PARAGANGLIOMAS OF THE HEAD & NECK: AN OVERVIEW
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Dr. Michelle Williams declares she has no conflict(s) of interest to disclose.

A century of observations
Early 20th century
Kohn coined ‘Chromaffin reaction’ &
- Paraganglion
  - chromaffin tissue complexes form ganglion-like bodies
- Watzka-divided into
  - Chromaffin &
  - Non-Chromaffin

Neural crest derived
- Autonomic nervous system
  - Sympathetic
  - Pre-/paravertebral
  - Pelvis/retroperitoneum
- Parasympathetic
  - Cervical
  - Thoracic

A century of observations
FOUR main sites
1. Carotid Body 60%
2. Middle ear 30%
  - Tympanic/jugular
3. Vagus nerve (vagale)
4. Larynx
  - Supraglottic
  - Infraglottic (may involve thyroid)

Paragangliomas in the Head & Neck

PLEASE TURN OFF YOUR CELL PHONES
Paragangliomas of the Head & Neck

**Origin-etiology**
- Paraganglioma in the H&N non-secretory (99%)
- Most common presentation (carotid body, vagal) painless mass in anterior neck near jaw
- Presentation 5th-6th decade with female predominance (3:1)
- Decade younger in hereditary cases
- 30-40% are now known to be hereditary
  - **most common hereditary syndrome to date**

**Imaging & gross findings: Carotid body**

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Carotid body</th>
<th>Vagal</th>
<th>Middle ear</th>
<th>Laryngeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of H&amp;N PGL</td>
<td>60%</td>
<td>10%</td>
<td>30%</td>
<td>Very rare</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Asymptomatic neck mass near angle of jaw</td>
<td>70% asymptomatic, high-risk mass, cranial nerve palsies; &lt;4% clinically functional</td>
<td>4% clinically functional; hearing loss, facial paralysis</td>
<td>Spinal cord compression; rarely metastasis; cranial nerve palsies</td>
</tr>
<tr>
<td>Bilaterality/multifocal</td>
<td>10-25%</td>
<td>20-40%</td>
<td>yes often with carotid body, &lt; vagal PGLs</td>
<td>rare</td>
</tr>
<tr>
<td>Metastatic risk</td>
<td>4-6%</td>
<td>10%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>% hereditary</td>
<td>At least 1/3 (SDH, TMEM127, VHL)</td>
<td>At least 1/3 (SDH, TMEM127, VHL)</td>
<td>1/3 (SDH, NF1)</td>
<td>Limited information</td>
</tr>
</tbody>
</table>

*Metastasis versus second primary (multifocal) tumor was not always clarified.*

**Paragangioma**

**Histologic features**
- Growth pattern nested
  - Zellenballen surrounded by rich vasculature
  - Reticulin highlights pattern
- Background
  - Post embolization
  - Inflammation

**Paragangioma**

**Histologic features**

1. Neuroendocrine “Chief cells”
   - Also known as:
     - Type I cells
     - Chromaffin or chromaffin-like
     - Granule containing cells
     - Glomus
   - Variable pleomorphism
   - Salt & pepper nuclei
2. Sustentacular cells (peripheral in nests)

**Variability**

- Vascular predominating
  - Look for intervening cells
- Sclerosing
  - Fibrosis
  - Immunostudies (CK+)
  - (mimics malignancy)

*Multifocality/bilateral tumors is associated with hereditary syndromes in the majority of cases. Metastasis versus second primary (multifocal) tumor was not always clarified.*
Paraganglioma HN
Histologic features CANNOT PREDICT behavior
- Local invasion
- Bone invasion
- Cytologic atypia
- Sclerosis
- Necrosis (uncommon)

Lymph node metastasis

Paragangliomas of the Larynx: Why all of the confusion?
- Over 20 years
- Dr. Leon Barnes wrote numerous articles and editorials
- Trying to get pathologists and clinicians to get this RIGHT!

Letters to the Editor

Differential diagnosis
- Carotid Body
- Vagus nerve (vagale)
- Middle ear
- Tympanicum/jugularus
- Larynx
- Supraglottic larynx
- Inferior (may present in thyroid)

Other neuroendocrine tumors (CK+)
- Medullary thyroid carcinoma
- Neuroendocrine carcinoma
- Carcinoid/Atypical carcinoid/Merkel cell

Metastases (on small biopsies)
- Renal Cell, Melanoma
- EAR – middle ear adenoma
WHO Updates in Head & Neck PGLs

- **Histology/biology**
  - PGLs are now considered to represent a continuum of risk, and are assessed in terms of risk stratification based on genetic associations and therefore should not be termed “benign”.
  - There is no validated histopathologic risk assessment score for head and neck PGLs.
  - Thus histopathologic features (i.e. soft tissue involvement, vascular invasion, mitoses, necrosis) are insufficient to determine risk for distant metastases.
  - Mutations also risk stratify PGLs.
  - Loss of SDHB expression by immunohistochemistry is a valuable screening tool to identify any succinate dehydrogenase gene mutation (SDHA, B, C, D, SDHAF2) in tumors.

