CASE REPORT

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Neuroendocrine pancreatic tumor – diagnosis circumstances, staging and treatment: a case report

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Abstract

Neuroendocrine neoplasms (NENs) of the pancreas are rare and frequently malignant. Our presentation of a pancreatic NEN analyzes the diagnosis circumstances, staging, treatment, one-year evolution and disease particularities. A 39-year-old nonsmoker patient was admitted in the Clinic of Pulmonology, Tirgu Mures, Romania with a pneumonia suspicion (fever, thoracic pain irradiated below the diaphragm, mild dyspnea). The chest X-ray showed a rise of the left diaphragm. Abdominal ultrasound revealed a large pancreas-related tumor. Computerized tomography (CT) scan with contrast confirmed a well-vascularized pancreatic tumor, which invades spleen, collateral circulation of the splenic vein, enlarged liver without secondary lesions and no retroperitoneal adenopathies. The patient was referred to the surgery where there was performed total tumor resection, spleen resection, and large lymphadenectomy. Histopathology and immunohistochemistry revealed the pancreatic NEN G2 grade, T3N1M0 and allowed accurate treatment. 2010 *World Health Organization* (WHO) NENs classification recommends further treatment-related biomarkers determination only in selected cases. Our case evolution after one year was favorable without local tumor relapse or metastases. The close survey of the patient (by clinical exam, imaging and biological markers) is ongoing. The onset of asymptomatic pancreatic tumor may have atypical respiratory symptoms. Imaging methods (ultrasound, contrast CT) are recommended in borderline symptomatology. Radical surgical resection of the tumor with lymphadenectomy, histopathology with immuno-histochemistry play an essential role in the correct diagnostic, grading, staging and treatment of pancreatic NENs. Close survey of the clinical, imagistic and biological markers is recommended.

Keywords: neuroendocrine pancreatic tumor, NEN G2, histopathology, immunohistochemistry.

Introduction

Currently, neuroendocrine neoplasms (NENs) or neuro-endocrine tumors (NETs) develop throughout the body from cell with special "hormone-producing" function. These tumors can be found mostly in the gastrointestinal system, pancreas, lung or gonads.

Pancreatic NETs rarely occur (1–2% of the total pancreas neoplasms), and usually have a late diagnosis [1, 2]. The prevalence of digestive NENs has worldwide increased in the last decades at least because of the improvement of the diagnostic methods (especially immunohistochemistry, blood markers, and modern imaging methods).

Pancreatic NENs have a malignant potential, therefore tumors have to be very well characterized. The last 2010 *World Health Organization* (WHO) NENs classification and the Consensus of the *European Neuroendocrine Tumor Society* (ENETS 2007) recommend that NENs have to be characterized by several mandatory criteria to evaluate the malignant potential [2–5]. The most important one is the location (the primary involved organ), followed by tumor differentiation (degree of similarity of the tumor with the original tissue of provenance and the degree of organization in cognoscible pattern).

NENs can be either well or poorly differentiated. Well-differentiated pancreatic NENs look like the normal tissue it came from (they have an "organoid pattern") [2]. They grow and spread slower than the poorly differentiated tumors, they cause symptoms when they become big enough to compress/invade the surrounding organs or by various hormone-like substances secretion.

The well-differentiated tumors have intracellular granules with neuroendocrine markers expression and hormonal immunoexpression (chromogranin A, synapto-physin) [5].

NENs can be functionally or non-functionally active. Some active NENs have been called from long time ago "carcinoid tumors" and may secrete particular substances (low molecular weight polypeptides – serotonin, bradykinin, histamine, prostaglandins) [5]. The "carcinoid syndrome" (flushing, diarrhea, nausea, vomiting, bronchoconstriction with wheezing and dyspnea, heart failure) occurs especially in highly secreting tumors or when the malignant tumor has spread into the liver and blood stream [5]. The ancient name "carcinoid tumor" is not any more in current use (it does not establish the differentiation, clinical evolution or the malignant aspect of the tumor).

"Tumor grade" expresses the degree of tumor aggressi-veness upon cell proliferation index (Ki67 marker). The differentiation criteria are linked to tumor grading (after

ENETS 2007, WHO 2010, AJCC – *American Journal of Critical Care* 2010) [3, 4, 6–8].

