Radiologic diagnosis in multiple endocrine neoplasia type 1 syndrome. A case study based on the medical history of a father and his two children.

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ABSTRACT

Multiple endocrine neoplasia syndrome type 1 (MEN1) is an autosomal dominant inherited disease. Typical tumours present in patients are parathyroid adenomas, pancreatic neuroendocrine tumour and pituitary adenoma, which may be accompanied by other tumours. The aim of this study was to analyse the clinical cases of a family – a 49-year-old father, a 24-year-old son and a 20-year-old daughter – for the diagnosis of MEN1 syndrome, after confirming the presence of MEN1 in the father. In each of the patients, a mutation in one allele of the MEN1 gene was detected in a heterozygous pattern, which confirmed the diagnosis of endocrine adenomatosis type 1 syndrome. Prior to the diagnosis, none of the children presented with distressing clinical symptoms, despite the presence of numerous lesions visualised by radiological examinations, which obtained different histopathological diagnoses. Radiological screening of patients after treatment allows early detection of new lesions, which improves prognosis.

INTRODUCTION

Multiple Endocrine Neoplasia Type 1 (MEN1) syndrome, or Wermer syndrome, was first reported by pathologist Jakob Erdheim, in 1903 as an autopsy description of a patient with acromegaly and enlarged parathyroid glands. And in 1927, Harvey Cushing and Leo Max Davidoff described a case of a patient with the classic MEN1 triad: primary hyperparathyroidism, pancreatic neuroendocrine tumor and pituitary tumor [1,2]. In contrast, 20 years later, Laurentius Underhal's research team presented a study of 8 cases whose histopathological diagnoses corresponded to MEN1 syndrome, for the first time using the term "multiple endocrine adenomas," literally "multiple endocrine adenomas" [3]. It is now accepted that mutation of the *MEN1* suppressor gene, encoding menin, located on chromosome 11 (11q13), facilitates the formation of neoplasms in certain endocrine organs, which can be adenomas or carcinomas. In addition, these patients may develop skin lesions in the form of neurofibromatosis or collagenoma tumors, as well as thyroid tumors, adrenal tumors, lipomas, pheochromocytoma or meningiomas. The disease is inherited in an autosomal dominant manner, as first described by Paul Wermer in 1954 [4-8]. Clinical manifestation occurs in 98% of carriers of the mutated gene, and usually reveals itself in the fifth decade of life. Parathyroid tumor (95% of patients), pancreatic neuroendocrine tumor (40-70% of patients) and pituitary tumor (30-40% of patients) are the most common [5,9]. The criteria for the diagnosis of MEN1 syndrome are shown in table 1, with only one of the criteria needing to be met for diagnosis [10].

Treatment methods for tumors are similar to those for isolated lesions; however, the prognosis of patients with MEN1 is worse due to more frequent recurrences, more aggressive course, increased incidence of metastasis and greater resistance to treatment [5,11]. Radiological studies used for imaging diagnosis are endoscopic ultrasound (EUS), computed tomography (CT), positron emission tomography (PET), pituitary magnetic resonance imaging (MRI), and scintigraphic studies [1,7,12,13]. The radiological surveillance requires the same tests to be conducted annually. However, there is no consensus on the use of ^{68}Ga-DOTA-TATE PET/CT examination in the prospective evaluation of the disease [14].

AIM OF STUDY

The purpose of our study is to analyze the clinical cases, particularly imaging studies, of a father and his two children, a son and a daughter, in whom the MEN1 gene mutation was confirmed by genetic testing.

MATERIALS AND METHODS

The analysis includes the medical histories of 3 patients hospitalized at the Prof. K. Gibinski University Clinical Center in Katowice due to the presence of multiple endocrine neoplasia syndrome type 1. A general description of the patients' hospitalization is included in the study. All patients underwent

endoscopic ultrasound, chest and abdominal computed tomography, ^{68}Ga PET-CT and genetic testing for MEN1. In addition, two patients underwent magnetic resonance imaging evaluation of the pituitary gland.

CASE DESCRIPTIONS

The case reports presented here concern the clinical manifestation of multiple endocrine neoplasia type 1 (MEN1) syndrome found in a father and two children and their radiological features of the lesions.

