Surgical Management of VHL Endocrine Manifestations
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Disclosure
Nothing to disclose

Overview

- Diagnosis of VHL-associated
  - Pheochromocytoma/paraganglioma (PCC/PGL)
  - Pancreatic lesions
- Important consideration when management VHL-associated endocrine neoplasms
- Precise surgical intervention for VHL-associated PCC/PGL and PNETs.

Pheochromocytoma/paraganglioma (PCC/PGL)

Diagnosis
- Symptomatic - Surveillance/screening
  - 18% - 30% (depends on follow up or cross-sectional study)
- 24 h urinary or plasma free fractionated normetanephrine/metanephrine
- Preop alpha-blockade and volume repletion essential

Localization studies
Although practice guidelines recommend biochemical and radiological screening every 1–2 years for pheochromocytoma in patients with VHL. - there are limited data on the optimal age and frequency for screening.

A total of 273 patients diagnosed with VHL
- Thirty-one percent (84) were diagnosed with PCC/PGL
- Mean age of diagnosis was 28.8 ± 13.9 years
- Earliest age at diagnosis was 5.5 years
- Median follow-up for the cohort was 116.6 months (range, 0.1–613.2)

Twenty-five percent (21) of PCC were diagnosed in pediatric patients younger than 19 years of age
- 86% and 57% of pediatric patients had an elevation more than two times and more than four times upper limit of normal, respectively
- 62 (74.7%) unilateral and 22 (26.3%) bilateral
- 17 (20.5%) patients developed a contralateral second primary tumor requiring surgical intervention.

Operative approach
- Is partial adrenalectomy reasonable?
  - Avoid need for steroid replacement
- Total adrenalectomy
  - Avoid risk of recurrence in remnant gland

Lateral or posterior approach
- Unilateral vs. bilateral
- Previous laparotomy

What extent of adrenalectomy is need? VHL-associated PCC
What is the risk of recurrence after partial adrenalectomy in VHL-associated PCC

- Eight patients had nine total recurrences
- The shortest recurrence interval in the cohort was 0.5 years and the longest was 39.7 years after the primary PCC removal.
- Four (50%) of the nine patients with recurrence were pediatric patients and developed their recurrence before age 19.
- None developed metastatic disease or had malignant recurrences.

What extent of adrenalectomy is needed?

VHL-associated PCC

- Partial adrenalectomy is the best approach if no signs of malignancy and no family history of malignant PCC
- Easiest when small tumor
- Ultrasound is useful
- Gland will often contain multiple nodules
- All PGL should be completely resected.

VHL-Associated Pancreatic neuroendocrine tumor (PNETs)

- Types of pancreatic lesions:
  - Cysts – 70%
  - Serous cystadenomas 6-8%
  - PNETs – 8-12%

Clinical Dilemma

None that are functional
Metastatic/malignant?
Growth
Best way to detect metastases
VHL-Associated Pancreatic neuroendocrine tumor (PNETs)

Risk Factors for PNETs

Distribution of blood type (non-O types vs. O type) in study cohort stratified by manifestation of VHL syndrome

### Disease manifestation

<table>
<thead>
<tr>
<th>Disease present (n)</th>
<th>Non-O blood type (%)</th>
<th>O blood type (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas Yes (155)</td>
<td>47.7</td>
<td>52.26</td>
<td>0.047</td>
</tr>
<tr>
<td>No (24)</td>
<td>70.8</td>
<td>29.17</td>
<td></td>
</tr>
<tr>
<td>Cystic disease Yes (123)</td>
<td>52.9</td>
<td>47.15</td>
<td>0.046</td>
</tr>
<tr>
<td>No (32)</td>
<td>31.3</td>
<td>68.75</td>
<td></td>
</tr>
<tr>
<td>Solid tumors Yes (111)</td>
<td>41.4</td>
<td>58.56</td>
<td>0.0084</td>
</tr>
<tr>
<td>No (46)</td>
<td>65.2</td>
<td>34.78</td>
<td></td>
</tr>
</tbody>
</table>

VHL disease manifestations in study cohort. The categories tested for association with blood type are not mutually exclusive as some patients will have multiple manifestations. Thus, subcategories may not add up to 100% or the total number of the category heading because of missing data for some cases.

