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Multiple endocrine neoplasia type 1: a case report and review of the literature

Case Report

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Abstract: Multiple endocrine neoplasia syndrome, type 1 (MEN1) is an underdiagnosed autosomal dominant inherited cancer predisposition syndrome with inter- and intrafamilial variability without a known genotype-phenotype correlation. Disease is caused by mutations in the MEN1 gene located on chromosome 11, but other genes (CDKN1B, AIP) and mechanisms might be involved too. We performed retrospective case series study of MEN1 syndrome patient and his family and present our experience of management of genetically confirmed 9 MEN1 syndrome large family members from Lithuania with novel MEN1 gene mutation (MEN1 exon 6 – c. 879delT (p.Pro293Profs*76)) and delineate its clinical phenotype. At present the diagnosis of MEN1 syndrome must be established by direct mutation testing. MEN1 syndrome patients, their relatives and patients suspected of MEN1 are eligible for mutation testing. Patients with MEN1 have a shorter life expectancy than the general population. MEN1 patients and mutation carriers should be subjected to periodic screening in order to detect manifestations in an early stage. Early genetic diagnosis and subsequent periodic screening is associated with less morbidity and mortality at follow-up. Our study confirmed the absence of genotype-phenotype correlation and showed high intrafamilial clinical expression variability of the MEN1 syndrome.

Keywords: *Multiple endocrine neoplasia type 1 • Pancreatic neuroendocrine tumours • Pituitary tumours • Primary hyperparathyroidism*

1. Introduction

Multiple endocrine neoplasia syndrome, type 1 (MEN1, s. Wermer) is a rare underdiagnosed autosomal dominant inherited disease [1] with inter- and intrafamilial variability, without a known genotype-phenotype correlation. Syndrome is caused by mutations in the MEN1 gene on chromosome 11 (over 1000 MEN1 gene mutations have been reported to date), but other genes (CDKN1B, AIP, etc.) and mechanisms might be involved too. It is characterized by the occurrence of varying combinations of primary hyperparathyroidism (pHPT), duodenopancreatic neuroendocrine tumours (pNET), pituitary tumours (PIT), adrenal adenomas (ADR) and neuroendocrine tumours (NET) of the stomach, bronchus and thymus [1]. Signs and symptoms occur from overproduction of hormones, tumour growth and malignancy and also from complications of (surgical) treatment [1]. Recognition of the syndrome is important both for treatment and for evaluation of family members [2].

2. Case presentation

The 22-year-old man had an injury and the subsequent surgery for perforated jejunum. Later he was

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operated for adhesive intestinal obstruction and accidentally enlarged lymph nodes at the stomach were found. Histological examination revealed metastases of neuroendocrine carcinoma (Figure 1). Since then he was examined and treated in our hospital. During esophagogastroduodenoscopy the tumour in the gastric body was found. Gastric resection by Billroth I was performed and the diagnosis of well-differentiated neuroendocrine tumour secreting gastrin was established after histological evaluation. Following a computer tomography scan of the abdomen multiple foci in the pancreas were found (Figure 2). MEN1 syndrome was clinically suspected. Additionally hyperparathyroidism and hypocalcaemia were diagnosed. Patient was referred for oncogenetic counselling and further molecular genetic testing of genomic DNA isolated from peripheral blood leukocytes was initiated. MEN1 gene screening by HRM (high-resolution melting analysis) using exon and exon-intron borders flanking primers and SYTO9 intercalating dye was performed on LC480 thermocyler (Roche) and aberrant melting profile harbouring amplicons were subjected for downstream direct sequencing under established diagnostic protocols. Direct sequencing of the MEN1 gene 6 exon on ABI 3500 (Applied Biosytems) genetic analyser revealed novel deletion c.879delT (p.Pro293Profs*76) (Figure 3). This frame shifting mutation is predicted to induce premature "stop" codon at the downstream 369 amino acid level, which results in truncated MEN1 protein, presumably further degraded by nonsense mediated decay (NMD).

