Multiple endocrine neoplasia 1 (MEN1) is a hereditary syndrome associated with a number of endocrine and nonendocrine tumors. Unfortunately, a diagnosis of MEN1 often is delayed until after the patient has developed an advanced or second MEN1-related tumor. Nurses need to be familiar with hallmark signs of this syndrome to facilitate an early diagnosis and appropriately refer families for genetic assessment and, ultimately, develop a long-term plan for early detection and intervention for all family members at risk for MEN1.

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, and Laura Waldman, MS

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B.T., a 38-year-old woman, initially presented to her primary care physician with a six-month history of abdominal pain and diarrhea, which she had been attributing to stress because of her recent divorce. A subsequent upper endoscopy revealed duodenal ulcers and a computed tomography scan of the abdomen showed a 3 x 4 cm mass near the pancreatic head. She also had an elevated fasting serum gastrin level. Exploratory surgery showed three duodenal masses, all of which were excised. Pathology reported that all of the duodenal lesions were consistent with gastrinoma. B.T. was then referred to the oncology clinic to discuss prognosis and possible treatment options.

Nursing Assessment and Physical Examination

On assessment, the nurse reviewed B.T.’s past medical and family history. B.T. had a history of hypercalcemia caused by hyperparathyroidism for which she underwent a subtotal parathyroidectomy at age 25. B.T. also reported a one-year history of oligomenorrhea. Review of the family history reveals that B.T.’s father and paternal uncle had a history of kidney stones. Her father died at the age of 35 in a motor vehicle accident. B.T. had limited information about her father’s family history, but her paternal grandmother died of “stomach ulcers” (see Figure 1). On physical examination, B.T. is noted to have six facial cutaneous tumors (angiofibromas) that she states “have always been there.” The remainder of her physical examination is unremarkable. B.T. is a grocery store cashier and a single parent. She has a 12-year-old son and an 18-year-old daughter. She expresses to the nurse that she is very concerned about the impact of her recent diagnosis on her children.

In B.T.’s case, the history of hyperparathyroidism and gastrinoma are classic clinical features of multiple endocrine neoplasia 1 (MEN1) (see Figure 2). Her initial diagnosis of hyperparathyroidism together with the family history of kidney stones and an ulcer were previously unrecognized red flags for MEN1. Given the family and medical history, B.T. was referred for a genetic assessment and was found to have an MEN1 mutation. Subsequent biochemical testing revealed elevated prolactin levels as well as elevated parathyroid hormone and serum calcium levels. Magnetic resonance imaging showed a pituitary adenoma. B.T. was referred to an endocrinologist for management of the pituitary tumor and recurrent hyperparathyroidism.

Figure 1. Pedigree of B.T.’s Family

Note. Circle = female, square = male, slash = deceased. The arrow points to the proband who was the first individual tested in this family. The proband developed hypercalcemia from hyperparathyroidism and underwent a subtotal parathyroidectomy. The proband subsequently developed a gastrinoma.

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B.T.’s children were tested for the MEN1 mutation that was identified in B.T. Her daughter was found to have the mutation and, therefore, began the recommended MEN1 tumor surveillance (Doherty, 2005; Falchetti, Marini, & Brandi, 2005; Rich & Perrier, 2008). Her son did not inherit the mutation and, therefore, did not need to undergo MEN1 tumor screening.

Etiology of the Problem

MEN1 is primarily characterized by tumors of the parathyroid glands, endocrine pancreas/duodenum, and anterior pituitary (Lindor, McMaster, Lindor, & Greene, 2008). This disorder is caused by mutations that lead to the inactivation of the MEN1 gene, which codes for a tumor-suppressor protein, menin. MEN1 follows Knudson’s “two-hit” model for carcinogenesis. In inherited cases, the first hit is a MEN1 germ line mutation, which results in inactivation of one copy of the menin protein-coding alleles (Rich & Perrier, 2008). The second hit is a somatic mutation that inactivates the remaining allele and, thereby, allows malignancies and tumors to develop. More than 400 different germ line mutations in MEN1 have been reported, and most mutations are unique to individual families (Rich & Perrier, 2008). The disease patterns and expressivity are variable even within families (Akerström & Stålberg, 2009).

