MEN in black and white (and sometimes in color)

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Learning objectives

- Recognize pathophysiology, clinical manifestations and endocrine tumors associated with multiple endocrine neoplasia syndrome.
- Describe the multimodality imaging features of the endocrine tumors constituting MEN syndrome.
- Understand the role of follow up imaging and screening in patients with known or suspected gene mutations.
Background

Multiple endocrine neoplasia (MEN) syndrome comprises a spectrum of hormone secreting tumors, usually of autosomal dominant transmission within families [1-4]. The two primary subtypes, MEN 1 and MEN 2, are associated with characteristic benign and malignant endocrine tumors. Imaging plays a vital role in the multidisciplinary treatment approach to these complex tumors. Therefore, it is critical for the radiologist to understand the range of anatomic and functional imaging findings for each tumor type associated with MEN syndrome.
In 1953, Paul Wermer first described a familial syndrome of primary hyperparathyroidism (PHPT), pituitary adenoma and pancreatic neuroendocrine tumor (pNET) which was termed Wermer Syndrome [4-7]. This combination of hormone secreting tumors was later distinguished as multiple endocrine neoplasia type 1, which carries autosomal dominant penetrance with a gene locus on chromosome 11.

**PRIMARY HYPERPARATHYROIDISM (PHPT)**

*Biochemical Markers* - The hallmark of hyperparathyroidism is elevation of serum parathyroid hormone (PTH). Primary hyperparathyroidism is further delineated by elevation of serum calcium in response to high serum PTH. In the setting of hypercalcemia, PHPT may present with normal range hypercalcemia. In this context, PTH levels are inappropriately suppressed in the setting elevated serum calcium [8].

*Ultrasound* - Sensitivity for sonographic evaluation of parathyroid adenoma causing PHPT can be as high as 82% [1]. Parathyroid adenomas appear as an ovoid homogeneously hypoechoic nodule posterior to the thyroid gland [FIGURE 1]. Peripheral hypervascularity and feeding vessels at color Doppler imaging have also been described [9].

*Functional imaging* - Functional imaging techniques with $^{99m}$Tc-sestamibi offer superior detection for parathyroid adenoma compared with anatomic imaging alone. Sensitivity for solitary adenoma detection with sestamibi has been reported as high as 88% [10]. $^{99m}$Tc-sestamibi uptake occurs in normal thyroid and parathyroid tissue, with more avid uptake in adenomatous parathyroid tissue. On delayed planar images, tracer is retained in hyperfunctioning parathyroid glands [FIGURES 1-3]. SPECT imaging increased sensitivity of detection by allowing differentiation of hyperfunctioning parathyroid from residual overlying thyroid activity and providing better localization of metastatic disease [FIGURES 2-4].

*CT* - 4-dimensional CT protocols may be useful for detection of adenomatous PHPT in cases of suboptimal first line imaging, post-operative imaging and detection of ectopic
tissue [11]. 4D CT technique refers to three planes of CT reconstruction with the fourth dimension of multiphasic image acquisition. Parathyroid adenoma enhances earlier than native thyroid tissue and is most readily identified on the arterial phase.

**MRI** - MRI may be utilized in cases of persistent or recurrent hyperparathyroidism for location of ectopic parathyroid tissue [9]. Parathyroid adenomas demonstrate intermediate to low T1 with corresponding intermediate to high T2 signal characteristics. Routine use of contrast has not been established.

**PITUITARY IMAGING**

**Biochemical** - Incidence of functional adenoma is higher in patients with MEN syndrome compared with sporadic pituitary adenoma. The majority of hormone secreting pituitary tumors in MEN1 syndrome are prolactinomas, up to 60% [1]. The remaining tumors are composed of growth hormone secreting adenomas (approximately 24%) and adrenocorticotropic tumors (less than 5%). A small percentage of tumors are nonfunctioning [6,7].

