

CASE REPORT

Adenocarcinoma versus pancreatic neuroendocrine tumor – case report

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Abstract

Pancreatic cancer represents one of the most aggressive types of cancer, resulting in a late diagnosis and rapid death (poor overall survival). After adenocarcinoma (counting almost 80% of cases of pancreatic cancer), the second category, as frequency, is represented by the family of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Pancreatic cancer is characterized by genetic heterogeneity and may result in different evolution among metastases, which may acquire driver mutations with the ability to transform under the action of several cancer treatments. Here we report a case of a 64-year-old patient diagnosed with pancreatic tumor localized on the body and tail, invasive in the splenic and portal vein, pT3pN0M0 (adenocarcinoma pancreatic cancer), treated with a multimodal approach: surgery (splenectomy and distal pancreatectomy, with suture of the portal vein), chemotherapy, in 2010, that relapsed in 2015, with local recurrence that was resected and distant liver metastases. Immunohistochemistry of the recurrence tumor showed a neuroendocrine transformation of the tumor, with major implications in treatment and prognosis. Computed tomography examination, as well as histopathological and immunohistochemically testing, sustained positive and differential diagnosis.

Keywords: locally advanced pancreatic tumor, neuroendocrine pancreatic tumor, immunohistochemistry, multimodal treatment.

Introduction

Pancreatic cancer is one of the most fatal cancer in men and women after lung, colorectal, breast and prostate cancers, with a poor prognostic and a low life expectancy of nearly 5% at five years [1, 2]. Ninety-five percent of pancreatic cancers arise in the exocrine portion from ductal epithelium, acinar cells, or connective tissue, the most frequent pancreatic cancer being the adenocarcinoma (~80%). Other variants of pancreatic cancer requiring differential diagnosis should be taken into consideration like adenosquamous carcinoma or undifferentiated carcinoma. Neuroendocrine tumors of the pancreas are the second most frequent pancreatic cancers and are included in the family of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) heterogeneous group. Their phenotype has immunoreactivity for pan-neuroendocrine markers including chromogranin A and synaptophysin (SYN), neuron-specific enolase (NSE) and CD56 [1, 2]. Genomic instability that persists after cancer dissemination is characteristic for pancreatic cancer, resulting in different evolution among metastases. There is evidence that metastases have genetic heterogeneity and they may acquire driver mutations beyond those acquired for primary

tumors [3]. Multiple combinations of genetic mutations are commonly found in pancreatic cancers (mutational activation of oncogenes, predominantly KRAS, inactivation of tumor suppressor genes TP53, p16/CDKN2A, and SMAD4, inactivation of genome maintenance genes, such as hMLH1 and MSH2, that control the repair of DNA damage) [1, 2]. Another important feature is the heterogeneity of these tumors and their ability to transform under the action of cancer treatments, hypothesis proven by numerous literature data. Most cases are diagnosed in advanced stages, thus surgery is the main therapeutic modality regarding curative treatment. The main causes for the poor prognosis of the disease are the absence of specific symptoms, rapid progression of the disease with local extension and dissemination and intrinsic resistance to conventional chemotherapeutic regimens [4–7].

Here we report a case of a patient diagnosed with pancreatic tumor of the body and tail invasive in the splenic an portal vein, T4N1M0 (adenocarcinoma pancreatic cancer) treated with a multimodal approach: surgery (splenectomy and distal pancreatectomy, with suture of the portal vein), chemotherapy, in 2010, that relapsed in 2015, with local recurrence that was resected and distant pulmonary metastases. The recurrence tumor immuno-

histochemistry showed a neuroendocrine transformation of the tumor.

☞ Case presentation

For this specific case, informed consent for publication of medical data was obtained, besides the compulsory informed consent for initiating specific oncological treatment required in every oncological center in Romania.

