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Clinical case and review of literature

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Acute pancreatitis secondary to non-functioning pancreatic neuroendocrine tumor: uncommon clinical presentation. Clinical case and review of literature

BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) are uncommon, representing <5% of all pancreatic neoplasms, divided into functioning PNETs with secreted hormone cause of specific symptoms, and non-functioning PNETs (nf-PNETs) characterized by delayed diagnosis with metastases and clinical manifestations of compressive effects. Surgical approach is recommended for functioning and nf-PNETs >2 cm in diameter.

CASE REPORT: A 76-year-old woman was admitted to the UOC-University-Surgery Hospital "A. Fiorini" in Terracina for nausea and pain in the upper abdominal quadrants with dorso-lumbar irradiation, arising after the evening meal. After the haematochemistry tests and the instrumental investigations, the diagnosis of acute, severe halitiasic pancreatitis was made. Conventional US, CCT, CE-MRI and EUS showed a 2.8cm diameter lesion in the head-body junction of the pancreas. FNA-cytological examination did not found the presence of atypical pancreatic cells. Total-body scintigraphy with Octreoscan® documented a pathological hypercaptation area located in correspondence with the neof ormation. The patient underwent a body-tail spleno-pancreatectomy. The histological examination showed an intermediate grade (G2) nf-PNET infiltrating the lienal vein and stenosing the Wirsung duct, with perilesional pancreatitis. Immunohistochemistry showed CAM 5.2, Synaptophysin (>95%) and Chromogranin (60%) positive immunophenotype, with negative intratumoral Somatostatin expression.

CONCLUSION: Although rarely, nf-PNETS may be the cause of severe non-biliary acute pancreatitis from pancreatic ductal system compression. In cases where PET/CT⁶⁸Ga cannot be performed, total-body scintigraphy with Octreoscan® remains the most widely used method for the diagnosis of PNETs and the identification of extra-pancreatic lesions. Chromogranin and Synaptophysin are confirmed as specific markers of neuroendocrine differentiation.

KEY WORDS: Acute pancreatitis, Chromogranin, Pancreatic neuroendocrine tumor, Synaptophysin, Somatostatin

Introduction

Pancreatic neuroendocrine tumors (PNETs) are uncommonly found neoplasms representing less than 5% of all

pancreatic neoplasms, with an incidence of 1-1.5 cases/100.000¹. They are divided into functioning and non-functioning bases on the released hormone, which is the cause of specific symptoms². In more than half of the cases the PNETs are non-functioning (nf-PNETs), and the diagnosis is delayed when the lesion reaches large size with mass effect or develops metastasis³⁻⁵.

The diagnosis of PNET is based on hormonal tests, imaging and histological evidence⁶⁻⁷. At Contrast enhanced Computed Tomography (CCT) and Contrast Enhanced

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Magnetic Resonance Imaging (CE-MRI), PNETs have typical features that allow differential diagnosis with adenocarcinoma⁸. Total-body scintigraphy with injection of 111-In-pentetreotide (Octreoscan®) is an excellent tool for diagnosis, staging of the lesion, treatment planning and evaluation of the clinical response⁹⁻¹⁰.

More recently, Positron Emission Tomography/Computed Tomography with ⁶⁸Gallio (PET/CT⁶⁸Ga) has been shown to have higher sensitivity for PNET detection and is currently routinely used¹¹.

The endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) allows to diagnose the degree of malignancy, to evaluate the presence of genetic mutations and to make the correct pathological diagnosis¹². The decrease in plasma Chromogranin A (CgA) levels, points to a favorable response to treatment¹².

PNETs with a diameter of more than 3 cm have a tendency to metastasize, and imaging show a heterogeneous post-contrastographic enhancement.

Surgery is the treatment of choice for resectable tumors, generally associated with long survival, consisting of open or laparoscopic enucleation of the primary lesion or pancreatic resection associated in some cases with splenectomy, and liver resection in cases with resectable liver metastases¹²⁻¹⁵.

Regardless of differentiation grade, surgical approach is recommended for functioning, non-functioning PNETs larger than 2 cm in diameter or symptomatic for compression disorders^{14,16}.

Palliative therapy is applied in cases of disseminated disease and unresectable liver metastases^{4,14,15}.

Patients with well differentiated PNETs (G1-G2) present better responses to medical treatment than patients with poorly differentiated forms (G3)¹². The poorly differentiated form (G3) is treated with chemotherapy with a worse prognosis³.

Case Report

The authors report a case of PNET in a 76-year-old patient with clinical and laboratory picture of onset of acute pancreatitis (amylase 12.262U/L; lipase 2.688U/L; C-reactive Protein 3.65 mg/dl).

