Mixed adenoneuroendocrine carcinoma (MANEC) is a rare malignant neoplasm of a complex pathomorphological pattern combining the features of adenocarcinoma with a neuroendocrine component. According to the new classification of the World Health Organization (WHO) from 2010, the nomenclature of neuroendocrine neoplasms (NEN) was changed using this name for the entire group of neoplasms. The name ‘neuroendocrine tumours’ covers highly diversified neoplasms, determined in the pathomorphological comparison as G1 (NET G1) or G2 (NET G2). In addition, neuroendocrine carcinomas (NEC) and mixed adenoneuroendocrine carcinomas (MANEC) are differentiated.

In a search of the PubMed database, approximately 50 reports about this carcinoma were found, mainly with the location in the stomach, lymph nodes, intestines, liver, peritoneum, gallbladder, pancreas, oesophagus. We have not found a description of the metastatic lesions typical of MANEC in the meninges, brainstem, and lungs.

We present the case of a 63-year-old patient who was admitted to the Department of Neurology due to increased dizziness with accompanying diplopia, headache, nausea, and numbness of the hands. These symptoms appeared one day prior to admission, with intensification at night. The patient was initially diagnosed at the Department of Laryngology due to deafness of the right ear and deep hearing loss in the left ear four weeks prior to admission to our department. In the neurological examination, the following findings were detected: conscious, anxious, dysarthric speech, insignificant inspiratory dyspnoea, deafness of the right ear, deep hearing loss in the left ear, pharyngeal and palatal reaction, weak tension of the palato-pharyngeal fold, bilateral signs of central damage of the seventh nerve, insignificant deviation of the tongue to the left, muscle tone of the limbs without deficit, insignificantly decreased muscle tone in the left limbs, ataxia in the lower limbs, bilateral plantar reflex. In the admissions ward, CT examination of the head was performed and a hypodense focus in the left cerebral hemisphere, hypodense foci around the frontal horn of the lateral ventricles and small malacia cavities at the level of the subcortical nuclei were detected. A lumbar puncture was performed obtaining fluid with increased cytosis and a decreased glucose level. On the second day of hospitalisation, the general and neurological condition of the patient significantly worsened and a ‘sympathetic storming’ appeared followed by circulatory arrest. The patient was efficiently resuscitated, but then there was another sudden cardiac arrest and despite a long period of CPR, cardiac and respiratory action was not restored. After pathomorphological examination it was established that the whole image corresponded to MANEC located in the stomach, with dissemination mainly to the meninges, brainstem and lungs.

In differential diagnosis rare causes of diseases must always be taken into consideration. An additional difficulty in diagnosing MANEC is a difference in the names depending on literature and country of the origin of the article, as well as the lack of Polish equivalents of some names of neoplasms. Only a reliable histopathological analysis is able to detect neoplasms from this group.

Key words: MANEC, NEN, NET, NEC
Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumour of a complex pattern consisting of adenocarcinoma and neuroendocrine components. The incidence of neuroendocrine tumours (on the basis of SEER/Surveillance Epidemiology and Results/ database) has increased five times over the past thirty years, which is connected with better diagnostics. For this reason, it is worth getting acquainted with the characteristic signs of this proliferative process and the accompanying wide spectrum of clinical symptoms.