Well-differentiated pancreatic neuroendocrine tumours (somatostatinoma, gastrinoma) were enucleated from head, body and tale of pancreas (Figure 4). Recently subtotal parathyroidectomy for hyperparathyroidism was performed. Further cascade presymptomatic oncogenetic testing of familial mutation was initiated to the relatives of the proband after the comprehensive genetic counselling and additionally 8 family members were found to be mutation carriers (Figure 5). All of them were found to have clinical symptoms and characteristic biochemical abnormalities after laboratory investigations. The detailed treatment and follow up of the relatives is described in the Table 1.

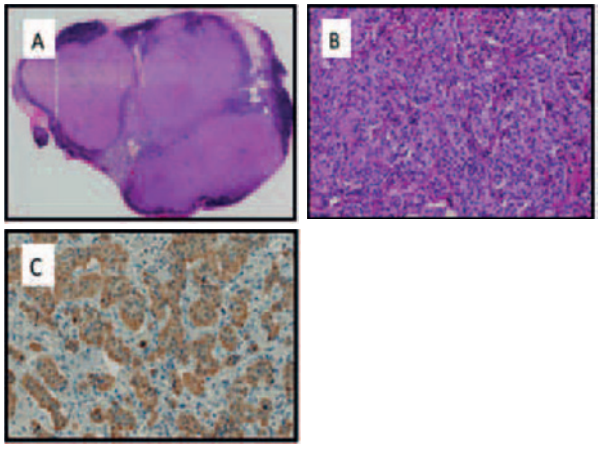

Figure 1. Metastasis of neuroendocrine carcinoma (A. HE 5x. Lymph node metastasis, detected first; B. HE 100x. Lymph node metastasis: trabecular and nested structures of monotonous eosinophilic NE cells; C. IH 200x. Gastrin positivity in cytoplasm of the tumor cells). HE – Hematoxylin and eosin staining; IH – Immunohistochemical staining.

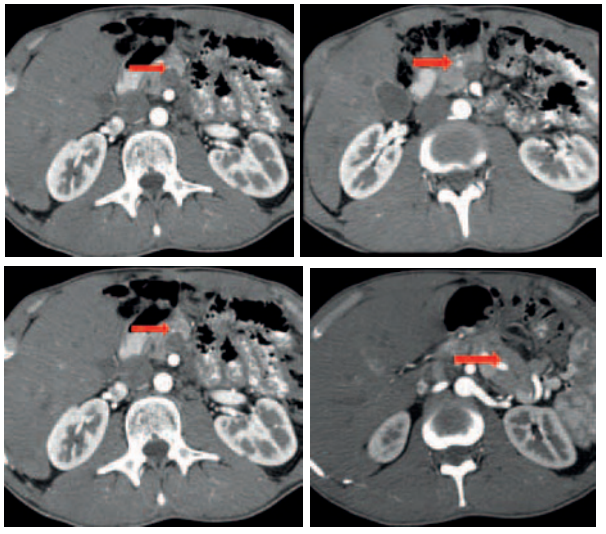

Figure 2. Computer tomography scans of the abdomen (multiple foci in the pancreas).

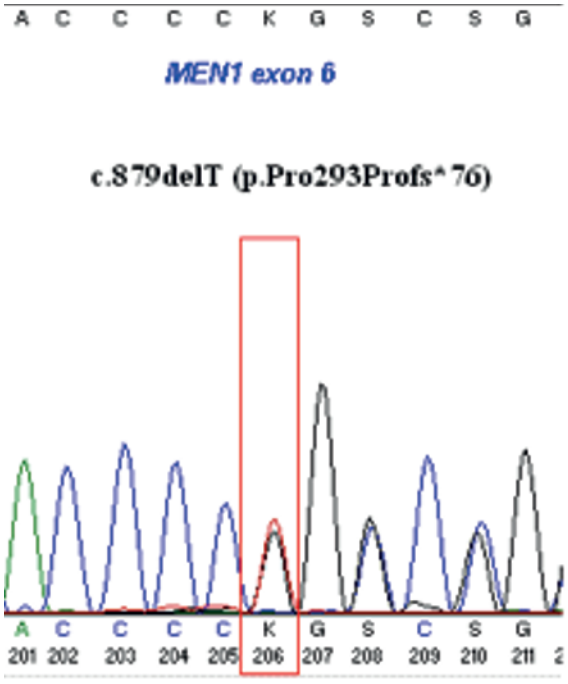

Figure 3. Sequence analysis of MEN1 gene showing heterozygous mutation c.879delT (p.Pro293Profs*76).

