



Received: 2016.04.12
Accepted: 2016.07.18
Published: 2017.03.01

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Disseminated Pancreatic Neuroendocrine Neoplasm (NEN) with an Uncommon Localisation in the Central Nervous System. A Case Report

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Summary

Background:

Neuroendocrine neoplasms (NEN) are rare neoplasms that originate from neuroendocrine cells and are characterized by the potential of hormonal activity. Approximately 70% of these tumours are located in the gastrointestinal system (GI), followed by the bronchi, endocrine glands-like C cells of the thyroid (medullary carcinoma), the parasympathetic and sympathetic system (paragangliomas, pheochromocytoma) and other very rare locations. The prevalence of cerebral metastases in neuroendocrine tumours is estimated by various authors to be approximately 1.5–5%. When the primary tumour is located in the pancreas, it is associated with a risk of cerebral metastases lower than 2%.

Case Report:

We describe a patient with a disseminated pancreatic NEN that presented with an isolated lesion in the brain. We gathered the important data via medical history, observation, analysis of medical records, imaging and others diagnostic tests. Despite the fairly rare prevalence of cerebral metastases in NENs, a neurological work-up should be performed. This should include neuroimaging of the brain, preferably with MR, together with the somatostatin receptor scintigraphy (SRS), in each clinically suspicious case.

Conclusions:

A histopathological examination of the CNS tumour can confirm a dedifferentiation of NEN in the direction of a neuroendocrine carcinoma (NEC – neuroendocrine carcinoma) with a poor prognosis.

Cerebral metastases are diagnosed in 1.5–5% of patients with a neuroendocrine neoplasm. In each case suggestive of a dissemination into the central nervous system, MRI of the brain should be performed.

MeSH Keywords:

Neoplasm Metastasis • Neuroendocrine Tumors • Neuroimaging

PDF file:

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Background

Neuroendocrine neoplasms (NENs) represent relatively uncommon neoplastic tumours, and almost 70% of these rare tumours are of a gastro-entero-pancreatic (GEP) origin [1,2].

These tumours reflect the wide distribution of neuroendocrine cells in the human body, especially in the diffuse endocrine system located in the pancreas and the gastrointestinal (GI) tract (e.g. gastrin cells, insulin cells and other cell such as enterochromaffin cells), which plays a crucial role in the processes of secretion and regulation in

Table 1. Biochemical and imaging data including: CgA, CT and somatostatin receptor scintigraphy (SRS) during Somatulin Autogel therapy.

Date	Chromogranin A CgA (N <98 ng/ml)	Somatostatin Receptor Scintigraphy (SRS) results	CT (RECIST)
10/2011	156.5	Positive scan (Krenning scale of radionuclide uptake – 3)	Initial pancreatic tail tumour size – 30 mm
07/2012	83.9	Equivocal results with an uptake of radiotracer – Krenning scale 2	SD
12/2012	288.8	N.D.	SD
05/2013	104.3	Negative results with a very weak uptake of the radiotracer (Krenning 1 to 2)	SD
11/2013	83.2	N.D.	SD

the GI tract. Otherlocalisations of NENs include, e.g., the bronchopulmonary system, adrenals (pheochromocytoma), paraganglioma, medullary cell carcinoma (MTC). Based on the pTNM classification, there are 4 groups of NENs, depending on tumour cell characteristics and the degree of differentiation. These are – (1) well-differentiated tumours NETG1 (Ki-67 \leq 2%), (2) moderately differentiated tumours NETG2 (2<Ki-67 \leq 20), (3) poorly differentiated carcinomas NECG3 (Ki-67 >20%, and (4) mixed neuroendocrine and adenocarcinomas (MANEC) [3,4].

