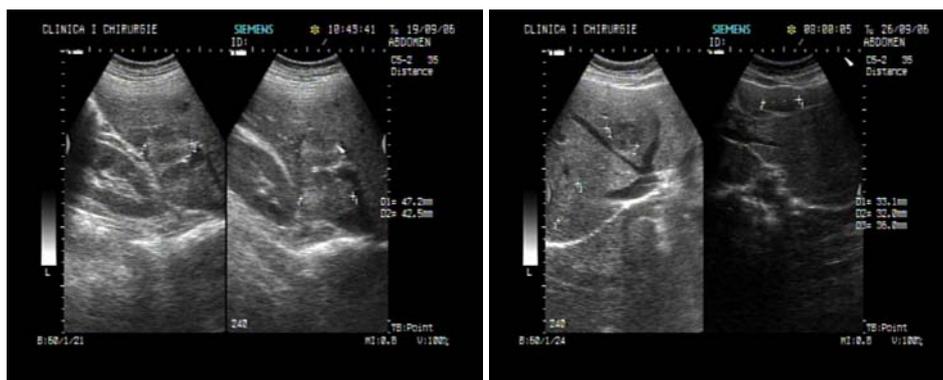


Fig. 1 Ultrasound exam

Multiple hypoechoogenous tumors disseminated in the liver in segments VI, VII and III with different dimensions (30-45 mm).

CT scan also confirmed the number and sites of liver tumors, but no other abdominal tumors were found and pancreas was described as “normal”.

We performed a diagnosis laparoscopy associated with non-anatomic metastasectomy using a LigaSure[®] device (for histological exam); for the other liver tumors thermonecrosis with overheated steam has been performed (Fig. 2).

Histopathological exam revealed metastasis from a malignant endocrine tumor confirmed by immunohistochemistry (the tumour was chromogranin positive, neuron specific enolase positive and citokeratine positive (Fig. 3).

The diagnosis was hepatic metastasis from a malignant endocrine tumors and ectopic (neoplastic) Cushing syndrome.

