Disclosure of Commercial Interests

Neither I nor my immediate family members have a financial relationship with a commercial organization that may have a direct or indirect interest in the content.
The Case

• **History:**

62 year old female presents with 6 month history of left facial fullness, trismus and left V3 distribution numbness
Left parotid mass
Enhanced T1WI
Foramen ovale
Case of the Day

• Considerations:
  – Parotid mass - nonspecific
  – Curvilinear structure - to cavernous sinus
  – Clinical features are concerning
    • Trismus, numbness
  – Dealing with a neoplasm - malignant
Parotid Malignancy

- Perineural disease
  - Facial nerve
Pierces parotid fascia
Into the gland
Communicates with CN 7
via two rami
Perineural Tumor Spread

- Adenoid cystic carcinoma – parotid mass
- Perineural tumor spread
  - Auriculotemporal nerve
  - Cavernous sinus
Highlight

Perineural Disease
Perineural Disease

• Spread of tumor along nerves
  – *Neurotropic carcinomatous spread*
  – First described in mid-1800’s

*Arch Pathol Anat.* 1862;24:201-201.

Secundäre Cancroidinfiltration des Nervus mentalis bei einem Fall von Lippencancroid.

Von Dr. E. Neumann in Königsberg i. Pr.

Nerve Sheath Anatomy

- **EPINEURUM** around the entire nerve
- **PERINEURIUM** around a fascicle
- **ENDONEURIUM** around an individual axon
- Blood vessels
- Axon
Perineural Invasion

- Liebig et al, 2009 *Cancer*
  - Tumor cells within any of the **three layers** of the nerve sheath
  - Tumor foci outside of the nerve with involvement **> 33%** of the nerve’s circumference
Perineural Invasion

- Physiological basis
  - Due to reciprocal nerve signaling interactions between tumor and nerves

<table>
<thead>
<tr>
<th>Factor</th>
<th>Possible Function in Cancer</th>
<th>Expression in Cancer</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>BDNF</td>
<td>May be overexpressed by tumor cells to promote neurite growth; stimulates tumor cell invasion at low-to-moderate concentrations</td>
<td>Overexpressed in pancreas cancer and adenoid cystic carcinoma; expression does not correlate with the presence of PNI, suggesting that the BDNF-expressing phenotype may appear before nerves</td>
<td>Ketterer 2003, Zhu 2002, Kowalski 2002, Miknyoczki 1999</td>
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<tr>
<td>GDNF</td>
<td>Exhibits a chemotactic and chemokinetic effect on tumor cells and mediates increased MMP-9 expression and activity</td>
<td>Overexpressed in specimens of human neural plexi; multiple pancreatic cancer cell lines express the RET protein tyrosine kinase receptor for GDNF</td>
<td>Okada 1999, Okada 2003</td>
</tr>
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<td>NT-3</td>
<td>Stimulates tumor cell invasion at low-to-moderate concentrations</td>
<td>Overexpressed in pancreas cancer specimens</td>
<td>Ketterer 2003, Miknyoczki 1999</td>
</tr>
</tbody>
</table>

NGF indicates nerve growth factor; trkA, tropomyosin receptor kinase A (a high-affinity catalytic receptor for nerve growth factor); MAPK, mitogen-associated protein kinase; MMP-2, matrix metalloproteinase 2; BDNF, brain-derived neurotrophic factor; PNI, perineural invasion; GDNF, glial cell line-derived neurotrophic factor; NT-3, neurotrophin 3.
Perineural Invasion

• Tumor cells express **proteinases**
  – Help migrate through extracellular matrix and nerve sheath
Perineural Invasion

• What it does *not* involve
  – Not tracking along **lymphatics**
    • Lymphatics do not penetrate into the nerve sheath
  – Not due to spread along **path of least resistance**
    • Collagen, basement membrane
Perineural Invasion

- Pathologist:
  - Perineural invasion is a contiguous process
Perineural Invasion

- Significance of PNI
  - 3x increased rate of local recurrence
  - Decreased survival 30% 5yr
  - Increased LN recurrence
  - Influence therapy
    - Can make disease unresectable
    - Influence surgical approach
    - XRT, chemotherapy
Perineural Tumor Spread