Well-differentiated tumors are considered as low grade ENETS – NET G1 ("typical carcinoid"). The moderately differentiated tumor corresponds to the intermediate grade ENETS – NET G2 with Ki67 index above 2% (grade 2, between 2–20%. This grade corresponds to the old "atypical carcinoid tumor"). The poorly differentiated tumor corresponds to high grade ENETS – NET G3 (small cell or large cell NE carcinoma).

Tumor staging can be site specific, such as the 7th TNM Staging by AJCC/UICC (*Union for International Cancer Control*) [5–8].

Tumor staging can be established by modern methods, such as contrast-enhanced computerized tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasono-graphy (EUS) with tumor or lymph nodes biopsy or ^{111}In-DTPA (diethylenetriaminepentaacetic acid)-octreotide scintigraphy [5]. The first indicator, T corresponding to the size of the tumor (a size above 2 cm and the vascular invasion are severe prognosis factors), N – lymph nodes invasion and M – characteristic for metastasis [2].

Investigations for targeted therapy and prognostic markers are not on routine use neither very good stand-ardized [3–5]. The most prominent marker is cytokeratin 19, which is associated with poor outcome [9, 10]. Ki67 – the proliferative cell index (% of positive cells per 100 counted cells) may assess the severity if it is raised ≥3% (Ki67 is considered the best prognostic/predictive para-meter for NETs [11–13]. Blood expression of some common neuroendocrine markers such as [5]: CgA or CgB chromogranins (plasma CgA is elevated in 60–100% of NEN patients with either functioning or non-functio-ning NETs) and synaptophysin can be used. Hormones immunoassays (somatostatin receptor SSTR2) assess the need of chemotherapy in liver metastasis or in tumors with hormonal expression [11]. Pancreastatin level above 500 pmol/L is an independent indicator of poor outcome (it correlates with liver metastasis; it is used in the follow-up of NENs patients) [5]. Immunohistochemistry – expression of somatostatin receptor type 2A is well correlated with somatostatin receptor scintigraphy (77%), and with therapeutic response (75%) [12, 13]. Somatostatin-receptor scintigraphy with ^{111}In-labeled pentreotide can exclude metastases [14]. Gene expression profiling by RT-qPCR (reverse transcription quantitative polymerase chain reaction) on formalin-fixed paraffin-embedded tissues [13].

Gold standard treatmentt consists in total tumor removal. Hepatic metastasis may benefit from hepatic artery embolization, which relieves symptoms and delay disease progression [14].

Current additional therapy options in pancreatic NENs include somatostatin analogues (octreotide/Sandostatin), which inhibit the growth of tumor with specific receptors expression [13, 14]. Cytostatics in advanced stages and grades [14–16] can also present as a useful therapy. Monoclonal antibodies (bevacizumab exerts an action on endothelial growth factor receptors) [14].

⊟ Case report

A 39-year-old nonsmoker patient was admitted in the Clinic of Pulmonology, Tîrgu Mureş, Romania with a left pneumonia suspicion (fever, thoracic left pain with irradiation below the diaphragm, mild dyspnea and dry cough).

The chest X-ray showed a raised left right hemi-diaphragm. The abdominal ultrasound revealed a large tumor in the retroperitoneal space aroused from the corpus and the tail of the pancreas, 13/10/7 cm, apparently well delimited, isoechogenic well vascularized (during Doppler ultrasound).

The contrast-enhanced CT scan confirm a well vascularized pancreatic tumor with minimally invasion of the spleen, collateral circulation of the splenic vein to superior cave vein, homogeneous enlarged liver without secondary lesions or retroperitoneal adenopathies.

The patient did not present any symptoms related to hormone secretion or other pathology. Blood and urine analysis was normal, viral hepatic marker negative, *Helicobacter pylori* positive.

At that time there were not possible to perform PET (positron emission tomography)–CT. The patient was referred to the surgery where there was performed total tumor resection, medio-distal pancreatectomy (pancreas body and tail removing), spleen resection and lymph-adenectomy.

Gross examination of the surgical specimen revealed a relatively well-demarcated pseudoincapsulated 135× 110×75 mm-sized white-yellow tumor weighing 550 g. The tumor involved the distal part of the pancreatic body and pancreatic tail and crossed the pancreatic capsule with direct invasion in the splenic hilum (30×8×3 mm) and focal involvement of the spleen parenchyma, respectively.

