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Review

Multiple endocrine neoplasia 1: a broad overview

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Abstract: This review article discusses the diagnoses and treatment of patients with multiple endocrine neoplasia type 1 (MEN 1). The most common tumors associated with MEN 1 are located in the pancreas, pituitary, and parathyroid glands. Less common tumors include neuroendocrine tumors of the lung and thymus, adrenal tumors, and cutaneous lesions. This article describes the diagnosis, clinical manifestations, treatment, and surveillance of tumors associated with patients who are diagnosed with MEN 1.

Keywords:
Multiple Endocrine Neoplasia I, MEN 1, pancreatic neuroendocrine tumor, pituitary, primary hyperparathyroidism, parathyroid, adrenal tumor, bronchial carcinoid, thymic carcinoid

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Introduction

First described in in the early 1900s, multiple endocrine neoplasia type 1 (MEN 1) is a rare endocrine syndrome characterized by a combination of pituitary, parathyroid, and pancreatic tumors. In 1954, Paul Wermer, an internist who practiced at Columbia University Presbyterian Hospital in New York, found the syndrome to be transmitted in an autosomal dominant fashion.[1] Though many other scientists and physicians have contributed to its discovery, the syndrome still carries his name, Wermer syndrome. More commonly, the syndrome is referred to as MEN 1. The prevalence of MEN 1 worldwide is 1 in 30,000.[2] There is no demonstrated predilection for sex, age, or gender in patients with MEN 1.[2] The diagnosis of MEN 1 is established when a patient has a combination of at least two of the three classic MEN 1 tumor subtypes from the pituitary, pancreatic, and parathyroid glands. Approximately 20 different other endocrine and nonendocrine tumors have been associated with MEN 1.

In 1997, the MEN 1 gene was found to be located on chromosome 11q13.[3] The MEN 1 gene consists of 10 exons that encode the protein menin. Menin is an amino acid protein that is involved in transcriptional regulation, genome stability, cell division, and proliferation.[4] Hundreds of germline or somatic mutations have been reported in both MEN 1 families and sporadic cases.[5,6] These mutations can be located across the entire coding region rather than a specific location.[6] Concolino *et al.* reported that 42% of these mutations are frameshift mutations, 25.5% are missense mutations, 14% are nonsense mutations, 10.5% are splice-site mutations, 5.5% are in-frame deletions, and the remaining 2.5% are gross deletions.[5] Most of these mutations lead to truncated forms of menin.[4] In addition, as many as 10% of MEN 1 mutations arise *de novo* and can be passed on to future generations.[5] Confirming the genetic mutation in a patient with the clinical diagnosis of MEN 1 can be challenging at times. As many as 10–20% of patients who meet clinical criteria for MEN 1 may not have mutations within the coding region of the MEN 1 gene. As a result, genetic testing is negative. These patients may have mutations within the promoter region of the MEN 1 gene or in an untranslated region.[7] In addition, it is possible that there is another tumor suppressor gene in this region that has not been identified.[6] Regardless of the genetic testing result, all patients who meet the clinical criteria for MEN 1 or at-risk family members, should meet with a genetic counselor.

Another syndrome carrying a similar presentation as MEN 1 is familial isolated hyperparathyroidism (FIHP). As its name suggests, FHIP is characterized by hyperparathyroidism alone. These patients

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do not develop pituitary or pancreatic tumors. On occasion, individuals who are thought to have FIHP are actually patients showing early manifestations of MEN 1.[7]

Primary hyperparathyroidism

Primary hyperparathyroidism is found in greater than 95% of patients with MEN 1. The majority of patients have four-gland hyperplasia. Primary hyperparathyroidism is often the first clinical manifestation of MEN 1 as the average age of onset is from 20 to 25 years old.[8,9] Symptoms associated with primary hyperparathyroidism include nephrolithiasis, osteoporosis (defined as T-score less than −2.5), fragility fractures, bone pain, pancreatitis, myopathy, fatigue, functional deficits such as problems with balance, difficulty sleeping, inability to focus or concentrate, or depression.[10] Primary hyperparathyroidism is often identified in patients who were found to have hypercalcemia on routine laboratory tests. Diagnosis is confirmed with an inappropriately elevated parathyroid hormone (PTH) and elevated calcium in the setting of a normal vitamin D. Patients may additionally have normocalcemic hyperparathyroidism, where serum calcium levels will be normal and PTH will be inappropriately elevated.