In November 2010, the 58-year-old female, smoker patient, with no other comorbidities, presented at the primary care physician accusing acute abdominal pain, fatigue, asthenia, symptoms appearing three months earlier. After complete clinical and paraclinical (tumor marker CA19.9: 38.3 U/mL) evaluation, there was a suspicion of pancreatic cancer of body and the tail and the patient underwent radical surgery. The computed tomography (CT) examination detected a tumor of 6.5 cm in diameter located in the tail of the pancreas, which marks the duodenum and splenic vein and compress the stomach, without any other pathological changes, except regional lymph nodes having a maximum of 5–6 mm in diameter. Intraoperative surgical protocol described a voluminous 10/15 cm tumor in the body and tail of the pancreas, adherent to the posterior gastric, with central necrosis, invasive in the splenic and portal vein and with normal macroscopic liver and accessory spleen located at the great omentum. Surgery consisted in splenectomy and distal pancreatectomy, with suture of the portal vein and multiple peritoneal drainage. Pathological report described a globular macroscopic tumor of 10/13 cm in diameter; sections reveal whitish nodules of varying sizes between 0.3 to 1.5 cm, isolated or confluent in lobular areas and tumor necrosis.

Microscopic examination described pancreatic carcinoma with acinar cells, infiltrative in the peripancreatic fat tissue and small outbreaks of neuroendocrine differentiation. Intravascular tumor emboli, perineural invasion, tumor permeation of the pancreatic ducts, areas of necrosis were described. Two peripancreatic lymph nodes were examined, with reactive component and the splenic tissue with congestive red pulp. Conclusion: pT3N0, G1 pancreatic adenocarcinoma and immunohistochemical tests were recommended. Immunohistochemical tests showed cytokeratin (CK) 19, CK7 positive in small areas, carcinoembryonic antigen (CEA) weakly positive in tumor cells, chromogranin A negative, insulin negative, Ki67 positive 15–20%, thus concluding that neuroendocrine different-

iation of the tumor was not sustainable. Positive diagnosis was established: pT3N0M0 adenocarcinoma pancreatic cancer, without a neuroendocrine component.

The patient was treated with six cycles of Gemcitabine (1000 mg/m², d1,15) and Cisplatin (50 mg/m² d1,15), repeated every four weeks, and for four years there was no evidence of any relapse. Following treatment, a check-up CT examination without relapse was performed in 2012 (Figure 1).

In January 2015, at her regular follow-up, she was diagnosed with local recurrence of the pancreatic tumor. The CT scan examination, in January 2015, described post-splenectomy and distal pancreatectomy status, but with a bulky tumor mass at pancreatectomy and splenectomy lodge, with a maximum axial dimension of 11/12 cm and 12.2 cm in craniocaudal dimension, with heterogeneous structure, with lobular cystic component, with solid nodules, invasive in the stomach, left hemidiaphragm and anterior renal fascia, with anterior perirenal extension; compression and caudal displacement of the left kidney was detected; macronodular lesions located in the VI, VII and V right hepatic segments, with axial dimensions of 50/58 mm; right arm of the portal vein was undetectable, most likely thrombosed (Figure 2).

The patient resumed chemotherapy to reduce tumor volume, with a more aggressive chemotherapeutic regimen type – FOLFIRINOX [5-Fluorouracil (5FU) 400 mg/m² i.v. bolus d1 and 2400 mg/m² i.v. 46 h d1,2; Leucovorin 400 mg/m² d1; Oxaliplatin 85 mg/m² d1; Irinotecan 180 mg/m² d1], repeated every two weeks. After six months of treatment, there was a good clinical outcome and tomography-imaging examination performed in July 2015 showed that the tumor mass from the spleno-pancreatectomy lodge presented a solid regression compared to the January examination, but with progression of right liver lesion, with infiltrating area in the sixth segment.