**MRI** - MRI is the mainstay for imaging diagnosis of pituitary adenoma. Imaging features on MRI are divided by microadenoma or macroadenoma. Microadenomas are isointense to the adjacent pituitary parenchyma on T1- and T2-weighted sequences. However, these lesions enhance slowly compared with background pituitary parenchyma and appear as hypointense on post contrast sequences [FIGURE 4]. A small portion of pituitary microadenomas are imperceptible on single phase post contrast imaging. In those cases, a dynamic protocol increases sensitivity for differences in enhancement of the pituitary microadenoma against the normal pituitary background tissue [12].

Pituitary macroadenomas are defined by size greater than 1 cm. These lesions are typically isointense to grey matter on T1 sequences and demonstrate heterogeneous enhancement [FIGURE 5]. Intrinsic T1 hyperintense signal may result from areas of necrosis and hemorrhage.

**CT** - There is limited role for CT in the prospective workup for pituitary adenoma. Lesions are typically isodense to the adjacent brain matter. Enhancement pattern varies by the amount of necrosis; however, most adenomas enhance avidly. Remodeling of the sella turcica is another common feature [FIGURE 6].

**PANCREATIC NEUROENDOCRINE TUMOR**
Biochemical - The majority are non-functional. Biochemical derangement results from mass effect from primary tumor or metastatic disease, such as elevated bilirubin from obstruction of the extra-hepatic biliary ducts or acute pancreatitis with elevated lipase secondary to compression of the main pancreatic duct. The specific biochemical derangement of the primary tumor is dependent on the histologic subtype. The most common functional pNETs are insulionomas and gastrinomas, followed by VIPomas, glucagonomas and somatostatinomas [TABLE 1] [13].

Table 1. Pancreatic neuroendocrine tumor subtypes, biomarkers and associated clinical findings.

<table>
<thead>
<tr>
<th>Tumor Subtype</th>
<th>Associated peptide or hormone</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Hypoglycaemia [13]</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>Refractory gastric and duodenal ulcers [13]</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>Necrotizing migratory erythema, diabetes, anemia and weight loss [14]</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Vasoactive intestinal peptide (VIP)</td>
<td>Profuse watery diarrhea, hypovolemia, hypokalemia and acidosis [15]</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>Diabetes or glucose intolerance, cholelithiasis, weight loss, diarrhea, hypo- or achlorhydria [16]</td>
</tr>
</tbody>
</table>

Ultrasound - Transabdominal ultrasound has relatively low sensitivity for detection of pNET, particularly for tumors less than 2 cm in size [17]. Endoscopic ultrasound is far superior for detection of pNET with sensitivity rates reported as high as 93%, with the added benefit of direct needle sampling at the time of the procedure [18]. Tumors usually appear as solid hypoechoic masses with variable amounts of hypo- to anechoic cystic foci and calcification [FIGURE 4].

CT - Dual phase CT is the mainstay for localization and follow up of pNET. Tumors are typically hypervascular and often better visualized on arterial phase imaging; however, portal venous phase imaging is complementary as some tumors may only be seen on the portal venous phase [19,20]. Heterogeneous enhancement is a common feature with varying degrees of cystic degeneration, fibrosis and calcification [FIGURE 4-5, 7-9].
Metastatic disease from pNET will also be hypervascular and better visualized on the arterial phase.

**MRI** - Offers increased sensitivity compared to CT for detection of small pNETs [1,21]. Rounded lesions of low T1 signal are present on both fat saturated and non-fat saturated sequences. Lesions also demonstrate increased T2 signal compared with the normal surrounding pancreatic parenchyma. The pattern of enhancement on post contrast sequences closely mirrors that of CT with increased enhancement on arterial phase relative to normal parenchyma and heterogeneous enhancement on successive phases [FIGURE 8]. Liver metastases usually demonstrate similar features of low T1 and high T2 signal with ring like peripheral enhancement. Fat saturated T2 sequences tend to be the most sensitive [19]. The use of hepatobiliary agents such as gadoxetic acid demonstrates relative hypoenhancement of tumor on the hepatobiliary phase, as these tumors do not contain hepatocytes.

