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CASE REPORT PEER REVIEWED | OPEN ACCESS

Pancreatic serous cystadenoma with a high ^{68}Ga DOTATOC-uptake mimicking a pancreatic NET

Erling A Bringeland, Elin Rønne, Åse Kjellmo, Thomas M Keil

ABSTRACT

Introduction: ^{68}Ga-DOTATOC positron emission tomography (PET) has replaced octreotide scintigraphy as method of choice in detecting and staging most neuroendocrine tumors (NETs). With a better signal-to-noise ratio and improved spatial resolution, sensitivity is increased. However, several non-NETs express surface somatostatin receptors, challenging the positive predictive value of a DOTATOC scan regarding a NET diagnosis. This is of particular concern in pancreas as NET is a frequent differential diagnosis, as is a variety of cystic neoplasms increasingly often diagnosed as incidental findings.

Case Report: A 66-year-old man was diagnosed with an asymptomatic cystic tumor in the pancreatic neck. At computed tomography scan (CT) a 4 cm P-NET was suspected as an incidental finding. The diagnosis was supported by a positive ^{68}Ga-DOTATOC scan, with a high DOTATOC-uptake in the pancreatic tumor and in a local interaortocaval node. The tumor was radically resected. At pathologic examination a pancreatic serous cystadenoma (SCN) was unexpectedly diagnosed, with the regional nodes proven only to harbor granulomatous inflammation.

Conclusion: A rare case of a ^{68}Ga-DOTATOC positive SCN is reported. Diagnostic workup was confounded by a local node exhibiting a high DOTATOC-uptake. Radiologists, nuclear medicine physicians, and pancreatic surgeons must be aware of this diagnostic pitfall to avoid unnecessary surgical procedures.

Keywords: ^{68}Ga-DOTATOC PET-CT, Pancreatic cystic neoplasm, Pancreatic neuroendocrine tumor, Pancreatic nuclear imaging, Pancreatic serous cystoadenoma

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INTRODUCTION

Pancreatic serous cystadenoma (SCN) is a rare entity belonging to the group of cystic pancreatic neoplasms. It is typically found in females aged 50–70 years, but cannot be ruled out in younger patients or in males. The tumor consists of small serous cysts each ranging from one to a few millimeters in diameter. An oligocystic version with fewer and larger cysts is sometimes found [1]. At radiology it is classically characterized by a central fibrous scar, at times calcified, which is considered patognomonic. However, this finding is lacking in the majority of cases [2, 3]. The lesion is predominantly located in the pancreatic head, but may be found at any location of the pancreas. It is a benign disorder, and diagnostic ambiguities is the main reason for concern.

Mucinous cystic neoplasms (MCN) and branch-duct type intraductal papillary mucinous neoplasms (Br-IPMN) are the main differential diagnostic entities [3], but some solid neoplasms, primary or metastatic, may on occasion present themselves with central necrosis and a deceptively cystic appearance at computed tomography (CT) [1, 2, 4]. Pancreatic neuroendocrine tumor (P-NET) is such an entity. Some 20% of P-NETs are functional tumors producing hormones causing clinical symptoms, the remaining 80% are non-functional tumors. The non-functional NETs are most often incidental findings, and may reach diameters of several centimeters as they are allowed silently to grow with no clinical symptoms to give them away [5]. At computed tomography (CT), typical findings include a well demarcated, hypervascular lesion with an intense contrast enhancement in the arterial phase, contrasting the pancreatic adenocarcinomas which are typically hypovascular [6, 7]. However, the picture may be confounded by entities such as hypervascular adenocarcinomas or pancreatic metastases from renal cell carcinoma. Magnetic resonance imaging (MRI) may aid in the differential diagnostic workup, but once a P-NET is suspected a DOTATOC PET-CT (positron emission tomography) is indicated to support the diagnosis and identify any involved regional lymph nodes or distant organ metastases. DOTATOC PET-CT is a nuclear medicine technique for detecting tumors expressing somatostatin receptors at their surface, a feature thought to distinguish a NET from the non-endocrine entities [5]. Based on the diagnostic workup, proper decisions can be made as to operate, control, or dismiss the patient. However, as the case presented will prove, matters are not always that clear.