Once the diagnosis of primary hyperparathyroidism is confirmed, patients will need additional workup to determine if surgical intervention is indicated. Patients who have a calcium greater than 1 mg/dl above the upper limits of normal, osteoporosis, fragility fractures, 24-h urine calcium greater than 400 mg/day, age less than 50 years, creatinine clearance less than 60 cc/min, presence of nephrolithiasis on imaging, or significant cognitive deficits meet criteria for parathyroid exploration.[11] A dual energy X-ray absorptiometry (DEXA) scan is used to evaluate for osteoporosis in three sites, which includes the lumbar spine, total hip, femoral neck, or distal one-third of the radius (as this is one of the first bones affected by hyperparathyroidism).[11,12]

A 24-h urine calcium level is recommended to rule out benign familial hypocalciuric hypercalcemia (FHH). FHH is a rare autosomal dominant disorder characterized by hypercalcemia and a normal or mildly elevated PTH.[13] There are three subtypes of FHH. Patients with FHH1 have mutations in the calcium-sensing receptor (CASR) gene on chromosome 3, while patients with FHH2 and FHH3 have mutations on chromosome 19.[13] Patient with FHH are usually asymptomatic with hypercalcemia and a normal PTH. Typically, 24-h urine calcium is less than 100 mg/24 h. Urinary calcium excretion is not usually altered in patients with FHH who receive a calcium infusion. On the other hand, patients with primary hyperparathyroidism who receive calcium infusion will have an increase in urinary calcium excretion.[13] Patients with FHH are usually asymptomatic and typically do not need treatment. Subtotal parathyroidectomy does not cure this disorder.

Once a decision is made to proceed with surgery, ultrasound of the thyroid is recommended to evaluate for thyroid nodules, enlarged parathyroid glands or intrathyroidal parathyroid glands.[14] Patients who have thyroid nodules that meet criteria for FNA should undergo evaluation prior to parathyroidectomy since some of these patients will require concomitant thyroidectomy depending on cytology of the thyroid nodules. Additional imaging of the parathyroid glands is not necessary since these patients require a four-gland parathyroid exploration. MEN 1 patients who undergo parathyroid localization studies such as sestamibi single-photon emission CT (SPECT) and four-dimensional (4D) CT often will not localize because these patients have four-gland parathyroid hyperplasia.[15]

The surgical approach to patients with known MEN 1 disease can be managed in a variety of ways. Because the majority of patients with MEN 1 have four-gland parathyroid hyperplasia, total parathyroidectomy with or without autotransplantation is the standard of care.[16] However, patients who undergo total parathyroidectomy will require a significant amount of calcium and vitamin D supplementation while waiting for the grafted parathyroid tissue to become functional. Autografted parathyroid tissue can sometimes take years to be functional.[17] Some of these patients may develop permanent hypoparathyroidism due to autograft failure.[17] Surgeons who perform total parathyroidectomy should consider cryopreservation of parathyroid tissue during parathyroid exploration in case the patient is found to be aparathyroid after surgery. Cryopreserved parathyroid tissue may lose cell viability after 12 months. As a result, a larger amount of parathyroid tissue must be reimplanted if autografted over 12 months.[18] Another surgical option is to perform a subtotal parathyroidectomy, which carries a lower chance of permanent hypoparathyroidism, but as many as 13% may develop

recurrent primary hyperparathyroidism.[19,20] A new method of resection suggested by some endocrine surgeons is a minimally invasive approach to parathyroidectomy where they undergo a lateral approach with intraoperative i-PTH assay.[21] This occurs in select patients only if a single parathyroid gland is confirmed to be hyperplastic by concordant preoperative imaging.[22]

Regardless of the surgical approach, all of the patients who undergo parathyroid surgery for MEN 1 are at risk for recurrent disease. In fact, 15–20% of patients with MEN 1 have supernumery parathyroid glands within the thymus.[23] If unable to find all four glands, thymectomy at the time of parathyroidectomy is an approach to consider identifying supernumery parathyroid glands. Theoretically, this may help in early identification of thymic carcinoid tumors although this has not been proven.[24] Smokers or patients with strong family histories are at greater risk of developing thymic carcinoids.[25] However, some studies suggest that in patients with four-gland identification during initial operation, risks of thymic resection outweigh benefits.[24] Thymic resection at the time of initial operation increases operative time and increases the possibility to damage nearby organs and structures, chiefly the phrenic nerve or recurrent laryngeal nerve. In addition, thymic carcinoids have developed after resection of thymus at the first parathyroid operation.[26]

Pancreatic neuroendocrine tumors

The second most common classic tumor associated with MEN 1 is a pancreatic neuroendocrine tumor (PNET). A PNET is a category of tumors associated with both nonfunctioning and functioning pancreatic endocrine tumors differentiated by the different cell types of the pancreas. Over 80% of MEN 1 patients will develop a PNET. The average age of diagnosis is earlier (10–50 years old) than sporadic PNETs (50–80 years old).[27] PNETs are cited as the most common cause of death in MEN 1 patients.[28] The symptoms of different subtypes are variable based on which hormone is overproduced (Table 1).