**Functional Imaging** - Expression of somatostatin receptor (SSTR) on the surface of pancreatic neuroendocrine tumors has been utilized for imaging with $^{111}$In-octreotide. Planar and SPECT imaging demonstrate uptake in tumor cells [FIGURE 4-5, 9]. Recently, PET/CT imaging with Ga$^{68}$-Dotatate has gained favor due to its increased specificity, imaging efficiency and better safety profile compared with $^{111}$In-octreotide [FIGURE 9] [22]. This is also an excellent modality when evaluating for metastatic disease.

**MEN 2**

MEN 2 is a less common variant hormonal tumors characterized by the presence of medullary thyroid carcinoma (MTC), pheochromocytoma and parathyroid adenoma. This familial syndrome was first reported by John Sipple in 1953 and termed Sipple Syndrome [1]. This syndrome is caused by a genetic defect of the RET protooncogene on chromosome 10 [23,24]. MEN2 is further divided into MEN2A and the less common variant MEN2B. MEN2A is comprised of MTC, pheochromocytoma and parathyroid adenoma. MEN2B is similar to MEN2A, but without parathyroid adenoma and added features of marfanoid habitus and multiple ganglioneuromas. These features are important to obtain from the referring clinician, as it is difficult to detect these on imaging.

**MEDULLARY THYROID CARCINOMA**

**Biochemical**- Pre- and post-operative measurement of plasma calcitonin is an important predictor of disease prognosis, response to treatment and recurrence. Serum
carcinoembryonic antigen (CEA) levels have also been utilized to monitor MTC; however, its sensitivity and specificity is lower compared with plasma calcitonin [25].

**Ultrasound** - First line study for diagnosis of thyroid nodules. Sonographic findings of MTC are similar to other thyroid malignancy with hypoechoigenicity, calcification, internal vascularity and spiculated margins predictive of malignancy [FIGURE 10] [26].

**CT** - Limited role in the workup of patients with MTC. CT is predominantly used for evaluation of metastatic disease. Current American Thyroid Association (ATA) guidelines only recommend CT workup for MTC in patients with extensive neck disease or distant metastasis. Alternately MRI may be performed [FIGURE 11] [27].

**PHEOCHROMOCYTOMA**

Pheochromocytomas are found in up to 50% of patients with MEN2 and are present bilaterally in up to 80% of cases [28-30]. Clinical features include a triad of headache, palpitations and sweating. Imaging evaluation complements biochemical evaluation and modalities of CT, MRI and functional imaging are often utilized for diagnosis and surgical planning.

**Biochemical** - Plasma free metanephrines and urinary fractionated metanephrines are most sensitive biochemical markers. Urinary vanillylmandelic acid and urinary total metanephrines are most specific [28-30].

**Ultrasound** - Yields relatively low sensitivity and is rarely used. When encountered, pheochromocytomas appear as an ovoid iso-to hyopoechoic suprarenal mass with variable internal echoes depending on the degree of intralesional hemorrhage.

**CT** - Pheochromocytoma attenuation can vary, but imaging features of pheochromocytoma and lipid poor adenoma rarely overlap. Almost all pheochromocytomas measure greater than 10 HU [28,31]. Patterns of enhancement can also vary, but most pheochromocytomas demonstrate similar washout characteristic to adrenal cortical carcinomas (<60% absolute and <40% relative washout). [FIGURE 12]

**MRI** - Imaging study of choice for pheochromocytomas due to its superior sensitivity [28]. Pheochromocytomas demonstrate low T1 signal and very bright T2 signal. Slight variations in T2 signal characteristics may occur depending on the degree of necrosis, calcification and hemorrhage. Intrinsic high T1 signal is usually indicative of intralesional hemorrhage. [FIGURE 13-14]
**Functional Imaging** - A variety of functional imaging techniques and tracers are available for detection of pheochromocytoma, but the most common and most sensitive/specific agent remains $^{123}$-MIBG, either by planar or SPECT imaging [FIGURE 14] [1,28]. Imaging with $^{111}$In-octreotide has significant lower sensitivity (approximately 25%) for non-metastatic tumor. However, this tracer does provide benefit for MIBG-negative or metastatic tumor. Similar to octreoscan, $^{18}$F-Fluorodeoxyglucose PET imaging may be utilized for evaluation of metastatic disease or dedifferentiated tumor. Several additional PET ligands including $^{18}$F-fluorodopamine and $^{18}$F-dehydroxyphenylalanine show promise for increased sensitivity and specificity for pheochromocytoma detection, however these studies are not yet routinely used in clinical practice [28,32].