CASE REPORT

We report the case of a 66-year-old man with no prior medical history apart from medication with mianserin hydrochloride 30 mg vesp and citalopram hydrobromid 40 mg vesp for mental depression. Due to sustained abdominal pain following a minor abdominal trauma, he received an abdominal CT scan with the incidental finding of a 4.0 cm tumor in the pancreatic neck, abutting the coeliac trunk and its hepatic and splenic branches without infiltrating any of them. The tumor had a cystic, non-enhancing central core with a hypervascular peripheral rim, raising the suspicion of a pancreatic NET with central necrosis (Figure 1A and B). Relevant blood samples were normal, including several tumor markers: S-CEA 2.2 (<5.0), S-NSE 11 (<17), Ca 19-9 <2 (<27) and S-Chromogranin A 58.9 (<101.9). A DOTATOC PET-CT was obtained to secure the diagnosis and provide a TNM-staging. A total of 158 MBq ^{68}Ga-DOTATOC were administered intravenously, with a PET-CT performed after 60 minutes. SUV_{max} was adjusted for bodyweight. The pancreatic tumor showed an intense peripheral DOTATOC-uptake with a central photopenia (Figure 2A). Likewise, a normal

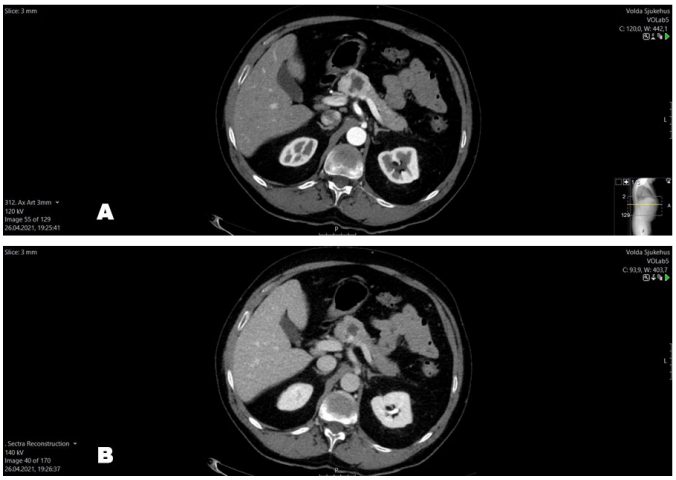

Figure 1: (A) Arterial phase imaging showing a 4 cm well demarcated hypervascular lesion in the pancreatic neck, with a non-enhancing central core. (B) Portal venous phase imaging with the same lesion showing isoattenuation. The central core is still non-enhancing.

sized interaortocaval node showed a high DOTATOC-uptake, suggesting the diagnosis of a malignant P-NET with a local metastatic node (Figure 2B). One month later the patient underwent a distal pancreatectomy with

