

# Metastatic Nonfunctional Pancreatic Neuroendocrine Tumor – Case Report and Review of the Literature

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Received May 31, 2015; Revised June 02, 2015; Accepted June 10, 2015

**Abstract** We present a 56-year-old patient with liver metastases from nonfunctional pancreatic neuroendocrine tumor. The disease is found incidentally in a patient with nonspecific symptoms. Conventional abdominal ultrasound establishes several liver lesions mimicking hemangiomas. On contrast enhancement ultrasonography hypervascularized secondary liver lesions are detected. Subsequent imaging methods and biochemical tests diagnose a pancreatic neuroendocrine metastatic tumor. Left-sided pancreatectomy with splenectomy is carried out. The patient is in good general condition six months after initiation of combination therapy with everolimus and sandostatatin LAR depot. Tc-99m-tektrotyd single photon emission computed tomography-CT hybrid imaging shows reduced accumulation of the radiopharmaceutical in the liver parenchyma without data of pancreatic tumor.

**Keywords:** neuroendocrine tumor, pancreas, liver metastases, imaging methods

**Cite This Article:** Ludmila Tankova, Vanya Gerova, Plamen Getsov, Radislav Nakov, Stanislav Churchev, Ivan Terziev, Irena Kostadinova, Miroslava Vitkova, Ventsislav Nakov, Damyan Damyanov, and Nina Topuzanska, “Metastatic Nonfunctional Pancreatic Neuroendocrine Tumor – Case Report and Review of the Literature.” *American Journal of Medical Case Reports*, vol. 3, no. 7 (2015): 205-208. doi: 10.12691/ajmcr-3-7-6.

## 1. Introduction

Pancreatic neuroendocrine tumors (PNETs) are a subgroup of NETs with unique tumor biology, natural history, and clinical management [1]. PNETs are rare neoplasms of the pancreas (incidence 1/100,000 x year) and account for about 1-2% of all pancreatic neoplasms [2,3,4]. There is an increase by 5 times in the detection rate of NET's in the last two decades, partly due to improved radiological diagnostic techniques [5,6].

## 2. Case Report

A 56-year-old patient with moderate non-specific abdominal pain lasting from several months was admitted in our Clinic. Physical examination was unremarkable. Routine laboratory test were within the normal range with the exception of slightly elevated bilirubin total/dir 28.9/9.3µmol/L. On the occasion of his complaint upper and lower endoscopy were conducted with data for hiatal hernia and dolichosigma. Conventional transabdominal ultrasonography (with ultrasound machine Hitachi Aloka<sup>®</sup> Prosound alpha 7) demonstrated several focal nonhomogenous predominantly hyperechogenic liver lesions with dimensions from 1 to 2.0 cm (Figure 1). The presumed

diagnosis was hemangiomas. Contrast-enhanced ultrasonography (CEUS, low mechanical index MI = 0.15), using 2.4ml bolus Sonovue<sup>®</sup> (sulfur hexafluoride with phospholipid shell) (Bracco, Milan, Italy) established six hypervascular liver metastases (Figure 2 & Figure 3). These metastases presented with a diffuse enhancement in the arterial phase and with a rapid and complete “washout” due to the absence of portal supply to the neoplastic lesions. A computed tomographic (CT) scan of the chest and abdomen (native and contrast enhanced) showed a small (2 cm in size) focal lesion in the tail of the pancreas that was not seen in conventional ultrasound (Figure 4). The multiple focal lesions in the liver were confirmed as hypervascular secondary lesions. PNET was considered as a possible cause of liver metastases. Blood chromogranin A (CgA) level was moderate elevated (177 ng/ml; normal range up to 100ng/ml). The 5-hydroxyindoleacetic acid urine test was within normal value ranges. The tumor markers Ca 19-9, CEA and  $\alpha$ -fetoprotein were strongly increased respectively 3520 U/ml (normal range <34); 2490 µg/l (normal range <5.5) and 32.2ng/l (normal range 0-8.1). The whole body scintigraphy using 99mTc-Tektrotyd and Single photon emission computer tomography (SPECT/CT) showed somatostatin receptor expressing lesions in the pancreatic tail as well as in the liver parenchyma (Figure 5). The diagnosis was confirmed intraoperatively and left-sided pancreatectomy with splenectomy were carried out. The

definite immunohistopathological report showed moderately differentiated neuroendocrine pancreatic carcinoma G2 expressing chromogranin and synaptophysin with weak focal expression of CK8 and missing expression of CK 7/19 (Figure 6 & Figure 7). The proliferation marker Ki-67 was 5% (Figure 8). Combination therapy with everolimus (10 mg/d) and sandostatin LAR depot 30mg/every 28 days was initiated. Tc-99m-tekrotyd single photon emission computed tomography-CT hybrid imaging, performed 6 months after therapy initiation showed reduced accumulation of the radiopharmaceutical in the liver parenchyma without data of pancreatic tumor (Figure 9). Six months after initiation of therapy the serum CgA levels were dropped to 40ng/ml. Currently (seven months after surgery) the patient is in good general condition.