Given this new imagistic development, the medical team, in accordance with the patient desire, decided surgical re-evaluation. Intraoperative tumor recurrence with invasion of the central part of the gastric wall and left kidney was diagnosed and the ablation of the relapsed tumor, including gastric wall, left nephroureterectomy and polar cystectomy were performed, with a latero-terminal mechanical gastroesophageal anastomosis and viscerolysis. The patient had no postoperative complications with full recovery. In October 2015, the patient has presented after surgical treatment for oncological follow-up with the pathological examination to establish therapeutic conduct.



Figure 1 – Abdominal CT scan (2012) with no signs of disease, only status modifications post-splenectomy and distal pancreatectomy.

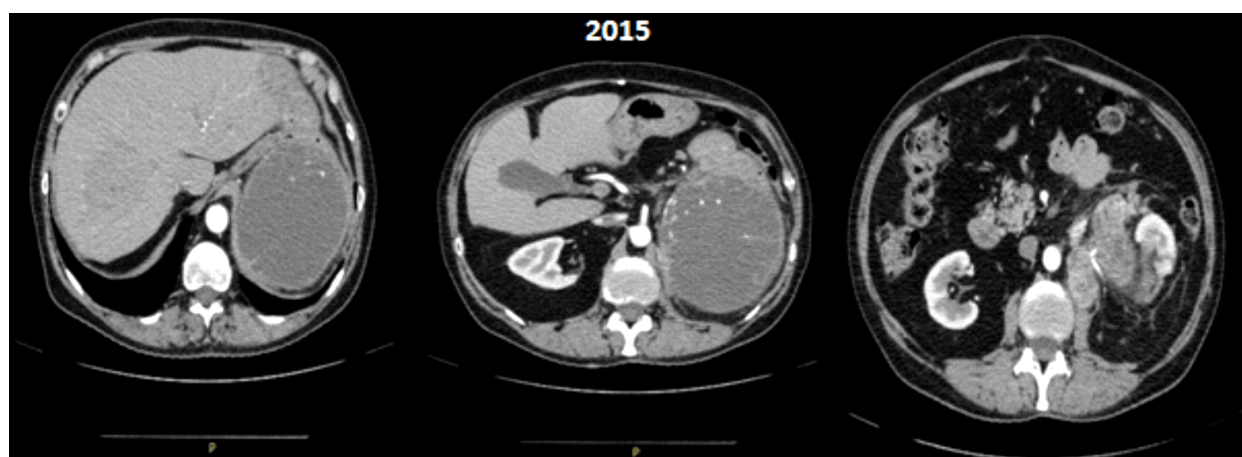


Figure 2 – Abdominal CT scan (2015) shows relapse of the disease: relapse tumor mass, invasive in the curve gastric, left hemidiaphragm and anterior renal fascia, macronodular lesions located in the VI, VII and V right hepatic segments.

Pathological examination described macroscopic tumor block with a left nephroureterectomy, including a kidney of 12/7/4 cm and ureter of 12 cm length, which shows a cystic tumor in the upper pole of 18/16/7 cm. The section highlights the wall with whitish areas alternating with yellowish areas and areas of necrosis. Gastric wall of 12/8 cm adhesion and whitish nodular renal sinus tumor of 2 cm are described. Microscopic tumor histology shows poorly differentiated carcinoma with solid and trabecular pattern with areas of clear cells, infiltrative in the renal pelvis and gastric wall, with cystic degeneration and necrosis that included frequent cholesterol crystals. Outstanding adrenal tumor tissue showed infiltration. The surgical limit of the ureteral resection was without tumor infiltration. One peritumoral lymph nodes had metastasis and three lymph nodes had reactive response. Immunohistochemical tests were recommended to establish histogenesis. Immunohistochemical tests of the relapsed tumor showed negative vimentin (VIM) in tumor cells, positive in stroma cells, CK7 positive in tumor cells, epithelial markers (epithelial membrane antigen – EMA), CD10, renal cell carcinoma (RCC) negative and melan A negative, inhibin positive in isolated tumor cells, PAX8 and S100 negative, SYN diffuse positive in tumor cells, Ki67 over 20%.