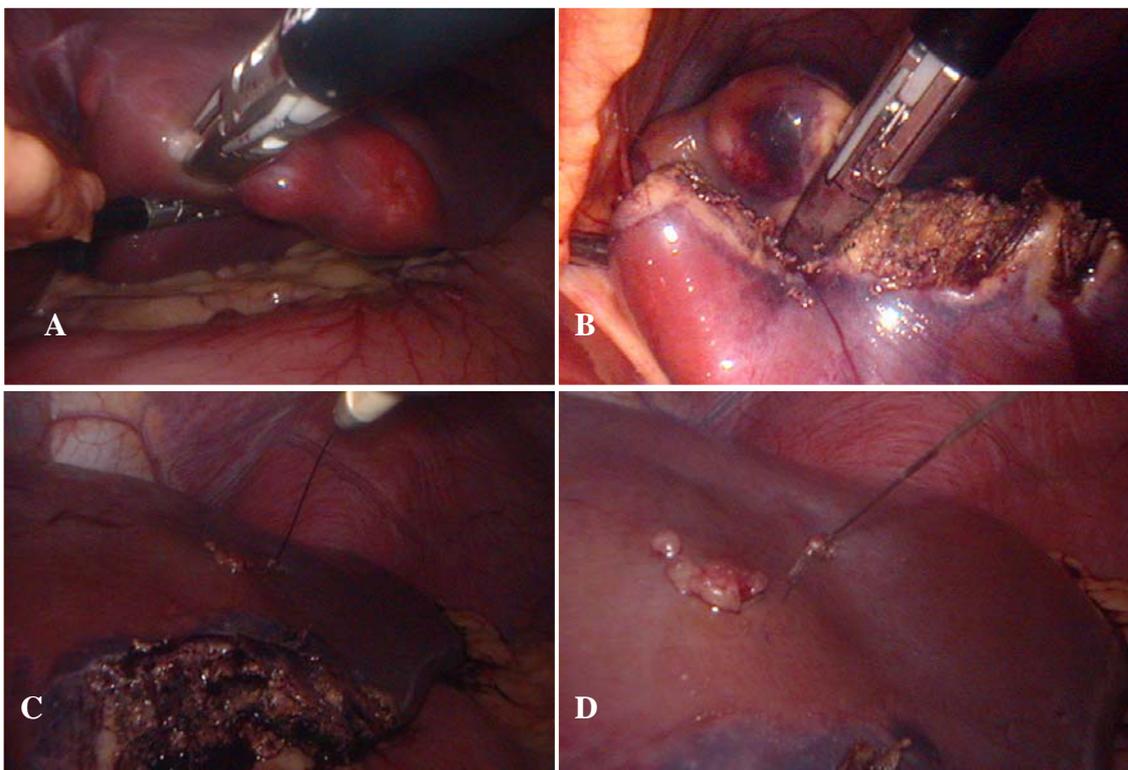


Fig. 2 Intraoperative view

A,B Metastasectomy, using LigaSure
C,D Thermonecrosis with overheated steam

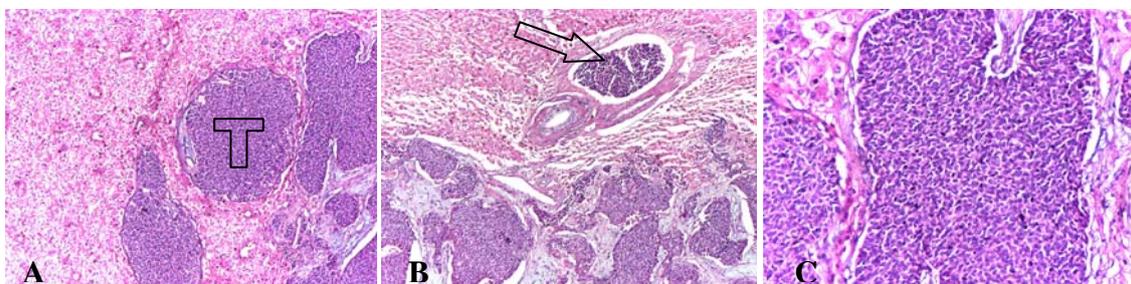


Fig. 3 Histopathological exam - metastasis of malignant endocrine tumor

A. tumour, HE, 4x; B. tumoral embolus in a portal vein HE, 10x;
C. detailed view of the tumor - monoclonal growth HE, 10x.

After a few weeks, she was admitted in emergency at the Gastroenterological Institute Iași, for acute pain in the upper abdominal region, Cushing syndrome, haematemesis and melena. The lab tests revealed hyperglycemia and hypokaliemia. A enteroscopy using videocapsule has been performed; multiple ulcers located on the duodenum and jejunal loop, some of them with diffuse bleeding, were diagnosed. She was treated with Octreotide, insulin and H⁺ pump blockers. She was then admitted at the Endocrinological Clinic to complete the tests (November 2006). The lab tests revealed a high cortisol levels – 754.56 ng/mL (60-285), a low kalium levels – 2.8 mEq/L and a high ACTH levels – 1141.82 pg/mL. The treatment was completed with ketoconazole and then, with Metirapone, obtaining the decreasing of cortisol plasma levels. Also, a new CT scan was performed and diagnose a pancreatic tumor (3x2.5x1

cm), situated in the pancreatic neck. A PET scan performed in Lyon (France) also revealed large adrenal glands with intense absorption of the marker, nodule of 7 cm in 6-th liver segment and other 2 nodules in 7-th segment, small pancreatic tumor (Fig. 4).