Patient I

A 49 year old patient was admitted to the Hospital Emergency Department for suspected ICU due to severe abdominal pain radiating to the lower back, nausea, vomiting, and fever. Abdominal CT revealed ambiguous cystic lesions, most likely of a post-inflammatory nature at the border of the body and tail of the pancreas measuring 13 mm and in the tail of the pancreas measuring 18 x 8 mm. The EUS performed revealed a pancreas of heterogeneous structure and echogenicity with four litho-cystic focal lesions located at the border of the body and tail of the pancreas measuring 6 to 12 mm in diameter. Histopathological examination of EUS-guided biopsy specimens revealed pancreatic neuroendocrine tumor, neuroendocrine tumour (NET) G2 with a Ki-67 mitotic index of 4.1%. The patient was referred to the Division of Endocrinology and Neuroendocrine Tumors, where a contrast-enhanced CT scan of the chest showed submillimeter nodules in the lungs and subpleural with unclear etiology. An abdominal CT scan revealed nodularly remodeled adrenal glands, with a prominent hypodense lesion of the right adrenal gland measuring 19 mm and a density of -12 Hounsfield units (HU), as well as a hypodense lesion in the body of the left adrenal gland measuring 12 mm. During hospitalization, genetic testing was performed, which revealed a pathogenic variant in one allele of the *MEN1* gene, in a heterozygous pattern, confirming the clinical diagnosis of endocrine adenoma syndrome. In January 2016, the patient underwent parathyroidectomy for primary hyperparathyroidism. A follow-up PET-CT performed 11 months later with ^{68}Ga showed foci of radiopharmaceutical accumulation in the body and tail of the pancreas consistent with NET, without features of disease dissemination. In July 2017, the patient was hospitalized in the Endocrinology Department for hypercortisolemia, with an abnormal rhythm of cortisol secretion. The patient was consulted surgically, but did not consent to adrenalectomy. Follow-up abdominal CT and PET-CT with ^{68}Ga performed since then showed no disease progression.

Patient II

A 24-year-old patient, whose father was diagnosed with multiple endocrine adenoma syndrome, was admitted to the Endocrinology Department in 2013 for symptoms of paroxysmal hypoglycemia. Due to a positive family history of MEN1 syndrome, the patient underwent genetic testing, which revealed a pathogenic variant in one allele of the MEN1 gene in a heterozygous pattern, confirming the diagnosis of MEN1. A contrast-enhanced CT scan did not reveal pancreatic pathology, but a ^{13}F-DOPA PET-CT scan showed increased metabolism in the head and hook-like process of the pancreas measuring 30x16mm with Maximum Standardized Uptake Value (SUV_{max}) 3.2. The patient was treated symptomatically with diazoxide and remained under constant follow-up at the endocrinology clinic. A follow-up abdominal CT scan showed no pancreatic abnormalities, but a focal lesion in the head of the pancreas measuring 12-13mm was revealed in the EUS performed. Due to the difficult anatomical conditions, an aspiration biopsy was abandoned. A receptor scintigraphy study with tectreotide revealed a pathological focus within the pancreas showing increased expression of the somatostatin receptor. Glucagon-Like Peptide-1 Receptor (GLP1) PET/CT with ^{68}Ga revealed a focus of radiopharmaceutical accumulation in the head of the pancreas measuring 10x13x14 mm SUV_{max}=5.5. The patient was referred for parathyroid scintigraphy, which showed a focus measuring 4x8 mm below the lower pole of the left lobe, consistent with a parathyroid adenoma. A follow-up abdominal CT scan with contrast showed a focus of arterial phase enhancement 1 cm in diameter in the head of the pancreas, and a second focus of similar nature and size was suspected at the border of the head and body of the pancreas. The patient was qualified for surgery. The histopathological specimen retrieved showed pancreatic head tumor: NET G2, Ki-67 3%; hook process tumor: NET G2, Ki-67 about 4%; tumor from the body, tail: NET G1, Ki-67 1%; duodenal tumor - NET G2, Ki-67 about 5%. In the 6 lymph nodes taken, the presence of tumor metastases was found. The stage of the disease according to the TNM classification was defined as pT3N1Mx. A postoperative abdominal CT scan showed hypodense lesions located in the head of the pancreas with a probable cystic nature. The patient underwent a postoperative abdominal CT scan about a year later, which showed a strongly hyperdense lesion measuring 9x13x8 mm in the arterial phase of the pancreatic head. A ^{68}Ga-DOTA-TATE PET-CT scan showed a focus of increased receptor expression (SUV_{max}=10.8) in the anterior part of the pancreatic head, corresponding to the location of the lesion from the previous abdominal CT scan - the images were consistent with the recurrence of a neuroendocrine tumor of the pancreatic head. The patient, as part of the Multispecialty Neuroendocrine Tumor Consortium, was referred for ablative stereotactic radiotherapy of the pancreatic tumor recurrence focus, but was disqualified from treatment due to the high risk of damage to the postoperative anastomosis. Follow-up CT scans of the chest and abdomen showed no signs of tumor spread. Due to confirmed MEN1, the patient underwent pituitary MR imaging, which showed an indistinctly demarcated area of weaker contrast enhancement of 3.0x1.7 mm in the pituitary parenchyma on the right side, corresponding to a microglandular lesion.