Microscopically, the tumor consisted of solid nests intermingled with trabecular areas. The small uniform tumor cells showed finely granular eosinophilic cytoplasm with the specific "salt and pepper" aspect and central round centrally located nuclei with well-defined nucleoli. The mitotic rate was relatively low (<10 mitoses per HPF – high power field). No vascular or perineural invasion was detected. The proximal and distal pancreatic margins were free of tumor cells; the splenic invasion was micro-scopically confirmed.

Immunohistochemically, the tumor cells diffusely expressed AE1/AE3 keratin and the neuroendocrine markers synaptophysin and chromogranin (Figure 1).

Based on the uniformity of the tumor cells, the low mitotic rate, low-grade of nuclear pleomorphism and minimal necrotic areas, the final diagnosis was "mode-rately-differentiated (G2) NET of the pancreas". Direct invasion of the spleen and identification of metastasis in one perisplenic lymph node, without involvement of the celiac axis or superior mesenteric artery, and no CT-detected distant metastases, allowed inclusion of the case in the stage IIB (pT3N1M0).

The biological markers – urinary 5-hydroxy-indole-acetic acid (5-HIAA) and seric chromogranin A (CgA) – were negative. The tumoral biomarkers were negative, thereby the oncology service did not consider at that moment biological treatment.

The six-month and the one-year postoperative evolution were evaluated by clinical exam and CT scan. Both clinic aspects and CT scan showed a very good evolution, without local relapse or secondary determination. The patient

performed at one year after surgery oncologic markers for prognostic (serum CgA, urinary 5-HIAA). The biomarkers were in normal limit. The clinical, imagistic and biological follow-up was very close. Systematic chemotherapy and biotherapy (with somatostatin analogues and interferon-α) will be used if after surgery recurrence will appear.
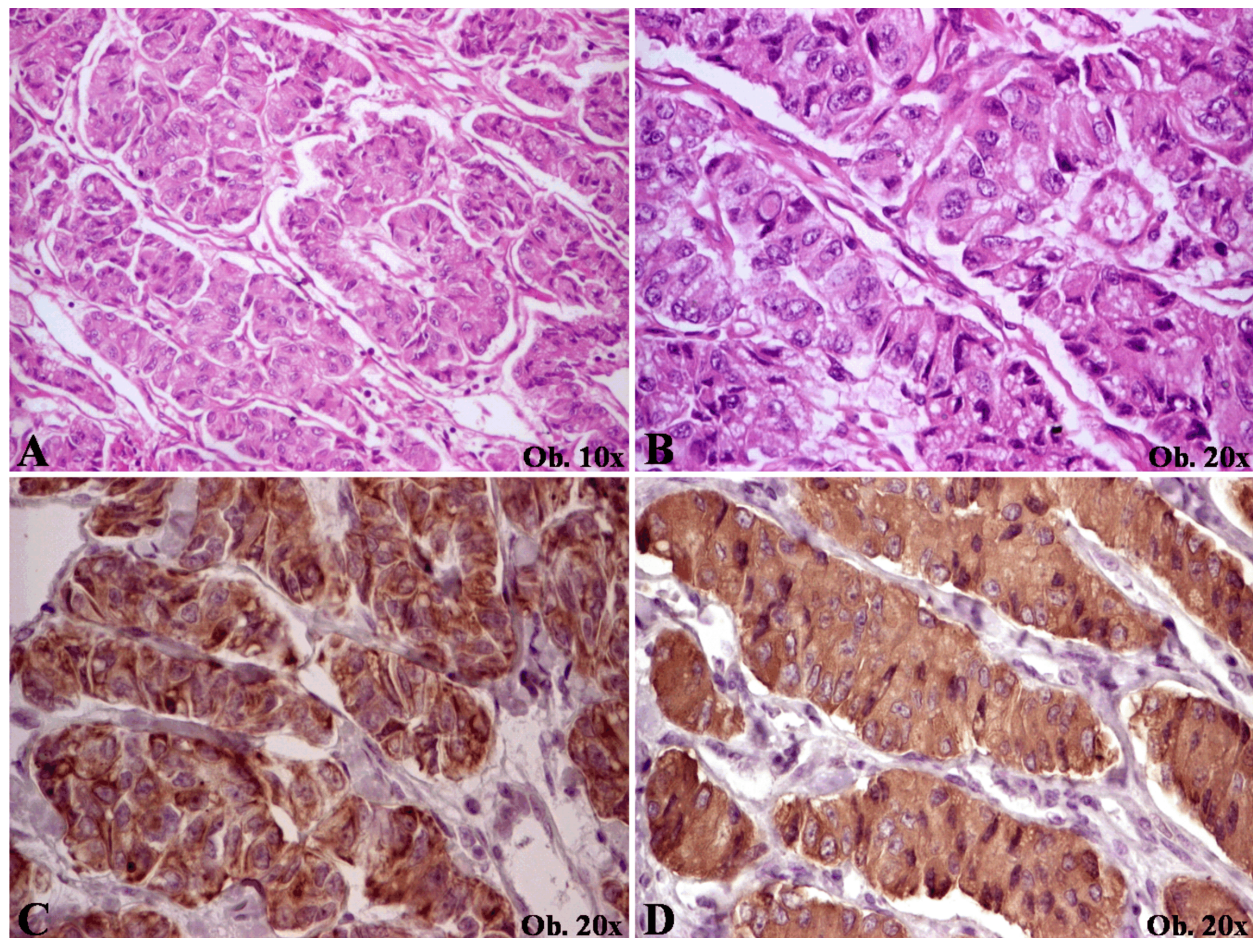
Figure 1 – The moderately differentiated pancreatic neuroendocrine tumor consists of proliferation of solid tumor areas with trabecular architecture and low grade of nuclear pleomorphism (A–D). The tumor cells are reactive for keratin AE1/AE3 (C) and synaptophysin (D).