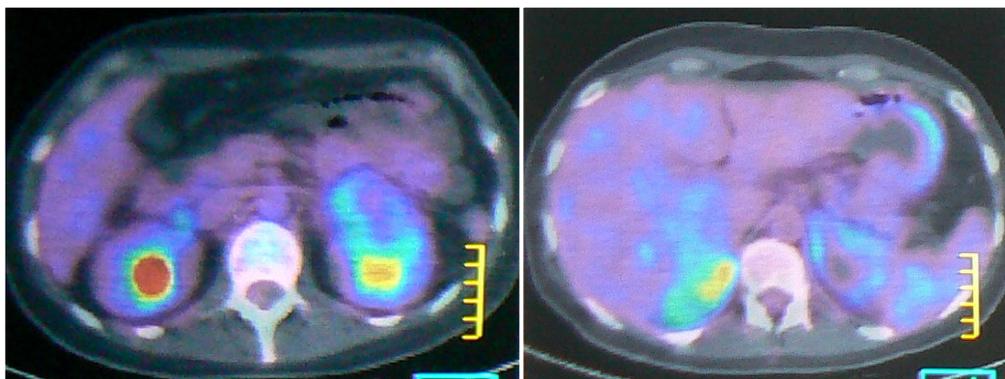


Fig. 4 PET scan

Large adrenal glands with intense absorption of the marker; nodule of 7 cm in 6-th liver segment

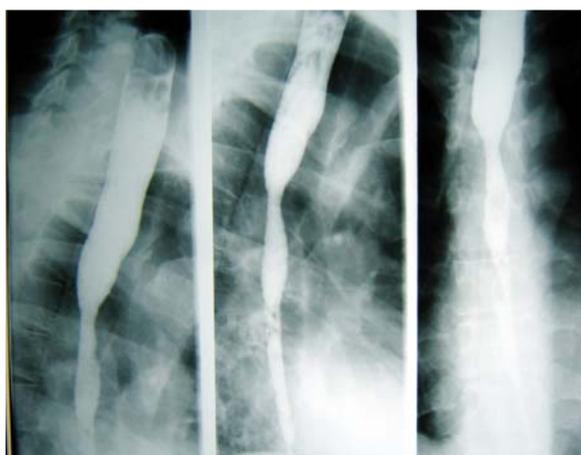


Fig. 5 Barium meal

Stenosis of the esophagus

Octreoscan with Indium 111-Pantetide diagnosed 5 nodules in the liver, one nodule in the pancreas (body), and a right pelvic nodule into the right ovary.

In evolution the patient present a new episode of upper digestive bleeding and dysphagia. A upper GI tract endoscopy diagnosed acute esophagitis, esophageal stenosis and Barrett esophagus, confirmed by barium meal (Fig. 5).

Another three operations have been performed: bilateral ovariectomy (Fig. 6), jejunostomy and bilateral adrenalectomy for a better control of cortisol secretion and to exclude a metastasis. Histopathological exam revealed in resected ovary a metastasis of endocrine tumor (Fig. 6) and hyperplasia in adrenal gland.

Complete diagnosis of this patient is: Pancreatic ACTH-oma with liver and ovarian metastasis; Ectopic Cushing syndrome; Peptic esophagitis, Barrett esophagus; Esophageal peptic stenosis; Upper GI tract bleeding.

She was proposed for Yttrium Octreotide radiotherapy ... BUT bone (vertebral) metastasis with paraplegia complicated the course and she died after 18 months from the diagnosis of the liver metastasis!

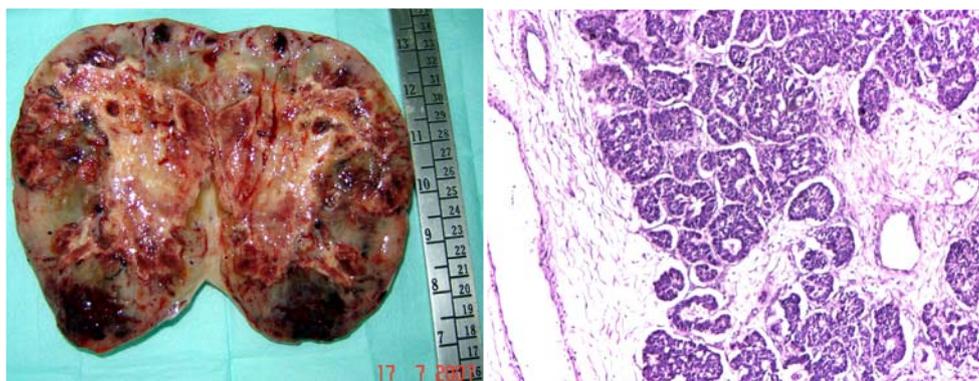


Fig. 6 Histopathological exam
Resected ovary - metastasis of endocrine tumor (HE 4x):
macroscopic (left) and microscopic (right) views

