Multiple Endocrine Neoplasia Type 1 Associated with Spinal Ependymoma


A 51-year-old man was hospitalized with a gait disturbance and hypoesthesia below the level of his chest. These symptoms were due to a spinal tumor which was surgically resected and identified as an ependymoma. Additionally, the patient had hypercalcemia and a family history of insulinoma. An endocrine evaluation revealed parathyroid hyperplasia and a pancreatic islet cell tumor. Magnetic resonance imaging disclosed a pituitary microadenoma. He was diagnosed with spinal ependymoma and multiple endocrine neoplasia type 1 (MEN 1). A review of the literature revealed that chromosome 11q13 abnormalities have been reported in both ependymoma and MEN 1. We discuss the pathogenesis of these diseases.

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Introduction

The familial association of parathyroid, pancreatic islet, and pituitary hyperplasia or neoplasia is called multiple endocrine neoplasia type 1 (MEN 1) (1). The predisposition to these neoplastic lesions is inherited in an autosomal dominant manner (2). In 1988, the MEN 1 locus was first mapped to chromosome 11 by linkage analysis of affected families (3). It has subsequently been mapped to band q13.1 of chromosome 11, within the 8 cM region between D11S480 and D11S546 (4, 5). Although the gene responsible for the disease remains to be identified, predictive DNA testing using restriction fragment length polymorphism (RFLP) is now possible (6).

Structural abnormalities affecting chromosome 11q13 have been reported in a variety of human tumors (7). Karyotypic analysis of solid tumors has demonstrated that 11q13 is a relatively frequent site of chromosome breakage (8). Several patients with chromosome 11q13 abnormalities have also been diagnosed with ependymomas (9), and translocations containing chromosome 11q13 have been reported in two patients with childhood supratentorial ependymoma (10, 11). These chromosome abnormalities have been suspected to play a role in the pathogenesis of ependymoma.

We present a patient with MEN 1 associated with spinal ependymoma and discuss the pathogenesis of these diseases.

Case Report

In June 1991, a 51-year-old man was admitted to our hospital with a gait disturbance and hypoesthesia below the level of his chest. This hypoesthesia had first appeared in 1989 and had gradually worsened. His gait became clumsy in the spring of 1991. Spastic paraplegia of both lower extremities and hypoesthesia below the level of thorax were first noted on examination in May 1991. His past medical history was significant for a painful attack of urolithiasis. The patient’s family history was significant for insulinoma in his two sons and his paternal cousin, each of whom had undergone tumor resection (Fig. 1). His paternal cousin (III-1) had been surgically treated for a pancreatic insulinoma at 26 years of age in 1970 and died 2 weeks after the surgery from acute pancreatitis. The elder son of the patient (IV-1) had experienced hypoglycemic symptoms including coma and seizures at 7 years of age. He was clinically diagnosed with an insulinoma and the tumor was surgically enucleated from his pancreas and pathologically diagnosed as a benign insulinoma at 9 years of age in 1981. The elder son has no abnormalities detected on follow-up to 1995 on either brain magnetic resonance imaging (MRI) or endocrinological screening examinations except for a slightly elevated serum prolactin concentration (19.1 ng/ml). The younger son of the patient (IV-2) had experienced hypoglycemic symptoms at age 16. He was
clinically diagnosed with insulinoma and underwent surgical enucleation of three tumors of his pancreas at 17 years of age in 1991. All tumors were immunoreactive for insulin on histochemical staining, and one revealed evidence of tumor invasion. This tumor was diagnosed as a malignant insulinoma. The younger son has had no abnormalities in follow-up to 1995 on either brain MRI or endocrinologic screening examinations except for a slightly elevated serum growth hormone concentration (10.1 ng/ml).

Evaluation of the neurologic deficits of the patient included a lumbar puncture revealing xanthochromic cerebrospinal fluid with a total protein concentration of 1,200 mg/dl. Myelography and MRI demonstrated a cervico-thoracic intramedullary spinal lesion with syringomyelia (Fig. 2). Serum analysis during hospitalization revealed hypercalcemia (level 12.0 mg/dl), but further evaluation revealed no evidence of tumor by neck and mediastinal scintigraphy. The intramedullary cord tumor (C5 to T2) was completely removed following laminectomy and the tumor specimen was identified as a benign ependymoma (Fig. 3). Though spastic paraplegia remained, the patient could walk with assistance.