Case study

A 63-year-old male patient was admitted to the Department of Neurology due to intensified dizziness with accompanying diplopia, headache, nausea and numbness of the hands. The symptoms appeared one day prior to admission with intensification after the night. The patient was initially diagnosed at the Department of Laryngology due to deafness of the right ear and profound hearing loss in the left ear. Four weeks prior to admission, MRI of the brain, CT angiography of the head and ultrasound examination of the internal carotid and vertebral arteries were performed, the results of which were normal. Furthermore, the patient was not chronically treated. The patient did not report allergies or intolerance of any medications or other substances. The patient did not follow any diets and he also denied any addictions or use of stimulants. The community and family interview was unremarkable. On admission, high values of arterial pressure (170/110 mmHg) and tachycardia (110/min) were observed. In the neurological examination, the following were confirmed: patient was conscious, restlessness, his speech was dysarthric, mild inspiratory dyspnoea, deafness of the right ear, profound hearing loss in the left ear, pharyngeal and palatal reflexes were present, he was weakly flexing the glossopalatine folds, bilateral signs of the central damage to nerve VII, insignificant tongue deviation to the left side, muscle strength of the limbs without deficit, insignificantly reduced muscle tone in the left limbs, lower limb ataxia, plantar reflex was bilaterally present. In the admissions ward, CT examination of the head was present and the following were confirmed: a hypodense focus in the right hemisphere of the cerebellum, hypodense foci around the frontal horns of both lateral ventricles and small malacic cavities at the level of subcortical nuclei. A lumbar puncture was performed, obtaining fluid with elevated cytosis (66 cells/µL), decreased glucose level (< 20 mg/dL), an increased level of lactic acid (9.6 mmol/L), and an insignificantly higher protein level (67 mg/dL). In the CSF smear, the following were detected: 2% segmented neutrophils, 6% mesothelial cells, 92% lymphocytes. A RT23 test was performed. In laboratory tests the following were confirmed: hyperthyroidism (546 × 10^3/µL), leukocytosis (23 × 10^9/µL), decreased uric acid (3.0 mg/dL), hyponatremia (133 mmol/L), prolonged prothrombin time (12.9 sec.), and increased fibrinogen (451 mg/dL). The following were administered in the treatment: ceftazidime, metronizadole, acyclovir, dexamethasone, mannitol, enoxaparin, furosemide, atorvastatin, perindopril, diazepam, acetylsalicylic acid. A nasogastric tube was inserted due to difficulty swallowing. Because of decreased oxygen saturation — up to 86% — passive oxygen therapy was administered. On the second day of hospitalization, the general and neurological condition of the patient considerably worsened, swallowing problems intensified, sympathetic storming appeared. Despite the administration of beta-blocker infusions, it was not possible to reduce the heart rate. Sudden cardiac arrest was observed. The patient was efficiently resuscitated and afterwards sudden cardiac arrest appeared once again and despite the long-term duration of cardiopulmonary resuscitation, it was not possible to restore heart rate and breathing. General autopsy and post-mortem examination of the brain were requested. After pathomorphological examination it was established that the whole image suggested a neoplasm of MANEC type located in the stomach, with metastasis mainly to the meninges, brainstem and lungs (Figs. 1–4).

In the immunohistochemical examination, a positive chromogranin marker (CHR) and cytokeratin market CK20 as well as negative cytokeratin CK 7 marker were confirmed (Fig. 5).

The short period of hospitalization in our department did not allow the diagnostics to be broadened with comparative MRI of the brain or other measures. In the subsequently obtained test results, a normal level of Borrelia antibodies and a negative result of the CSF culture were obtained.

Description

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumour of a complex pattern consisting of adenocarcinoma and neuroendocrine components. According to the new classification of the World Health Organization (WHO) from 2010, the nomenclature of the neuroendocrine neoplasms (NEN) was changed using this term for the whole group of these neoplasms. The term ‘neuroendocrine tumours’ (NET) includes well-differentiated neoplasms described in the pathomorphological comparison as G1 (NET G1) or G2 (NET G2). Additionally, we can differentiate neuroendocrine carcinomas (NEC) and mixed adenoneuroendocrine carcinomas (MANEC).

Having searched the PubMed database, we have not found a description of the metastatic lesions typical of MANEC in the meninges, brainstem and lungs.

The term ‘MANEC’ includes carcinomas with a pattern of differentiated adenocarcinoma and neuroendocrine carcinoma of high malignancy (alternative historic name). Ex-goblet cell carcinoid constitutes a separate clinical and...
pathological entity which in the past was not included in the MANEC group. Neuroendocrine tumours (NETs) are characterized by mechanisms of collecting the precursors of biogenic amines and expression of specific receptors on their cell membranes, which is helpful in locating the tumours and determining the treatment strategy. Neoplasms of NET

Figure 1. Visible infiltration from the signet-ring cells in the meninges (autopsy preparation of the patient)

Figure 2. Visible oedema in the brainstem and a focus of encephalomacia with infiltration from atypical signet-ring cells (autopsy preparation of the patient)

Figure 3. Visible infiltration from atypical signet-ring cells in the cerebellar meninges (autopsy preparation of the patient)

Figure 4. Visible histopathological picture of the stomach tumour (autopsy preparation of the patient)

Figure 5. A. Visible infiltration from the signet-ring cells in the cerebral meninges after mucicarmine staining for the presence of mucous cell; B. Visible positive staining for the presence of non-specific marker of neuroendocrine tumours, i.e. chromogranin A (CgA, chromogranin A), i.e. protein which is produced, stored and released from the neuroendocrine tissues
Amphicrine carcinoma

Mixed adenoma/adenocarcinoma — NEC

Mixed adenocarcinoma — G1/G2 NET*

Types of mixed exocrine-neuroendocrine neoplasms of the pancreas, genetically conditioned tumours, e.g. VHL (von Hippel-Lindau syndrome), MEN1 (multiple endocrine neoplasia type 1) [1] may constitute 10–15%. They appear approximately 15 years earlier than sporadic tumours.