In the USA, the incidence of the disease in the years 2003-2007, based on the 2007 National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) data base, was 5.76/100,000. This classification is currently used to characterize the tumours, which is relevant for choosing optimal methods of treatment and improving prognosis [5]. Metastatic disease is commonly seen in both the intestinal and pancreatic NENs. [1,2,5,6]. At initial diagnosis, 40–50% of patients with GEP-NEN have a disseminated disease, with an increasing prevalence over time [1,2,5,6]. Cerebral metastases in disseminated NENs are an uncommon finding. There are different reports on the incidence of brain metastases ranging between 1.5–5%. The primary pancreatic localisation in case of brain metastases is seen in less frequently than 2%. Cerebral metastases of NENs incur a much worse prognosis with respect to patient survival than metastases in other locations [7,8].

Case Report

This is a case report of a patient with a history of a pancreatic well-differentiated NEN in the pancreatic tail. The initial diagnosis indicated a spleen tumour, which was followed by a splenectomy performed on the 10/01/2011. The procedure included an R2 resection of the tumour located in the hilum of the spleen. However, the histopathological examination reported a NETG1 pancreatic tail tumour with the mitotic index of 2 per 10 HPF (Ki-67 <2%). Due to the R2 resection, the patient had another surgery performed in another hospital on the 04/04/2011. The second surgery was a distal pancreatectomy. Due to an altered anatomy after the first surgery, no tumour was found during the second surgery, which was confirmed on a histopathological examination. The patient was referred to the Memorial Cancer Center for further evaluation and treatment. In order to

identify the remaining tumour mass, a full diagnostic imaging work-up was performed, which involved both structural (CT) and functional SRS (somatostatin receptor scintigraphy) studies. Both CT and SRS showed a tumour mass in the pancreatic tail. There was a positive high expression of somatostatin receptors (SST) on the SRS study after an injection of a standard dose of ^{99m}Tc HYNICTOC (Tektrotyd, NCBJ; Polatom, PL). The whole-body tomographic acquisition (WB-SPECT technique) showed a pathological uptake of grade 3 in the Krenning scale (pronounced pathological accumulation, indirectly confirming the presence of a neuroendocrine tumour). Contrast-enhanced CT showed a hypervascular focal lesion, 30mm in diameter, visible in both the arterial and venous-portal phases, which was consistent with a pancreatic NEN.

The patient underwent another surgery with the removal of the tumour that was previously seen on both CT and SRS. Because of the prior surgery, the resection was not radical (R2). The histopathological examination indicated a NETG2 tumour, with an increased proliferation index of Ki-67=15%. The final diagnosis based on the surgery was pTxN0Mx, as there was no lymph node involvement. In subsequent studies, the level of chromogranin (CgA) decreased initially after the surgery (CgA) and then increased and decreased after starting the treatment with somatostatin analogues. The patient began the treatment with the somatostatin receptor analogues (Somatuline Autogel 120 mg every 4 weeks) in 04/2012, which was continued until 11/2013. During the 20 months of treatment with Somatuline, no significant adverse effects were noted. Based on CT, the disease was stabilized – SD (RECIST). On the control SRS, there was no new significant accumulation of the radiotracer, despite an early pathological uptake. However, a SRS study performed in November 2013 was negative, which could result from an effective treatment with an SST analogue or from a dedifferentiation of the primary NETG1 into a NETG2 tumour. The dates of examinations of CgA, SRS and CT with respective results are presented in Table 1.

During the therapy with SST analogues in November 2013, the patient was admitted because of seizures. A CT (Figure 1) and MRI (Figure 2) scans showed a tumour of the right fronto-temporal lobe, 55mm in diameter, with a high vascular bed after i.v. contrast enhancement. The tumour



Figure 1. An axial CT scan of the head after i.v. contrast enhancement showing tumour mass located in right fronto-temporal region of the brain.

was surrounded by quite an extensive zone of oedema (Figure 1).

Due to the extensive brain oedema and the clinical life-threatening signs, an urgent neurosurgery was performed in the University Clinical Hospital, Olsztyn on the 1/20/2014. Before surgery, the patient had undergone an MRI of the brain with 3T system (Magnetom Skyra; Siemens, AG; Germany). The Sono Wand navigation system was used to plan the surgery.

