



## LIVER METASTASIS WITH UNKNOWN PRIMARY ORIGIN

Constantin Alina<sup>1\*</sup>, Plotogea Oana<sup>1\*</sup>, Ilie Mădălina<sup>1\*</sup>, Constantinescu G.<sup>1\*</sup>, Macovei R.<sup>1\*</sup>,  
Stănculescu Elena-Luminița<sup>1\*</sup>, Diaconu Camelia<sup>1\*</sup>, Popa B.<sup>1\*</sup>

<sup>1</sup> Clinical Emergency Hospital Bucharest, Romania

\* all authors equally contributed to this work

**Abstract.** Pancreatic neuroendocrine tumors (pNETs) are usually slow growing tumors and their malignant potential is often underestimated. Most of them are malignant at diagnosis (50-80%, except for insulinoma) and have an aggressive course with liver metastases as well as other sites. These heterogeneous neoplasms are divided into two groups: functioning tumors, which secrete a variety of peptide hormones and non-functioning tumors (up to 90% of pNETs), which often show metastases at the time of diagnosis. We report a case of 44 years old male, non-smoker, recently diagnosed with type II diabetes mellitus, admitted for fatigue, loss of appetite and severe weight loss. Laboratory tests showed discrete inflammatory syndrome, while chest X-ray was normal. Abdominal ultrasound revealed hyperechoic lesions in both liver lobes. Tumor markers (carcinoembryonic antigen, alpha-fetoprotein and CA19-9) were elevated. The upper endoscopy and colonoscopy described no lesions. Abdominal computed tomography (CT) revealed hepatic metastases with unknown primary site, while contrast-enhanced ultrasound (CEUS) highlighted a hypoechoic hypervascular mass in the pancreatic tail. Chromogranin A, urinary 5-hydroxyindoleacetic acid, serotonin and neuron-specific enolase were normal. Ultrasound-Guided Liver Biopsy from the hepatic metastases was performed in order to establish the diagnosis. The histopathological and immunohistochemical results were decisive. Poorly differentiated pancreas neuroendocrine tumor (G3) was the diagnosis supported by the Ki67 index > 20 %.The patient was referred to medical oncology.

**Keywords:** liver metastasis, pancreatic neuroendocrine tumors, ultrasound-guided liver biopsy

### Introduction

Pancreatic neuroendocrine tumors (pNETs) are relatively rare representing approximately 2% of all pancreatic neoplasms, having an incidence and prevalence that have increased substantially [1]. Their clinical incidence is reported to be of 1-5 new cases/100,000 population per year with a prevalence of 10/100,000 population[2]. These heterogeneous neoplasms can be classified in those associated with a functional syndrome and those that are not associated with a functional syndrome. Those associated with a functional syndrome secrete a variety of peptide hormones (insulin, gastrin, glucagon, vasoactive intestinal peptide, somatostatin or combination of them). Non-functioning tumors may also secrete a number of other substances, for example: chromogranins, neuron-specific enolase,

subunits of human chorionic gonadotropin, neurotensin, and grehlin, although, by definition, nonfunctioning pancreatic NET do not secrete or do not lead to a clinical syndrome. Non-functioning pancreatic tumors often show metastases at the time of diagnosis, most of them being liver metastases; up to 90% of pNETs are non-functioning [3, 4].



Fig.1. Ultrasound image of liver with multiple hypoechoic masses

### Mădălina Ilie

8 Calea Floreasca, 1<sup>st</sup> District, Bucharest, Romania  
e-mail: m\_ilie2001@yahoo.com

## Case Report

We present the case of a 44 years old male patient, non-smoker, recently diagnosed with type 2 diabetes mellitus, who was admitted to our hospital for fatigue, appetite loss and severe weight loss. He denied alcohol consumption. The clinical exam did not reveal any abnormalities, except for a low body mass index. Laboratory tests showed only a discrete inflammatory syndrome, while chest X-ray was normal. We performed an abdominal ultrasound which revealed multiple hyperechoic masses in both liver lobes (Figure 1)

