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A calcitonin secreting pancreatic neuroendocrine tumor with liver metastasis and hepatic vein thrombosis: a case report

Nina Piłka [1], Mateusz Drabczyk [2]

Affiliations:

[1] Bonifrater Medical Center Branch in Katowice, Markiefki 87, 40-211 Katowice, https://orcid.org/0009-0006-7482-2666, nina572@interia.pl

[2] Bonifrater Medical Center Branch in Katowice, Markiefki 87, 40-211 Katowice, https://orcid.org/0000-0003-3354-5982, matidra@poczta.fm

Abstract

Pancreatic neuroendocrine neoplasms (PanNEN), accounting for only 1-2% of all pancreatic tumors, are slow-growing and capable of secreting substances that can cause characteristic clinical syndromes, with an increasing prevalence estimated at around 8-10 million cases per year. We report the case of a pancreatic neuroendocrine tumor with high calcitonin levels and distant metastases without clinical manifestation. The correct diagnosis

of a neuroendocrine tumor was established based on histopathologic examination and immunohistochemical assessment of the expression of neuroendocrine markers. The presence of somatostatin receptors led to the initiation of treatment with somatostatin analogues and radionuclide therapy. No increase in neuroendocrine tumor markers was observed. However, follow-up abdominal CT imaging performed after the completion of radionuclide therapy showed an unsatisfactory response with an increase of liver metastases and an increase in the size of the primary tumor in the pancreas. Our case report contributes to the literature on the diagnostic challenges of neuroendocrine tumors and highlights the current debate regarding tumor mass cytoreduction.

Keywords Endocrine System Diseases, Pancreatic neuroendocrine tumours , Calcitonin

Case presentation

33-year old woman with the diagnosis of non-functional well-differentiated pancreatic neuroendocrine tumor (PanNET) was referred to our Department of Endocrinology and Neuroendocrine Tumors to be evaluated for treatment management with a view to establish potential therapeutic perspectives. The PanNET was a fortuitous finding on computed tomography (CT) imaging examination 2 months prior to the current admission.

On admission the patient reported nausea and loss of appetite, she noted a 19-kg weight loss in the recent 6 months. She had not experienced flushing attacks, diarrhea or wheezing. Physical examination revealed abdominal pain and tenderness in the left upper quadrant. The mentioned symptoms were described by the patient as the most frequent within a half year and with no correlation to any known triggering. Physical inspection of other body parts revealed no abnormalities, neither the liver nor spleen were enlarged.

The patient’s medications comprised Eliquis (5mg; 2 tabs per day) and Asertin

(50mg; 2 tabs per day). As a consequence of clinical presentation of portal and splenic veins thrombosis she had discontinued oral contraception (OC) 2 months ago. Furthermore, she had suffered from DM2, cholelithiasis, gallbladder polyps, kidney stones, endometriosis and mental disorders, particularly anxiety and depression.The patient had notable family history for breast cancer in mother and prostate and larynx cancer in father, whereas the family history of endocrine diseases was negative.

Two months before hospitalization in our Department of Endocrinology and Neuroendocrine Tumors, she reported by herself to the emergency department with cramping abdominal pain. The diagnosis of acute cholangitis was based on the presence of clinical and laboratory findings of systemic inflammation and cholestasis, combined with computed tomography (CT) imaging findings of obstruction. An endoscopic retrograde cholangiopancreatography (ERCP) was performed and in order to relieve compression a stent in the common bile duct was deployed. The patient was discharged from the hospital in a stable condition with a referral letter to magnetic resonance imaging (MRI) and biopsy of incidentally discovered mass lesions in pancreas and hepatis in CT imaging.

The MRI of the pancreas revealed a focal mass formation in the body and tail of size 94 mm x 42 mm with supposed focal inflammatory enlargement and infiltration into surrounding tissues. Moreover, the MRI confirmed several masses in the liver, the biggest one in segment V/VI, 17 mm x 16 mm in size. Endoscopic ultrasound (EUS) based biopsy revealed neuroendocrine tumors G2 with mitotic activity identified as Ki-67 index 6%.The splenic and portal vein was also infiltrated.