DISSCUSIONS

The estimated incidence of digestive endocrine tumors is 1.5/100,000 [1]. The small bowel was the most common site (38.9% of cases), preceding large bowel localisations (27.1%) and pancreatic localisations (20.5%) [2]. The other sites were much less frequent: stomach (6.1%), gallbladder (2.2%), liver (1.8%), oesophagus (0.4%), peritoneum (0.4%), and digestive localisation not otherwise stated (2.6%) [2]. Appendix malignant endocrine tumors represented 8.1% of large bowel localisations [2].

These tumors are more frequent in men and the age specific incidence rates of malignant digestive endocrine tumors in men and women [1] are 60-80 years.

Most malignant digestive endocrine tumors were already at a late stage at the time of diagnosis. In this way, only 26.6% did not extend beyond the organ, 20.1% had lymph node metastases, and 53.3% had visceral metastases or were unresectable. Among the metastatic cases, the proportion of patients with hepatic metastases was 59.7% [2]. The other main metastatic sites were peritoneal carcinosis (23.2% of cases), lung (3.7%), skin (2.4%), bone (1.2%), and other sites (9.7%) [2].

As we previous noted, PEnTs can be classified in secreting or non-secreting, unique or multiples, associated with MEN or alone, tumoral or diffuse [3]. All these PEnTs are possible to be benignant, border-line, malignant [3]. The diagnosis algorithm for these tumors include: recognition of the clinical syndrome (especially for the functioning PEnT), laboratory tests to identify the hormones or the biochemical parameters influenced by the hormones, topographic diagnosis and histological diagnosis.

Even the clinical signs of the PEnTs are for only one type of hormone these tumors usually have a multiple endocrine secretion: 52% form secreting PEnTs and 50% from non-secreting PEnTs produce hormones without any clinical sign [3]. In a series, Heitz cited by Jensen and Norton [4] describe that 33% from insulinomas excrete glucagone, 100% from glucagonomas excrete insuline, 22% from insulinomas +

glucagonomas excrete somatostatine, 35% from insulinomas + glucagonomas excrete PP and 5% from insulinomas + glucagonomas excrete gastrine.

Ectopic ACTH syndrome (EAS) occurs in about 5–10% of all patients with ACTH-dependent hypercortisolism, and 64% of affected patients presented hypokalemia, rarely seen in patients with Cushing's disease and highly suggestive of EAS [5]. The intense hypokalemia in EAS can be explained by the mineralocorticoid effect of cortisol, which in EAS tends to be higher than in Cushing's disease and because the activity of 11-hydroxysteroid dehydrogenase type 2, for reasons yet to be clarified, is decreased in patients with ectopic secretion of ACTH [6].

Regarding the topographic diagnosis, CT, MRI, and scintigraphy with radioisotopes can be used [3,4]. In Salgado series [6], CT was positive in 15 out of 21 cases and MRI in 8 out of 17 cases and the latter was unable to identify any case not identified by CT. Both scans failed to localize the tumor in 5 out of 25 (20%) of our patients [6]. Positron emission tomography has been used in oncology and whole body scintigraphy with fluorodeoxyglucose (FDG) is presently the most broadly used method to identify occult tumors, although it has little accuracy [8]. Scintigraphy with somatostatin analog (111 In-pentetreotide scintigraphy) identified some occult tumors not identified by conventional CT or MRI scans [4,9].

During the localization diagnosis period, even in occult cases, given the severity of the case, clinical treatment was necessary with cortisol synthesis blockers, ketoconazole being the most often used due to its efficacy [7]. After the localization of ACTH-secreting tumor source was accomplished, surgical removal of these lesions is the treatment of choice [6]. Another therapeutic alternative was the use of octreotide, as ectopic ACTH-producing tumors can express receptors for somatostatin and thus, respond to the administration of this polypeptide [10].