Most MEN1-related tumor growth occurs in hormone-secreting glands, so tumors often become clinically evident because of symptoms related to hormone overproduction. The incidence of tumors associated with MEN1 is shown in Table 1. Hyperparathyroidism is the presenting symptom (65%) and is diagnosed simultaneously with the presenting symptom in 94% of the cases (Lindor et al., 2008). The average age of onset is at ages 20–25, and 90% will display hypercalcemia by age 50. Most individuals with MEN1 present in late adolescence or early adulthood; however, reports exist of children as young as age 5 presenting with MEN1-related disease. Occasionally the diagnosis can be delayed until later in life (Rich & Perrier, 2008). Penetrance (i.e., the proportion of individuals who have a disease-causing mutation and show signs or symptoms of the disease) of MEN1 is high and is estimated to be 45% by the age of 30, 82% by the age of 50, and 96% by the age of 70; therefore, almost all who carry the mutation will eventually develop one or more cancers (Lindor et al., 2008).

The diagnosis of MEN1 often is missed or delayed because it can be associated with a mix of both benign and malignant tumors. In addition, patients may not always accurately report or know their family history, which can result in missing information that would otherwise lead to recognition and diagnosis of MEN1. This can be compounded if family members do not communicate well with each other. About 10% of the mutations are de novo, so the family could not anticipate the diagnosis (Lindor et al., 2008).

A clinical diagnosis of MEN1 can be made when there are two major tumors involving the parathyroid, endocrine pancreas, or anterior pituitary, or one major MEN1-related lesion is present in an individual who has a first-degree

<table>
<thead>
<tr>
<th>TUMOR/CLINICAL FINDING</th>
<th>INCIDENCE (%)</th>
<th>SYMPTOM</th>
</tr>
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<tbody>
<tr>
<td>Parathyroid</td>
<td>88–97</td>
<td>Symptoms of hypercalcemia include lethargy, depression, confusion, anorexia, constipation, nausea and vomiting, altered diuresis with increased risk for kidney stones, dehydration, hypertension, and shortened QT interval.</td>
</tr>
<tr>
<td>Pituitary</td>
<td>30–84</td>
<td>Prolactinoma manifested as oligomenorrhea/amenorrhea; galactorrhea in females and sexual dysfunction in males</td>
</tr>
<tr>
<td>Gastroenteropancreatic gastrinoma</td>
<td>40</td>
<td>Manifestations can include abdominal pain, diarrhea, esophageal reflux, acid peptic ulcers, vomiting, and anorexia.</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>16–36</td>
<td>Primary hypercortisolism; primary hyperaldosteronism</td>
</tr>
<tr>
<td>Carcinoid tumors (bronchial, thymic, gastric)</td>
<td>10</td>
<td>Carcinoid tumors do not manifest as recognizable hormonal syndrome, but symptoms may be caused by tumor mass or metastasis</td>
</tr>
<tr>
<td>Gastroenteropancreatic insulinoma</td>
<td>10</td>
<td>Results in hypoglycemia after fasting or exertion</td>
</tr>
<tr>
<td>Nonendocrine tumors</td>
<td>88</td>
<td>- Facial angiofibromas</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>- Collagenomas</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>- Lipomas</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>- Ependymomas</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>- Meningiomas</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>- Leiomyomas</td>
</tr>
</tbody>
</table>

Note. Based on information from Doherty, 2005; Falchetti et al., 2005; Rich & Perrier, 2008.
Table 2. Recommended Screening for Patients With a Multiple Endocrine Neoplasia 1 Mutation

<table>
<thead>
<tr>
<th>TEST OR EXAMINATION</th>
<th>AGE TO INITIATE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum prolactin</td>
<td>5</td>
</tr>
<tr>
<td>MRI head</td>
<td>5</td>
</tr>
<tr>
<td>Serum glucose, insulin, and proinsulin</td>
<td>5</td>
</tr>
<tr>
<td>Serum concentrations of calcium</td>
<td>8</td>
</tr>
<tr>
<td>Serum parathyroid hormone</td>
<td>8</td>
</tr>
<tr>
<td>Monitoring of fasting and meal-stimulated pancreatic polypeptide</td>
<td>10–20</td>
</tr>
<tr>
<td>Abdominal CT or MRI</td>
<td>20</td>
</tr>
<tr>
<td>Fasting serum gastrin: If gastrin is elevated, a secretin-stimulated gastrin test is indicated.</td>
<td>20</td>
</tr>
<tr>
<td>Somatostatin receptor SRS/CT of thorax and abdomen every 2–3 years</td>
<td>20</td>
</tr>
</tbody>
</table>

*Annually unless noted otherwise

CT—computed tomography; MRI—magnetic resonance imaging; SRS/CT—scintigraphy with computed tomography

Note. Based on information from Doherty, 2005; Falchetti et al., 2005; Rich & Perrier, 2008.