In the updated histopathological classification of GEP-NENs published in 2010, the degree of histological maturity of the tumour was considered to be the main element as it is — unlike other parameters of the pathomorphological assessment of GEP-NENs — mutual for the whole group and is based on criteria independent of the tumour location. Due to the indolent course of the disease, diagnosis in the majority of patients is made as late as in the metastatic stage.

Clinical signs may be non-specific, and may result from tumour mass or (in 20–50% of the cases) substance secreted by GEP-NENs [2]. Occurrence of signs dependent on active substances is more frequently observed in patients with neuroendocrine neoplasms of the pancreas as well as mid-gut neoplasms (midgut — distal small intestine, appendix and an initial part of the large intestine) than in patients with tumours coming from the foregut (foregut — stomach, duodenum) and the hindgut (distal part of the large intestine and rectum) [1]. Clinically, the following are most frequently diagnosed: the carcinoid syndrome dependent mostly on secretion of serotonin, such as flush, diarrhoea, valvular lesions in the right part of the heart, stomach-ache, bronchospastic signs, muscle contractions, telangiectasias, edema, cyanosis, myopathy and joint symptoms, which are present more rarely. Clinical signs of pancreatic NENs depend on the substances produced by particular neoplasms, such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP) or somatostatin. According to the current guidelines of the European Neuroendocrine Tumor Society (ENETS) from 2011, the site of the lesion which is often decisive of clinical signs of the disease as well as degree of advancement of proliferation process are of great importance [3].

From the clinical point of view, unambiguous differential diagnosis between poorly-differentiated large cell neuroendocrine carcinoma, small neuroendocrine carcinoma and mixed mixed adenoneuroendocrine carcinoma is not necessary. All three neoplasms demonstrate a similar level of aggressivity and they are treated in a similar way. The exception is MANEC of the oesophagus, the prognosis of which is slightly better than that of the two other neoplasms, despite the fact that treatment results remain unfavourable [4]. In the differential diagnostics, the above-mentioned criteria allow differentiation of MANEC from signet-ring cell carcinoid and adenocarcinoma, as none of these possess a poorly-differentiated neuroendocrine component [5].

In MANEC diagnostics, standardization of Ki-67 expression methods (proliferative activity described with Ki-67 proliferation index on the basis of the immunohistochemical test with the application of MIB1 antibody) as currently — in most centres — this test is based on subjective pathomorphological assessment (Tab. I).

It is necessary to note that there is a significant range of clinical signs depending on the secretory structures within the tumour.

The treatment process depends on histopathological diagnosis. Radical surgical treatment constitutes the only effective method and the result depends on the correct pre- and intra-operative location of the neoplastic lesion. The surgical procedure is possible at each stage of disease advancement. In the limited disease, this constitutes a chance for recovery. In the advanced process — due to specificity of NENs — biotherapy with the application of labelled somatostatin analogues, isotopic radiotherapy, chemotherapy and new methods of targeted therapy are used [3]. In the case of patients with metastatic lesions limited to the liver, surgery with an intent to cure improves prognosis (the five-year sur-
vival rate of patients is 60–80%) and it is a method which is preferred over ablation methods [7]. However, qualification of patients for surgical removal of hepatic lesions is possible if there is a high grade or a middle grade of differentiation of the neoplasm (G1 or G2) and the lesions are operable, the patient does not suffer from right-ventricular heart failure (cardiac carcinoid syndrome) and non-operable metastases in the lymph nodes or distant metastases beyond the abdominal cavity or peritoneum have not been diagnosed [7]. Liver transplantation can be offered to patients with NEN metastases in the liver who have life-threatening signs related to hormonal activity of NENs which are resistant to other available treatment methods and, also, in patients who are hormonally inactive, have generalized inoperable metastatic lesions in the liver, and are also non-responsive to previously applied available treatment forms [8].