- **Genetics**
  - 30-40% of HNPGLs are familial.
  - Gene mutations involving the succinate dehydrogenate (SDH) pathway predominate, most commonly SDHD.

- **Paraganglioma (PGL) syndromes and their associated genetic and clinical associations**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>% of patients with HNPGLs</th>
<th>Risk for metastasis</th>
<th>PHEO +/- Thoraco/abdominal PGL</th>
<th>Associated tumors</th>
<th>FACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGL1</td>
<td>SDHD</td>
<td>79-89% 4%</td>
<td>12-33%</td>
<td>Renal, GIST, Pituitary</td>
<td>Rare</td>
<td>85%</td>
</tr>
<tr>
<td>PGL2</td>
<td>SDHAF2</td>
<td>73-86% low</td>
<td>5%</td>
<td>Renal, GIST, Pituitary</td>
<td>Usually solitary PGLs</td>
<td></td>
</tr>
<tr>
<td>PGL3</td>
<td>SDHC</td>
<td>88% 5% Rare &lt; 3%</td>
<td>18-84%</td>
<td>Renal, GIST, Pituitary</td>
<td>More common in thoraco/abdominal &amp; pelvic PGLs</td>
<td></td>
</tr>
<tr>
<td>PGL4</td>
<td>SDHB</td>
<td>27-42% highest risk</td>
<td>32%</td>
<td>Renal, GIST, Pituitary</td>
<td>Rare</td>
<td>85%</td>
</tr>
<tr>
<td>PGL5</td>
<td>SDHA</td>
<td>7 low</td>
<td>4%</td>
<td>Renal, GIST, Pituitary</td>
<td>Possible</td>
<td></td>
</tr>
</tbody>
</table>

*These genes are inherited with imprinting, requiring parenteral inheritance for associated PGL. Tumors in ( ) are rare; GIST=gastrointestinal stromal tumor; HN= head and neck.

Paraganglioma syndromes associated tumors
- Renal cell carcinoma
  - Monomorphic polygonal eosinophilic, bubbly/vacuolated cytoplasm
  - RCC Associates with all SDH genes/ PGL syndromes
- Pituitary adenomas

Paraganglioma syndrome associated tumors
- Gastrointestinal stromal tumors
  - Often childhood/young adults
  - Gastric wall
  - Multifocal, plexiform
  - Epithelioid
  - 30% SDHA

- Renal cell carcinoma
  - Mean age of 40 years
  - Monomorphic polygonal eosinophilic, bubbly/vacuolated cytoplasm
  - RCC Associated with all SDH genes/ PGL syndromes

- Pituitary adenomas

From Hornick et al, Modern Pathology (2014) 27, S47–S63
Immunohistochemical screening

**Broad ‘genetic’ screening utilizing SDHB antibody**
- Normal SDHB expression is cytoplasmic and granular (fig. B)
- Loss is noted with mutations in any SDHx gene member (fig. C, D)
- Internal positive control must be present (fig. C arrows)
- Subset of ‘loss’ may be secondary to gene methylation (Carney’s)
- Caution inflammatory (positive expression) obscuring tumor cells (fig. D)

**Immunohistochemical screening**

**Reporting considerations**
- Abnormal – Immunohistochemical evaluation for SDHB expression is lost in the paraganglioma cells with positive internal control identified. This immunohistochemical study is a general screening process and is not specific for mutations in the SDHB gene but is seen when any of the SDH family of genes is altered (SDHA, B, C, or D). As the vast majority of SDH mutations are familial in paraganglioma further genetic evaluation is advised.

**Carney-Stratakis syndrome**

**Paragangliomas and GISTS**
- IHC screening? YES
- SDHB immunohistochemistry loss (further genetic counseling)

**Clinical considerations**

**Genetic screening-impacts individuals and families**
- Imaging
  - Multifocal Head & Neck PGL
  - Thoracic/abdominal PGL-PHEOs
  - Secondary malignancies
    - Renal cell, GISTs, Pituitary adenoma
  - ~10% of apparent sporadic PGL will be hereditary

**Imprinting & Paternal inheritance for Paragangliomas (PGLs)**
- SDHD- autosomal dominant
- White= non-carriers
- Yellow=carrier
- Black= effected(PGL)
- Circles= females
- Squares= males

*As many head and neck PGL are watched. Tissue biopsy for SDH mutation evaluation or genetic counsel may improve patient triage based on risk stratification.*
Moving Ahead

- Pathologist play a key role in assessing paragangliomas
- Histologic confirmation of disease
- Importantly considering the differential diagnosis by site
- Risk stratification for possible aggressive disease & comorbidities requires genetic assessment
- Immunohistochemical evaluation of SDHB screens for majority of genetic associations in H&N paragangliomas
  - Though notably lower in middle ear site (also associated with NF1)
- SDHB mutated paragangliomas identifies the highest risk patient population for metastasis.

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