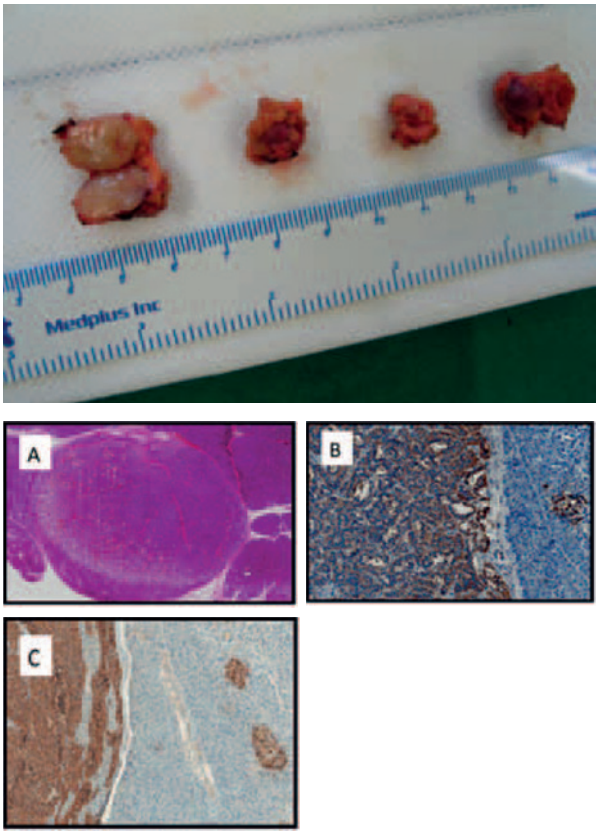

Figure 4. Well-differentiated pancreatic neuroendocrine tumor (somatostatinoma, gastrinoma). A. HE 20x. The tumor nodule (0.3 cm); B. IH 100x. Diffuse glucagon expression in the tumor (left) and Langerhan's island (right); C. IH 100x. Diffuse somatostatin positivity in the tumor (left) and Langerhan's islands (right). HE - Hematoxylin and eosin staining; IH - Immunohistochemical staining.

3. Discussion

In 1903, Erdheim published the first case of multiple endocrine neoplasia type 1 (MEN1) [1,3]. In 1953, Underdahl et al. introduce the term "multiple endocrine adenomas" and reported the first familial occurrence of this syndrome [1,4]. In 1954, Wermer postulates that this syndrome is caused by a mutation in a single gene and inherited in an autosomal dominant fashion [1,5].

MEN1 is a rare heritable disorder with a prevalence of 1–10/100000 [1,2,6,7]. Of the mutation carriers 82–99% has at least one manifestation of the disease at the age of 50 [1,2,8-10]. Patients with MEN1 have a shorter life expectancy than the general population [1, 11-13] with the most important causes of MEN1-related death is malignant pNETs and thymic NETs [1,11-14].

The MEN1 gene is a classic tumour suppressor gene which encodes the menin protein [1]. The site of the "MEN1 gene" is region on the long arm of chromosome 11 (11q13) [2]. Menin is a ubiquitous nuclear protein involved in regulation of gene transcription [1]. More than 1000 different germline MEN1 gene mutations have been reported that inactivate or disrupt menin function [1,2]. MEN1 is caused by inactivating germline mutations in the MEN1 gene. In accordance with Knudson's ''two-hit'' hypothesis, both MEN1 alleles need to be inactivated before a MEN1 tumour can develop. Loss of the wild-type MEN1 allele (loss of heterozygosity (LOH)) is observed frequently in MEN1 tumours [1]. Most of the MEN1 gene mutations found in MEN1 patients would be expected to inactivate or disrupt menin function [2].