PNETs are generally found on CT or magnetic resonance imaging (MRI) and are described as a well-circumscribed, hyperenhancing lesions. The sensitivity of CT and MRI for PNETs varies between 63–82% and 85–100%, respectively.[29] Endoscopic ultrasound (EUS) is helpful for tumors less than 1 cm in size.[29] Biopsy at the time of EUS can be used for definitive diagnosis. EUS has an approximately 90% detection rate, making EUS the most sensitive imaging technique.[29] Specialized imaging, namely the somatostatin receptor scintigraphy or octreotide scan, can be used for metastasis. However, its sensitivity is variable among PNET subtypes.[29] Newer technologies, such as the gallium dotatate positron emission tomography (PET)-CT scan, can be helpful in patients with symptomatic patients with negative imaging.[30] As the PNET subtypes are characterized on individual hormone oversecretion, workup and diagnosis will align with detecting these individual abnormalities. However, it is important to note that testing for chromogranin A, pancreatic polypeptide, glucagon, and gastrin testing has been shown to have a low yield in diagnosis of PNETs in MEN 1.[31]

Table 1. Pancreatic neuroendocrine tumors.

Tumor subtype	Labs utilized for diagnosis
Nonfunctioning PNET	Serum pancreatic peptide Chromogranin A
Gastrinoma	Serum gastrin (>1000 pg/ml)
Insulinoma	Serum insulin (>3 microU/ml) Pro-insulin (>5 pmol/l) C peptide (0.2 nmol/l)
Glucagonoma	Serum glucagon (>500 pg/ml)
Somatostatinoma	Serum somatostatin (>30 pg/ml)
VIPoma	Serum VIP (>75 pg/ml)

PNET, pancreatic neuroendocrine tumors; VIP, vasoactive intestinal peptide.

Nonfunctioning PNETs. Nonfunctioning PNETs, either sporadic or syndromic, are frequently found incidentally on imaging performed for other medical indications.[27] Nonfunctioning PNETs make up the majority (60–90%) of tumors found within the pancreas among patients with MEN 1.[32] Because they do not produce hormonal symptoms, nonfunctioning PNETs are often diagnosed late in their course. Biochemical markers such as chromogranin A, pancreatic polypeptide, and neuron specific enolase have been used as potential markers of less well-differentiated or tumors of unknown origin.[33] Higher levels have been associated with poorer prognosis

but can be elevated in patients with hepatic or renal impairment or in those taking proton-pump inhibitors.[32] Depending on the location of the tumor, patients may develop obstructive jaundice, gastric outlet obstruction, vague abdominal pain, fatigue, weight loss, or other nonspecific symptoms.[32] Patients may also develop symptoms from metastatic disease including anorexia, nausea, intra-abdominal bleeding, abdominal pain, jaundice, or a palpable mass.[32] The most common site of primary metastasis is the liver.

Functioning PNETs. Functioning PNETs are present in a variable number of patients with MEN1 (20–80%).33 MEN1 patients with functioning PNET tumors are generally diagnosed at a younger age than sporadic counterparts and may encounter recurrence at a higher rate than non-MEN1 patients.[34] The subtypes are based on overproduction of hormone based on the cell subtypes in the pancreas. These include gastrinoma, insulinoma, glucagonoma, somatostatinoma, and VIPoma. There are a variety of subtypes that can all be present within the same patient, although one is generally the most prevalent. Each tumor is associated with its own set of symptoms.

Gastrinoma. The most common PNET in MEN1 is the gastrinoma. A patient with a gastrinoma generally presents with recurrent gastric and duodenal peptic ulcer disease and gastric hypersecretion. Patients may complain of diarrhea, heartburn, and abdominal pain; 20–61% of patients with MEN1 will have a gastrinoma.[35] The majority of these tumors are malignant and metastasize to lymph nodes in 45–85% of patients. Gastrinomas are frequently missed as they are very small tumors and are located in the wall of the duodenum.[34] EUS is often unable to detect tumors within the duodenal wall. CT and MRI will localize between 10% and 40% of gastrinomas. Somatostatin receptor scintography will localize tumors 60–70% of the time.[35]

Patients will demonstrate high gastrin levels in the setting of hyperchlorhydria and a low gastric pH.[36] Basal maximal acid output ratios may be helpful to demonstrate inappropriately high acidity. In addition, gastric aspirates during endoscopy can be used to estimate acidity.[36] A 12-h nocturnal gastric acid secretion test will demonstrate levels of gastric acid greater than five times the normal range.[36] Imaging modalities most commonly utilized to localize gastrinomas are CT, MRI, and esophagogastroduodenoscopy (EGD) with endoscopic ultrasound. A selective arterial secretagogue injection (SASI) may also be used to localize gastrinomas, especially in the case of a small or duodenal gastrinoma.[37] Of the patients who are operated on for a gastrinoma, 30–50% will have regional lymph node metastasis at time of resection.[38]