The MRI of pancreas identified a focal mass formation measuring 94 mm x 42 mm in the body and tail, suggesting localized inflammatory enlargement and infiltration into adjacent tissues. Furthermore, multiple richly vascularized liver masses were confirmed, with the largest one measuring 17 mm x 16 mm in segment V/VI. Additionally, infiltration into the splenic and portal vein was observed with the presence of thrombosis in both vessels. The histopathological findings of EUS based biopsy of pancreas revealed NET G2 with mitotic activity Ki-67 6% and for hepatis NET G2 Ki-67 12%.

During current hospitalization the patient underwent positron emission tomography (PET) scan using somatostatin analogues labeled with gallium-68 (68Ga-DOTA-TATE PET/CT) as well as laboratory tests. PET-CT reported accumulation of radiotracer in the liver and sustained radiotracer uptake of the tail and body of the pancreas. Biochemical examination revealed significantly increased secretion of calcitonin 1310pg/ml [<4,80].

Insulin, gastrin, VIP, glucagon, serotonin, chromogranin A, 24 h urine 5 HIAA were undetectable. Elevated plasma concentration of calcitonin levels extended diagnosis into thyroid examination. However, thyroid hormones and antibodies were within normal range as well as thyroid ultrasound examination ruled out any abnormalities.

A calcitonin-producing PanNET with liver metastases was diagnosed. Due to high density of somatostatin receptor expression treatment by long-acting somatostatin analogues - lanreotide was initiated at dose 120 mg every 28 days to reduce tumour size. By the decision of the multidisciplinary tumor board , the patient has been qualified for peptide receptor radionuclide therapy (PRRT).

Discussion

Pancreatic neuroendocrine neoplasms (PanNEN) comprise only 1-2% of all pancreatic tumors. Their prevalence is increasing and is estimated at around 8–10 million cases per year [11]. Neuroendocrine tumors (NETs) are slow-growing neoplasms with the ability to secrete special substances that can lead to characteristic clinical syndromes. According to the latest World Health Organisation (WHO) classification from 2019 the histological classification of PanNENs depending on degree of histological maturity (G, Grade) is divided into three subtypes: Neuroendocrine tumour G1 (NET G1); Neuroendocrine tumour G2 (NET G2) ;Neuroendocrine carcinoma (NEC); and Mixed adenoneuroendocrine carcinoma (MANEC) [19].

In general pancreatic neuroendocrine neoplasms (PanNENs) may be divided into two groups: functional pancreatic neuroendocrine neoplasms (F-PanNENs) and non-functional pancreatic neuroendocrine neoplasms (NF-PanNENs). Non-functional PanNEN remaining the most frequent ones, due to their slow growth and uncharacteristic symptoms may be initially unnoted, thus assessment of pancreatic polypeptide (PP), chromogranin A (CgA) and neuron specific enolase (NSE) is supposed to be relevant in these patients. Clinical presentation of functional PanNENs depends on the amount and type of secreted hormones. Functional NENs remain more uncommon and are usually associated with the secretion of insulin, gastrin, glucagon, VIP, GHRHoma — growth hormone-releasing hormone (GHRH)-producing tumour, ACTHoma — adrenocorticotropin hormone (ACTH)-producing tumour. Reliable

knowledge of the specific NENs markers is useful identifying all NET types and controlling the effectiveness of treatment [10].

Thyroid C-cells secrete a calcitonin, the peptide hormone which plays the main role in decreasing calcium level through its action on the kidneys and bone by inhibiting bone resorption, promoting renal excretion of calcium and stimulating phosphaturia [2].
Interestingly, in our case despite elevated calcitonin level there was no abnormalities in calcium and phosphate metabolism: calcium - 2,53 mmol/l [2,20-2,65 mmol/l], phosphorus - 2,99 mg/dl [2,50-4,50 mg/dl], however PTH was slightly decreased - 4,83 pg/ml [15-65 pg/ml]. The elevated level of calcitonin should always raise a suspicion of medullary thyroid carcinomas [3].