In July 1992, the patient was readmitted for further examination of persistent hypercalcemia and suspected MEM 1 (Table 1). Evaluation for primary hyperparathyroidism included cervical ultrasonography (US) which showed areas of low-echogenicity behind both lower poles of the thyroid gland. One of these areas demonstrated abnormal uptake on thallium-technetium subtraction scintigraphy. He was diagnosed with primary hyperparathyroidism. Additional evaluation by abdominal US demonstrated bilateral renal calculi. Despite a mildly elevated serum alkaline phosphatase concentration, musculoskeletal complaints were absent and normal vertebral bone density was demonstrated radiographically. His parathyroid tissue was completely removed and small packets of the tissue were transplanted to the non-dominant forearm. Pathologic analysis revealed nodular hypertrophy of the oxyphilic cells in each gland. A diagnosis of parathyroid hyperplasia was made and the serum calcium concentration returned to normal after a short period of hypocalcemia.

Because of the parathyroid hyperplasia of each gland and the family history of multiple insulinomas, a thorough endocrine evaluation was performed. The patient lacked hypoglycemic symptoms and a 30-hour fast did not cause marked hypoglycemia. However his serum insulin concentration was inap-
Table 1. Diagnosis of Multiple Endocrine Neoplasia Type 1

<table>
<thead>
<tr>
<th>Organs</th>
<th>Endocrinological findings (normal range)</th>
<th>Imagings</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid</td>
<td>Calcium (albumin adjusted) 11.8 mg/dl (8.6-10.1)</td>
<td>TI-Tc scintigraphy</td>
<td>Hyperplasia</td>
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<td></td>
<td>Phosphorus 2.1 mg/dl (2.4-4.3)</td>
<td>Ultrasonography</td>
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<td></td>
<td>Alkaline phosphatase 283 U/l (102-249)</td>
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<td></td>
<td>Intact parathyroid hormone 120 pg/ml (15-50)</td>
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<tr>
<td>Pancreas</td>
<td>Insulin 21 µU/ml (−17)</td>
<td>Angiography</td>
<td>Islet cell tumor</td>
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<td></td>
<td>Glucagon 200 pg/ml (40-180)</td>
<td>Ultrasonography</td>
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<td></td>
<td>Gastrin 76 pg/ml (−200)</td>
<td>Ultrasound</td>
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<tr>
<td>Pituitary</td>
<td>Growth hormone 31 ng/ml (−5)</td>
<td>Magnetic resonance</td>
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<td></td>
<td>Somatomedin-C 360 ng/ml (100-315)</td>
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<td></td>
<td>Prolactin 15 ng/ml (1.5-9.7)</td>
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<td></td>
<td>TSH 3 LiU/ml (0.34-3.5)</td>
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<td></td>
<td>ACTH 20 ng/ml (9-52)</td>
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Propriately elevated and the ratio of insulin (µU/ml) to glucose (mg/dl) reached 0.47 (normal ratio <0.3). Abdominal computed tomography (CT) demonstrated a small enhancing lesion in the pancreatic body which corresponded to a small hypervascular lesion supplied by a branch of the splenic artery visualized on angiography (Fig. 4). An arterial stimulation and venous sampling (ASVS) method was applied (12). Calcium gluconate (0.025 mEq Ca²⁺/kg) was rapidly injected through a catheter positioned proximally in the superior mesenteric artery and branches of the celiac artery. Samples of blood were obtained from the right hepatic vein prior to the initial injection and at 0.5 and 1 minute after the calcium injection. Concentrations of glucose, insulin, gastrin and glucagon were measured. Over a 10-fold rise in the insulin concentration was observed in blood samples obtained 0.5 and 1 minute after the calcium injection into the splenic artery supplying the pancreatic body and tail (Fig. 5). A rise of greater than 2-fold was not observed in the other samples. A preoperative diagnosis of pancreatic insulinoma was made. A tumor measuring 12 mm in diameter was subse-

Figure 4. Abdominal angiography demonstrating a small hypervascular lesion (arrow) supplied by a branch of the splenic artery.

