Case # 2

Yun Gong M.D.
UT M. D. Anderson Cancer Center
Department of Pathology
Clinical History

A 42-year old woman with a non-tender neck nodule found incidentally by self-palpation

She had no past family or personal history of malignancy
Congo red
Medullary thyroid carcinoma (MTC)

- Account for 5-10% of all thyroid carcinomas
- Arising from parafollicular (C) cells which secrete calcitonin (causing elevated serum calcitonin)
- **Sporadic MTC**: ~80%, affecting adults (mean age: 45 years), slightly more common in women, usually unilateral and solitary
- **Familial MTC**: ~20%, affecting younger patients (mean age: 35 years), often bilateral and multifocal
Medullary thyroid carcinoma (MTC)

**Familial MTC**: inherited in an autosomal dominant fashion and present as a part of multiple endocrine neoplasia type 2 syndrome (MEN II), caused by germ-line mutations in *RET* proto-oncogene which codes for a tyrosine kinase receptor.
Molecular study of MTC

_Somatic_ \textit{RET} mutations occur in 20-80\% of sporadic MTC (mostly at codon 918)

_Germ-line_ \textit{RET} onco-gene mutations are found in all hereditary MTC (in different codons and with different degrees of penetrance)
Cytologic features of MTC

**Cellularity:** usually hypercellular

**Arrangement:** isolated cells or loosely cohesive clusters

**Cell shape:** round/oval, plasmacytoid, short to long/slim spindle

**Nucleus:** round or elongated
stippled or “salt & pepper” chromatin
inconspicuous nucleoli
± intranuclear pseudoinclusions
± binucleated and multinucleated

**Cytoplasm:** ± metachromatic red granules on DQ slide

**Background:** amyloid (~80%), colloid absent
Spectrum of cell type of MTC

- Plasmacytoid or oval-shaped (conventional)
- Small cell
- Oncocytic cell
- Squamoid cell
- Clear cell
- Giant/anaplastic cell
- Pigmented cell
- Spindle cell
“plasmacytoid with pleomorphism”
“oval and uniform”
“small cell”
“oncocytic”
MTC, oncocytic type  Hurthle cell carcinoma
“spindle cell”
“long/slim spindle cell”
Differential diagnosis of spindle cell MTC

Mesenchymal origin (primary or metastatic)
- Solitary fibrous tumor
- Peripheral nerve sheath tumor
- Smooth muscle tumor

Epithelial origin
- Primary thyroid tumor with spindle features (anaplastic, Hurthle cell)
- Metastatic spindle cell carcinoma

Metastatic spindle cell melanoma
Hurthle cell neoplasm, spindle cell type
Hurthle cell neoplasm, spindle cell type

TGB

TTF-1
Metastatic spindle cell melanoma
Metastatic metaplastic breast carcinoma to thyroid
Differential diagnosis of amyloid material in the anterior neck region
Amyloid
Degenerated colloid
Hyaline cartilage
Skeletal muscle
Myxochondriod material from a metastatic tumor
Immunoperoxidase study and special staining of MTC

**Positive:** Calcitonin
CEA
Chromogranin
Synaptophysin
TTF-1
Keratin
Congo red*

**Negative:** thyroglobulin

*apple-green birefringence with polarized light microscopy
Treatment and prognosis of MTC

• Treatment: total thyroidectomy with regional lymph node dissection
• 5-year survival rate: 70%-80%
• Spread:
  Locaregional: cervical and mediastinal lymph node
  Distant: lung, liver, bone
Medullary thyroid carcinoma: clinical, histologic and cytologic features

