Diagnosing Distinctive Lesions of the Head and Neck

Evaluation of a Sinonasal Tract Case

Lester D. R. Thompson

Learning Objectives

Following the presentation, participants should be able to:

1. Develop a clinical, imaging, and histopathology differential diagnosis for small round blue cell lesions of the sinonasal tract
2. Understand the fundamental treatment differences between the various diagnoses and how to reach a diagnostic category based on selecting special studies to aid in separation

Case History

- 28 year old woman
- Presented with progressive sinus pain
- Recent onset of diplopia and headaches
- Left proptosis and exophthalmos were noted
- By computed tomography, there is a 1.8 x 1.1 cm left frontoethmoid sinus mass
- During physical exam, there was a palpable mass through the left upper eyelid nasal side
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USCAP – Diagnosing Distinctive Lesions of the Head and Neck
Best diagnosis based on the H&E findings:

1. Melanoma
2. Mesenchymal chondrosarcoma
3. Rhabdomyosarcoma
4. Epithelial: Sinonasal undifferentiated carcinoma/Squamous cell carcinoma/NEC
5. Small cell osteosarcoma
6. Lymphoma
7. Olfactory neuroblastoma
8. Ewing sarcoma
9. Pituitary adenoma

Small Round Blue Cell Tumors

Small Blue Round Cell: **MR SLEEP**

- Melanoma, Mesenchymal chondrosarcoma
- Rhabdomyosarcoma
- Sinonasal undifferentiated carcinoma (SNUC)/Squamous cell carcinoma/Small cell osteosarcoma
- Lymphoma
- Esthesioneuroblastoma (Olfactory neuroblastoma)
- Ewing sarcoma
- Pituitary adenoma/Plasmacytoma
Differential Diagnosis: Mesenchymal Chondrosarcoma

- Malignant mesenchymal tumor with cartilaginous differentiation
- Rare, but 2nd - 3rd decades
- Cartilage is frequently limited, requiring many sections or levels
- Biphasic microscopic pattern:
  - Abrupt islands of cellular hyaline cartilage
  - Small, undifferentiated round to spindled cells
- Cell arranged in a solid pattern with staghorn-shaped vessels
- **Positive:** CD99, Sox9, CD56, NSE
- **Variable:** GFAP, Desmin, synaptophysin
- **Negative:** S100 protein (small blue cells)
- **HEY1/NCOA2** fusion detected by FISH in ~80%
- Surgery and radiation

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Differential Diagnosis:
Ewing Sarcoma/PNET

- High-grade primitive small round cell sarcoma with (variable) neuroectodermal differentiation defined by presence of translocation (EWSR1)
- Small round blue cell tumor, sheets, tumor necrosis, finely distributed chromatin, mitoses
- **Positive**: CD99, FLI1, Erg, SNF5, p63 (~20%)
- **Variable**: NSE, S100 protein, synaptophysin, CD56, NFP or GFAP
- **Negative**: myogenic, hematolymphoid, keratin (focal up to 30%)
- **EWSR1/FLI1** translocation most often
- Multimodality therapy, primarily chemotherapy
Differential Diagnosis:
Extranodal NK/T-cell lymphoma, Nasal Type

- Extranodal, NK/T-cell lymphoma, nasal type
  - 6th decade; M > F (3:1); Midline destructive
  - Dyscohesive, cytologic atypia, perivascular distribution, geographic necrosis
  - Often shows pseudoepitheliomatous hyperplasia
- **Positive:** CD3ε, CD56, EBER, TIA-1, perforin, granzyme-B,
- **Negative:** CD20, CK-pan, desmin, vascular markers
- Chemotherapy and radiation
**Differential Diagnosis:**

**Sphenoid Sinus Pituitary Adenoma**

- **Benign pituitary gland neoplasm occurring separately from and without involvement of sella turcica (a normal anterior pituitary gland)**
  - Direct extension from intrasellar pituitary tumors in about 2% should be excluded

- **Incidence:** Rare in ectopic locations
- **Age:** Wide range: 16–84 years
  - Mean: 54 years
- **Gender:** Female > Male (1.3:1)
- **Symptoms:** Obstruction, sinusitis, pain, discharge, headache, visual disturbances, endocrine syndrome
Ectopic Sphenoid Sinus Pituitary Adenoma
Imaging Findings

- Intrasphenoidal mass with expansion and/or erosion
  - Sella may be involved by upward extension, but usually normal
  - Strong enhancement post contrast
- Define extent and location of tumor
- Imaging usually suggests chordoma, nasopharyngeal carcinoma, or metastatic tumor

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Pituitary Adenoma
Pathology Findings