Thermal ablation of the metastatic lesions in the liver may not only decrease or remove the neoplastic foci; however, in specific cases, it may decrease intensification or result in complete resolution of symptoms related to hormonal activity of the advanced NEN [9]. The basic method of reducing the signs related to hormonal activity of NENs is the application of somatostatin analogues (with long-term effects) once a month either in an intramuscular dose of 20–30 mg (octreotide) or in a subcutaneous dose of 90–120 mg (lanreotide). Periodically, e.g. during the pre-operative period, it may be necessary to administer (subcutaneously or intravenously) the preparations with short-term effects for prevention of a possible breakthrough related to rapid release of serotonin. In the event of the ineffectiveness of somatostatin analogues, application of IFN-α can be considered [10]. Systemic chemotherapy is recommended for pancreatic NEN, diffuse foregut G2 NET and G3 NEC, regardless of the point of origin of the neoplasm. We can choose streptozocin with 5-fluorouracil or doxorubicin, temozolomide and capecitabine; it is also recommended to use cisplatin and etoposide [11]. Isotopic radiotherapy with the application of somatostatin analogues (DOTA-TOC, DOTA-TATE) labelled 90Y or 177LU can be used when we deal with diffuse G1–2 NETs, with both active and inactive hormonal activity, regardless of the point of origin of the neoplasm, yet, with required expression of the somatostatin receptors confirmed with imaging tests (scintigraphy with the application of somatostatin analogues or (68Ga-DOTA-TATE PET/CT) or an immunohistochemical test [12]. The mToR kinase inhibitor (everolimus) and numerous tyrosine kinase inhibitors (sunitinib) provide entirely new possibilities for targeted treatment of the patients with advanced NENs [13]. Control examinations of the patients with advanced NENs include imaging tests (CT, MRI) and determination of the specific markers for this group of neoplasms (cgA and possibly specific markets for particular types of tumours) — for G1–2 NET these tests should be performed every 3–6 months. Assessment of the expression of the somatostatin receptors (scintigraphic or with the application of 68Ga-DOTA-TATE PET/CT) should be carried out once in the period of 18–24 months or earlier, depending on the results of imaging tests or marker levels. For G3 NEC, the above-mentioned tests should be performed every 2–3 months [14].

The percentage of five-year survivals in the metastatic neuroendocrine neoplasms is similar to the percentage of five-year survivals in other metastatic neoplasms, ranging from 4% in neuroendocrine carcinomas to 35% in G1 and G2 NETs [3]. To demonstrate how rare these neoplasms are, it is worth referring to the German research including patients from the National Centre of Neoplastic Diseases that gathered the data about 30 patients over a period of three years [15].

In the above-mentioned case, it is necessary to consider the onset of symptoms, from the causes of hospitalization at the Department of Laryngology related to deafness and hearing impairment. The neuroimaging tests performed at that time did not display pathologies, probably due to the short course of the disease. During hospitalization at the Department of Neurology, an ischaemic stroke of the left cerebellar hemisphere was diagnosed. Due to the image of the CSF, empirical treatment of the bacterial meningitis was applied. Intensified vegetative symptoms, non-responsive to treatment, swallowing difficulties, saturation loss suggested pathology within the brainstem. Taking into account the whole clinical image and the results of the post-mortem examination, it is always necessary to include rare causes of diseases in differential diagnostics.

Conclusions
1. It is always necessary to include rare causes of diseases in differential diagnostics.
2. The difference in the names depending on literature and country of origin of the article, as well as a lack of Polish equivalents of particular names of neoplasms constitutes an additional difficulty in diagnosing MANEC.
3. Only reliable histopathological analysis can allow detection of neoplasms from this group.

Conflict of interest: none declared

Mariusz Głuszak, MD
Neurology Department, Clinical Hospital No. 1 in Rzeszów
Szopena 2, 35–055 Rzeszów, Poland
e-mail: mariusz-gluszak@wp.pl

Received: 12 Sept 2016
Accepted: 21 Feb 2017
References
4. Rouse RV. Mixed adenoneuroendocrine carcinoma (MANEC) of the GI tract, Department of Pathology, Stanford University School of Medicine. (original posting/last update: 1/25/15).