Medullary thyroid carcinoma (MTC) accounts for 5-10% of all thyroid carcinomas and derives from parafollicular (C) cells which secrete calcitonin.[1, 2] There are two forms of MTC: sporadic and familial forms. Sporadic MTC comprise about 80% of the cases, which affect adults (mean age: 45 years), slightly more common in women and is almost always unilateral and solitary. Familial MTC comprise up to 20% of the cases, which affect younger patients (mean age: 35 years), often bilateral and multifocal. Familial MTC is inherited in an autosomal dominant fashion with high penetrance and usually present as a part of multiple endocrine neoplasia type 2 syndrome (MEN IIA and MEN IIB), caused by germ-line mutations in \textit{RET} proto-oncogene. The \textit{RET} proto-oncogene, located on chromosome 10q11.2, codes for a tyrosine kinase receptor and plays a key role in the genesis of MTC. Notably, somatic mutations in the \textit{RET} gene can be found in 20-80% of sporadic MTC, mostly at codon 918 of exon 16. Its prognostic significance is controversial.[3-8] Clinically, MTC usually presents as a firm painless thyroid nodule. Most tumors are located in the lateral upper two-thirds of the thyroid, the region where the C-cell concentration is highest. Approximately 50% of patients show lymph node metastases and up to 15% can show distant metastases at presentation. Serum calcitonin levels are elevated in around 90% of patients. Grossly, the typical tumor is solid, firm and relatively well circumscribed and has a tan-yellow cut surface. Histologically, tumor is characterized by a solid proliferation of neoplastic cells separated by richly vascularized stroma and amyloid. Various histologic growth patterns of MTC have been described including glandular/tubular/follicular, papillary or pseudopapillary, carcinoid-like, paraganglioma-like, hyalinizing trabecular adenoma-like. Various cell types can also be seen in MTC. Conventional MTC cells are typically oval or plasmacytoid; the tumor cells may be spindle-shaped, oncocytic, squamoid, small cell, giant cell/anaplastic, clear cell, and pigmented.[9-17] These variants can be seen in focal areas of an otherwise conventional MTC or seen exclusively in an entire tumor. Tumor cells usually have ill-defined cell border, finely granular cytoplasm, medium-sized round or oval nucleus with mild to moderate pleomorphism, typically possess stippled or “salt & pepper” chromatin and indistinct nucleolus. Sometimes, tumor cells show nuclear grooves and intranuclear pseudo-inclusions, which can be mistaken for papillary thyroid carcinoma.[18, 19] The FNA cytologic features of MTC are summarized in the following table.

Amyloid can be seen in approximately 80% of MTC and, if present, is an important diagnostic clue.[1] It appears as homogenous amorphous extracellular material. It can be seen in both Diff-Quik-stained or Papanicolaou-stained smears and can be highlighted by Congo red staining which demonstrates typical apple-green birefringence under polarized light microscopy. Amyloid is sometimes associated with foreign body-type giant cell reaction and calcification. There is no colloid in the background, but clumps or spheres of amyloid may somewhat be misinterpreted as colloid. The material resembling amyloid in the anterior neck aspiration also includes hyaline cartilage and fragments of skeletal...
muscles and extracellular matrix from metastatic malignancy. Necrotic debris may be found in large tumors.

Most of the morphologic variants are of no prognostic importance, but they can pose challenges in histologic and cytologic recognition. The differential diagnosis of MTC is broad depending on the morphologic variant seen in each case. For example, oncocytic variant showing voluminous eosinophilic granular cytoplasm and prominent central nucleolus, mimicking oncocytic/Hurthle cell neoplasm of follicular cell derivation; small cell variant may resemble small cell carcinoma of lung or neuroblastoma. Spindle cells are not uncommon in MTC, but some MTCs are composedly exclusively of plump or slender spindly cells arranged in intersecting fascicles or wholes, which may be indistinguishable from primary or metastatic mesenchymal tumors, spindle cell carcinoma and spindle cell melanoma. Immunoproxidases study is important to confirm or refute a diagnosis of MTC. MTC is typically positive for keratin; calcitonin, TTF-1, chromogranin, synaptophysin and CEA and generally negative for thyroglobulin.[20-28]

The treatment option is total thyroidectomy and central lymph node lymph node dissection.[29] Recent studies showed that tyrosine kinase inhibitors, particularly those affecting RET activity such as vandetanib, sorafenib and sunitinib, are promising.[30] Local regional metastasis occurs in cervical and mediastinal lymph node and distant metastasis is mostly found in lung, liver, and skeletal system. The 5-year survival rate varies between 70% and 80%. [31-33] Good prognostic factors are young age, female sex, occurrence in familial setting, small tumor size, and tumor confinement to the gland. The poorer prognosis of sporadic cases may be related to the older age at detection, advanced tumor stage at diagnosis, tumor with high mitotic activity, necrosis, squamous pattern, small cell type, poor immunoreactivity for calcitonin.[34-36]

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FNA cytologic features of MTA [37, 38][39-40]

<table>
<thead>
<tr>
<th>Cellularity</th>
<th>usually high</th>
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<tbody>
<tr>
<td>Arrangement</td>
<td>single cells or loosely cohesive clusters</td>
</tr>
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<td>Cytoplasm</td>
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</tr>
<tr>
<td>Background</td>
<td>amylloid (~80%), colloid absent</td>
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