Multiple Endocrine Neoplasia Type 1 Presented with Manic-Depressive Disorder: a Case Report with an Identified MEN1 Gene Mutation

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We report a case of multiple endocrine neoplasia type 1 who had repeated hypoglycemic episodes and had previously been diagnosed with bipolar manic-depressive disorder. The patient had a positive family history of multiple endocrine neoplasia type 1 and had multiple pancreatic endocrine tumors, hyperparathyroidism and possibly a pituitary tumor. The pancreatic tumors were resected by subtotal pancreatectomy and examined by histochemical staining and gene analysis. The tumor cells were positive for immunoreactive insulin and glucagon. A microsatellite polymorphism analysis revealed loss of heterozygosity on 11q13 in the tumors. By polymerase chain reaction-based nucleotide sequencing, we identified a germline mutation 483del2 of the MEN1 gene in the normal pancreatic tissue of the patient. This mutation causes a shift of the reading frame of menin mRNA at codon 125. It seems that the wild type allele of the MEN1 gene had been lost in the tumor cells whereas the mutant allele remained intact. This is the first identified MEN1 gene mutation in Japanese families and is different from all MEN1 gene mutations reported previously.

Key words: multiple endocrine neoplasia type 1 – hypoglycemia – insulinoma – MEN1 – hyperparathyroidism

INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant familial cancer syndrome characterized by neoplasia or hyperplasia of the parathyroids, enteropancreatic endocrine tissues, anterior pituitary and other tissues (1,2). Hyperparathyroidism is the most common and usually the first manifestation of MEN1, followed by endocrine syndromes of enteropancreatic tumors, including insulinoma, Zollinger–Ellison syndrome, watery diarrhea hypokalemia achlorhydria (WDHA) syndrome and glucagonoma (1,2). The responsible MEN1 gene has been localized to chromosome 11q13 (3,4) and is considered to be a tumor suppressor gene based on loss of heterozygosity (LOH) for polymorphic markers on 11q13 in pancreatic islet tumors and parathyroid tumors (3,4). Recently, Chandrasekharappa et al. (5) cloned the MEN1 gene, which encodes menin, a 610-amino acid protein of unknown function. Forty different germline MEN1 mutations have so far been identified in individuals affected by MEN1 (6).

Here we report a case of familial MEN1 whose proband had been diagnosed with manic-depressive illness. The germline mutation of the MEN1 gene was identified in the normal and the tumor tissues from the patient by nucleotide sequencing.

CASE REPORT

Because of sudden unconsciousness and jerking movement of the entire body, a 31-year-old man was brought to a nearby hospital by ambulance in July 1995, where examination revealed that he had hypoglycemia (blood glucose 23 mg/dl). He was referred to Self Defense Forces Central Hospital for etiological diagnosis of the hypoglycemic attack. He had been diagnosed as having manic-depressive illness at the age of 26 and had been treated with tranquilizers and antidepressants by psychiatrists. He attempted suicide once at the age of 27.
Family history disclosed that his siblings and paternal relatives had tumors suggestive of MEN1 (Fig. 1). His father had a malignant thymoma and urinary calculosis. His sister showed the signs of acromegaly caused by a pituitary tumor and underwent an operation. His brother had urinary calculosis. An aunt had a pituitary tumor and a gastrinoma, and another aunt had a parathyroid tumor. An uncle died of metastatic liver tumors and another uncle and a grandfather each had a gastric tumor.

On admission, physical examination showed no abnormalities except that he was emotionally agitated. He showed stereotyped movements and was incoherent and uncooperative. Fasting plasma glucose was 56 mg/dl. Serum calcium (corrected to an albumin of 4.0 g/dl) was 5.7 mEq/l (normal range 4.5–5.5) and plasma phosphorus was 3.1 mg/dl (normal range 2.5–4.5). He often became semiconscious and blood glucose levels then were below 50 mg/dl. Endocrinological data were as follows (normal ranges in parentheses): growth hormone, 5.0 ng/ml (<1.5); prolactin, 6.9 ng/ml (1.5–9.7); follicle-stimulating hormone, 8.5 mIU/ml (1.8–13.6); luteinizing hormone, 1.6 mIU/ml (1.1–8.8); intact parathyroid hormone, 84 pg/ml (14–66); parathyroid hormone measured by a high sensitivity assay, 580 pg/ml (90–270); free triiodothyronine, 2.8 pg/ml (2.5–4.3); cortisol, 15.4 µg/dl (<20); insulin, 58 µU/ml (5–11) when plasma glucose was 80 mg/dl; gastrin, 92 pg/ml (<200). A contrast-enhanced abdominal CT scan revealed a tumor mass in the body of the pancreas (Fig. 2). CT and MRI scan of the pituitary and ultrasonography of the parathyroid glands did not reveal an abnormal mass. Based on the clinical and laboratory findings as well as his family history, a diagnosis of MEN1 presenting with insulinomas and hyperparathyroidism was made. In addition, the existence of a growth hormone-secreting pituitary adenoma was suggested.