Patient III

A 20-year-old female patient with a father and brother diagnosed with multiple endocrine adenoma type 1 syndrome, previously presenting no clinical symptoms of the syndrome was referred for genetic testing, which showed mutations in one allele of the MEN1 gene in a heterozygous pattern, confirming

the diagnosis of MEN1. For diagnostic purposes, an abdominal CT scan was performed, which showed an intensely enhanced head of the pancreas with an 18x21-mm contracture defect, consistent with a nodular lesion. The patient was diagnosed with obstructive hydrocephalus three weeks later. An urgent MRI scan of the head showed a quadriplegic plaque tumor occluding the cerebral hydrocephalus. The patient underwent trepanopuncture of the right frontal region and endoscopic ventriculostomy of the third ventricle of the brain. A PET-CT scan with ^{18}F-Deoxyglucose visualized a 22x21x22 mm (SUV_{max}=2.17) tissue foci in the pineal region and quadricuspid plaque. There was a 14x15 mm (15 HU; SUV_{max}=15.24) hypodense focus in the tail of the pancreas, near the border of the pancreas, as well as metastatic foci in the bones. One month later, the patient underwent a circumferential resection of the tail of the pancreas. Histopathological examination revealed a pancreatic neuroendocrine tumor of the glucagonoma NET G2 type, Ki-67 3%. 2 months later, the patient underwent a suboccipital craniotomy to remove the tumor of the pineal region, quadricuspid lamina and ventricle III. Histopathological examination revealed WHO GI ganglioglioma. The patient presented primary hyperparathyroidism during treatment, so it was decided to perform a total parathyroidectomy on her. A follow-up PET-CT scan with ^{68}Ga showed increased receptor expression in the head of the pancreas and at the border of the body and tail, as well as in a single node on the left iliac-lumbar muscle. The patient achieved a three-year freedom from disease progression until two confluent focal lesions of the pancreatic head measuring 20x19 mm and 10x15 mm were found. On CT scan, the lesions are poorly differentiated from their surroundings, modeling and compressing the superior mesenteric vein, the venous tributary draining the hepatic fold, and modeling the portal vein. A biopsy of the lesions under EUS guidance showed recurrence of NET G1 pancreatic neuroendocrine tumor, Ki-67 1.6%.

DISCUSSION

The diagnosis of patients with MEN1 syndrome is not straightforward due to the multiplicity of symptoms presented. In the presented patients, complaints included symptoms similar to acute pancreatitis, episodes of hypoglycemia, hyperparathyroidism, but it should be mentioned that the latent form of the disease does not give any complaints. In the cases described, it can be seen that all 3 criteria for the diagnosis of MEN1 were applied [10], i.e. diagnosis of 2 of the 3 most common tumors (patient No. I - pancreatic neuroendocrine neoplasm and parathyroid adenoma); occurrence of one characteristic pathology in a person who is a first-degree relative of a patient diagnosed with MEN1 syndrome (patient No. II), detection of a germline mutation of the MEN1 gene in a person without biochemical, radiological or clinical symptoms (patient No. III). New data even discuss the need to test asymptomatic individuals with a heavy family history as early as age 5 [9,15]. Finally, in all 3 family members, MEN1 syndrome was confirmed by positive genetic testing with the presence of one pathogenic allele of the MEN1 gene in a heterozygous pattern.

