Sinonasal Undifferentiated Carcinoma

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CASE 1

HPI:
• 71yo F with history of GERD and HTN
• Presented with nausea and dizziness after bumping her head on windowsill
• Denied visual changes or any other neurological symptoms

Pertinent exam findings:
• General- appears in no distress, ECOG 0
• HEENT– slight ptosis of right eye, pupils equal and reactive to light, no facial numbness, other CN II-XII grossly intact, vision intact, negative anterior nasal exam, OC/Ophx clear, no palpable LAD
• Neuro: sensation intact throughout, 5/5 strength all extremities, gait/balance intact
• Remainder of exam was normal
• Nasal Endoscopy Under Anesthesia: visible tumor erosion of the posterior wall of the right maxillary sinus. There was also tumor in the ethmoid cells exposing anterior and posterior ethmoid cells, sphenoids, and skull base. There was no orbital fat involvement from the nasal cavity seen.

Patient H&P, treatment planning details: Courtesy of Dr. William Regine, Professor and Chair, Dept. of Radiation Oncology, University of Maryland, Baltimore
**IMAGING**

**Description:** MRI shows a solid enhancing lesion centered in the posterior superior right nasal canal with extension into the pterygoid palatine fossa measuring 3.0cm in greatest dimension. There is bony invasion of the maxillary sinus and sphenoid. There is no intracranial or orbital involvement. There is also a borderline enlarged right retropharyngeal lymph node (RPLN).

**Other imaging:** PET-CT – no evidence of nodal or distant disease.
CASE 2

HPI:

• 27yo F with no significant medical history, presents with worsening headaches over the last several days-wks, first started about 6-8 months ago
• Sudden, severe respiratory distress at an outside institution, requiring intubation

Pertinent exam findings:

• **General**: appears stated age, intubated, ECOG 4
• **HEENT**: left pupil was 5mm and reactive to 3mm sluggishly, right pupil was 3mm and reactive to 2mm
• **Neuro**: ptosis on left, left VI cranial n. palsy
• **Extremities**: Patient localizes to pain and moves all 4 extremities
• **Remainder of exam was normal**
• **Nasal Endoscopy Under Anesthesia**: left anterior nasal cavity normal, a large hyperemic mass was visualized in posterior left nasal cavity that extended into posterior nasopharynx.
**Description:** MRI shows a heterogenously enhancing mass, 8 cm in greatest dimension, located at the base of the skull with bony invasion of the clivus, sella and sphenoid sinus as well as significant intracranial extension. The mass also extends into the nasal cavity, nasopharynx and orbit.

**Other imaging:** PET-CT – no evidence of nodal or distant disease.
WORK-UP FOR PARANASAL SINUS MASS

• Detailed H&P with a complete HEENT/Neurological examination
• Baseline ophthalmology consult to document visual function including visual field testing
• Fiberoptic nasopharyngoscopy
• Biopsy (trans-nasal or endoscopic-guided)
• CT or MRI Head-Neck with IV contrast
  – To assess primary tumor and nodal disease
  – MRI if base-skull/orbital/intracranial involvement to delineate primary tumor extent for operative assessment and/or radiation planning
• Consider PET-CT scan for Stage III or IV
  – assess regional and distant staging
• Chest imaging as clinically indicated
• Dental exam if clinically indicated
PATHOLOGY FROM BIOPSY (case 1 and 2)

- Medium-sized, cohesive cells
- Arranged in nests and trabeculae
- High mitotic rate, high nuclear:cytoplasm ratio, necrosis, prominent vascular invasion
- Reactive for cytokeratin, epithelial membrane antigen and neuron-specific enolase
- **Final diagnosis:** Sinonasal Undifferentiated Carcinoma (SNUC)

Pathology Images: Courtesy of Dr. Christine Yoo, Department of Pathology, University of Maryland Medical Center, Baltimore
DDX: High-Grade, Anaplastic Neoplasms of the Sinonasal Tract

- Sinonasal Undifferentiated Carcinoma (SNUC)
- Olfactory Neuroblastoma or Esthesioneuroblastoma (ENB)
- Neuroendocrine Carcinoma
- Small Cell Carcinoma
- Lymphoma
- Mucosal Melanoma
- Rhabdomyosarcoma
- Lymphoepithelioma (Nasopharyngeal Undifferentiated Carcinoma)

* Teaching point: Diagnosis of SNUC can be difficult because it may resemble other neoplasms clinically and radiographically. The diagnosis can usually be made with light microscopy alone if adequate tissue samples are obtained.
SNUC – INTRODUCTION

• Very rare tumor of the paranasal sinus (<3% of head and neck cancers) – classified as undifferentiated neuroendocrine tumor
• Originates from nasal cavity/paranasal sinus epithelium
• Disease is typically locally advanced at presentation – often into adjacent sinuses or beyond – can involve orbit/skull/brain
• 10-30% present with clinically positive lymph nodes
• Distant metastasis at diagnosis is very unusual; however, distant mets can occur with recurrent disease, most often to lung and bone
• Local and distant recurrence both may be important causes of treatment failure
STAGING NASAL CAVITY/ETHMOID SINUS