Figure 5. Arterial stimulation and venous sampling (ASVS) method disclosing over a 10-fold rise in insulin concentration in blood samples obtained after injection of calcium into the splenic artery. In the other samples, an insulin concentration increase of greater than 2-fold was not observed.
sequently surgically enucleated from the pancreatic body. Pathologic analysis of the tumor revealed a partial loss of the tissue capsule and evidence of intravascular tumor invasion. Immunopathologic analysis revealed that the tissue lacked staining for many substances including: insulin, glucagon, somatostatin, vasoactive intestinal polypeptide, calcitonin, and pancreatic polypeptide. A diagnosis of malignant nonfunctional pancreatic islet cell tumor was made. The patient developed diabetes mellitus after the surgery, however, good glycemic control was obtained with diet therapy alone.

Further endocrine evaluation included a gadolinium-enhanced T1-weighted MRI which disclosed a small low-signal lesion in the anterior pituitary suggestive of a pituitary microadenoma. Despite the fact that the serum growth hormone and serum somatomedin-C concentrations were both elevated, a 75-g oral glucose load suppressed the growth hormone (level 0.35 ng/ml at 1 hour after the glucose load) and complications of the tumor (including acromegaly and visual field defects) were absent. Additional studies included an abdominal CT, MRI, and US which demonstrated mild bilateral enlargement of the adrenal glands, but adrenal function was normal. The patient was diagnosed with both benign spinal ependymoma and the MEN 1 syndrome consisting of: pituitary microadenoma, hyperplasia of the parathyroid gland with hyperparathyroidism, and malignant nonfunctional pancreatic islet cell tumor.

Discussion

A patient with the MEN 1 syndrome associated with spinal ependymoma is presented. The diagnosis of MEN 1 was made on the basis of the pathological findings of parathyroid hyperplasia, a nonfunctional malignant pancreatic islet cell tumor, and an anterior pituitary microadenoma.

MEN 1 syndrome is so rare that only 106 cases have been reported in Japan between 1966 and 1989 (13). Although the gene responsible for the syndrome remains unknown, the locus has been mapped to chromosome 11q13 (3–5), and predictive DNA testing by RFLP is now possible (6). Additionally, a point mutation of the Gs alpha gene on chromosome 22 has been reported in an MEN 1 patient with a growth hormone-secreting pituitary adenoma. A multi-step gene defect has been suggested to be responsible for the oncogenesis of this syndrome (14).

Ependymoma is also a rare tumor presenting most commonly as a medullary spinal tumor (15). The oncogenesis of ependymoma remains to be clarified, although, several genomic analyses have been reported. DNA sequences similar to a segment of the T-antigen gene related to a monkey polyomavirus, simian virus 40 (SV40), have been reported in some patients with ependymoma in childhood (16). Additionally, a germ-line mutation of exon 7 of the p53 gene, the most common region of mutation in patients with the Li-Fraumeni cancer syndrome, has been reported in one patient with a malignant ependymoma of the posterior fossa in childhood (17). Chromosomal abnormalities involving chromosome 9, 20 or 11 have also been reported in patients with ependymomas (9). Finally, translocations containing chromosome 11q13: t(11; 17)(q13; q21) and t(10; 11; 15)(p12.2; q13; p12) have been reported in two patients with childhood supratentorial ependymoma (10, 11). These chromosome abnormalities have been thought to play a role in the pathogenesis of ependymoma.

This is the first reported case of MEN 1 syndrome associated with an ependymoma (13, 18). A relationship in the pathogenesis of MEN 1 and ependymoma can be considered because chromosome 11q13 abnormalities have been reported in both diseases. However, chromosome 11q13 is a long site containing 15Mb and it is a relatively frequent site of chromosome breakage. Additionally, the reported genomic analyses of ependymoma patients are not constant. The detection of loss of heterozygosity or rearrangement on chromosome 11q13.3 of the ependymoma tissue may support a common etiology. Unfortunately, limited ependymoma tissue from the patient remained when the diagnosis of MEN 1 was made, thus full investigation was not possible. Further genomic analysis and follow-up of the patient and other family members are currently under way to search for a common etiology.

References

MEN Type 1 with Spinal Ependymoma