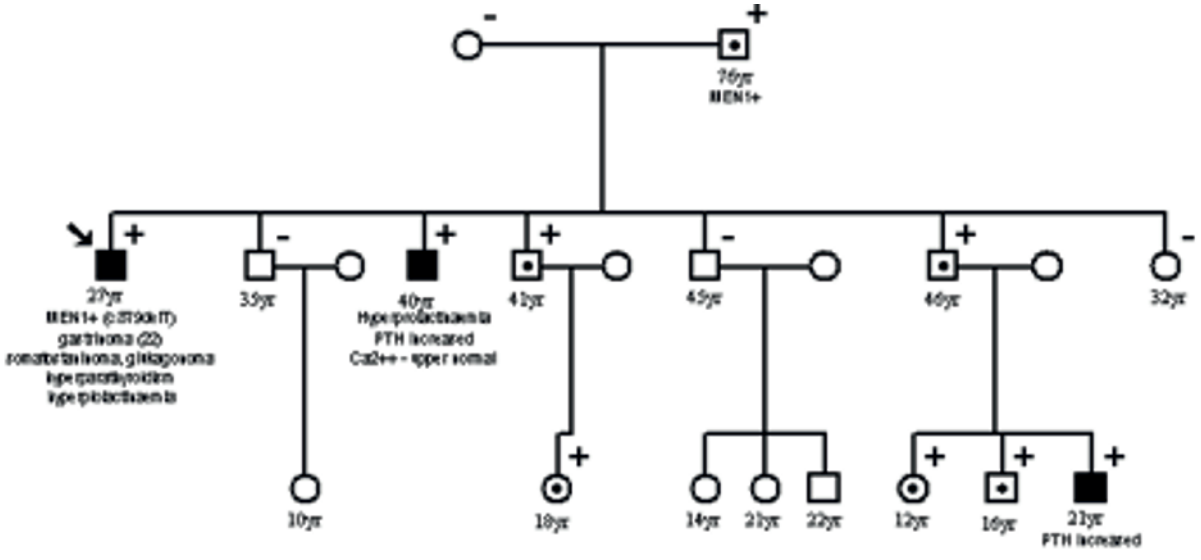

Figure 5. Pedigree of the family with MEN1 c.879delT mutation. Proband is represented by an arrow. Circles represent females, squares – males; „+" and dots in the centre denotes confirmed mutation carriers, „-" tested negative patients; filled symbols represent affected patients; Age and brief phenotypic description is given near the symbols.

Table 1. Relatives and treatment.

Patients	Age	Diagnosis	Treatment
Father	76 yr.	Hyperparathyrosis primaria Multiple pancreatic neuroendocrine tumours (1.7; 1; 0.4 cm) Prolactinoma	Refused surgical treatment Refused surgical treatment Dopamine agonist therapy
Son VI	46 yr.	Hyperparathyrosis primaria Multiple pancreatic neuroendocrine tumours (0.7x0.5; 0.2x0.4; 0.6 cm)	2011 Parathyroidectomia subtotalis Follow-up
Son IV	41 yr.	Hyperparathyrosis primaria Ca neuroendocrinicum corporis pancreatis T3N0M0 G2 (5x6x5 cm) Bronchial carcinoids	Follow-up 2012 Hemipancreatectomia sinistra, splenectomia, cholecytectomia Follow-up
Son III	40 yr.	Hyperparathyrosis primaria Prolactinoma	2011 Parathyroidectomia subtotalis Dopamine agonist therapy
Proband	27 yr.	Hyperparathyrosis primaria Multiple pancreatic neuroendocrine tumours (0.6x0.6; 0.4x0.2; 0.3; 0.4 cm) Prolactinoma Gastrinoma	2011 Parathyroidectomia subtotalis, istmectomia 2010 Enucleatio tumoris ex capitis, corporis et caudae pancreatis Dopamine agonist therapy 2009 Resectio venrticuli m. Billroth I
Grandson III	21 yr.	Hyperparathyrosis primaria Tumor neuroendocrinicum corporis pancreatis (1.5 cm)	2011 Parathyroidectomia subtotalis Follow-up
Granddaughter II	18 yr.	Prolactinoma	Dopamine agonist therapy
Grandson II	16 yr.	Hyperparathyrosis primaria	Follow-up
Granddaughter V	12 yr.	Hyperparathyrosis primaria	Follow-up