Radiological diagnosis plays an important role in establishing a correct diagnosis and planning appropriate therapeutic management [9]. In the imaging and histopathological studies performed, typical proliferative lesions accompanying MEN1 have been visualized. The most clinically and radiologically prominent tumor in each patient was a pancreatic neuroendocrine neoplasm, which occupied the borderline of the body and tail in all cases, and the head of the pancreas in two. It is the second most common neoplasm in MEN1 syndrome (30-80%) [10,16]. Histopathologic examination with Ki-67 index determination assessed G2 grade lesions in all patients and G1 for one lesion on the borderline of the body and tail in patient No. II. In addition, a G2 grade neuroendocrine tumor of the duodenum was found in patient No. II. Both children of patient No. I underwent head MR imaging and were diagnosed with a pituitary adenoma in the male and a quadriplegic lamellar tumor in the female. Pituitary tumors are among the common lesions of MEN1 (30-40%) [6,10]. Patients II and III showed and lymph node and bone metastases, respectively, while patient I visualized multiple subpleural nodules. In this patient, EUS furthermore visualized nodularly altered both adrenal glands with manifest hypercortisolemia, which may also be a component of MEN1 syndrome [10].

The treatment of MEN1 is not fundamentally different from the management of patients without the syndrome [10]. All patients were treated with surgery to remove endocrine tumors. Patient No. II was treated with diazoxide, which is used in the treatment of insulinomas, before surgery [17]. Despite the treatment administered, patients suffering from MEN1 have a shorter life expectancy, and treatment may not be successful due to the aggressiveness of the tumors and their localization in different organs - recurrent neuroendocrine tumors with different histopathological diagnoses have been diagnosed in children [18].

SUMMARY AND CONCLUSIONS

Multiple endocrine tumor syndrome type 1 is a rare disease that shows a predisposition to familial occurrence. Radiological diagnosis is helpful in establishing a correct diagnosis and planning therapeutic management, and is important in identifying lesions in asymptomatic patients, which enables the implementation of treatment and limits the growth of tumors. Covering patients with systematic radiological screening increases the likelihood of early detection of new lesions.

TEACHING POINTS

Multiple endocrine neoplasia syndrome type 1 (MEN1) is an autosomal dominant inherited disease. Typical tumours present in patients are parathyroid adenomas, pancreatic neuroendocrine tumour and pituitary adenoma, which may be accompanied by other tumours. The presence of changes on imaging studies may precede the clinical manifestation of symptoms. Prognosis of patients with MEN-1 is generally worse than patients with isolated lesions, therefore lesions in MEN1 syndrome require

immediate diagnostic evaluation using multiple radiologic imaging techniques.

QUESTIONS

Which of the following answer choices is false?

1. MEN1 syndrome is autosomal recessive inherited disease. [The disease is inherited in an autosomal dominant manner]

2. MEN1 is a genetic disorder [It is now accepted that mutation of the MEN1 suppressor gene, encoding menin, located on chromosome 11 (11q13), facilitates the formation of neoplasms]

3. In addition to typical tumors, there may be skin lesions, among others [these patients may develop skin lesions]

4. The most common tumor is parathyroid adenoma [Parathyroid tumor (95% of patients)]

5. MEN-1 is suppressor gene [mutation of the *MEN1* suppressor gene]

Which of the given neoplasms is not typical of the MEN1 syndorme:

1. Parathyroid adenoma [Parathyroid tumor (95% of patients)]

2. Pancreatic neuroendocrine tumor [pancreatic neuroendocrine tumor (40-70% of patients)]

3. Pituary gland adenoma [pituitary tumor (30-40% of patients) are the most common]

4. Collagenoma [In addition, these patients may develop skin lesions in the form of neurofibromatosis or collagenoma tumors]

5. Hepatoblastoma

In radiology diagnosis of MEN1 syndrome we commonly use:

1. EUS [Radiological studies used for imaging diagnosis are endoscopic ultrasound (EUS)]

2. CT [computed tomography (CT)]

3. X-rays picture

4. PET/CT [positron emission tomography (PET/CT)]

5. MRI [pituitary magnetic resonance imaging (MRI)]

Choose wrong answer about MEN1:

1. Neoplasms in MEN1 syndrome occures in almost all patients at the age 50 [usually reveals itself in the fifth decade of life]

2. The risk of metastasies is higher than in isolated neoplasm [the prognosis of patients with MEN1 is worse due to more frequent recurrences, more aggressive course, increased incidence of metastasis and greater resistance to treatment]

3. Patients' prognosis is generally worse [patients suffering from MEN1 have a shorter life expectancy]

4. Chemotherapy has very good effects

5. Patients with a history of a burden should undergo genetic testing at 5 years of age [New data even discuss the need to test asymptomatic individuals with a heavy family history as early as age 5]

To the diagnosis of the disease MEN1 syndrome:

a. Diagnosis 2 of 3 most common neoplasms is sufficient [Diagnosis of 2 of the 3 most common tumors: parathyroid adenoma, pancreatic neuroendocrine neoplasm or pituitary adenoma]

b. Confirmation of germ mutation of MEN-1 is sufficient [Detection of a germline mutation of the *MEN1* gene in a person without biochemical, radiological or clinical symptoms]

c. All diagnostic criteria have to be met

d. Occurrence of one characteristic pathology in a person who is a first-degree relative of a patient diagnosed with MEN1 syndrome is sufficient [occurrence of one characteristic pathology in a person who is a first-degree relative of a patient diagnosed with MEN1 syndrome]

e. Meeting only one of the diagnostic criteria is sufficient

AUTHOR CONTRIBUTION

Conceptualization- J.H.; methodology, J.H., K.J., J.C.; Investigation- J.H., J.P.K.; Writing—original draft preparation- J.H., K.J., J.C.; Writing—review and editing- J.P.K.; visualization, J.H. All authors have read and agreed to the published version of the manuscript.

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FIGURES

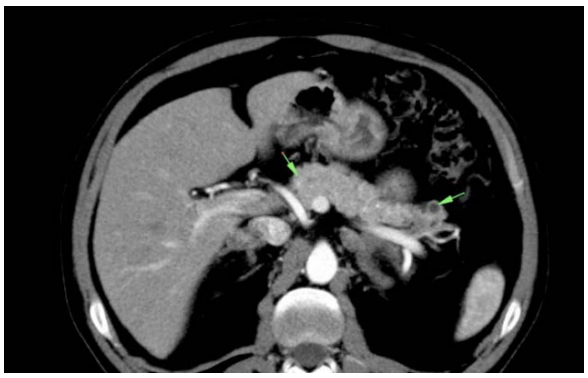

Figure 1: Arterial phase CT of the abdomen, transverse section shows two nodules with different morphologies: a solid tumour in the isthmus and a cystic tumour in the tail region.

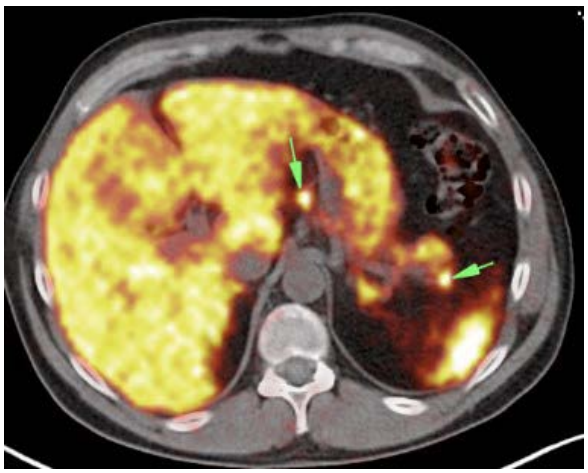

Figure 2: PET-CT with 68Ga shows that the tumour from Figure 1 exhibit overexpression of somatostatin receptors.