In conclusion, immunohistochemical tests and pathological examination indicated large cell neuroendocrine carcinoma with possible pancreatic origin in the anatomical-clinical context. Evolving transformation of the mixed acinar carcinoma and neuroendocrine pancreatic tumor operated in 2010 to a neuroendocrine carcinoma large cell can be considered.

Histopathological evaluation

Serial 3 µm sections had been cut from paraffin blocks and stained with Hematoxylin and Eosin (HE). Pathological report concluded that histological features of the tumor varied slightly from the initial pancreatic localization to the last metastasis. The initial tumor was acinar, mostly solid type and the neuroendocrine markers (chromogranin A, insulin) were negative. The relapsing tumor and its metastases showed some change in morphology and immunoprofile.

HE-stained sections showed in the stomach and metastatic nodules, tumor infiltration with large and small cells in the wall of a cystic cavity straight attached to the wall (Figure 3); the large cells were poorly differentiated, with pink or clear cytoplasm, vesicular nuclei and a lobulated pattern of growth; sometimes the pattern of growth became more regular with acinar aspects (Figure 4); the small cells had round dark nuclei and trabecular disposition; the mitoses number of both type were reduced (<2 mitoses/10 high power fields – HPFs); the tumor stroma is desmoplastic, partly hyalinized; the cyst centre was necrotic with cholesterol crystals.

Immunohistochemistry (IHC) evaluation

According to the IHC method, 3 µm sections from 10% formalin-fixed paraffin-embedded tissues were used for the IHC, using a polymer based detection system (Max Polymer Detection System – Leica Ref. RE7280-k) for an indirect bistadial technique. Tissue sections were spread on poly-L-lysine-coated slides immersed in three changes of xylene and rehydrated using a graded series of alcohol. Antigen retrieval was executed in microwave oven. In each section, 20 minutes incubation in 3% hydrogen peroxide was used to block the endogenous peroxidase. The sections were incubated for 60 minutes, at room temperature, with primary antibody: chromogranin A (Thermo Houston CA, USA, 1:800, LK2H10), synaptophysin (Leica, UK, 1:100, 27G12), CD56 (DAKO, Carpinteria CA, USA, 1:100, 123C3) and Ki67 (DAKO, 1:100, Mib-1), then the Max Polymer Detection System (Leica Ref. RE7280-k) was applied for 30 minutes. Finally, the sections were incubated in 3,3'-diaminobenzidine for 5 minutes, counterstained with Mayer's Hematoxylin and mounted. A Leica DM750 microscope was used for examination and photography of the slides. Replacement of primary antibody with non-immune serum was used for negative controls, while a section of pancreatic tissue provided positive control.

IHC showed VIM positive in small areas in large cells (Figure 5); epithelial markers were constantly negative (EMA), or weakly positive (CK 7). All general neuroendocrine markers (chromogranin A, synaptophysin, CD56) were positive, but not diffusely; the vaguely acinar structures showed a patchy staining, some cells being

negative (Figure 6, a–c). The markers for renal origin (CD10, PAX8), cortical adrenal (inhibin, melan A) were

negative as specific neuroendocrine one, as insulin. Ki67 was positive in ~20% of the tumor cells.

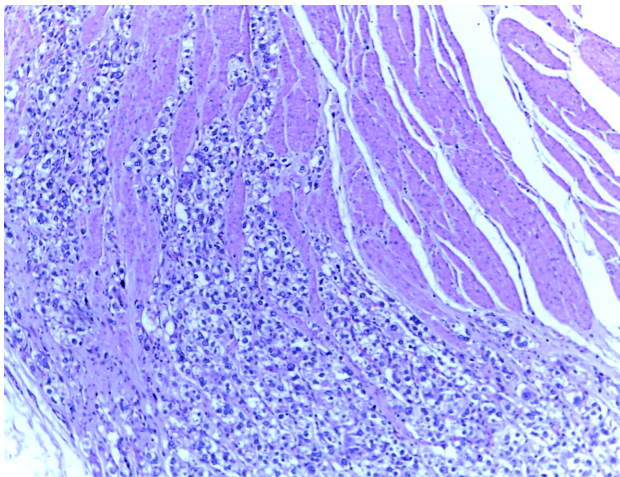


Figure 3 – Tumor infiltration with large and small cells in the wall of a cystic cavity straight attached to the wall (HE staining, $\times 100$).