Insulinoma. As many as 10% of patients with an insulinoma will have MEN1, and these tumors can be located throughout the pancreas.[39] These tumors are generally small – less than 2 cm.[40] Patients generally will present with hypoglycemic symptoms and fasting blood glucose levels less than 50 mg/dl. Hypoglycemic symptoms may include diaphoresis, tremor, and palpitations, confusion, behavioral changes, personality changes, visual disturbances, seizure, and coma.[40] Patients occasionally may also express symptoms of a sympathetic overdrive associated with insulin surge. Symptoms are rapidly relieved with intravenous glucose administration.

An insulinoma is diagnosed with a 72-h fast. Plasma glucose, C-peptide, pro-insulin, and insulin levels should be drawn every 6 h throughout the time period. All patients will develop symptoms within 72 h. A third of patients will become symptomatic within the first 12 h of testing, 80% will become symptomatic within 24 h, and 90% within 48 h.[10] Testing should be continued until blood glucose drops below 45 mg/dl and the patient develops symptoms of hypoglycemia. Long duration testing is difficult because the test requires hospital admission. For the diagnosis of insulinoma, the serum insulin will be greater than 5 mIU/l. The C-peptide level is greater than 0.6 ng/ml. Insulin to C-peptide ratio will be less than 1.0. Finally, the proinsulin level is greater than 20 nmol/l.[10] These patients should also be tested for plasma sulfonylurea causing hypoglycemia to rule out medication-induced hypoglycemia. A C-peptide level is helpful to rule out exogenous insulin use. More recently, a functional test combining a 48-h test with a glucagon load test has been suggested as more accurate and less invasive method for diagnosis.[41] After diagnosis, helpful imaging modalities that can be used to locate an insulinoma include CT, MRI, and endoscopic ultrasound. It is important to note that an octreotide scan is generally unhelpful in localizing

insulinomas as these tumors have a low density of somatostatin receptors.[42] Intraoperative US may be helpful to find tumors that are difficult to localize despite perioperative imaging. The median overall survival is 61% at 5 years with disease recurrence of 85% over the same time period.[43]

Glucagonoma. Glucagonomas are large tumors with an average size of 5 cm.[44] Glucagonomas are generally malignant and are found in variable locations in the duodenum or pancreas. The most common location is the tail of the pancreas.[44] These tumors are typically diagnosed when they are larger and can cause symptoms of compression. Patients may also present with symptoms of abdominal pain, diarrhea, ulcers, heartburn, and glucose intolerance. They may additionally have neuropsychiatric disturbances, venous thrombosis, or the pathognomonic symptom of necrolytic migratory erythema (NME). NME is a superficial epidermal necrosis that may spontaneously go into remission or relapse.[44] NME is present in approximately 70% of patients who have been diagnosed with glucagonomas. Glucagonomas are diagnosed with high glucagon levels in the setting of clinical symptomology. Fasting zinc and amino acid levels should be checked as many patients have deficiencies secondary to large volume diarrhea. Anemias may be present on laboratory evaluation as well.[44]

VIPoma. A VIPoma is characterized by a large volume of secretory diarrhea associated with hypokalemia, dehydration, and hypochlorhydria and is also known as Verner–Morrison syndrome. Patients also may demonstrate hyperglycemia and flushing. Many of these tumors are large (greater than 3 cm) and metastatic at time of presentation (60–80%) with the primary tumor located within the pancreas.[45]

VIPomas are diagnosed with a fasting VIP level greater than 500 pg/ml in the setting of high-volume diarrhea, usually 6–8 L a day.[45] It is important to note that electrolyte losses will occur with diarrhea and will be found on routine labs. These tumors can be seen on CT, MRI, or endoscopic ultrasound. However, if unable to find by those modalities, octreotide scans, mesenteric arteriography, and portal venous sampling can also be used. Overall 5-year survival for patients with VIPomas is 69%. In patients without metastasis at time of diagnosis, overall survival is 95% compared with 60% in patients with metastasis.[45]

Somatostatinoma. Somatostatinomas are extremely rare, with an incidence of 1 in 40 million,[46] and only 10% of these tumors are associated with familial disorders such as MEN 1. Generally, patients present with hepatobiliary obstructive symptoms as these tumors are large in size.[47] Additionally, patients may present with new onset diabetes mellitus, cholelithiasis, steatorrhea, weight loss, anemia, and diarrhea. Most are found within the pancreatic head or duodenum, and greater than 90% are malignant.