The surgery was performed under general anaesthesia and involved an extensive right fronto-temporo-parietal craniotomy to reach basal part of anterior and middle cranial fossa. After removing the bone flap, visualisation of dura, which was tense. After forming radial flap of dura, cortical surface of right hemisphere was seen. Because of features of increased intracranial hypertension (distended surface of cortical gyres), there was carried out a resection of the right temporal lobe in the range of 5.5 cm. During resection temporal part of tumour was visualized. Tumour mass was hard, solid, cohesive, richly vascularized, with a visible border of surrounding zone of swollen white matter. Under the control of neuro-navigation with bipolar coagulation, ultrasonic aspirator and with the assistance of an operating microscope there was performed resection of tumour mass visualized in the base of the middle cranial fossa. During resection of tumor there was shown complex of the right middle cerebral artery at its branches, which were overgrown by the tumour mass. The tumour was removed gradually and leaving intact main trunk and branches of the right middle cerebral artery. Due to the infiltration by tumour of visualized trunk of the right middle cerebral artery, part of the tumour had to be left. In a next step with intraoperative ultrasound frontal part of the tumour was located. Then next part of removing the tumour located at the base of the right frontal region. After resection of frontal part of tumour, the main part of operation was done. Cerebral cortex with no signs of swelling. Next step of suturing watertight of dura with use of patch of perios-teum. Bone flap suturing. Skin clousure.

A histopathological examination described a metastatic neuroendocrine carcinoma with foci of necrosis and significant polymorphism, i.e. NECG3. Immunohistochemistry (IHC) was as follows: CKAE1/3 +, CK 19+, chromogranin + Synaptophysin +, CD56 +, CK7, Ki-67=55%.