(AJCC 7th ED., 2010)

T stage

T1: restricted to 1 subsite +/- bone invasion
T2: involves 2 subsites in single region or
extends to involve adjacent region +/- bone invasion
T3: involves medial wall or floor of
orbit/maxillary sinus/palate/cribiform plate
T4a: invades any of following – anterior
orbital contents, skin, minimal extension
into anterior cranial fossa, pterygoid plates, sphenoid or frontal sinus
T4b: invades orbital apex, dura, brain, middle cranial fossa, cranial nerves (other than V₂), nasopharynx or clivus

N stage

N1: single ipsilateral lymph node involvement ≤ 3cm
N2: none greater than 6cm in greatest dimension
  N2a: single ipsilateral > 3cm but < 6cm
  N2b: multiple ipsilateral
  N2c: bilateral or contralateral
N3: lymph node > 6cm in greatest dimension

Overall Stage

Stage I: T1 N0 M0
Stage II: T2 N0 M0
Stage III: T1-2 N1 M0, T3 N0-1 M0
Stage IVA: T4a N0-2 M0, T1-3 N2 M0
Stage IVB: T4b Any N M0, Any T N3 M0
Stage IVC: Any T, Any N, M1
## ALTERNATIVE STAGING: KADISH

* Teaching Point: Kadish staging was originally described for esthesioneuroblastoma (ENB), but has shown to correlate with outcomes in SNUC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Confined to nasal cavity</td>
</tr>
<tr>
<td>B</td>
<td>Confined to nasal cavity and paranasal sinus</td>
</tr>
<tr>
<td>C</td>
<td>Beyond nasal cavity and paranasal sinus</td>
</tr>
</tbody>
</table>
SNUC – GENERAL MANAGEMENT

- Trimodality therapy results in the best outcomes
- Surgery, when feasible, may improve local control (Reiersen et al)
- Resectable or marginally resectable:
  - Primary surgery followed by adjuvant chemo-radiotherapy may be preferable
  - May consider induction chemotherapy (Cyclophosphamide/Doxorubicin/Vincristine) followed by re-assessment for surgery (Musy et al)
- Unresectable:
  - Concurrent chemoradiation
  - Induction chemotherapy followed by concurrent chemoradiation (Rischen et al)
- Optimal sequence of modalities and choice of chemotherapy regimen is still unclear
### GENERAL OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Control (2-year)</td>
<td>60%</td>
<td>43-83%</td>
</tr>
<tr>
<td>Regional Control (5-year)</td>
<td>84%</td>
<td>78-90%</td>
</tr>
<tr>
<td>Distant Metastasis-Free Survival (5-year)</td>
<td>75%</td>
<td>35-90%</td>
</tr>
<tr>
<td>Overall Survival:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year</td>
<td>63%</td>
<td>45-74%</td>
</tr>
<tr>
<td>5-year</td>
<td>43%</td>
<td>20-74%</td>
</tr>
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- This table compiles the data of 10 retrospective case studies.⁴-¹³
- This demonstrates the wide range of outcomes that have been observed.
- Generally, local and distant recurrence are more common causes of distal failure in this disease.
TRIMODALITY THERAPY IMPROVES CHANCE OF SURVIVAL

BACK TO THE CASES

Case 1

• Deemed unresectable due to involvement of the base skull
• Initiated on concurrent chemo-radiotherapy with curative intent

Case 2

• Due to significant intra-cranial extension, upfront radiotherapy to definitive doses was not feasible
• In the setting of bulky disease and limitations of normal tissue constraints, she was initiated on induction chemotherapy to be followed by re-assessment for sequential radiotherapy
RADIATION PLANNING

• **Simulation:**
  – Supine, head neutral, shoulder traction, thermoplastic immobilization mold
  – Planning CT with IV contrast

• **Contouring:**
  – Diagnostic MRI co-registered with planning CT for contouring

• **Radiation doses from literature:**

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant (Musy et al)</th>
<th>Post Op-RT (Tanzler et al)</th>
<th>Definitive (Tanzler et al)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Dose</td>
<td>50 Gy</td>
<td>64.8</td>
<td>70.8Gy BD/QD</td>
</tr>
<tr>
<td>Range</td>
<td>50-54 Gy</td>
<td>62.4-74.4 Gy</td>
<td>70-74.8 Gy</td>
</tr>
</tbody>
</table>

* Teaching Point: Standard 1.8-2 Gy, once daily fractionation is most commonly used. In situations with close proximity to the neural structures, hyperfractionation with twice daily fractions can be used to reduce the risk of late toxicity or in this case, blindness.
RADIATION PLANNING: CASE 1

• **Target Volumes:**
  – Sequential phase IMRT plan was developed*
  – GTV = nasal mass + right retropharyngeal LN
  – CTV1 = (GTV + 1 - 1.5 cm margin, modified at natural barriers) + ENI (Bilateral RP + level II-IV**)
  – Phase I (Initial Volume): 48.4 Gy in 44 fx, @ 1.1Gy BID***

* Sequential phase plan per institutional practice. May also be performed with differential dose-per-fraction, dose-painting IMRT techniques.