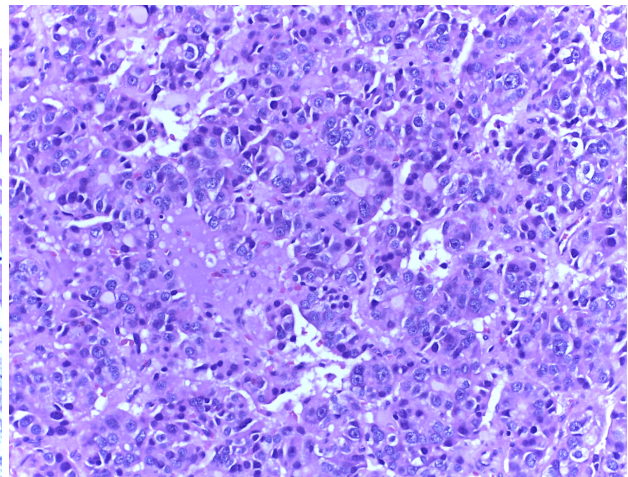


Figure 4 – Acinar structure in the metastatic tissue (HE staining, $\times 100$).

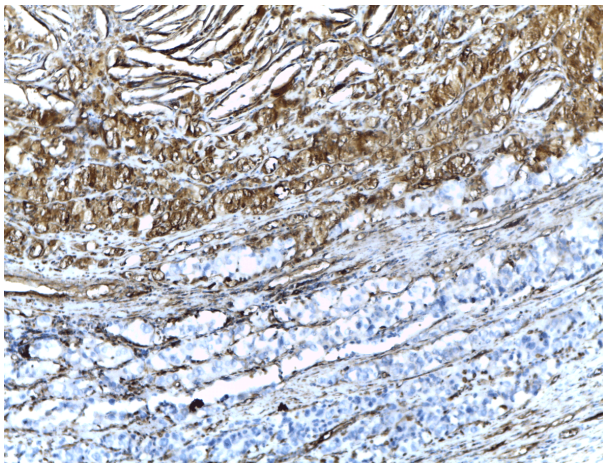


Figure 5 – Vimentin positive in small areas in large tumor cells (Immunohistochemistry, $\times 100$).

After IHC and pathology report were obtained, a complete biochemical analysis of relevant biomarkers for neuroendocrine tumors, such as plasma chromogranin A

(pCgA – which is a general NET marker), plasma serotonin and urine 5-hydroxy-indole acetic acid, was performed in November 2015. The only raised neuroendocrine marker was chromogranin A. The patient did not present any carcinoid syndrome symptoms. Due to neuroendocrine differentiation of the recurrence, the treatment for the patient was per NETs (neuroendocrine tumors) guidelines. The complete CT scan examination, in January 2016, showed no evidence of relapse and the biomarkers for NETs (chromogranin A, plasma serotonin and urine 5-hydroxy-indole acetic acid) performed were in normal range (Figure 7).

The original histopathological and IHC reports of this case belong to the Department of Pathology, “Floreasca” Emergency Hospital, Bucharest, Romania (in 2010) and to the Department of Pathology, “Sf. Maria” Hospital, Bucharest (in 2015). All the histopathological and IHC reports have been re-evaluated at Onco Team Diagnostic Laboratory within the “Monza” Hospital, Bucharest.