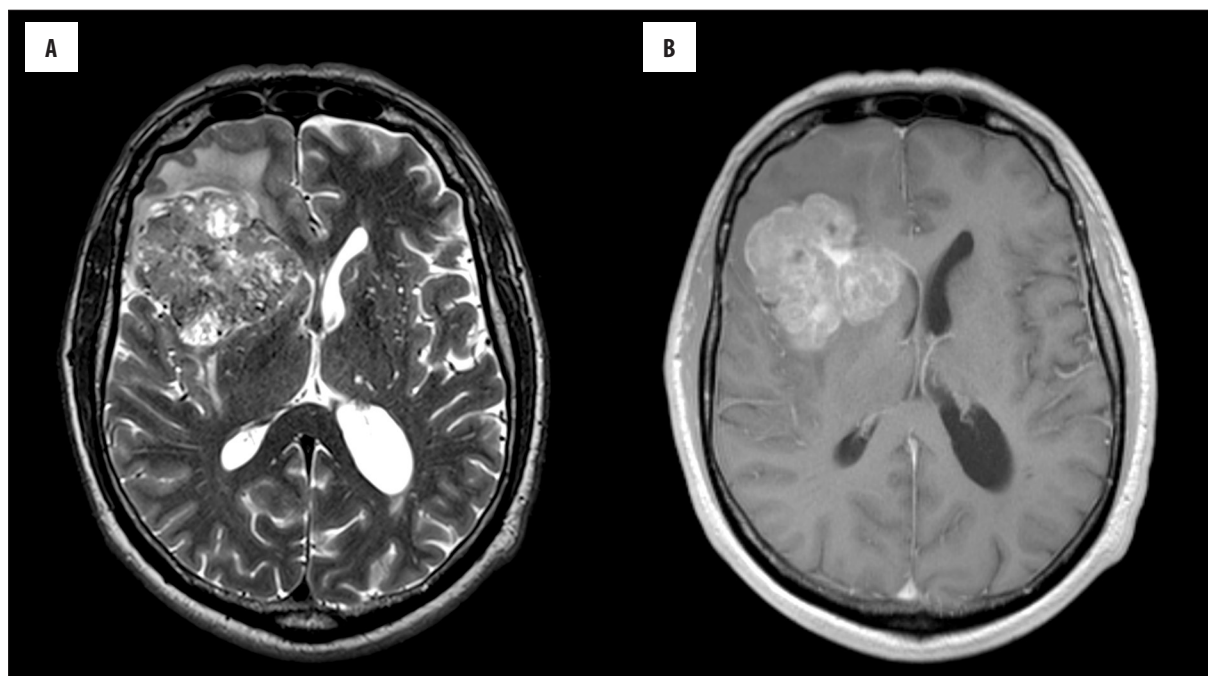


Figure 2. MRI brain scan showing tumour mass located in the fronto-temporal region of the brain. (A) T2-weighted image and (B) T1-weighted image after i.v. contrast enhancement

On the fourth day after the surgery, the patient had an oedema of the right hemisphere of the brain. A revision of the tumour bed and left decompression were performed. Due to a severe clinical condition (GCS 15, deep hemiparesis of the left hand) the patient was transferred to an ICU, where he stayed for a week. Subsequently, he was transferred to the Department of Neurosurgery and after 2 weeks to the Department of Clinical Neurological Rehabilitation where he stayed until 10.03.2014.

On admission to the rehabilitation ward, a physical examination showed features of a massive paralysis of the left upper limb. In the left lower limb, there were limited movements in all the joints. In the upper limb, there were only traces of active movements in the shoulder joint and the elbow, there were no active movements of the wrist = and fingers.

On the neurologopedic examination, a left-sided weakness of the articular muscles and facial muscles was found.

The patient was wheelchair-bound. He scored 3 points on the Barthel ADL scale. The patient did not control the bladder and was catheterized. The neuropsychological diagnosis revealed a working memory deficit, low resistance to distractors, significantly impaired visuospatial functions (Benton Visual Retention Test BVRT + 3–15), impaired ability to recognize visual stimuli with the preservation of normal vision, deficit of executive function – in particular planning, initiating and sustaining activities (Color Trails Tests: CTT1, CTT2 <1 percentile), rigid thinking, slowing down, difficulty with concentrating on the task, problems with selective attention and increased levels of anxiety. After physical rehabilitation, the muscle strength in the left limbs and the postural muscles improved. The patient gained muscle mass in the left lower limb, and there was a slight improvement in the left upper limb dexterity and a decreased facial asymmetry. The patient could walk short distances with the help of a therapist, and over longer distances the patient used a wheelchair. He scored 7 points on the Barthel ADL scale.

The WAIS-R (EN) intelligence test conducted at the end of the hospitalization determined the verbal intellectual functioning of the patient to be high and his executive functions to be average. The overall IQ score was above the average. As regards the specific factors, the patient received high scores in tests of verbal comprehension and memory and resistance to distractors. His results in perceptual organization were below the average.

After surgery and rehabilitation, the patient standard radiotherapy due to the R2 resection, which took place from 03/2014 to 05/2014. During follow-up, a control MRI scan performed in 10/2014 showed no further local recurrence, but new lesions in the medulla were found (Figure 3). The patient deteriorated rapidly and died in 03/2015.

Discussion

NENs are difficult to diagnose because of an uncharacteristic and often variable symptomatology and difficulties in the interpretation of axillary tests [2,5,6,11,12]. In addition,

there are no specific laboratory tests for the identification of NEN cerebral metastases to the brain. Similarly, there are no methods that could determine the activity of the cancer [6–9,12,12]. In the event of metastatic changes in the liver and in the CNS, the optimal imaging technique is MRI [6,11,13].