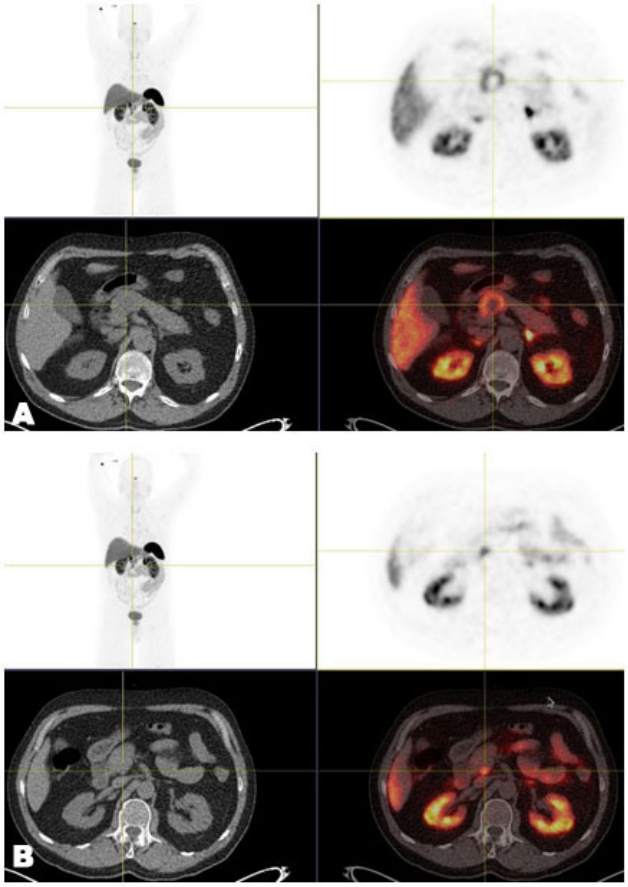

Figure 2: (A) PET-image and fused PET/CT with saturation at SUV = 20. Primary tumor has SUV_{max} = 12.8. (B) PET-image and fused PET/CT with saturation at SUV = 20. Interaortocaval lymph node has SUV_{max} = 12.2.

splenectomy en bloc. Following a Kocher maneuver, the retropancreatic interaortocaval nodes were removed separately. The recovery was uneventful, with no need for endocrine or exocrine substitution.

Unexpectedly, the pathology report concluded with a radically resected pancreatic serous cystadenoma of microcystic type (Figure 3A). Due to the discrepancy between this finding and the preoperative positive DOTATOC PET-scan, the histologic diagnosis was secured with immunohistochemical analyses for chromogranin A and synaptophysin (Figure 3B). Both proved to be negative, ruling out the possibility of a mixed serous-neuroendocrine neoplasm, which is acknowledged as a rare, but distinct pancreatic entity [8]. The final twist to the case was that none of the removed interaortocaval nodes proved to harbor any malignancy. Only non-caseous granulomatous inflammation was found, judged not to be indicative of tuberculosis, but rather to point at sarcoidosis. The patient was subsequently referred to the internists for further diagnostic workup.

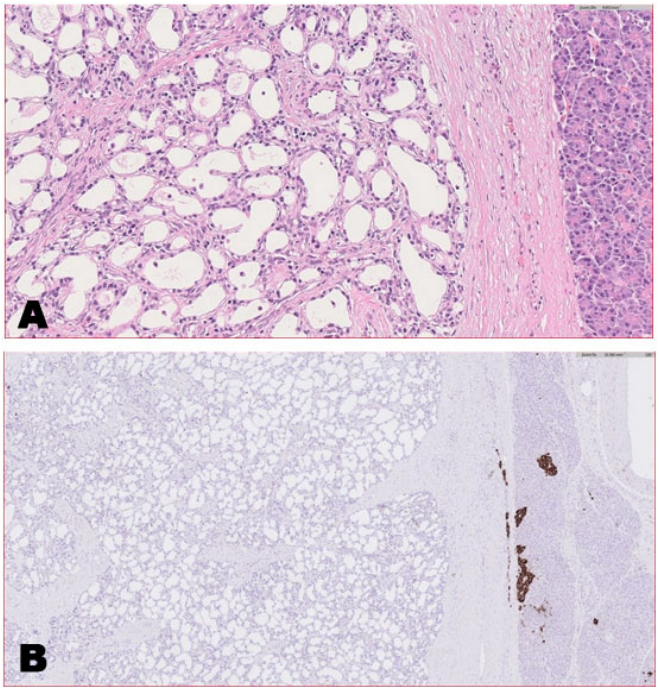

Figure 3: (A) Resected specimen showing microcystic serous cystadenoma, normal pancreatic tissue at the far right (HE ×200). (B) Chromogranin A immunohistochemical staining of resected specimen. Negative staining in tumor tissue, positive staining of the islets of Langerhans at the right.

DISCUSSION

DOTATOC is physiologically accumulated in several organs and tissues, such as the liver, spleen, gastric mucosa, adrenals, neural tissue, etc. Receptors may be expressed in a variety of tumors emanating from these tissues, such as intestinal neuroendocrine tumors and adrenal pheochromocytomas, but may also be found abundantly in tumors of other origin such as breast or pulmonary cancer [9]. Receptors may also be expressed in inflammatory tissue, further adding to the diagnostic challenges. They are not expressed in pancreatic adenocarcinoma, but are found in some 90% of the P-NETs [5, 9]. They have not been known to be expressed in pancreatic cystic neoplasms, and when reported by Nappo et al. in 2020 this was claimed to be the first report of this finding in a *serous* cystadenoma [10]. No somatostatin positive pancreatic *mucinous cystic* neoplasm has been reported, and to our knowledge, nor in the cystadenomatous analogues originating from other organs such as the ovaries. However, a dominant pancreatic uncinate process or a pancreatic tail splenosis may cause diagnostic challenges due to a substantial physiologic DOTATOC uptake [11]. To our knowledge, there is no interaction between the use of selective serotonin reuptake inhibitors (SSRI) and tetracyclic antidepressant medication (TCA) as in the present case, and the findings at DOTATOC PET-scans have been reported.