⊟ Discussion

Clinical particularities

The patient was long time asymptomatic and we noted an incidental finding. The patient had a NEN without symptoms related to serotonin secretion (nonfunctional tumor) [15]. The very slow evolution may be explained by the left-sided pancreatic location without jaundice or celiac compression. We noted a completely unusually onset mimicking a left basal pneumonia.

The favorable evolution may be explained by distal location of the tumor (half of the corpus and tail), stage N1, M0 in the absence of other organ invasion (outside the spleen which benefited of splenectomy). There still is a hope for a good prognostic due to young age at the moment of diagnosis, absence of metastases, intermediate tumor grade (2), surgery total resection, low mitotic index, non-functioning endocrine tumor, negative biological markers.

Particularities of the laboratory issues

CT with contrast combined with abdominal ultrasound offered a well preoperative diagnosis for location and tumor staging. The patient could not perform at that time the PET–CT exam for a more accurate preoperative staging but the CT with contrast offered good criteria for surgical resecability – absence of the celiac adenopathies and absence of liver metastasis [16–19].

The use of PET scanning is more usefully in undifferentiated tumors, which have higher FDG ([18]Fluoro-deoxyglucose)–PET uptake. PET with tracers based on metabolic features (5-HTP – 5-hydroxy-tryptophan) and receptor characteristics for hormone-like substances has shown promising results in a limited number of studies.

Blood CgA and 5-HIAA from 24 hours urine were performed for prognosis assessment and follow-up reasons. 2010 WHO NENs classification and current guidelines do not recommend routine use of prognostic or treatment related biomarkers (outside of specific research settings) [3–5]. Detecting high level of CgA (>156.5 ng/mL) is usefully for metastasis prediction [18, 20, 21].

⊟ Conclusions

The clinical "apparent" onset of pancreatic tumor may have atypical respiratory symptoms. Evolution of non-functional NEN (without serotonin secretion) may be long time very noiseless. Imaging methods (ultrasound, contrast CT) are recommended in borderline clinical symptoms and when PET–CT scan is not accessible. Radical surgical resection of the NEN with lymphadenectomy and spleen

resection played in our case the main role in the treatment of this rare tumor. The future favorable evolution and good prognostic are due to young age at the moment of diagnosis, surgery total resection, absence of metastases, intermediate tumor grade (2), low mitotic index, non-functioning endocrine tumor, negative biological markers. Histopathology and immunohistochemistry have a decisive role in the correct diagnosis, grading, staging and treatment of pancreatic NENs. The clinical, imagistic and biological follow-up has to be very close and will contribute to correct assessment of case evolution.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors had an equal contribution in preparing this manuscript.