Somatostatinomas are diagnosed with a markedly elevated somatostatin level in the plasma.[47] They are localized in a manner similar to other PNETs through CT, MRI, endoscopic ultrasound or EGD. In addition, an octreotide scan can be useful. Somatostatinomas have 100% 5-year overall survival if found before metastasis. However, if metastasized, overall survival is reduced to 60%.[48]

Surgical management of PNETs

PNETs present at variable stages in their growth so management must be customized based on presentation. The surgical management of a nonfunctioning PNET is based on the size and location of the tumor. The operative indication based on size is controversial depending on which guidelines [National Comprehensive Cancer Network (NCCN) or European Neuroendocrine Tumor Society (ENETS)] are used. Tumors greater than 1 cm (NCCN) or 2 cm (ENETS) in size, those with invasion, or node-positive tumors should be resected with regional lymph node dissection.[48] Smaller tumors can be monitored closely.[48] Location of the tumor will determine whether the patient needs a total pancreatectomy, distal pancreatectomy, duodenectomy, pancreaticoduodenectomy, or Thompson procedure. The Thompson procedure is comprised of a distal pancreatectomy plus enucleation of tumors in the pancreatic head to avoid total pancreatectomy.[49] In general, syndromic PNETs grow more slowly than sporadic tumors so close monitoring may be appropriate in select scenarios.[50] Tumors that are refractory to medical management or with rapid growth within 6–12 months require resection.

Functioning PNETs are also treated with surgical intervention as described above. Ideally, hormones secreted by these tumors will normalize after resection. If there is persistent elevation of the affected

hormone, further evaluation is required to evaluate for additional disease. Insulinomas with close proximity to the pancreatic duct or invasive tumors are treated with complete resection. Small tumors may be enucleated.[50]

Surgical treatment for gastrinomas includes resection with regional lymph node dissection.[50] Intraoperative ultrasound is helpful to have available at the time of operation since many of these tumors are difficult to find. For occult tumors, a systematic approach to localizing these tumors is suggested starting with exploring the lesser sac, followed by a Kocher maneuver. A duodenotomy can be performed if the tumor has not been localized. If still not found, extrapancreatic locations must be explored, including the duodenum.[35]

If amenable for surgery, glucagonomas also are treated with resection and lymph node dissection.[49] Unresectable disease is treated with somatostatin analogues, for example octreotide, especially for patients with necrolytic migratory erythema. Patients with VIPomas will need preoperative rehydration and octreotide to control diarrhea symptoms. Once diagnosed, surgical resection with lymph node dissection is indicated.[49] Somatostatinomas are treated with simple resection.[49] In addition, at time of surgery, patient will need to undergo cholecystectomy if they have not previously for cholelithiasis.

For nonfunctioning PNETs, median survival for localized disease is 240 months. Overall survival for those with locoregional disease decreases to 90 months, and survival is 25 months in unresectable metastatic disease.[51] These patients need long-term follow up as many of them develop metachronous liver metastasis. Liver metastasis in patients with PNET can be managed with resection, microwave, or radiofrequency ablation. Other methods including transarterial chemoembolization or yttrium-90 radioembolization may be utilized as well.[52] Peptide receptor radionuclide therapy (PRRT) can be an effective treatment modality for patients who are not surgical candidates or for patients who have advanced and/progressive disease on somotostatin receptor imaging.[53] In patients with metastatic disease, options for systemic therapy include octreotide, everolimus, sunitinib, streptozocin, temozolomide, and capecitabine. Other chemotherapy regimens include combinations adriamycin and streptozocin or 5-FU and streptozocin.[54]

Pituitary adenoma

Pituitary adenomas are present in 30–50% of patients with MEN 1.[55] In 10% of patients, this tumor is the first indication of MEN 1.[55] Pituitary adenomas are diagnosed early, generally around age 35 and are more common in women.[55] Like the pancreatic tumors, there are different subtypes characterized by the hormones produced. Tumors of the pituitary gland are best seen using MRI of the brain with gadolinium contrast. Pituitary adenomas with prolactin levels less than 100 ng/ml and those without other endocrine features are nonfunctioning. Any of these tumors can present with symptoms of headache, visual field deficits such as bitemporal hemianopsia, cranial nerve dysfunction, or seizures secondary to mass effect. Pituitary tumors associated with MEN 1 tend to be more aggressive and resistant to standard treatments, requiring closer clinical follow up.[55]

The most common subtype to present in MEN 1 is a prolactinoma. Prolactinomas may cause galactorrhea, amenorrhea, sexual dysfunction, gynecomastia, infertility, or osteoporosis secondary to prolactin overproduction. Prolactin levels greater than 200 ng/ml confirm the diagnosis.[56]

Somatotropinomas cause gigantism and acromegaly secondary to growth hormone (GH) or insulin-like growth factor 1 (IGF-1) overproduction. Somatotropinomas are diagnosed by increased levels of growth hormone or IGF-1. Specifically, IGF-1 levels of 250% of the upper limit of normal and GH levels of 35 ng/ml suggest adenomatous source.[57] Increases in levels of prolactin may occur as well.