Somatostatin receptors (SSTRs) bind circulating somatostatins. In recent years synthetic analogues with improved binding capacity to subgroups of the somatostatin receptor family have been available, increasing the signal-to-noise ratio. The DOTA-conjugated somatostatin analog octreotide is such a ligand, with DOTA acting as a chelator carrying the ^{68}Gallium atom like a Trojan horse. The improved binding capacity between the SSTR 2 receptors and this ligand combined with significantly improved spatial resolution of PET-CT compared to the older gamma camera, radically improves sensitivity, now reported at 86–100% for even smaller P-NETs with a specificity of 79–100% [5]. In clinical use, the method is more rapid and overall cheaper than the single photon emission CT (SPECT) octreotide scintigraphy, and ^{68}Ga-DOTATOC has largely replaced the ^{111}In-octreotid scintigraphy as the method of choice. Inevitably, this will increase the detection of somatostatin positive tumors, including some non-NETs as well. In parallel, increasingly often incidental findings of pancreatic NETs and pancreatic cystic lesions like the present can be expected, reflecting an abundance of abdominal CT/MRI scanners in use [12], and findings of a positive DOTATOC-scan in pancreatic SCNs do raise diagnostic concerns. Adding to this, a rare pseudo solid variant of SCN has been described, with solid components without secretory activity traversing the regions of microcystic clusters. The stromal components are contrast enhancing at CT, and may impose a false impression of a P-NET [13]. Pancreatic SCN is considered a benign neoplasm and only resected if rapidly increasing in size or producing symptoms by mass effect [4]. On the other hand, a P-NET of 2 cm or more will largely be recommended for radical surgery. The dilemma is underscored by the fact that the diagnostic failure is not a matter of cut-off values to declare a positive scintigram, but rather the abundant expression of somatostatin receptors in tumors other than P-NETs, as illustrated by the present case. It is important for pancreatic surgeons to be aware of such diagnostic pitfalls and secure the

diagnosis with MRI and/or endoscopic ultrasound (EUS) with fine needle aspiration cytology or biopsy when needed. Neither of these modalities came to use in the present case as the positive DOTATOC PET-CT was taken to prove the diagnosis of a P-NET. The final twist to the case was the local retropancreatic node that enhanced significantly at DOTATOC-PET. Retrospectively, this finding acted as a confirmation-bias to the preoperative diagnosis. Inflammatory engaged lymph nodes are well known at times to induce surface expression of somatostatin receptors. DOTATOC-uptake may be lower and more diffusely located as opposed to a more intense and sharply demarcated uptake in a malignant node. However, any conclusion on a malignant or a reactive node based on findings at DOTATOC alone must be warned against. Any finding of enhancing nodes must be correlated to the diagnostic information obtained from other sources, such as tumor markers, known former or present malignant disease, known patterns of local lymphatic spread, findings at plain CT/MRI, etc. [14]. In the present case the interaortocaval node was deemed to be locoregional to a pancreatic primary and to have a high, demarcated uptake, rendering any distinction between a reactive or a malignant node very difficult.

CONCLUSION

A pancreatic serous cystadenoma may display a high ^{68}Ga-DOTATOC-uptake, falsely giving the impression of a pancreatic neuroendocrine tumor. Radiologists, nuclear medicine physicians, and pancreatic surgeons must be aware of this diagnostic pitfall to avoid unnecessary surgical procedures.

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Author Contributions

Erling A Bringeland – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Elin Rønne – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Åse Kjellmo – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Thomas M Keil – Acquisition of data, Interpretation of data, Revising the work critically for important

intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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All relevant data are within the paper and its Supporting Information files.