On admission, the patient complained of pain in the upper abdominal quadrants with dorso-lumbar irradiation and nausea after the evening meal. To the conventional ultrasound scan (US) of the abdomen the gallbladder appeared not distended and without stones, and the intra-extra-hepatic bile ducts appeared not dilated. At the level of the pancreas body the presence of a hypoechoic neoformation with a diameter of 2.8 cm was found.

The CCT of abdomen showed a swelling of 2.8 cm in diameter at the junction of the head and pancreatic body, and CE-MRI showed small pancreas in fibroadipose involution and solid nodular formation of the size of 2.8 cm located at the head-body passage. The lesion had regular

margins and inhomogeneous structure, with hyperintense component in the T2-weighted sequences and homogeneously hypointense in the T1-weighted sequences. After administration of contrast medium, the nodular lesion exhibited hypervascular behavior. The set of findings indicated the diagnoses of PNET.

EUS-FNA confirmed the presence in the pancreatic body of a hypoechoic neoformation with irregular limits of about 2 cm in diameter, infiltrating the splenic vein. The cytological examination revealed the presence of epithelial cells referable to pancreatic parenchyma free of atypia.

The patient underwent a total-body scintigraphy with an intravenous 162MBq 111-In-Octreoscan. The investigation was performed by means of total body scans in anterior and posterior detections, and by SPECT technique of the abdomen, at 4 and 24 hours after the administration of the radiopharmaceutical. Since the early acquisitions, the scintigraphic assessment documented the presence of a pathological hypercaptation area of the marked somatostatin analogue, located in the right paramedian epigastric region, in correspondence with the neoformation described in the CCT, CE-MRI and EUS (Fig. 1). The finding of hypercaptation the radiopharmaceutical is an expression of high density of somatostatin receptors. Indication was given to the open surgical approach of the lesion on the basis of the following evidences: a) symptomatic nf-PNET for acute severe pancreatitis; b) lesion with diameter of more than 2 cm; c) not diriment cytological examination.

After assessing the risk-benefit ratio, indication was given to the spleno-pancreatectomy body-tail¹⁷.

After bilateral subcostal laparotomy, a 3 cm diameter neoformation was found on the head-body of the pancreas with an irregular surface and hard consistency, infil-

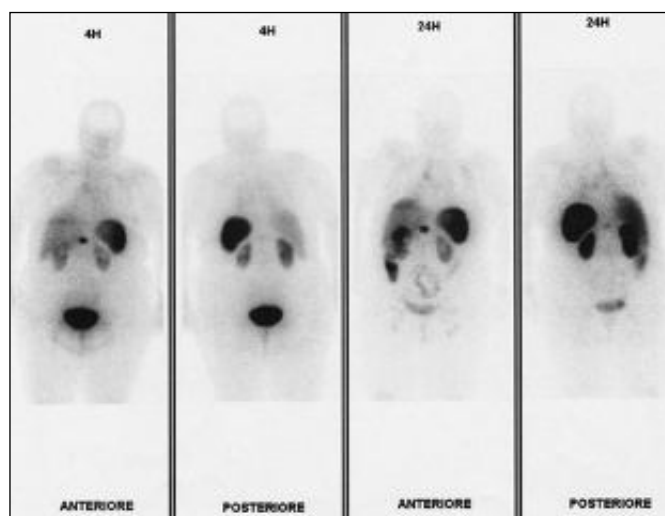


Fig. 1: Octreotide scintigraphy, SPECT technique of the abdomen 4 and 24 hours after the administration of the radiopharmaceutical. Presence of a pathological hypercaptation area located in the right paramedian epigastric region between the head and body of the pancreas.



Fig. 2: Distal splenopancreasectomy for head-body pancreas neuroendocrine tumor.

trating the lienal vein. Resection of pancreas body-tail and spleen was performed.

At the macroscopic histological evaluation the nodular lesion had a diameter of 3 cm, grayish-brown color, expansive margin (Fig. 2).

MICROSCOPIC DIAGNOSIS: PNET with CAM5.2, Synaptophysin (>95%) and Chromogranin (60%) positive immunophenotype; the expression of Somatostatin was negative; finding of vascular invasion (V1) of the lienal vein; absence of perineural invasion (Pn0); chronic granulomatous non-caseating phlogosis with giant cells was found in 15 lymph nodes of the splenic hilum; perilesional PNE microadenomas finding.

EVALUATION OF PROGNOSTIC FACTORS: mitotic count 3 mitosis /10 HPF; Ki-67 4%; CD99 and PgR weakly expressed in 5% of the neoplasm¹⁸⁻²¹; CK 19 widely expressed²¹⁻²⁴.