Patients with corticotropin-secreting tumors present with Cushing disease secondary to adrenocorticotropic hormone (ACTH) overproduction. They may have central weight gain, hirsutism, new onset diabetes mellitus and hypertension, striae, and easy bruising. Corticotropin-secreting tumors require a more complex workup. Initial screening is completed by measuring midnight salivary cortisol levels. Levels greater than 4.3 nmol/l suggest Cushing's syndrome.[56] Confirming the diagnosis requires a urinary free cortisol level, plasma adrenocorticotrophic hormone level, or a dexamethasone suppression test.[58] Patients may require inferior petrosal sinus sampling to verify the diagnosis.

Pituitary adenomas are treated with transsphenoidal tumor resection. Three approaches may be

used including sublabial, anterior nasal aperture, and posterior nasopharynx.[59] Prolactinomas may also be treated with bromocriptine or cabergoline.

Other tumors associated with MEN 1

Other tumors associated with MEN 1 include gastric carcinoids, neuroendocrine tumors of the lung and thymus, adrenal adenomas or carcinomas, and lipomas and cutaneous angiomas.[60] Thyroid adenomas have also been linked to MEN 1; however, some sources state that this may be an incidental finding and not associated with the syndrome.[61] Some studies have suggested that breast cancer may be associated with MEN 1 as well.[62]

Gastric carcinoid. Gastric carcinoid tumors are indolent, small, and found throughout the gastrointestinal tract including the gastric fundus. They are derived from enterochromaffin-like cells and cause achlorhydria and atrophic gastritis due to chronic hypersecretion of gastrin.[61] There are different subtypes of gastric carcinoid, which include type 1, 2, and 3.[61] Type 1 gastric carcinoids, the most common subtype, generally present as multiple tumors in the setting of long-term atrophic gastritis and low acid secretion. Generally, type 1 lesions are slow growing with low malignant potential. Type 2 gastric carcinoids are the subtype most prevalent in MEN 1. Type 2 lesions grow in the setting of gene inactivation rather than lack of stomach acid.[61] Type 3 gastric carcinoids are sporadic, solitary, and present with atypical carcinoid syndromes. Gastric carcinoids are most commonly diagnosed on endoscopic ultrasound, which demonstrates lesions in the deep mucosa or submucosa.[63]

The management of gastric carcinoids are dependent on the subtype and size of the tumor.[61] Type 3 gastric carcinoids are treated with subtotal or total gastrectomy. Type 1 and type 2 carcinoids are dependent on the size, number and growth over time. Larger lesions with less than six total polyps can be resected endoscopically. However, in instances of greater than six polyps, partial or total gastrectomy is recommended. Consideration of more extensive resection may be discussed in the case of MEN syndromes though it is important to note that many type 2 gastric carcinoids have been seen to regress after successful resection of gastrinoma.[61] Patients with gastric carcinoid tumors should be monitored annually for growth and recurrence.[61]

Thymic carcinoids. Neuroendocrine tumors of the thymus and lung are present in less than 8% of MEN 1 patients but 25% of all occur within the context of MEN 1.[64] Thymic carcinoids comprise less than 5% of anterior mediastinal tumors and have a male predominance of 2:1 in patients with concurrent MEN 1 syndrome.[65] Thymic carcinoids are the second most common cause of death in MEN 1 patients.

Carcinoid tumors of the thymus generally present as large masses, often with local invasion and distant metastasis. Thymic carcinoid tumors are aggressive; they have a 23.4% 5-year overall survival.[66] Over 50% of thymic carcinoids are functional, producing ACTH with a resulting Cushing syndrome.[67] Patients also present with chest pain, cough, and respiratory distress. Additionally, patients may have dysphagia or other mediastinal symptoms secondary to mass effect.