Calcitonin-secreting PNETs is associated with secretion of other hormones such as intestinal peptide (VIP), somatostatin or pancreatic polypeptide [6-8]. However, coexpression of these several peptides is likely to be very common, in our case such a phenomenon was not observed.

Symptoms of PanNET mostly include water diarrhea which affects half of all individuals [9]. Interestingly, higher levels of calcitonin secretion have been observed in patients with water diarrhea than in those without such symptoms [3]. Although our patient had a significantly elevated calcitonin level, she did not suffer from any diarrhea symptoms. On the other hand, the absence of neoplasm-associated symptoms is connected with a better prognosis, regardless of cancer stage [10].

Recent clinical trials confirmed that pancreatic cancer promotes hypercoagulability mainly associated with a high tumoral expression of tissue factor (TF) which elevated level has been documented across various cancer types [15]. Given our patient's clinical presentation indicating portal and splenic vein thrombosis, it may support a potential correlation between pancreatic cancer and increased blood clotting.

Identifying PanNETs continues to pose a significant challenge. The use of biochemical diagnostic methods particularly chromogranin A levels (CgA) is recommended as the first line of examination and considerably improves the chances of early detection [18]. Clinical presentation depends on whether the tumor is functional or not. The concentration of some peptides may suggest a particular tumor type [10]. Nevertheless, when conducting differential diagnoses, it is imperative to measure the concentration of specific markers (such as gastrin, insulin, serotonin, VIP, glucagon, etc.) regardless of the functional status [11].

When it comes to diagnostic management, it is essential to highlight that the biochemical markers currently in use cannot be solely linked to establishing the final diagnosis [10].

Imaging methods are essential to establish the localization of the lesion and the stage of PanNENs [20]. Ultrasound examination is an accessible and widely applicable first choice tool that may detect the location of the lesion. Next step of investigation should require CT and MRI to assess the stage of the disease progression [11]. Moreover, EUS and EUS-based biopsy, which sensitivity and specificity are over 84% and 92.5% for detection of PanNETs, should be performed [16]. The EUS-based biopsy is especially significant in case of detection of hormonally non-functional PanNETs and distinguishing ordinary neoplasms from adenocarcinomas [10].

Advancements in contemporary histopathological and imaging methods have not only enhanced diagnostic capabilities but also contributed significantly to therapeutic decisions [11]. The utilization of positron-labeled somatostatin analogues, specifically [68Ga]Ga-DOTA-SSA, in diagnostics is preferred for confirming somatostatin receptor expression prior to scheduled PRRT [17].

The choice of specific treatment of NF-PanNETs depends on the tumor size. For neoplasms < 2 cm in diameter further control of symptoms is recommended while in case of tumors > 2 cm or symptomatic and functional tumors regardless their size, surgical resection is required [13, 14]. Somatostatin analogues (SSAs) are recommended as first-line therapy for controlling tumor growth in highly differentiated PanNENs G1 and PanNENs G2 with strong somatostatin receptor (SSTR) expression in receptor or immunohistochemical examinations, and a Ki-67 value up to 10%. In second-line treatment for PanNETs with a Ki-67 value below 10%, PRRT can be considered as an alternative to the use of tyrosine kinase inhibitor (TKIs) and chemotherapy [10].

Conclusions

In the literature, the most cases of pancreatic neuroendocrine neoplasms (PanNET) were treated by radical surgery [23,24]. In our case, with somatostatin receptor-positive disease, we introduced a somatostatin analogues treatment followed by PRRT to reduce the tumour mass.

The use of somatostatin analogs therapy for the treatment for well-differentiated, metastatic PanNET has been reported and it has been generally associated with satisfactory

outcomes [22]. Based on the research published so far, we can say that there are several PanNET treatments with proven efficacy, however in our case cytoreduction of the tumour mass resulted in progression of the disease accompanied by new liver metastasis.

Author's contribution

Conceptualization, NP and MD; methodology, NP; software, MD; check, NP; formal analysis, MD; investigation, NP and MD; resources, NP; data curation, NP and MD; writing - rough preparation, NP and MD; writing - review and editing, NP and MD; visualization, NP; supervision, NP; project administration, MD. All authors have read and agreed with the published version of the manuscript.

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