The Current Strategy for Managing Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1


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Multiple endocrine neoplasia type 1 (MEN1) is an inherited autosomal dominant disease presenting with pancreatic neuroendocrine tumors (pNETs), parathyroid tumors, or pituitary tumors. Using the PubMed database, we reviewed the literature on information regarding the proper diagnosis and treatment of MEN1-associated pNET. Many cases of MEN1-associated pNET are functioning pNETs. Gastrinomas and insulinomas tend to occur frequently in the duodenum and pancreas, respectively. In addition to diagnostic imaging, the selective arterial secretagogue injection test (SASI test) is useful for localizing functioning pNET. The standard treatment is surgical resection. However, in the case of a functioning pNET, the tumor should first be accurately located using the SASI test before an appropriate surgical method is selected. In cases of a MEN1-associated non-functioning pNET that exceeds 2 cm in diameter, the incidence of distant metastasis is significantly increased, and surgery is recommended. In cases of unresectable pNET, a somatostatin analog has been shown to demonstrate antitumor effects and is considered to be a promising treatment. In addition, molecular-targeted drugs have recently been found to be effective in phase III clinical trials. (Gut Liver 2012;6:287-294)

Key Words: Multiple endocrine neoplasia type 1; Pancreatic neuroendocrine tumor; Multiple tumors; Selective arterial secretagogue injection test

INTRODUCTION

Multiple endocrine neoplasia (MEN) is an autosomal dominant inherited disease presenting with tumorous lesions, mainly in various endocrine organs. In 1954, Wermer first indicated that patients with multiple tumors in the parathyroid gland, pituitary gland, and pancreatic islets of Langerhans were actually suffering from an autosomal dominant inherited syndrome instead of simple concomitant onset of the tumors. In 1961, Sipple reported a syndrome complicated with medullary thyroid carcinoma and pheochromocytoma. A syndrome consisting of mainly pancreatic neuroendocrine tumor (pNET), parathyroid tumor, pituitary tumor, etc., that was formally called “multiple endocrine adenomatosis,” which was found to be hereditary by Wermer, was subsequently classified as MEN type 1 (MEN1). A syndrome consisting of mainly medullary thyroid carcinoma and pheochromocytoma, as reported by Sipple, was classified as MEN2.

Patients with MEN1-associated pNET often have multiple tumors or malignant tumors that determine patients’ prognosis for survival. Therefore, it is considered important to make a cautious diagnosis and select the most appropriate treatment method for each patient. In light of this, we used the PubMed database to review the literature on MEN1-associated pNET and examine the diagnosis and treatment methods appropriate for MEN1-associated pNET.

ETIOLOGY OF MEN1

MEN1, which was identified by Chandrasekharappa et al. in 1997 as the gene that causes MEN1, is located on the long arm of chromosome 11 (11q13). This gene, which is also called menin, consists of about 10 exons dispersed over a region of approximately 7,000 base pairs, and encodes a 610-amino acid protein. Menin mRNA has been found in all normal human tissues thus far examined. Menin protein has also been found in pancreatic exocrine cells, where MEN1 tumors do not develop.
Menin protein is mainly located in the nucleus where it binds
with nuclear proteins, including JunD, NFκB, and Smad3, as
well as with histone deacetylase and histone methyl-transferase.
It is thought to be involved in cell growth, apoptosis, DNA re-
pair, and transcriptional regulation.5,6

In patients with MEN1, the inactivated MEN1 gene has ex-
isted heterozygously from the time of ontogeny, while the other
normal gene has lost function through somatic mutation, thus
causing tumor formation of specific cells.

In familial and non-familial MEN1, the detection rate of
MEN1 mutations is 90% and 70%, respectively,7 and the lifetime
incidence of MEN1 is nearly 100% in those with the mutations.
Therefore, if a patient clinically suspected of having MEN1 can-
not be definitely diagnosed, a genetic test is required.