DIAGNOSIS: intermediate grade PNET (G2) causing stenosis of the main pancreatic duct and perilesional pancreatitis; pTNM, UICC / AJCC 8th Edition: pT2 PN0 V1 Pn0^{18-20, 25-27}.

Discussion

The diagnosis of non-functioning PNETs has increased significantly in the last twenty years, and the prognosis is related to the size of the lesion less or greater than 2 cm²¹ and enhanced by the possibilities of imaging.

In the absence of distant metastasis, lymph node metastasis and local invasion, lesions less than 2cm in diameter are generally not associated with disease progression²¹. However, all PNETs should be considered potentially malignant, until the determination of the mitotic index and Ki-67¹³.

In the reported case, characterized at the onset by acute severe pancreatitis, trans-abdominal US, CCT and CE-MRI played a fundamental role in the differential diagnosis with adenocarcinoma, staging of the neoplasm and planning of therapy⁹.

Scintigraphy of somatostatin receptors (SRS) (Octreoscan®) is still the most widely used diagnostic technique in institutions where the PET/CT⁶⁸Ga is not available, and in the clinical case described it allowed to locate the pancreatic lesion, and to exclude the presence of occult extra-pancreatic lesions not identified with the conventional methods²¹. At surgery infiltration of the lienal vein described in echoendoscopy was confirmed, which required splenectomy as needed.

Splenic hilum lymphadenectomy with N parameter evaluation contributed to the accurate staging of the neoplasm. At immunohistochemistry, Chromogranin and Synaptophysin were confirmed being specific markers of neuroendocrine differentiation²³.

The onset of nf-PNET in acute pancreatitis, caused by stenosis of the Wirsung duct determined by the tumoral obstruction as in the case reported by the authors, is documented in literature in a rather limited number of patients^{24,28,29}.

Conclusions

Among the various etiopathogenetic causes of acute pancreatitis, stenosis of the caudal main pancreatic duct by nf-PNET should be hypothesized.

Total-body scintigraphy with Octreoscan® remains the most widely used method for the diagnosis of PNETs and the identification of extra-pancreatic lesions in cases where PET/CT⁶⁸Ga cannot be performed.

Chromogranin and synaptophysin are confirmed as specific markers of neuroendocrine differentiation.

Riassunto

I tumori neuroendocrini del pancreas (PNET) sono rari, e rappresentano <5% di tutte le neoplasie pancreatiche, suddivisi in PNET funzionanti con secrezione ormonale responsabile di sintomi specifici e PNET non funzionanti (nf-PNET) generalmente di diagnosi tardiva per la comparsa di metastasi o manifestazioni cliniche per effetti compressivi. L'approccio chirurgico è il trattamento di scelta per PNETs funzionanti, non-funzionanti di diametro superiore a 2 cm o sintomatici per disturbi da compressione.

Osservazione personale. Donna di 76 anni ricoverata presso la UOC-Università-Chirurgia Ospedale "A. Fiorini" di Terracina per nausea e dolore ai quadranti addominali superiori con irradiazione dorso-lombare, insorti dopo un pasto serale. Dopo gli esami ematochimici e le indagini strumentali, è stata fatta la diagnosi di pancreatite acuta severa. Gli US convenzionali, CCT, CE-MRI ed EUS hanno mostrato una lesione di 2,8 cm di diametro nella giunzione testa-corpo del pancreas. L'esame citologico FNA non ha rilevato la presenza di cellule pancreatiche atipiche. La scintigrafia total

body con Octreoscan® ha documentato un'area di ipercaptazione patologica situata in corrispondenza della neoplasia. La paziente è stata sottoposta a spleno-pancreasectomia corpo-coda.

L'esame istologico ha dimostrato un nf-PNET di grado intermedio (G2) stenotante la vena lienale e stenotante il dotto di Wirsung, con pancreatite perilesionale. L'immunoistochimica ha mostrato un immunofenotipo positivo per CAM5.2, sinaptofisina (> 95%) e cromogranina (60%), con espressione di somatostatina intratumorale negativa.

CONCLUSIONE: Sebbene raramente un nf-PNETS può essere la causa di grave pancreatite acuta non biliare da compressione del sistema duttale pancreatico. Nei casi in cui la PET / CT68Ga non può essere eseguita, la scintigrafia total body con Octreoscan® rimane il metodo più utilizzato per la diagnosi dei PNET e l'identificazione delle eventuali lesioni extra-pancreatiche. La cromogranina e la sinaptofisina sono confermate come marcatori specifici del differenziamento neuroendocrino.

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