Our mutation is predicted to cause protein truncation at 369 codon level with frameshift of upstream 76 amino acids sequence. This observed relatively long translational change in the sequence of peptide upstream the nonsense codon might be interferering with variable phenotypic expression due to dominant negative mutant protein effect.

A consensus statement from an international group of endocrinologists recommended that MEN1 syndrome clinically be defined as the presence of two of the three main MEN1 tumour types (parathyroid, entero-pancreatic endocrine, and pituitary tumours), hence, the mnemonic device of the “3 Ps”. Familial MEN1 was defined as an index MEN1 case with at least one first degree relative who has one of the three main MEN1 related tumours [1,2]. Syndromes clinically related to but genetically distinct from MEN1 do exist, and mutations in the MEN1 gene are not responsible for all individuals [2]. In most cases, primary hyperparathyroidism is the initial manifestation of MEN1, displaying almost 100 percent penetrance by age 40 to 50 years. The biochemical diagnosis of primary hyperparathyroidism is based, as it is in all patients with primary hyperparathyroidism, upon the demonstration of hypercalcemia with inappropriately high serum parathyroid hormone (PTH) concentrations. The most common type of pituitary adenoma in MEN1 is a lactotroph adenoma, but somatotroph, corticotroph, gonadotroph and clinically nonfunctioning adenomas can also occur. Functioning pancreatic islet cell or gastrointestinal endocrine cell tumours become clinically apparent in approximately one-third of patients with MEN1. The most common cause of symptomatic disease is the Zollinger-Ellison (gastrinoma) syndrome. The clinical spectrum of this disorder has been expanded [16].

At present the diagnosis must be established by direct mutation testing. Recent studies have shown that in some families where diagnostic MEN1 gene testing failed to detect a causal germ-line mutation, inherited mutations of other genes were identified: aryl hydrocarbon receptor-interacting protein (AIP) gene and four cyclindependent kinase inhibitor genes: CDKN1B (p27, Kip1), CDKN1A (p21, Cip1, Waf1) CDKN2B (p15, CDK4I) and CDKN2C (p18, INK4C) [1]. Literature suggests that the CDKN1B gene can be involved in the pathogenesis of sporadic parathyroid tumours and that CDKN1B V109G polymorphism may play a critical role in the outcome of MEN1 patients [17,18].

There are more possibilities of suspecting the NETs and subsequently MEN1 syndrome. The chromogranin family consists of at least three different water soluble acidic glycoproteins (Cg A, Cg B, and secretogranin II, sometimes called chromogranin C). Cg A is currently the best available biomarker for the diagnosis of NETs. It is useful in establishing the diagnosis, predicting disease recurrence, outcome and efficacy of therapy [19,20]. Urinary 5-hydroxyindoleacetic acid (5-HIAA) is

the urinary breakdown of serotonin. 5-HIAA is the most important marker for mid-gut tumors, often heralded by the carcinoid syndrome [21].

In our family there is a different phenotypic expression of the same mutation (MEN1 exon 6–c. 879delT (p.Pro293Profs*76)) (Fig. 3) in MEN1 gene, but we cannot exclude that other unknown molecular events (i.e. polymorphisms) may have influenced this different clinical expression. Some authors suggest the possibility of an environmental component to the predisposition of MEN1 related tumors (e. g. pNETs) [22], others assure the association between O blood type and the manifestation of a primary neuroendocrine tumour in patients with MEN-1 [23].