Following ultrasound, we decided to test digestive tumor markers - carcinoembryonic antigen, alpha-fetoprotein and CA19-9 which were elevated. Subsequently, we performed an upper endoscopy and colonoscopy, both showing no lesions. Our suspicion of liver metastases was then confirmed by computed tomography (CT) which revealed hepatic metastases (Figure 2), but without identifying the primary site. For a better description of the masses, we decided to repeat the ultrasound using SonoVue – a contrast substance. This time, the contrast enhanced ultrasound (CEUS) not only highlighted the metastases, but more important it revealed a hypoechoic hypervascular mass in the pancreatic tail (Figure 3).



Fig.2. CT image of hepatic metastases masses



Fig.3. CEUS image of hypoechoic hypervascular mass in the pancreatic tail

In order to have a precise diagnosis we performed an ultrasound-guided biopsy from the liver masses (Figure 4). The histopathological and immunohistochemical results were decisive and the final diagnosis was poorly differentiated pancreas neuroendocrine tumor (G3), supported by the Ki67 index which was positive in more than 20% of tumoral cells. Biochemical markers showed normal levels of Chromogranin A (CgA), urinary 5-hydroxyindoleacetic acid, serotonin and neuron-specific enolase. The patient was referred to medical oncology.

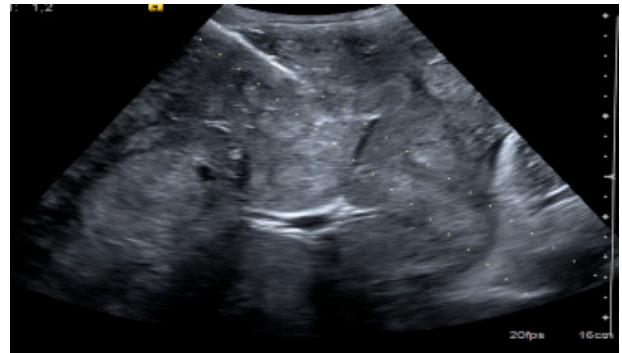


Fig.4. Ultrasound-Guided Liver Biopsy

## Discussions

As a consequence of the long delay between the onset of symptoms and the final diagnosis, many patients have advanced disease at the time of diagnosis. 32% up to 73 % of pNETs are metastatic at diagnosis. Nonfunctioning pNETs present with non-specific signs and symptoms like abdominal pain, weight loss, anorexia and nausea [5]. Our patient presented only with fatigue, appetite loss and weight loss, symptoms which might have occur in a variety of catabolic diseases.

Imaging techniques [i.e., ultrasound or contrast-enhanced computed tomography (CT), magnetic resonance (MRI) or contrast-enhanced ultrasound (CEUS)] are necessary to detect both the primary tumor and metastases. CT scan is usually the first imagistic method used for evaluating pNETs, with great accuracy; however, sensitivity is decreased for tumors smaller than 2 cm in diameter [6]. These small tumors can often appear as vascular, hypodense or cystic lesions.

Endoscopic ultrasonography (EUS) is considered highly accurate for detecting primary pancreatic NETs with high sensitivity (82%) and specificity (95%), and it can detect lesions as small as 2 to 3 mm in diameter (6). One report showed that EUS had higher sensitivity than helical, contrast-enhanced CT scan (92% versus 63%) [6], having the possibility to perform fine-needle aspiration (FNA) that provides a non-operative histologic diagnosis of pNETs. Another benefit of EUS is the capability to use elastography, which is a method for real-time evaluation of tissue stiffness. The disadvantages of this method are represented by cost and availability.

In functioning neuroendocrine tumors, somatostatin receptor scintigraphy (SRS/Octreoscan) is considered the gold-standard to detect metastases,

including extrahepatic ones, although there are studies which show that positron emission tomography (PET) using <sup>68</sup>Ga appears to be more sensitive, particularly in detecting small lesions.

Biochemical markers including CgA, pancreatic polypeptide and specific hormones depending on clinical presentation should be performed in all patients at the diagnosis and during follow-up [7,8].