**CLINICAL FEATURES OF pNET IN MEN1 PATIENTS**

It is reported that the prevalence of MEN1 is estimated to
be approximately 1 in 10,000 to 30,000, and that non-familial
MEN1 patients account for approximately 15% of total MEN1
patients.8 In people with MEN1 mutations, a few percent of
those 10 years of age and under develop MEN1, and while, by
40 years of age, nearly 100% of them develop the disease.9 Hy-
perparathyroidism is the most frequent initial disease in MEN1
(85%), and in people in their 40s, the incidence of parathyroid
adenoma is higher than that of other tumor types.10 Pituitary
adenoma and pNET are the second most frequent diseases.

According to a recent nationwide survey on gastroenteropan-
creatic neuroendocrine tumors in Japan,11 MEN1 was concur-
rently found in 10% of pNET patients. As for the breakdown of
pNET in MEN1 patients, gastrinoma was the most frequent (25%),
followed by insulinoma (14%). Interestingly, non-functioning
pNET (6.1%) occurred less frequently in Japan than in West-
ern countries.11 VIPoma and glucagonoma were also found,
although rarely, as other functioning pNET that present with
specific symptoms due to the hormones produced. Table 1 sum-
marizes the characteristics of the MEN1-associated functioning
pNET reported in literature.10-16

In cases of gastrinoma, refractory multiple ulcers and diar-
rhea, etc., develop due to increased gastrin concentrations in the
blood (Table 2).14,17,18 This disease is called Zollinger-Ellison syn-
drome (ZES). In gastrinoma, the incidence of concurrent MEN1
is as high as 20% to 38%;15,19 and therefore, gastrinoma should
be treated with MEN1 in mind. Gastrinoma is often found in the
duodenum of MEN1 patients. Since gastrinoma occurs as mul-
tiple tumors that are usually smaller than 0.5 mm in size, it is
sometimes difficult to detect by imaging.

Insulinoma often presents with symptoms of hypoglycemia
caused by an elevation of insulin levels in the blood. Insulinoma
usually develops as an isolated disease; however, a patient with
multiple pancreatic tumors is likely to have MEN1. Like gastrin-
oma, it is usually difficult to identify all the pancreatic tumors
by imaging studies in MEN1 patients.

The most characteristic sign of glucagonoma is necrotic mi-
gatory erythema. While glucagonoma is usually considered
malignant due to distant metastasis, MEN1-associated cases ap-
parently have tiny tumors with fewer symptoms.20

Most of endocrine tumors with MEN1 are benign, while

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Incidence of tumor type in MEN1, %</th>
<th>Incidence of MEN1 involvement in tumor, %</th>
<th>Site</th>
<th>Malignancy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>40-4710,12</td>
<td>19-2511,16</td>
<td>Duodenum (&gt;80%)</td>
<td>50-6013,15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreas</td>
<td></td>
</tr>
<tr>
<td>Insulinoma</td>
<td>10-1210,12</td>
<td>12-1411,12</td>
<td>Pancreas</td>
<td>12-2015</td>
</tr>
<tr>
<td>VIPoma</td>
<td>&lt;213,15</td>
<td>114</td>
<td>Pancreas</td>
<td>4014,15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duodenum (10%)15</td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>&lt;313,15</td>
<td>314</td>
<td>Pancreas</td>
<td>7014,15</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>&lt;213,15</td>
<td>114</td>
<td>Pancreas</td>
<td>70-8014,15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duodenum/jejunum (44%)13</td>
<td></td>
</tr>
</tbody>
</table>

MEN1, multiple endocrine neoplasia type 1.

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>Abdominal pain, diarrhea, heartburn, nausea, vomiting, gastrointestinal bleeding7,18</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Neuroglycopenic symptoms and hypoglycemia, corrected by administration of glucose13,18</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Severe watery diarrhea, hypokalemia, achlorhydria4,17,18</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Necrotic migratory erythema (rash), diabetes, thromboembolic disease14,17,18</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Steatorrhea, cholelithiasis, diabetes14,17,18</td>
</tr>
</tbody>
</table>

Table 1. The Characteristics of Functioning Pancreatic Neuroendocrine Tumors in Patients with MEN1

Table 2. The Symptoms and Signs of Functioning Pancreatic Neuroendocrine Tumors