Figure 1. Ultrasound image of multiple liver lesions resembling hemangiomas



Figure 2. CEUS image – Rapid complete contrast enhancement in the arterial phase (22 sec.)



Figure 3. CEUS image – Rapid complete wash-out in the early portal phase (57 sec.)

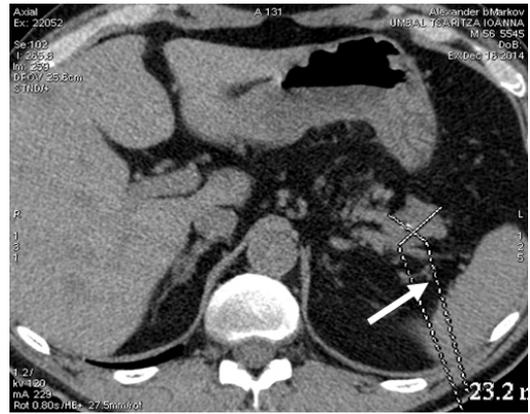


Figure 4. CT – Lesion in the pancreas tail (arrow)



Figure 5. Tc-99m-tekrotyd single photon emission computed tomography-CT hybrid imaging – before therapy

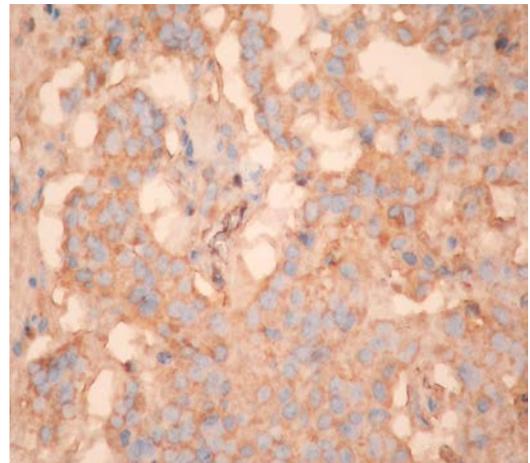


Figure 6. Positive immunohistochemistry reaction:

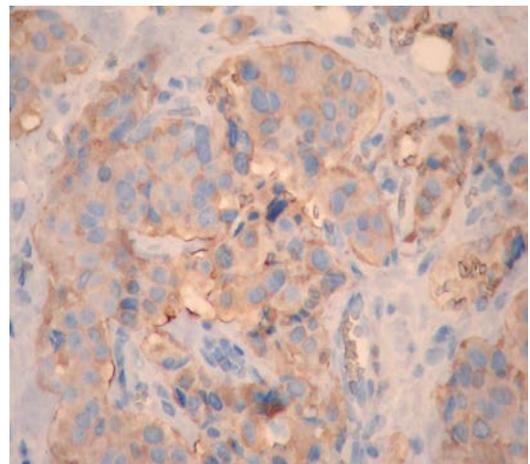
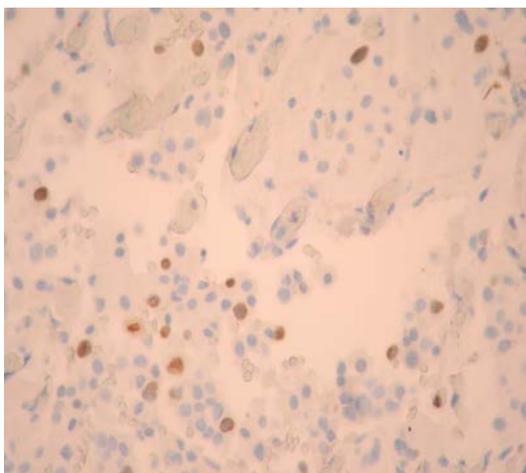
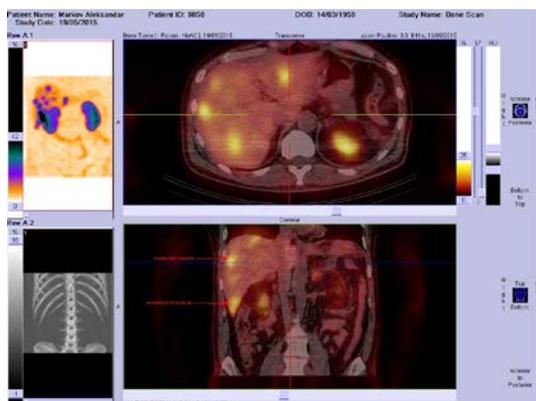


Figure 7. Positive immunohistochemistry reaction: synaptophysin positive



**Figure 8.** Ki-67 proliferative index (5%)



**Figure 9.** Tc-99m-tekrotyrd single photon emission computed tomography-CT hybrid imaging after 5 months therapy, demonstrating not only visual, but also quantitative reduction in radiotracer accumulation

### 3. Discussion

Based on the presence or absence of symptoms related to hormone production, PNETs are classified into functional and non-functional, respectively [7]. Non-functional PNETS (40-65%) present no clinical manifestation of hormonal oversecretion, however they may produce a precursor hormone that is functionally inert or is in too small amounts to be clinically relevant [3,7]. These patients often presents with advanced metastatic disease, similar to our case. Thus the diagnosis of non-functioning PNETS is a real challenge for the physician.