Best way to detect primary lesions and metastases

Table 8. Tumor detection by different modalities (n=81)

<table>
<thead>
<tr>
<th>Modality</th>
<th>No. of lesions detected</th>
</tr>
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<tbody>
<tr>
<td>CT</td>
<td>58</td>
</tr>
<tr>
<td>MRI</td>
<td>65</td>
</tr>
<tr>
<td>US</td>
<td>54</td>
</tr>
<tr>
<td>PET/CT</td>
<td>44</td>
</tr>
</tbody>
</table>

*New or small number of lesions by CT/US, and PET/CT. However, these were detected by MRI due to aggressive nature of the tumors. PET/CT lesions were seen at a later time in the disease progression and were not present at initial presentation.
VHL-Associated Pancreatic neuroendocrine tumor (PNETs)

Clinical Dilemma

Metastatic/malignant?

Best way to detect metastases

Enhancing solid pancreatic lesions on a coronal, b axial, c sagittal CT that was d 18F-FDG-avid on 18F-FDG PET/CT and e measured for metabolically active portions.

18 F-FDG 18F-fluorodeoxyglucose, PET/CT positron emission tomography/computed tomography

VHL-Associated Pancreatic neuroendocrine tumor (PNETs)

Role for MRI

Clinical Dilemma

Metastatic/malignant?

Best way to detect metastases

Comparison of PNETs not associated with metastatic disease and PNETs associated with metastatic disease by a TLG (p = 0.0092), and b TLG after outlier analysis (p = 0.0090). PNETs pancreatic neuroendocrine tumors, TLG total lesion glycolysis, SUV mean standardized uptake value

VHL-Associated Pancreatic neuroendocrine tumor (PNETs)

Role of (18)FDG-PET

Sadowski et al. JACS 2014

109 of 197 patients had solid pancreatic lesions

Both CT and (18)FDG-PET scanning

165 and 144 lesions, respectively.

Metastatic disease was detected by (18)FDG-PET in 3 patients in whom it was not detected by CT scan

Non-neoplastic disease in 3 patients.

PNETs pancreatic neuroendocrine tumors, TLG total lesion glycolysis, SUV mean standardized uptake value
**Optimal surgical approach & extent of resection for VHL-associated PNETs**

- Extent of resection
  - Enucleation
    - Low risk of malignancy (nonfunctioning PNETs < 3cm),
  - Pancreatectomy
    - High risk of malignancy
    - Involving pancreatic duct
    - Multiple lesions in region
    - Nodal involvement
  - Misense/exon 3 intermediate lesions

**Radioguided Surgery for PNETs using $^{68}$Ga-DOTATATE**

- Forty-four patients with 133 lesions on preoperative imaging
- Pancreatic NET (43%), gastrointestinal NET (50%), and pheochromocytoma/paraganglioma (7%)
- The omentum had a significantly lower count than other solid organs for background count activity 3 hours after injection (22.1 vs. 34.5; p < 0.001).

**Optimal surgical approach & extent of resection for VHL-associated PNETs**

- Open vs. minimally invasive surgery
  - Less morbidity/mortality?
  - Less pain/convalescence?

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- The lesions containing NETs had a higher TBR (18.9 vs. 4.4; p < 0.001).
- TBR of 2.5 and 16 showed a sensitivity of 90% and 25%, and a specificity of 54% and 81%, respectively.
- 13% of lesions not visible and or palpable.
Impact of surveillance and screening for PNETs

<table>
<thead>
<tr>
<th>Variable</th>
<th>VES Surveillance (n = 12,480)</th>
<th>VES Internal (n = 8,100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Younge: 55.0 (50.3 - 60.6)</td>
<td>54.5 (50.0 - 59.0)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Old: 60.0 (55.7 - 64.9)</td>
<td>58.5 (55.0 - 62.0)</td>
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<tr>
<td>Gender</td>
<td>Male: 54.6% (52.3 - 56.9)</td>
<td>58.2% (55.8 - 60.6)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Female: 45.4% (47.7 - 43.0)</td>
<td>41.8% (39.4 - 44.2)</td>
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<tr>
<td>Tumor size</td>
<td>&lt;1 cm: 31.0% (28.0 - 34.1)</td>
<td>33.5% (30.0 - 37.0)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>&gt;1 cm: 69.0% (66.0 - 72.0)</td>
<td>66.5% (63.0 - 69.0)</td>
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Table 1: Comparison between patients with PNETs in the VES Surveillance and VES Internal groups.

Summary

- Screening and Surveillance for PCC/PGL and PNETs is essential.
  - To reduce morbidity and mortality.
- Adrenal-preserving surgical intervention is optimal
  - Localized and low-risk tumors
- Pancreas preserving surgical intervention is optimal
  - Early detection is key
  - Accurate staging

Thank you!