He underwent a distal subtotal pancreatectomy and splenectomy in October 1995. There were two macroscopic...
Figure 5. Detection of MEN1 mutation by direct sequencing. Both coding (non-transcribed) and non-coding (transcribed) strands were sequenced by the dideoxy fluorescent dye terminator method with an automated capillary sequencer (8). The sequences are shown in the direction of 5′ (left) to 3′ (right) of the strand. Black, green, red and blue lines represent G, A, T and C respectively. Nucleotide position 483 is indicated by an arrow. The germline mutation involved deletion of either dinucleotide AT at 483 and 484 or dinucleotide AT at 485 and 486 and was designated as 483del2 according to the nomenclature described previously (6). (A) Control DNA from a normal individual. (B) DNA from the normal pancreatic tissue of the patient containing both normal as well as mutant sequences. (C) DNA from the pancreatic tumor of the patient, mainly consisting of the mutant sequence but also containing a small amount of the normal sequence.

tumors in the surgical specimen (Fig. 3). Microscopic examination revealed that there were at least 19 tumors in the resected pancreas specimens. Some tumors were immunoreactive for insulin (Fig. 4) and glucagon on histochemical staining. They were histologically diagnosed as islet cell tumors of the pancreas.

Although the serum insulin level was normalized and his hypoglycemic symptoms disappeared after the surgical treatment, the plasma growth hormone level remained high (4.2 ng/ml) and the serum gastrin level elevated (590 pg/ml). Therefore, he started to use octreotide (100 µg/day), which normalized his growth hormone and gastrin levels, although they elevated with cessation of therapy. The pancreatectomy and octreotide therapy did not alleviate his psychiatric symptoms of manic-depressive disorder.
We examined LOH on chromosome 11q13 by the procedure described previously (7) and found it in the two macroscopic pancreatic tumors from this patient (data not shown). We also analyzed germline and somatic mutations of the MEN1 gene in the normal and the tumor tissues of the resected pancreas (Fig. 5) by polymerase chain reaction (PCR)-based direct nucleotide sequencing (8). Analysis of DNA from the normal pancreatic tissue of the patient identified, in addition to a wild type sequence, a germline mutation 483del2, a deletion of two nucleotides at positions 483 and 484, in exon 2 of the MEN1 gene (Fig. 5). Both normal and mutant sequences were confirmed by cloning and sequencing of the PCR products. Thus, this mutation was heterozygous in the normal tissue of the patient. Analysis of the tumor DNA revealed that the 483del2 mutant allele was predominant in the tumor although a minor sequence of wild type allele was also observed (Fig. 5). This finding is in agreement with LOH on 11q13 in this tumor, assuming that the tumor contained a small number of normal cells, such as blood and connective tissue cells.

DISCUSSION

This patient had a strong family history of MEN1, experiences of hypoglycemic episodes and multiple pancreatic endocrine tumors which were positive for immunoreactive insulin and glucagon. He was diagnosed with hyperparathyroidism on the basis of persistent hypercalcemia and high plasma parathyroid hormone levels. He showed high basal plasma growth hormone levels which persisted after the elimination of hypoglycemic symptoms by pancreatectomy, suggesting the existence of a growth hormone-producing pituitary adenoma. His plasma gastrin levels elevated after pancreatectomy, implying the development of gastrinomas. Thus, this patient has a fully-fledged feature of MEN1 and is considered to be a definite case of this syndrome. The diagnosis of MEN1 is not difficult if a patient has multiple endocrine neoplasia with family history of parathyroid, enteropancreatic and pituitary lesions. However, endocrine neoplasia at a single site in a single individual without related family history is likely to be diagnosed as a sporadic tumor and may escape diagnosis of MEN1. Because the responsible gene has been identified (5), more MEN1 patients and carriers will be recognized by detecting a germline mutation of the gene.

We identified a heterozygous 483del2 germline mutation in the normal pancreatic tissue. Loss of the wild-type allele was demonstrated in the pancreatic tumor tissue, while the mutant allele remained intact in the tumor DNA. The 483del2 mutation causes a shift of the reading frame of mRNA at codon 125. These findings are compatible with the idea that MEN1 is a tumor suppressor gene and that 483del2 is a mutation that causes loss of function. This mutation is different from all MEN1 gene mutations reported previously (6). With this gene marker, MEN1 mutation carriers can be identified in this family by gene analysis. We are now investigating MEN1 gene mutations in other Japanese families at the National Cancer Center Research Institute, where the gene analysis was conducted in the present study.

Symptoms of hormone dysregulation may mimic nonendocrine diseases including neurologic or psychiatric disorders. For example, depression often associates with hyperparathyroidism (9) and hypercortisolism (10). Confusion and abnormal behavior characterize hypoglycemic episodes in patients with insulinomas (11). Our patient had been diagnosed with manic-depressive disorder, which might have been caused by the repeated hypoglycemic attacks or hyperparathyroidism although they may have occurred as a result of a simple coincidence. It should be noted that MEN1-associated tumors often produce hormones implicated in mood disorders. Although these psychological symptoms are considered to be caused by excessive hormone production, it might be possible that underlying gene mutations independently confer an inherited predisposition to psychiatric disorders.

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