Management, Prophylactic Strategies, and Outcomes

Care of the individual or family with MEN1 requires knowledge of the problems that may arise and the best approaches to detect and care for the manifestations of this incurable, but potentially manageable, syndrome. Aggressive screening in individuals known to have an MEN1 mutation leads to detection of tumors approximately 10 years earlier than without screening (Rich & Perrier, 2008). Surveillance of individuals who have MEN1 syndrome or are at high risk for its development typically includes a variety of laboratory tests and diagnostic tests. These are described in Table 2. Although some recommendations suggest when to begin screening, the age at which testing can be discontinued among individuals at high risk is unknown; it probably should be continued for life.

MEN1 syndrome-associated hyperparathyroidism treatment is complex and usually results in less than optimal results. Options include removal of three and a half glands, leaving a part of one gland in the neck (subtotal parathyroidectomy), or removing all four parathyroid glands with immediate autograft of some of the parathyroid tissue into the musculature of the nondominant forearm. The incidence of recurrent or persistent hyperparathyroidism is 16%–54%, and the incidence of hypoparathyroidism is 10%–25%. Prior to surgery, bone antiresorptive agents are used to reduce hypercalcemia and limit bone resorption.

Prolactinomas (pituitary tumors) are treated with dopamine agonists. Adrenocorticotropic hormone-secreting pituitary tumors associated with Cushing Syndrome are surgically removed; nonsecreting pituitary adenomas are treated by trans-sphenoidal surgery. The gastrinomas associated with MEN1 are not easily cured through tumor surgery because finding the many small gastrinomas in the pancreas, duodenenum, and lymph glands is very difficult. Proton pump inhibitors or H₂-receptor blockers are used to reduce gastric acid output caused by gastrinomas. Surgery is indicated for insulinoma and most other pancreatic tumors. Surgical removal of adrenocortical tumors that exceed 3 cm in diameter can prevent malignancy. Thymectomy may prevent thymic carcinoid in men, particularly in smokers.

Approximately 50% of people with MEN1 will eventually develop a malignant tumor (Falchetti et al., 2005). Because early detection affects medical management, genetic testing often is used to identify individuals at risk and implement aggressive screening and surveillance measures. Once a mutation is identified in a family, single-site specific testing can be used to identify other family members at risk. Because MEN1 is an autosomal dominant disorder, each sibling and offspring of an affected individual has a 50% chance of inheriting the mutation.

Conclusion

This case illustrates the importance of recognizing the clinical manifestations of MEN1 not only in the patient but in the patient’s family members. Figure 3 lists key features of MEN1 that serve as indications for referral for an MEN1 genetic evaluation.

Figure 3. Key Points About Multiple Endocrine Neoplasia 1 (MEN1)

- MEN1 is an inherited disorder that causes hormone-secreting tumors in the duodenum and the endocrine glands—most often the parathyroid, pancreas, and pituitary.
- Overactive parathyroid glands can lead to tiredness, weakness, muscle or bone pain, constipation, indigestion, kidney stones, or thinning of bones.
- Pancreatic and duodenal endocrine tumors called gastrinomas can cause dangerous stomach or intestinal ulcers.
- Pituitary tumors called prolactinomas can cause excessive production of breast milk or interfere with fertility in women or with sex drive and fertility in men.
- Although many tumors associated with MEN1 are benign, almost 50% of people with MEN1 will eventually develop a cancerous tumor. Although not all individuals with MEN1 will have an identified mutation, genetic testing often can confirm the diagnosis of MEN1.
- MEN1 cannot be cured, but regular testing can detect the problems caused by MEN1 tumors many years before serious complications develop. Careful monitoring enables doctors to adjust an individual’s treatment as needed.
- If there is a known mutation in a family, other family members at risk for developing MEN1 can be tested and appropriate surveillance initiated.

The following can be used as indicators for referral for an MEN1 genetic evaluation.

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evaluation. When a patient such as B.T. presents with a MEN1-type tumor, a detailed medical and family history should be taken, with particular attention to potential MEN1 clinical manifestations (e.g., renal stones because of hypercalcemia, peptic ulcers because of gastrinoma).

Knowledge of the MEN1 “red flags” enables oncology nurses to appropriately recognize and refer such patients for genetic evaluation. This, in turn, leads to early diagnosis and optimal medical management for individuals and families affected by MEN1.

In B.T.’s case, the diagnosis of MEN1 led to identification of and treatment for a pituitary adenoma as well as enabling other family members to be tested for the MEN1 mutation first identified in B.T. Detection of the MEN1 mutation in B.T.’s daughter resulted in the daughter being referred to an endocrinologist and initiation of screening for MEN1-related problems. Families such as B.T.’s can be counseled that, with early detection, monitoring, and appropriate treatment, the most harmful consequences of a MEN1 mutation can be significantly reduced.

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References


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