According to the World Health Organization (WHO) classification, three classes of NETs are identified (G1, G2, and G3): well-differentiated NETs can be classified as G1 tumors, when they express  $<2$  mitoses/10 HPF and  $\leq 2\%$  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 [8]. Based on the new WHO classification with respect to Ki-67 proliferative index slightly corrected cut-off values may allow a more precise prognostic stratification for pancreatic NET ( $<5\%$ , 5–20% and  $>20\%$ ) [9,10]. The low and intermediate grades (grade 1 and 2) are WD (well differentiated) NETs, and the high grade (grade 3) group consists of PD (poorly differentiated)

neuroendocrine carcinomas NECs [10]. Since well differentiated PNETs show a different behavior from poorly differentiated PNETs with a consequent different therapeutic approach, a complete histological assessment of the tumor by means of biopsy, including the detection of mitotic ki-67 index, is needed prior to treatment [9,10]. The minimal biochemical test for PNETs includes circulating CgA, expressed in 80-90% of all patients with pancreatic neuroendocrine tumors. Chromogranin A determination is also useful for staging, prognosis and follow up, since the serum concentration correlates to the tumor mass [6,10].

The use of second generation ultrasound contrast agents in combination with low MI contrast-specific US techniques has clearly improved ultrasound imaging of the liver. CEUS has improved the detection of liver metastases when compared to US itself, and it seems to have accuracy similar to that of CT. The typical vascular feature of a liver metastasis from PNETs is arterial phase hypervascularisation followed by rapid portal-venous washout. In our case contrast enhanced ultrasonography was the first method which showed highly vascularized liver lesions. The gold standard for the detection of pancreatic NETs are MRI, CT scan, and somatostatin receptor scintigraphy. Endoscopic ultrasound (EUS) is an excellent that has proved to be useful for pancreatic NET detection, particularly with small tumors that are unable to be detected by CT or MRI [11,12].

Nuclear medicine imaging consists of scintigraphy including single photon emission computed tomography (SPECT) with  $^{111}\text{In}$ -pentetretotide or PET with  $^{68}\text{Ga}$ -labeled somatostatin analogs (SSA),  $^{18}\text{F}$ -DOPA and  $^{11}\text{C}$ -5-HTP. A combination of anatomic and functional techniques is facilitated by the development of current hybrid scanners (SPECT/CT and PET/CT) [12].

At present, a variety of therapeutic options exist for metastatic PNETs, including surgery, loco-regional therapies, chemotherapy, biotherapy with somatostatin analogues and interferon (IFN) and, more recently, the novel molecular targeted therapies and the systemic peptide receptor radionuclide therapy [10,13]. Curative resection is considered as standard therapy in well-differentiated PNET G1/G2 with a Ki-67 index of  $<10\%$  [13,14,15]. PNET patients with liver metastases could have been a candidate for initial surgery for primary tumor and subsequent liver transplantation for unresectable metastases. Surgeons still have hesitation in deciding the best scenario in patients with PNET with liver metastases [13,14,16].

The dramatic increasing in the incidence of neuroendocrine tumors has led to the revitalization of the basic and clinical research into the molecular biology of NET and has resulted in the recent approval of new therapies, including the oral inhibitor of the mTOR – everolimus [17]. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that blocks the signal transduction in tumor cells and cells that play a role in tumor angiogenesis. Everolimus is a therapeutic option for neuroendocrine tumors (NETs), however, data in a real-world setting outside regulatory trials are sparse [18,19]. This medicine is a treatment option after failure of chemotherapy in pancreatic NET, but can be considered as first-line therapy in selected cases as an alternative

treatment to locoregional therapies or chemotherapy. The RADIANT-3 study includes 40% therapy-naive patients, and efficacy is equally good in therapy-naive patients as in patients with previous therapies [17]. Everolimus may be further considered in patients with advanced, progressive PNET [18,19]. In our case the combination therapy with everolimus (10mg/d) and sandostatin LAR depot 30mg/every 28 days was well tolerated by patient with good therapeutic response.

#### 4. Conclusion

Non functioning PNET are often found by chance and patients usually present with advanced disease. Distant spread to the liver may sometimes be the only manifestation of the tumor. PNETs demonstrate an increased somatostatin receptor expression both in primary and metastatic lesions. Multidisciplinary approach, in which nuclear medicine techniques play an important role in the detection, follow-up and therapeutic response of these tumors, is essential.

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