In patients with brain metastases, only about 1.3% have NENs, and of the patients with NENs only 1.5 to 5% have cerebral metastases [7]. A meta-analysis of 1,633 patients hospitalized in 1977–2003 in the Texas MD Anderson hospital, determined the incidence of NET cerebral metastases to be 1.5%, and in 46% of patients metastases were single and in 54% of multiple [7]. Most patients had primary lung NENs, and initially very often NEC, which has an aggressive behaviour. An earlier study published in 1986 determined the incidence of cerebral metastases of NENs to be 5% [10]. In our opinion and according to recent reports, these numbers are overestimated. The majority of cerebral NEN metastases were recognized as neuroendocrine carcinoma (NEC). Primary tumours frequently progressed from less malignant forms into more aggressive cancers. It is probably a natural behaviour of these tumours in terms of dedifferentiation of cancer cells during the course of the disease [9]. Our case was uncommon, because the brain lesion was the only single sign of dissemination of the disease on both clinical and imaging examinations. Moreover, the initial NETG1 progressed during a clinical follow-up over 2 years to a NECG3 tumour with a single brain metastasis. The neurological signs of brain metastases appeared very fast after the primary diagnosis, which initially was at the clinical stage of CS IIA (pT2N0M0). Based on the routine clinical and imaging follow-up, in patients with the pancreatic tumours at the stage of CS II, there is no need to perform routine brain imaging, which is reflected by the recent ENETS recommendation for the management of patients with pancreatic NEN that are well and moderately differentiated [11].

The median survival time of patients with NEN with cerebral metastases was assessed to be 7–10 months [7–9,12]. Despite disseminated disease, the cancer is often curable in terms of the long-term survival and a full activity of the patient [13]. The literature emphasizes that today, in patients with advanced nonresectable pancreatic NEN, there are several options that include a combination therapy with synthetic analogues of the somatostatin receptor (SSTR), and modern molecular target drugs such as those targeting the mTOR pathway (Everolimus) or multipotential VEGF and other receptor blocking agents (Sutent), as well as peptide receptor radionuclide therapy (PRRT) or cytotoxic chemotherapy [14–19].

After the initial diagnosis and the third surgery, the patient started a standard therapy with SSTR analogues and received a routine clinical and imaging approach [15]. It should be emphasized that the disease had a unique course. Initially, the tumour presented as a NETG1 pancreatic tumour, originally without the involvement of lymphatic nodes and distant metastases, and later progressed to a NECG3 tumour with an isolated distant metastasis in the brain.

After a further follow-up and the detection of the brain metastasis, the patient had a surgery with an intention to