• Perineural tumor spread: PTS
  – Different from *perineural invasion*
  – *Macroscopic* tracking of tumor along nerves
  – Tumor uses nerve as a scaffold
  – Visible on imaging
Clinical Symptoms

• Clinical features:
  – 40% asymptomatic - imaging may be the first to pick it up
  – Pain
  – Paresthesia
  – Muscle weakness
  – Diplopia
Disease Entities

- Squamous cell carcinoma
- Melanoma
- Adenoid cystic carcinoma
- Lymphoma
Imaging Features

- **Computed Tomography and MRI:**
  - Increased size of nerve, enhancement
  - Widened neuroforamen
  - Erosion of adjacent bony margins
  - Loss of normal fat planes
  - Muscle atrophy
How to Image

- MRI scan > CT scan
- Contrast enhanced scanning
- Narrow FOV 16-18cm
- High resolution matrix
- Slice thickness 3mm
Imaging Features

- Magnetic resonance imaging:
  - T1 pre gadolinium scan
  - T1 post gad ± fat saturation
Imaging Features

• Image all the way back along the course of the nerve
  – Antegrade as well as retrograde spread
Nerve enlargement
Denervation atrophy
Loss of fluid signal in Meckel’s cave
Conclusion

• ATN Perineural tumor spread
• **Significance** of PNTS
• **Anatomy** - knowing what to look for
• **Clinical history**
Pterygopalatine Fossa

- Space between posterior margin of maxillary sinus and the pterygoid process
- V2 as it exits foramen rotundum travels through here - predominantly fat density
Pterygoplatine Fossa

• The “relay station”:
  – Nasal cavity - sphenopalatine foramen
  – Masticator space - pterygomaxillary fissure
  – Orbit - Superior/inferior orbital fissure
  – Intracranial - Foramen Rotundum, Vidian canal
Enhancement and widening
Greater palatine foramen
Pterygopalatine foramen
V2 along foramen rotundum
Greater palatine foramen
Pterygopalatine fossa
Right sided ACC palate
Any palate tumor
Check the palatine foramen and PPF
**Conclusion**

- ATN Perineural tumor spread
- Significance of PNTS
- Imaging technique
- Knowing what to look for
- Clinical history
Perineural Tumor Spread

- Adenoid cystic carcinoma
  - Can we diagnose its full extent?
Perineural Spread of Head and Neck Tumors: How Accurate Is MR Imaging?

William R. Nemzek, Stephen Hecht, Regina Gandour-Edwards, Paul Donald, and Kevin McKenman


The Sensitivity and Specificity of High-Resolution Imaging in Evaluating Perineural Spread of Adenoid Cystic Carcinoma to the Skull Base

Ehab Hanna, MD; Emre Vural, MD; Emmanuel Prokopakis, MD; Ricardo Carrau, MD; Carl Snyderman, MD; Jane Weissman, MD

Arch Otolaryngol Head Neck Surg. 2007;133:541-545

DETECTING AND DEFINING THE ANATOMIC EXTENT OF LARGE NERVE PERINEURAL SPREAD OF MALIGNANCY: COMPARING “TARGETED” MRI WITH THE HISTOLOGIC FINDINGS FOLLOWING SURGERY

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Perineural Tumor Spread

- Retrospective studies
- Various histology of HN cancer
  - Except Hanna, et al - ACC
  - Gandhi, et al - cutaneous HN cancer
- Pre-operative MRI ± CT
- Surgical resection and pathology evaluation
Perineural Tumor Spread

• Nemzek et al, 1998
  – 65 pts → 19 patients - picked only those with (+) histo PNS and deemed resectable
  – MRI sensitivity for detection 95%
  – Sensitivity to map full extent 63%

• Hanna et al, 2007
  – 26 consecutive patients - all ACC → underwent resection
  – CT sens 88% spec 89%
  – MRI sens 100% spec 85%

• Gandhi et al, 2011
  – 25 patients - cutaneous malignancy, clinically suspected PND (+) MRI
  – MRI sens 100%
  – Sensitivity to map full extent 83.3%