References

[1] Dickson PV, Behrman SW. Management of pancreatic neuro-endocrine tumors. Surg Clin North Am, 2013, 93(3):675–691.
[2] Klöppel G. Classification and pathology of gastroentero-pancreatic neuroendocrine neoplasms. Endocr Relat Cancer, 2011, 18(Suppl 1):S1–S16.
[3] Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). WHO classification of tumours of the digestive system. World Health Organization (WHO) Classification of Tumours, 4th edition, vol. 3, IARC Press, Lyon, 2010.
[4] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas, 2010, 39(6):707–712.
[5] Vinik AI, Woltering EA, Warner RR, Caplin M, O'Dorisio TM, Wiseman GA, Coppola D, Go VL; North American Neuro-endocrine Tumor Society (NANETS). NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. Pancreas, 2010, 39(6):713–734.
[6] Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch, 2007, 451(4):757–762.
[7] Sobin LH, Gospodarowicz MK, Wittekind C (eds). TNM classification of malignant tumours. 7th edition, International Union Against Cancer (UICC), Wiley–Blackwell, 2009.
[8] Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds). AJCC cancer staging manual. 7th edition, American Joint Committee on Cancer (AJCC), Springer-Verlag, New York, 2010.
[9] Jain R, Fischer S, Serra S, Chetty R. The use of Cytokeratin 19 (CK19) immunohistochemistry in lesions of the pancreas, gastrointestinal tract, and liver. Appl Immunohistochem Mol Morphol, 2010, 18(1):9–15.
[10] Tomassetti P, Campana D, Piscitelli L, Casadei R, Santini D, Nori F, Morselli-Labate AM, Pezzilli R, Corinaldesi R. Endocrine pancreatic tumors: factors correlated with survival. Ann Oncol, 2005, 16(11):1806–1810.
[11] Papotti M, Bongiovanni M, Volante M, Allìa E, Landolfi S, Helboe L, Schindler M, Cole SL, Bussolati G. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohisto-chemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch, 2002, 440(5):461–475.
[12] Volante M, Brizzi MP, Faggiano A, La Rosa S, Rapa I, Ferrero A, Mansueto G, Righi L, Garancini S, Capella C, De Rosa G, Dogliotti L, Colao A, Papotti M. Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. Mod Pathol, 2007, 20(11):1172–1182.
[13] Volante M, Righi L, Berruti A, Rindi G, Papotti M. The pathological diagnosis of neuroendocrine tumors: common questions and tentative answers. Virchows Arch, 2011, 458(4):393–402.
[14] Petrányi A, Bodoky G. Pharmacologic therapy for neuro-endocrine tumours. Orv Hetil, 2011, 152(10):379–391.
[15] Gullo L, Migliori M, Falconi M, Pederzoli P, Bettini R, Casadei R, Delle Fave G, Corleto VD, Ceccarelli C, Santini D, Tomassetti P. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol, 2003, 98(11):2435–2439.
[16] Pregun I, Bodoky G, Rácz K, Tulassay Z. Carcinoid tumors. Orv Hetil, 2010, 151(46):1885–1894.
[17] Amador Cano A, García F, Espinoza A, Bezies N, Herrera E, De Leija Portilla J. Nonfunctional neuroendocrine tumor of the pancreas: case report and review of the literature. Int J Surg Case Rep, 2013, 4(2):225–228.
[18] Paik WH, Ryu JK, Song BJ, Kim J, Park JK, Kim YT, Yoon YB. Clinical usefulness of plasma chromogranin A in pancreatic neuroendocrine neoplasm. J Korean Med Sci, 2013, 28(5):750–754.
[19] Kimura W, Tezuka K, Hirai I. Surgical management of pan-creatic neuroendocrine tumors. Surg Today, 2011, 41(10):1332–1343.
[20] Poiană C, Neamţu MC, Avramescu ET, Carşote M, Trifănescu R, Terzea D, Neamţu OM, Ferechide D, Dănciulescu Miulescu R. The poor prognosis factors in G2 neuroendocrine tumor. Rom J Morphol Embryol, 2013, 54(3 Suppl):717–720.
[21] Mirancea GV, Moroşanu AM, Carniciu S, Dima S, Bacalbaşa N, Popescu I, Ionescu-Tîrgovişte C, Mirancea N. Relevant infra-structural alterations in a pancreatic neuroendocrine tumor: an insulinoma case. Rom J Morphol Embryol, 2014, 55(2 Suppl):659–668.

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