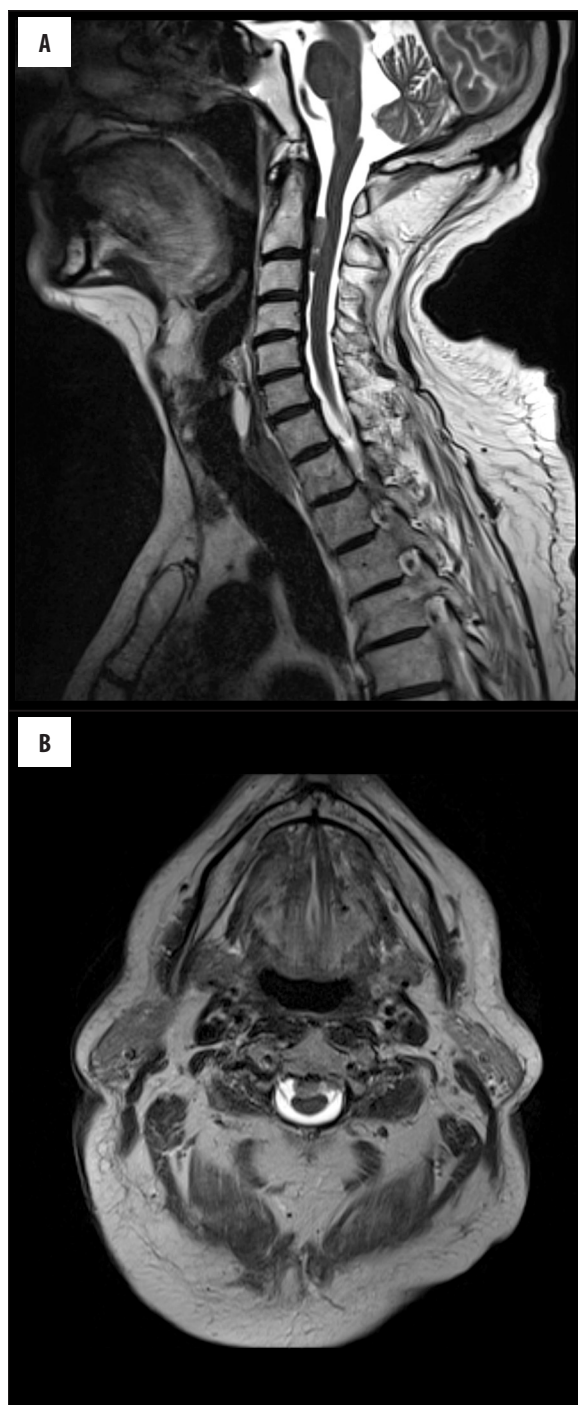


Figure 3. MRI of the cervical spine: Sagittal (A) and transverse (B) T2-weighted images of the cervical spine demonstrates two intradural extramedullary masses at the level of C2–C3 abutting the ventral aspect of the spinal cord. (C) Sagittal contrast-enhanced T1-weighted image shows an intense contrast enhancement of the masses, consistent with metastatic disease.

removed the brain tumour. Because of the infiltration of the right middle cerebral artery trunk, there was no possibility of a complete removal of the tumour. The size of the tumour required an extensive removal of the brain tissue and caused a large motor neurological deficit and an almost total dependence of the patient on other people as regards the basic life needs (Barthel ADL scale 3 points). The improvement was achieved through exercises such as breathing, passive proprioceptive priming by the PNF method, re-education, deep feeling by the Perfetti method, reinforcing the strength of the muscles of the left limbs and postural muscle using the platform and the rotor 4

limb with biofeedback. A verticalization and gait restoration were gradually conducted. In addition, neurologopedic treatment was carried out, to strengthen the weakened muscles of articulation and facial muscles. Psychological therapy was aimed at improving cognitive function and reducing the emotional tension. Applied comprehensive rehabilitation only slightly decreased cognitive behavioural dysfunctions and movement of the patient (Barthel ADL scale of 7 points).

In the event of metastatic changes, especially in the liver and in the CNS, the optimal imaging technique is MRI and the somatostatin receptor imaging (SRS) with SPECT or PET [6,11,13]. In our case, there was a gradual decrease in the uptake of radiotracer on the whole body (WB) SPECT (Single Photon Emission Computed Tomography). The reason could be a conversion into a more malignant tumour lacking of SST receptors or a change in the subtype of SST receptors [20]. Currently, both SPECT (^{99m}Tc HYNICTOC) and PET (^{68}Ga DOTATATE or DOTATOC) techniques use the dominant expression of subtype 2 receptors (SSTR2). This subtype of SSTR is more often seen in well and moderately differentiated NEN (NETG1 and NETG2), but not in NECG3 [1,3,5,6,]. In case of the overexpression of the other SSTR subtypes, both SPECT and PET are not helpful in assessing the stage of the disease. The final histopathological examination confirmed a NECG3 tumour, which very often loses overexpression of SSTR type 2, which could potentially explain the negatives result of our SPECT examination. Therefore, despite the relatively low percentage of

metastatic pancreatic NEN to the brain, we believe that in any case of NEN, the appearance of neurological symptoms and signs urgently require an MRI of the brain, which is the most sensitive method in diagnosis of brain tumours [21]. This may be very important for planning further treatment and improving the general and neurological condition and of the patient.

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Conclusions

Despite the fairly low percentage of NET metastases to the brain, in any case of neurological symptoms, MRI should be performed as the best neuroimaging modality of the brain.