In our case series study all family members had the same blood type. It is postulated that MEN1 patients have a shorter life expectancy than the general population, but our oldest patient is 76 years old and he is still alive, so in our case progression of the disease is very slow. We explored that the size and number of pancreatic tumours correlate with age. The younger the family member was the less tumours she or he had (Table 1).

Our study shows that the eldest member of the family has all three main MEN1 syndrome tumours. Practically all of his children have two main MEN1 syndrome tumours and grandchildren have one. This suggests that all three main tumours will occur with age. Therefore, periodic screening is necessary. Long life of the eldest member of the family prompts that MEN1 syndrome neuroendocrine tumours are low malignant. So the attitude that differs only clinical manifestation time, but the end result is the same – the three main MEN1 syndrome tumours can be correct. Despise that this study confirmed the absence of genotype-phenotype correlation and showed high intrafamilial clinical expression variability of the MEN1 syndrome.

Symptomatic treatment of the neuroendocrine tumours includes long-acting somatostatin analogues which provide good quality of life and temporary disease stabilization in patients with low-grade tumours [24]. For example octreotide is a safe and effective adjunct to surgical strategies for the management of GEP neoplasia in hypergastrinemic MEN-1 patients [25]. Despite that surgery should be offered when NETs are resectable and there is curative intent (or when debulking offers palliation) [26].

The indications for parathyroidectomy in patients with MEN1 include symptomatic hypercalcemia, nephrolithiasis, and evidence of bone disease, such as diminished bone density or fracture. For patients with MEN1 and indications for parathyroidectomy recommended subtotal (three and one-half gland) parathyroidectomy rather than removal of fewer glands including cervical thymectomy in this setting. Also acceptable is removal of all four glands with cervical thymectomy and autologous transplantation of parathyroid tissue. The choice of procedure depends upon the expertise of the parathyroid surgeon. Surgery should only be performed by surgeons highly experienced in parathyroid surgery. Pituitary adenomas in patients with MEN1 should be treated in the same way as sporadic pituitary adenomas. Zollinger-Ellison syndrome as part of the MEN1 syndrome should be treated primarily by proton pump therapy to limit the clinical manifestations and complications of peptic ulcer disease. If this treatment controls symptoms, the role of duodenal-pancreatic surgery to prevent metastatic disease is uncertain. Surgery is indicated for patients with MEN1 and insulinoma. Because patients with MEN1 often have multiple insulinomas, local excision of any tumors in the head of the pancreas plus a distal subtotal pancreatectomy is frequently performed [27]. Early resection of pNENs in MEN1 may prevent the development of distant metastases. However, the majority of patients develop new pNENs in the duodenopancreatic remnant which may require completion pancreatectomy in the long term [28].

The goal in surgically treating patients with MEN1 should be removal of dominant tumors. Most other functional and non-functional tumours are usually large at presentation and require formal surgical resection [29].

Care for MEN1 patients is complex and should be provided by a centre of expertise. Early genetic diagnosis and subsequent periodic screening are important pillars of the care for MEN1 patients [1].

4. Conclusion

With the development of imaging studies the diagnostics of neuroendocrine tumors improved and now it is possible to identify more patients with MEN1 syndrome. Patients suspected of having MEN1 should be examined genetically because to establish MEN1 diagnosis and select high risk family carriers by the oncogenetic verification is essential. It is known that MEN1 syndrome is caused by mutation in the “MEN1 gene” of the chromosome 11, but the large variety of clinical appearances of the syndrome and recent findings in research suggest that there are more mutated genes involved in development of the syndrome. MEN1 patients, their relatives and patients suspected of MEN1 are eligible for mutation testing. MEN1 patients and mutation carriers should be subjected to periodic screening in order to detect manifestations in an early stage. Early genetic diagnosis and subsequent periodic screening is associated with less morbidity and mortality at follow-up.

Conflict of interest statement

Authors state no conflict of interest.

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