**FAMILIAL NON-MEN MEDULLARY THYROID CARCINOMA**

This entity describes a clinical variant of MEN2A in which MTC is typically the only presenting feature. A mutation of the RET proto-oncogene is responsible for this disease; however, the specific codon mutation is distinctly different from that of MEN2A [33,34].

**MEN 4**

Recently, a new subset of MEN syndrome was described in a subset of mutation negative patients with MEN1-like features. This subset was termed MEN 4 and is caused by a separate gene mutation of tumor suppressor gene CDKN1B. Only 19 confirmed cases have been reported in the literature. Given the small subset, definite conclusions are difficult to draw regarding the clinical course of this disease. However, the most common phenotype is primary hyperparathyroidism and pituitary adenoma [23].

**SCREENING**

Individuals with known MEN gene mutations or those family members at risk for development of MEN related tumors undergo a combination of clinical, biochemical and radiologic screening [TABLE 2]. Specific regimens vary widely as no consensus guidelines are established.

Table 2. Suggested radiologic screening options.
<table>
<thead>
<tr>
<th>TUMOR</th>
<th>SCREENING SUGGESTION*</th>
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</thead>
<tbody>
<tr>
<td><strong>MEN 1</strong></td>
<td></td>
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<tr>
<td>Parathyroid Adenoma</td>
<td>None</td>
</tr>
<tr>
<td>Pituitary Adenoma</td>
<td>MRI every 3 years</td>
</tr>
<tr>
<td>pNET</td>
<td>MRI, CT or EUS annually</td>
</tr>
<tr>
<td><strong>MEN 2</strong></td>
<td></td>
</tr>
<tr>
<td>MTC</td>
<td>Annual US</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>MRI or CT**</td>
</tr>
</tbody>
</table>

* [6,7,35,36]

** For patients with abnormal biochemical testing only
Fig. 1: Parathyroid adenoma in MEN1 patient with hyperparathyroidism and prolactinoma. Transverse (A) and sagittal (B) ultrasound images demonstrate an ovoid iso- to hypoechoic mass posterior to the left thyroid lobe. Post injection planar scintigraphy image (C) with 99mTc-sestamibi radiotracer demonstrates avid asymmetric uptake within the thyroid (blue arrow) and parathyroid glands (yellow arrow). Delayed images (D) show retained radiotracer within the left parathyroid gland. Pathology from subsequent parathyroidectomy was consistent with parathyroid adenoma.

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Fig. 2: Parathyroid adenoma in MEN1 patient with parathyroid nodule on screening ultrasound. Nodule was not clearly evident on planar 99mTc-sestamibi delayed images (A-B) against background thyroid activity. However, SPECT images (C) show uptake within the parathyroid gland (yellow arrow). Subsequent resection and pathology results were consistent with adenoma.

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Fig. 3: Parathyroid adenoma in MEN1 patient with prior parathyroidectomy and persistent hypercalcemia. 99mTc-sestamibi planar (A-B) and SPECT imaging (C-D) shows ectopic parathyroid tissue in the mediastinum (yellow arrows). Subsequent resection and pathology showed adenoma.

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Fig. 4: Multimodality imaging features of pituitary adenoma, parathyroid adenoma and pNET in patient with MEN1. Sagittal (A) and coronal (B) contrast enhanced T1W MRI of the pituitary demonstrates focal hypoenhancement (yellow arrows), compatible with a pituitary microadenoma. Tc-99m Sestamibi SPECT image (C) shows uptake in the left parathyroid gland suggesting parathyroid adenoma (green arrow). Transabdominal ultrasound image (D) demonstrates hypoechoic lesion in the pancreas neck (red arrow). Subsequent arterial phase CT (E) shows lack of arterial phase enhancement (purple arrow), which is atypical. However, 111In-Octreotide SPECT study (F) demonstrates uptake within the lesion (blue arrow), in keeping with pancreatic neuroendocrine tumor.