Prognostic factors include histological grading, tumor differentiation and tumor staging. According to the recent World Health Organization (WHO) 2010 classification, three classes of tumors are identified (G1, G2, and G3): well-differentiated NETs can be classified as G1 tumors, when they express <2 mitoses/10 HPF and ≤2% Ki-67 index; as G2 tumors, when they express 2-20 mitoses/10 HPF and 3-20% Ki-67, whereas neuroendocrine carcinomas (NECs) usually belong to G3 category, with >20 mitoses/10 HPF and >20% Ki-67 index [9]. However, the presence of metastases, mainly liver metastases, represents one of the most important negative prognostic factor. In European and US referral centers, patients with pNETs often present with distant metastases at initial diagnosis (10). The occurrence of liver metastases is related to tumor extent (T-stage), differentiation, and grading (G1-G3); approximately 50% of poorly differentiated neuroendocrine carcinomas (NEC G3) are metastatic at initial diagnosis versus only 21% of well-differentiated and 30% moderately differentiated neuroendocrine tumors (NETs G1 and G2), respectively[10]. The site of the primary tumor also has prognostic significance, since pNETs are usually characterized by a more severe clinical course when compared with gastrointestinal tumors, with a 5-year survival rate of 30-60% versus a rate of 60-90% for carcinoids [11, 12].

At present, a variety of therapeutic options exist for metastatic pNETs, including surgery, loco-regional therapies, chemotherapy, biotherapy with somatostatin analogues (SSAs) and interferon (IFN) and, more recently, the novel molecular targeted therapies and the systemic peptide receptor radionuclide therapy. Also liver transplantation (OLT) may be evaluated in highly selected patients [12].

According to ENETS Consensus guidelines, systemic chemotherapy using various cytotoxic agents (i.e., streptozotocin, doxorubicin, 5-fluorouracil, cisplatin, etoposide, dacarbazine) is recommended in pNETs, metastatic foregut NET G2, and in NEC G3 of any site [10].

## Conclusion

The majority of pancreatic neuroendocrine tumors (PNET) are metastatic at diagnosis. Even if we don't have a primary site from the first evaluations, repeating ultrasound more accurately and adding contrast enhanced US can establish the diagnosis. Liver biopsy

in our case, ultrasound guided, conferred a good specimen for certifying the pathology diagnosis.

## References

1. **Franko J, Feng W, Yip L, et al.** Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg* 2010;14:541-8.
2. **Oberg K.** Pancreatic endocrine tumors. *Semin Oncol* 2010;37:594-618.
3. **Cusati D, Zhang L, Harmsen WS, et al.** Metastatic nonfunctioning pancreatic neuroendocrine carcinoma to liver: surgical treatment and outcomes. *J Am Coll Surg* 2012;215:117-24; discussion 124-5.
4. **Jensen RT, Cadiot G, Brandi ML, et al.** ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012;95:98-119.
5. **Fesinmeyer MD, Austin MA, Li CI, et al.** Differences in survival by histologic type of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14:1766.
6. **Rösch T, Lightdale CJ, Botet JF, et al.** Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med* 1992; 326:1721.
7. **Falconi M, Bartsch DK, Eriksson B, et al.** ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 2012;95:120-34.
8. **Massironi S, Sciola V, Peracchi M, et al.** Neuroendocrine tumors of the gastro-entero-pancreatic system. *World J Gastroenterol* 2008;14:5377-84.
9. **Rindi G, Arnold R, Bosman FT, et al.** Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, et al. eds. WHO classification of tumors of the digestive system. *Lyon: International Agency for Research on Cancer (IRAC)*, 2010:13-145.
10. **Pavel M, Baudin E, Couvelard A, et al.** ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012;95:157-76.
11. **Panzuto F, Nasoni S, Falconi M, et al.** Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005;12:1083-92.
12. **Tomassetti P, Campana D, Piscitelli L, et al.** Endocrine pancreatic tumors: factors correlated with survival. *Ann Oncol* 2005;16:1806-10.