During the management of the presented case, the topographic diagnosis of the primary tumor was delayed until the imagery tests performed in France (helical CT scan, PET and Octreoscan). In this time, the patient was treated with ketoconazole and somatostatin associated with H⁺ pump blockers. Unfortunately the topographic diagnosis of the primary tumor was established too late, after the diagnosis of extrahepatic metastasis.

In recent years, aggressive treatment of hepatic metastasis from neuroendocrine tumors has been shown to relieve symptoms [11,12]. With improved safety of liver resection and advances in technology, treatment of liver tumors has evolved into a more aggressive, multimodality approach, incorporating surgery, ablative techniques, and transarterial chemoembolization (TACE). Resection, ablation, and TACE for neuroendocrine hepatic metastases have been shown to be an extremely effective treatment of the symptoms related to the metastases [11,12]. We must note that the aggressive treatment of the liver metastasis from PEnTs is usefully only after the removal of the primary tumor. In these conditions the total hepatectomy and liver transplant could also be performed [13-15].

We reviewed the medical literature to find other cases of ACTH-oma.

Oberg KC et al [16] describe a case of a 41-year-old woman presented with hirsutism, a pelvic mass, and Cushing's syndrome. Imaging studies revealed bilateral ovarian masses and a solid and cystic mass within the pancreas. Partial pancreatectomy, bilateral oophorectomy, and excision of several peritoneal tumor nodules were performed. Pathological examination revealed a neuroendocrine islet cell tumor of the pancreas with bilateral ovarian metastases. The tumor was immunoreactive for ACTH,

chromogranin, neuron-specific enolase, and keratin. The patient received postoperative chemotherapy and has been disease-free for 6 years.

In another study, Amikura K et al [17] report 12 cases of ACTH-oma. From these, 83% had liver metastases at the time of diagnosis, like in our case. The management of the patients was different: 3 patients underwent distal pancreatectomy combined with hepatic resection; one patient underwent laparoscopic enucleation of a tumor from the pancreatic tail; 8 of 12 patients underwent bilateral adrenalectomy to control symptoms of Cushing's syndrome, including 3 patients who underwent concurrent distal pancreatectomy and hepatic resection.

Doppman JL [18] also report a series of 11 cases and his conclusion was “When ectopic ACTH production is caused by an islet cell tumor, the tumor is large and malignant and has usually metastasized to the liver by the time when Cushing syndrome is diagnosed”. The same author studied the hormones secretion of ACTH-omas and discovered a simultaneous secretion of gastrin in 8 from 11 cases [18]. In this way we think that our case could be also associated with hypergastrinemia, because of the severe esophagitis accompanied with Barrett esophagus and upper GI tract bleeding; unfortunately the gastrin wasn't measured.

The octreotide-targeted radiotherapy is the last choice for the last stage of malignant PEnTs [19,20].

Classically survival in patients with pancreatic neuroendocrine tumors is significantly better than pancreatic adenocarcinomas [3]. However, survival and quality of life are diminished in patients with neuroendocrine hepatic metastases, as in our case. Several groups have reported improved 5-year survival of 50% to 70% with R0 resection (primary pancreatic tumor resection associated with liver resection of the metastasis) [12].

CONCLUSIONS

PEnTs are rare tumors, and their management is always challenging. For these tumors it is necessary to recognize the clinical signs of the secreting tumors (inclusive carcinoid syndrome) and to carefully explore the patients. Unfortunately, Octreoscan and Positron Emission Tomography are not available in Romania.

Aggressive surgical treatment - excision of the primary lesion and multimodality approach of the liver metastasis (resection, ablative techniques, chemotherapy) - is indicated for PEnTs, even in advanced stages. Liver transplant for non-resectable liver metastasis from PEnTs, it is also recommended in selected patients (after resection of the primary tumor).

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Conflicts of interest

The authors have not conflict of interest in relation to this article.

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