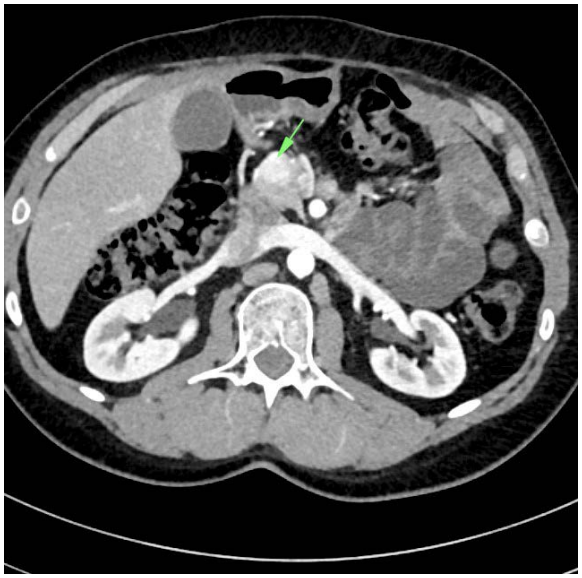

Figure 3: Late arterial phase CT of the abdomen, transverse section shows a hypervascular solid tumour in the pancreatic isthmus, indicative of PNET.

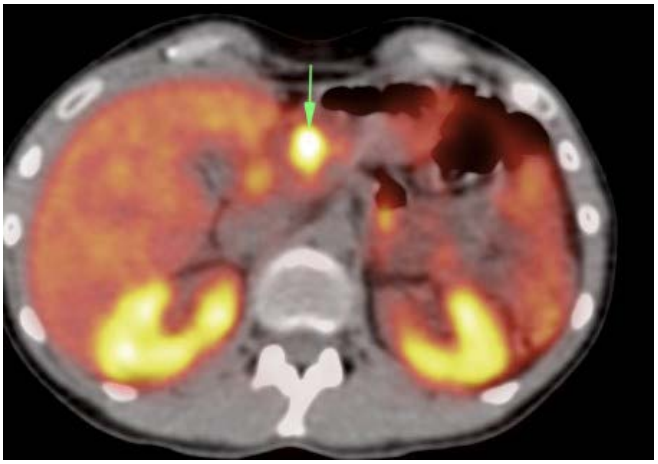

Figure 4: PET-CT with 68Ga shows that the tumour from Figure 3 exhibits overexpression of somatostatin receptors.

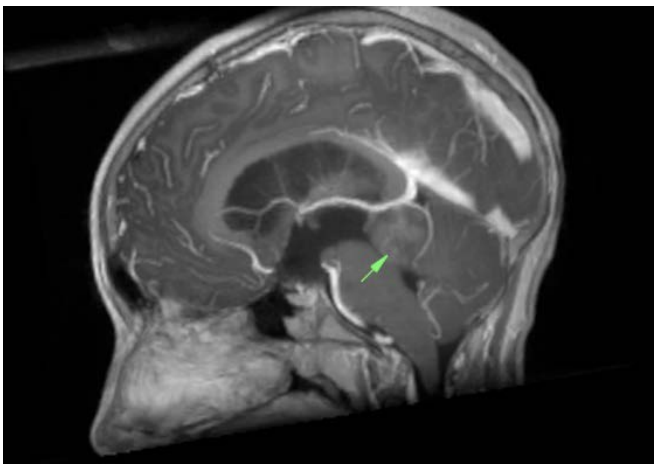

Figure 5: Head MRI with MPR reconstruction in the sagittal plane shows a ganglioglioma causing hydrocephalus.

Table 1: Criteria for the diagnosis of multiple endocrine neoplasia syndrome type 1.

Diagnosis of 2 of the 3 most common tumors: parathyroid adenoma, pancreatic neuroendocrine neoplasm or pituitary adenoma	The occurrence of one characteristic pathology in a person who is a first-degree relative of a patient diagnosed with MEN1 syndrome	Detection of a germline mutation of the *MEN1* gene in a person without biochemical, radiological or clinical symptoms

Source: own elaboration.

KEYWORDS

Multiple endocrine neoplasia syndrome type 1, Neuroendocrine tumors, Adenoma, MEN1 syndrome, Wermer syndrome