** While in nasopharyngeal carcinoma level V is considered a high risk site of involvement, nodal volumes of SNUC are based on the location and extent of the disease. In case 1, the tumor originated in the posterior nasal cavity, with only a borderline RPLN noted on MRI. Hence, the level V lymph nodes were excluded from the CTV.

*** Due to close proximity to neural structures, hyperfractionation with twice daily fractions were employed to reduce the risk of late toxicity. For sites not in proximity to critical structures, standard 1.8-2 Gy once daily fractionation is typically used.

Patient H&P, treatment planning details: Courtesy of Dr. William Regine, Professor and Chair, Dept. of Radiation Oncology, University of Maryland, Baltimore
RADIATION PLANNING: CASE 1

- $CTV_2 = GTV + 0.5 - 1\, \text{cm margin, modified at natural barriers}$
- Phase II (Small field boost): $24.2\, \text{Gy in 22 fx, @ 1.1\, \text{Gy BID}}$
- $PTV = CTV + 3\, \text{mm (institutional practice) }$
- Standard Head-Neck organs-at-risk (OAR) delineate
- Total PTV Dose: $72.6\, \text{Gy in 66 fx @ 1.1 \, Gy BID}$

Patient H&P, treatment planning details: Courtesy of Dr. William Regine, Professor and Chair, Dept. of Radiation Oncology, University of Maryland, Baltimore
IMRT PLAN – CTV1

Volumes:
GTV – Red
CTV1 – Yellow
PTV1 – Blue

Normal structures (in colorwash)

Brainstem – Purple
Optic nerve – Green
Chiasm – yellow-green

Absolute
4840.0 cGy
7623.0 cGy
7260.0 cGy
6897.0 cGy
6534.0 cGy
Patient H&P, treatment planning details: Courtesy of Dr. William Regine, Professor and Chair, Dept. of Radiation Oncology, University of Maryland, Baltimore
**DVH**

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dose Constraint (Gy)</th>
<th>Actual DVH Value (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Max &lt; 54</td>
<td>52.6</td>
</tr>
<tr>
<td>Cord</td>
<td>V50 &lt; 0.1%</td>
<td>V50: 0.0%</td>
</tr>
<tr>
<td></td>
<td>V48 &lt; 0.3%</td>
<td>V48: 0.0%</td>
</tr>
<tr>
<td>Chiasm</td>
<td>Max &lt; 55</td>
<td>54.9</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Max &lt; 55</td>
<td>*Right: 72.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: 54.3</td>
</tr>
<tr>
<td>Retina</td>
<td>Max &lt; 45</td>
<td>*Right: 69.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: 28.9</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Mean ≤ 35</td>
<td>*Right: 47.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: 33.3</td>
</tr>
<tr>
<td>Lens</td>
<td>Max &lt; 10</td>
<td>*Right: 45.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: 10.7</td>
</tr>
</tbody>
</table>

* Teaching Point: OARs on the left side were prioritized in order to preserve contralateral nerve function.

GTV (primary) – red
GTV (node) – orange
CTV2 – lavender
PTV2 – sky blue
Bright green – right optic nerve
Chiasm – yellow-green
Forest green – left optic nerve
Brainstem – purple
Spinal Cord – maroon
ON TREATMENT ISSUES/MANAGEMENT

- Mucositis – topical numbing mouthwash, oral hygiene, opioid based analgesics, baking soda and salt solution
- Dry mouth – lozenges
- Dry eyes – eye drops
- Maintain diet and hydration, PEG tube, IV fluid support PRN
- Skin care – non-alcoholic, water-based creams/lotions
- Monitor labs
- Case 1 needed a treatment break due to significant nausea/vomiting/failure to thrive, grade 3 weight loss requiring peg tube placement. Changes to her treatment included a switch from cisplatin to weekly carboplatin and a re-planning scan to account for >10% weight-loss. The remaining treatment course was given at a higher dose-per fraction, 1.5 Gy bid.
CASE-SPECIFIC POINTS

• These cases highlight the challenges in managing rare diseases in which there is little data available
• SNUC is rapidly progressive and presents with locally advanced disease
• Lymph node involvement at presentation is rare but associated with worse prognosis
• Elective nodal dissection/ irradiation recommended
• Studies have advocated for trimodality therapy with surgery having the most significant impact on overall survival
REFERENCES


Please provide feedback regarding this case or other ARRO cases to arrocase@gmail.com