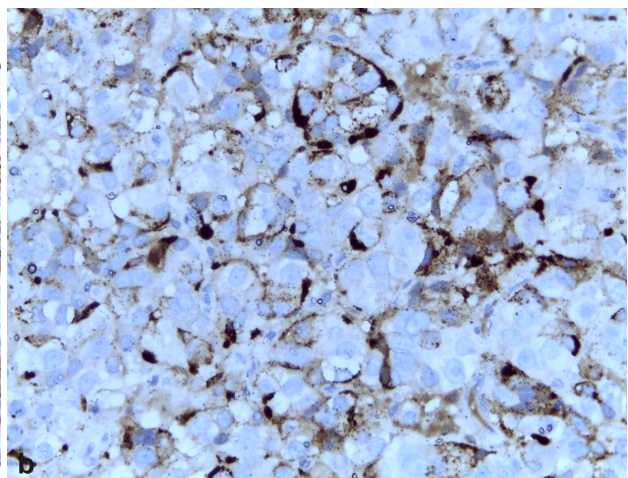
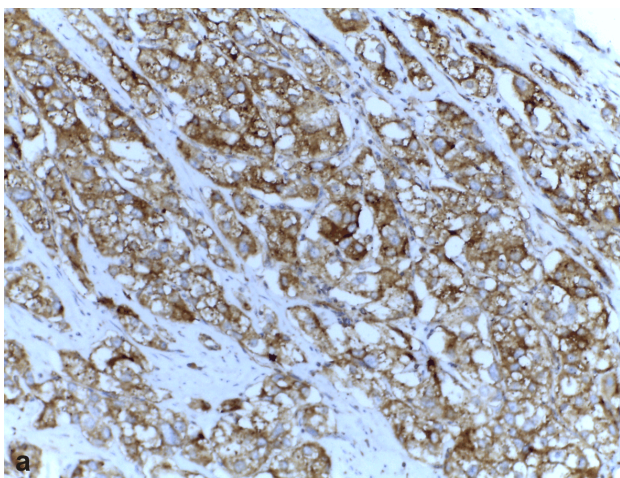


Figure 6 – (a) Vaguely acinar structures showed a patchy staining, some cells being negative (Synaptophysin immunohistochemistry, $\times 100$); (b) Neuroendocrine character of malignant cell proliferation at relapse demonstrated by acinar negative cells and neuroendocrine positive cells (Chromogranin A immunohistochemistry, $\times 100$).

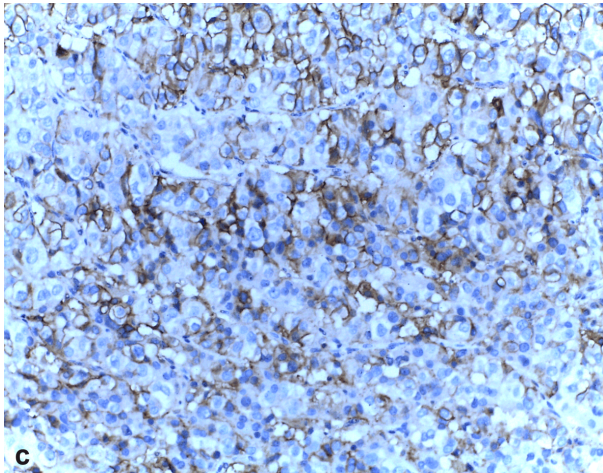


Figure 6 (continued) – (c) Focal positivity for neuroendocrine cells (CD56 immunohistochemistry, ×100).