Many neuroendocrine tumors of the thymus are found incidentally after screening chest X-ray or after symptoms of compression, displacement, or invasion of mediastinal structures prompting CT or chest radiography. On imaging, the tumor is lobulated and may have areas of necrosis or hemorrhage. An octreotide scan or 2-deoxy-2-fluorine-18-fluoro-d-glucose (18FDG) PET can be used to localize tumors and MRI can be helpful for surgical planning.[68] As with PNET tumors, in patients with symptomatic disease and negative imaging, a gallium dotatate PET-CT can be helpful to localize disease.[17]

Thymic carcinoids are treated with resection. Chemotherapy with cisplatin or carboplatin in combination with etoposide and radiotherapy can also be utilized but have been showed with mixed results.[66] Overall mortality of patients with neuroendocrine tumors of the thymus is high; approximately 25–36% 10-year survival.[66] Generally, completeness of resection is an indicator of overall survival.[66]

Bronchial carcinoids. Bronchial carcinoid tumors are more indolent in nature. Bronchial carcinoids are seen in 5–35% of patients with MEN 1 and they demonstrate a high recurrence rate.[69] Bronchial carcinoids are more commonly seen in males

and smokers. Clinical symptoms include hemoptysis or recurrent pneumonitis. Generally, bronchial carcinoids are small (less than 1 cm), multifocal, and are peripheral in the lungs.

Bronchial carcinoids may also be found on incidental imaging. For centrally located bronchial carcinoids, bronchoscopy may be helpful for biopsy and diagnosis. Biopsy of the lesion will demonstrate neuroendocrine cells. Treatment of bronchial carcinoids includes lobectomy with regional lymph node dissection. In patients where lobectomy is contraindicated, radiation therapy may be used. Chemotherapy regimens with cisplatin or carboplatin in combination with etoposide can be used in advanced disease.[33]

Adrenal disease. Adrenal disease such as hyperplasia, adenomas or carcinomas are found at a higher incidence in MEN 1 patients.[70] Symptoms can be subdivided based on endocrine functionality. Patients who are found to have an adrenal mass must undergo MRI or adrenal protocol CT scan. Adrenal adenomas will have high lipid content with high washout and can be observed if smaller than 3 cm and nonfunctional. Worrisome features of adrenocortical carcinomas include tumors greater than 4 cm in size, evidence of local invasion, Hounsfield units greater than 10, hypervascularity, or a heterogenous appearance.[71] If the adrenal tumor is functional, the treatment is surgical resection. Nonfunctional tumors with benign characteristics can be observed with serial imaging and subsequently removed if they grow in size.

Aldosteronomas. Aldosteronomas cause Conn syndrome, which is characterized by hypertension and hypokalemia. Often, patients with undiagnosed aldosteronomas have been placed on greater than three blood pressure medications without adequate blood pressure control, which prompts further clinical investigation.[72] Aldosteronomas are generally unilateral and are about 1–2 cm in size. In a functioning aldosteronoma, a patient's plasma aldosterone to renin ratio and plasma aldosterone level should be measured followed by adrenal phase CT.[70] A ratio of greater than 30 or an aldosterone level greater than 15 ng/dl are diagnostic.[70] Patients must be off of spironolactone for an accurate biochemical evaluation. Adrenal venous sampling may be used to confirm unilateral *versus* bilateral disease especially in those greater than 40 years old as the incidence of incidentalomas increases with age.[70] Preoperative spironolactone or epleronone is often prescribed for blood pressure control.[70]

Cortisol-producing adenoma. Cortisol-producing adenomas cause Cushing syndrome with weight gain, muscle wasting, fat deposition, dorsal kyphosis, osteoporosis, hyperglycemia/diabetes, hypertension, amenorrhea, and depression. A dexamethasone suppression test will fail to suppress cortisol levels below 1.8 μg/dl. Other useful laboratory tests include a morning cortisol, serial midnight salivary cortisol levels, ACTH level and a 24-h urinary free cortisol level.[70] Postoperative steroids are usually required due to adrenal atrophy from long standing disease.[70]

DHEAs adenoma. Dehydroepiandrosterone sulfate (DHEAs) tumor subtype is extremely rare within the context of MEN 1.[39] DHEAs tumors present with virilization including deepening of voice, hair production, menstrual irregularities, and acne. If suspected, plasma DHEAs levels can be tested to verify diagnosis.

Pheochromocytoma. Presentation of pheochromocytoma within MEN 1 syndrome has been reported only in fewer than 10 case reports.[73] Patients may develop intermittent heart palpitations, diaphoresis, and headaches.[74] The diagnosis is confirmed by measuring plasma and/or 24-h urinary metanephrines and normetanephrines followed by imaging studies including either adrenal phase CT or MRI. MIBG and PET scans can be used in to localize pheochromocytomas.[72] Pheochromocytomas can vary in size and have the ability to metastasize. Prior to surgery, patients must undergo alpha-adrenergic blockade, followed by beta blockade (if needed). They are ready for surgery once they develop orthostatic hypotension. A dedicated team of endocrinologists, surgeons, and anesthesiologists are imperative for a good outcome.