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**Fig. 5:** PNET and pituitary adenoma in patient with MEN1. Contrast enhanced CT (A) in the portal venous phase shows mass in the tail of the pancreas (yellow arrow). Complementary 111In-Octreotide SPECT (B) confirms pNET in the tail of the pancreas (green arrow). Pre-contrast T1W image (C) shows pituitary mass isointense to grey matter (purple arrow). Contrast enhanced T1W MRI (D) demonstrates heterogeneous enhancement of this lesion (blue arrow), compatible with a pituitary macroadenoma.
**Fig. 6:** Pituitary adenoma in patient with MEN1. CT with contrast (Left) shows enhancing suprasellar mass (yellow arrow) with remodeling of the sella turcica (red arrow) shown in the sagittal bone window (right), consistent with known pituitary adenoma.

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**Fig. 7:** PNET in a patient with MEN1. Arterial (left) and portal venous (right) phase CT images show typical findings of arterial phase enhancement (yellow arrow) and isoattenuation to background pancreatic parenchyma on the venous phase (blue arrow). Clinical and histologic features were consistent with insulinoma.

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Fig. 8: Pancreatic neuroendocrine tumor (pNET) in patient with MEN1. Arterial phase contrast enhanced CT (A) demonstrates avid enhancement of a pancreatic tail lesion (yellow arrow). Pre contrast (B) and post contrast (C) MRI in the arterial phase show similar findings with avid arterial phase enhancement (blue arrows), in keeping with pNET.

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Fig. 9: Metastatic pNET in patient with MEN1. CT with contrast demonstrates abnormal enhancing nodules near the site of previously resected pNET (yellow arrows) Octreotide scan (B) confirms the presence of metastatic lymphadenopathy (red arrow). Dotatate scan (C) further delineates activity in both lymph nodes seen on CT (blue arrows).

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**Fig. 10:** Medullary thyroid carcinoma (MTC) in patient with MEN2 presenting with palpable thyroid nodule. Thyroid ultrasound (A-B) demonstrates a complex cystic, solid nodule with echogenic foci in the left thyroid gland (yellow arrows) with interval vascularity (C). Pathology revealed MTC.

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Fig. 11: Metastatic medullary thyroid carcinoma (MTC) in MEN2. Numerous metastatic nodules (yellow arrows) are present shown on the coronal MIP image of the lungs in a patient with known MTC.

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Fig. 12: Pheochromocytoma in a patient with MEN2. Contrast enhanced CT examination demonstrates enhancing right adrenal nodule in the setting of elevated serum biomarkers. Subsequent resection revealed pheochromocytoma.

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**Fig. 13:** Pheochromoctyoma in MEN2. MRI shows a left adrenal nodule without microscopic fat indicated by the lack of signal drop out on the opposed phase imaging (A). The lesion is hyperintense on T2-weighted sequences (B) and demonstrates mild arterial phase enhancement (C and D), in keeping with a pheochromocytoma.

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**Fig. 14:** Bilateral pheochromoctyoma in a patient with MEN2. I123-MIBG planar imaging (A) demonstrates two discrete foci of uptake (yellow arrows). I123-MIBG SPECT image (B) confirm presence of uptake in the adrenal glands (red arrows). MRI sequences (C-E) demonstrate dark T1 (green arrows) and bright T2 (white arrows) enhancing nodules in the adrenal glands (blue arrows). Pathology results confirmed bilateral adrenal adenomas.

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Conclusion

Thorough knowledge of the spectrum of tumors associated with MEN gene mutations aids in the diagnostic workup, post treatment monitoring and screening in patients with MEN related gene mutations.
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References