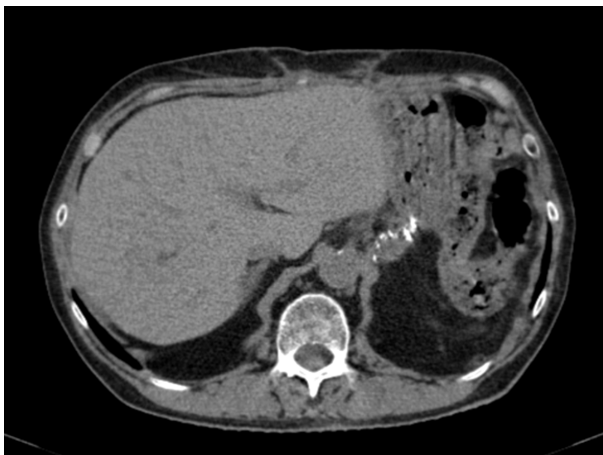


Figure 7 – Abdominal CT scan re-evaluation January 2016 showed no evidence of progression.

A comparative assessment of the criteria used for the initial positive diagnosis versus the recurrence diagnosis (a panel presentation)

Imaging criteria

The initial CT scan observed a tumor of 6.5 cm in diameter located in the tail of the pancreas, which compress the stomach and regional lymph nodes having a maximum of 5–6 mm in diameter (pT3N0M0, post-operative). At the time of the recurrence was described post-splenectomy and distal pancreatectomy status, but with a bulky tumor mass with axial dimension of 11/12 cm and liver metastases located in the V, VI and VII right hepatic segments, with axial dimensions of 50/58 mm (locoregional recurrence, liver metastases).

Histopathological criteria

First examination revealed pancreatic carcinoma with acinar cells, infiltrative in the peripancreatic fat tissue and small outbreaks of neuroendocrine differentiation (G1 pancreatic adenocarcinoma). Recurrent tumor analysis showed poorly differentiated carcinoma with solid and trabecular pattern with areas of clear cells, infiltrative in the renal pelvis and gastric wall, with cystic degeneration and necrosis with frequent cholesterol crystals (G3 carcinoma).

IHC criteria

The test performed in 2010 indicated CK19, CK7 positive in small areas, CEA weakly positive in tumor cells, chromogranin A negative, insulin negative, Ki67 positive 15–20% (these data confirm only an pancreatic adenocarcinoma without neuroendocrine differentiation). Recurrent tumor testing in 2015 showed positive general neuroendocrine markers (chromogranin A, synaptophysin, CD56), VIM positive in small areas in large cells, CK7 positive in tumor cells, epithelial markers (EMA), CD10, RCC and melan A negative, inhibin positive in isolated tumor cells, PAX8 and S100 negative, SYN diffuse positive in tumor cells, Ki67 over 20% (these results suggested neuroendocrine differentiation of the recurrence).

The initial diagnosis was pT3N0M0 adenocarcinoma pancreatic cancer, without a neuroendocrine component. Recurrence diagnosis was large cell neuroendocrine pancreatic carcinoma with liver metastases.

Discussion

Pancreatic cancer raises an important health problem, with few treatment options available in the past, with little impact on disease course and a limited prognosis. Recent years brought novelties in molecular biology and improved the knowledge of pathogenesis of pancreatic cancer. Mutations in the K-RAS oncogenes, tumor-suppressor genes can occur. New therapeutic strategies based on the molecular biology of pancreatic cancer seem to offer the greatest promise [8]. Defining the treatment strategy for patients suffering from pancreatic carcinoma requires a specialized multidisciplinary team that includes: surgeons, medical oncologists, gastroenterologists, radiation therapists, radiologists, pathologists and palliative care specialists.

Pancreatic NETs are still tumors with a low incidence. Few studies addressed to early detection and management are published. Surgical evaluation is preferred to be done in patients without imagistic evidence of unresectability, if we expect benefit on overall survival. Some pancreatic NETs are NF-PNETs (non-functional pancreatic neuroendocrine tumors) and make their detection difficult [9].

Well-differentiated neuroendocrine carcinomas have a good prognosis, with indolent biologic behaviors. Biopsy for immunohistology report is necessary to distinguish the various types of neuroendocrine carcinomas (epithelial *versus* neural origin or poor *versus* well differentiated). Additional laboratory workup is required to differentiate between functional and non-functional types of pancreatic endocrine tumors, which may associate neuroendocrine syndromes [9, 10].