Adrenal cortical carcinoma. Only about 19 cases of adrenocortical carcinoma have been associated with MEN 1.[70] Patients most commonly present with Cushing syndrome and prognosis is poor. These tumors are generally greater than 11 cm in size and should not be biopsied due of risk of tumor seeding. Open surgical resection is recommended to reduce the risk of capsule rupture and seeding; however, this recommendation is controversial.[70] Median 5-year overall survival is 15–44%.[75] Older age and incomplete resection are associated with worse outcomes. In addition,

functioning tumors tend to have worse outcomes. Mitotane has been used for metastatic disease not amenable to other forms of treatment.[76]

Cutaneous lesions

Multiple lipomas, angiofibromas, and collagenomas have been seen in patients with MEN 1.[77,78] Lipomas are fatty tumors that can be large in size and can be located anywhere on the body. Angiofibromas are small benign vascular tumors containing dermal tissue and blood vessels generally located on the face. Collagenomas are small benign collagen tumors that can be located anywhere on the body. Though not pathongnomic, the cutaneous symptoms are not to be overlooked, especially in families presenting for evaluation of MEN 1.

Surveillance

Patients with MEN 1 need surveillance of all classic tumors whether or not they have developed the tumor. In individuals who have a diagnosis of MEN 1, surveillance is key to an improved outcome (Table 2). Surveillance recommendations are often debated subjects, especially in the case of genetic testing and no clinical disease. The following are the recommendations by Thakker *et al.* based on a review of peer-reviewed publications.[16] After diagnosis, calcium levels should be tested annually. Patients with hypercalcemia should have intact PTH and vitamin D levels evaluated to determine if primary hyperparathyroidism is present. In addition, patients should undergo CT or MRI of the abdomen every 1–3 years to evaluate for pancreas tumors.[16] If a mass is present and has not been resected, a patient should undergo imaging every 6 months to monitor for progression. An additional imaging option for surveillance is serial endoscopic ultrasound. Patients with pituitary tumors should undergo pituitary or sella MRI every 3–5 years. Prolactin and IGF-1 levels should be ordered every 3–5 years in addition to any previous abnormal labs. Patients with bronchial or thymic tumors should undergo chest CT or MRI every 1–3 years after resection to monitor for recurrence.[16]

Patients and family members should be examined with the individual tumor subtypes in mind looking for any abnormal physical exam findings. Biochemical testing is also recommended to screen for tumors. Annual serum fasting glucose, insulin, gastrin, chromogranin-A, glucagon, and proinsulin levels should be obtained. In addition, starting at age 5 years, annual serum prolactin and IGF-1 levels should be added. At age 8 years, an annual serum calcium and PTH level is recommended. A brain MRI is recommended every 2–3 years and a CT or MRI of the abdomen every 1–3 years. In the instance a mass is found, the frequency increases to every 6 months. Other imaging and biochemical testing may be useful to detect less common tumors.[35]

Table 2. Surveillance.

Tumor type	Imaging and lab surveillance
Parathyroid disease	Annual calcium Annual PTH
Pancreatic disease	CT or MRI of abdomen every 1–3 years Serial endoscopic ultrasound Chromogranin-A
Pituitary disease	Pituitary/Sella MRI every 3–5 years Annual prolactin Annual IGF-1 Glucagon
Insulinoma	Annual serum glucose Serum insulin Pro-insulin
Gastrinioma	Annual gastrin
Glucagonoma	Annual glucagon

CT, computed tomography; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; PTH, parathyroid hormone.

Genetic testing and familial workup

In addition to the individual surveillance, patients with a clinical MEN 1 diagnosis should undergo genetic testing. Genetic counseling with a qualified genetic counselor should be provided to these patients. Immediate family members are also suggested to undergo testing. People who qualify for genetic testing are those with any of the following:

- Two or more tumors or one tumor with family history of MEN 1;
- One classic tumor and one non-classic tumor;

- One classic tumor and family history of classic tumor;
- High suspicion of MEN 1 even with initial negative MEN 1 genetic test;
- At risk family members in a high-risk patient currently undergoing genetic testing.[79]

The test is a blood test. In 10–20% of patients a pathogenic MEN 1 mutation cannot be identified so patients with a negative test and a high pretest probability of disease may still have MEN 1.[80] New advances in genetic testing allow for preimplantation testing to be performed on patients looking to test future pregnancies.[81]

Conclusion

MEN 1 is a complex disease syndrome requiring a multidisciplinary approach. The overall survival for patients with MEN 1 is based on the patient's individual tumor combination but is frequently dictated by the presence of PNETs.[82]

A multidisciplinary approach to intervention is appropriate and is recommended in management as patients may need input from a variety of specialists including endocrinologists, gastroenterologists, medical oncologists, genetic counselors, radiologists, pathologists, and surgeons.

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