Related to the origin of pancreatic adenocarcinoma, literature data concludes that there is overwhelming evidence showing the origin of the disease in islet cells and ductal epithelium of the pancreas [11]. The remarkable transdifferentiation tendency of islet cells to a variety of pancreatic and extrapancreatic cells, found also in both induced and human cancers, the presence of various drug-metabolizing enzymes in all tested species make this cell the most possible primary tumor origin. This striking transdifferentiation capability of islet cells into other cell types also indicates a close functional relationship between

the genes that are responsible for the differentiation toward acinar, ductal and islet cell phenotypes. The circumstances favoring the origin of cancer cells from islet cells could well be the environment rich on growth factors.

IL-8 and IL-8 receptors play important key roles in pancreatic cancer, up regulated in both pancreatic adenocarcinoma and neuroendocrine tumors, and indicate that this signaling pathway may modulate tumor behavior through autocrine and/or paracrine loops. The immunohistochemical analysis of the expression of IL-8, IL-8RA and IL-8RB in 52 pancreatic adenocarcinoma and pancreatic NETs demonstrated expression in 25%, 75% and 79% of pancreatic adenocarcinoma, respectively 21%, 63% and 92% of 52 pancreatic NETs [12].

Although it has low sensitivity, chromogranin A presents high specificity for NETs diagnosis (84–98%), being widely used as seric marker. Post-treatment monitoring can also provide prognosis usefulness, since the increase in the seric level is associated with disease progression, while its decrease is correlated with therapeutic response and/or improved outcome [13–15].

The prognosis seems to be determined by biological factors. Despite the clinical importance of metastasis, a fundamental question about the clone structures of metastatic tumor remains. The initial presence of rare micro-outbreaks with neuroendocrine differentiations may represent a factor for predicting future transformation from a typical common epithelial tumor of pancreatic adenocarcinoma into a predominant neuroendocrine phenotype. Recently, in the specific literature, an analysis was done on 44 cases reported until now and the conclusion was that the small number of cases does not allow a targeted therapy to be established for these patients. Chemotherapy has an impact on adenocarcinoma cells, with the reduction of the tumor volume, but probably selects the neuroendocrine cell clones, regardless of the use of platinum salt, that has some effect on PNETs tumors [16]. The new targeted molecular treatment methods (Sunitinib, Everolimus) have proved efficient both in advanced and metastatic forms, regarding progression free survival (PFS) and overall survival (OS) [17–19].

A recent literature search reveals three similar cases of mixed adenocarcinoma and neuroendocrine pancreatic tumor, with relative identically diagnostic characteristics. The only significant difference is in term of evolution: those three cases presented in 2016 in literature had a poor prognosis with rapid evolution, compared with our case, which seems to have a better prognosis. There are already two years since the recurrence has been diagnosed and patient is stable. The surgical treatment is the only difference in case management and this could support the use of this invasive treatment approach (when technical feasible) for obtaining a longer survival and a better quality of life [20–22].

✉ Conclusions

The acinar cell pancreatic carcinoma can have sometimes a mixed pattern of proliferation (acinar and neuroendocrine), and the neuroendocrine component can be represented by isolated cells, hybrid foci or large zones. The acquisition of genetic and molecular modifications

led to a phenotype strongly expressed by predominant neuroendocrine tumor. Immunohistochemical monitoring is recommended every six months through biopsy of tumoral form that was not surgically removed. These steps may help early highlighting of a well-differentiated neuroendocrine tumoral relapse, resulting in potential change of therapeutic approach as soon as possible. Future molecular analyses need to determine more accurate description of the genetic heterogeneity of pancreatic tumor metastases to adapt the new therapeutic strategies based on the molecular biology of pancreatic cancer cells.

Conflict of interests

The authors declare that they have no conflict of interests.

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