- Sphenoid sinus mass with bone erosion
- Size: Range: 0.5 to 8.0 cm (mean, 2.9 cm)
- Intact surface epithelium, unencapsulated tumor
- Necrosis (up to 25%); pleomorphism
- No perineural or vascular invasion
- No atypical mitoses
- Many patterns
  - Solid, organoid, glandular, insular, festoons, ribbons, single file, rosettes—pseudorosettes, papillary, cystic
- Epithelial cells
  - Polygonal, plasmacytoid, cuboidal, spindled, round or oval nuclei with “salt-and-pepper,” clumped chromatin, small nucleoli, intranuclear inclusions and variable cytoplasm
  - Profound pleomorphism
- Surgery or medical therapy (bromocriptine)
**Immunohistochemistry**

- **Positive:**
  - CK-Pan (AE1/AE3): 79%
  - Synaptophysin: 97%
  - CD56: 91%
  - NSE: 76%
  - Chromogranin-A: 71%
  - CD99: 40%
  - Prolactin: 59%
  - FSH: 47%
  - LH: 37%
  - ACTH: 33%
  - TSH: 29%
  - GH: 26%
- **Neuroendocrine +**
- **Epithelial markers +**

**Differential Diagnosis:**

**Neuroendocrine Carcinoma**

Malignant neoplasm showing neuroendocrine differentiation histologically and expressing epithelial and neuroendocrine markers immunophenotypically

- Multiple patterns: nests, ribbons, festoons, glands, rosettes, solid, papillary and even fascicular architecture
- **Crush artifacts**, tumor necrosis
- High mitotic index, including **atypical forms**
- **Lymphovascular invasion, perineural invasion**
### Differential Diagnosis: Neuroendocrine carcinoma

- Although different between tumors, cells range from round, polygonal to spindled
- Cytoplasm ranges from granular, eosinophilic to amphophilic and rarely oncocytic
- Salt-and-pepper nuclear chromatin (neuroendocrine features must predominate)
- Nucleoli generally only in large cell NEC
- **Positive:** CK-pan/CAM5.2: Cytoplasmic dot/punctate
  - Neuroendocrine markers:
    - Synaptophysin (neuronal synaptic vesicles)
    - Chromogranin (neurosecretory granules)
  - Non-specific: CD56, NSE
- **Negative:** HPV, NUT, CD34, pituitary hormones, muscle markers, hematologic, melanoma

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**Image 1:**

- **Image 2:**

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**Image 3:**

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**Differential Diagnosis: Olfactory Neuroblastoma**

- Arises from the specialized sensory neuroepithelial (neuroectodermal) olfactory cells
  - Basal reserve or olfactory stem cells
- Normally in upper part of the nasal cavity
  - Superior nasal concha, upper part of septum, roof of nose, cribiform plate of ethmoid sinus
- Age: Bimodal age presentation (young or old)
- Sex: Equal gender
- Symptoms: Non-specific; Anosmia <5%

**Imaging:** A “dumbbell-shaped” mass
- Extends across the cribiform plate of ethmoid sinus
- Bone erosion of the lamina papyracea
- CT may show speckled calcifications
- MR T1-weighted images after gadolinium show marked enhancement
Olfactory Neuroblastoma

Microscopic features

- Circumscribed lobules or nests of tumor in syncytial arrangement with neural processes
- Intact mucosa (olfactory mucosa in many cases)
- Tumor cells are “small, round, blue” cells
  - Slightly larger than mature lymphocytes
  - High nuclear to cytoplasmic ratio
  - Nuclei are small and uniform with hyperchromatic, delicate nuclear chromatin distribution
  - Nucleoli are inconspicuous
- Rarely, may show focal aberrant epithelial, myogenic or melanocytic differentiation
Olfactory Neuroblastoma
Microscopic features

- Two types of rosettes, although only in up to 30% of cases
  - Pseudorosettes (Homer Wright) common
    - The delicate, neurofibrillary and edematous stroma forms in the center of a cuffed or palisaded arrangement
  - True rosettes (Flexner-Wintersteiner) less common
    - “Gland-like” tight, annular arrangement
Olfactory Neuroblastoma
Hyams' Grading

- Grade based on the degree of differentiated, presence of neural stroma, mitotic figures, and necrosis
- Grade I to Grade IV
- Grade correlates with prognosis
- Increased grade of the tumor is more difficult to diagnose

<table>
<thead>
<tr>
<th>Feature</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
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<td>Architecture</td>
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<td>Mitoses</td>
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<td>Anaplasia</td>
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<td>Rosettes</td>
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<td>Necrosis</td>
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Sinonasal Tract Case

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Olfactory Neuroblastoma
Immunohistochemistry

Positive

♦ Synaptophysin, chromogranin, neuron specific enolase, NFP, CD56, calretinin
♦ S100 protein or GFAP found at the periphery of the tumor lobules and correspond to Schwann (sustentacular) cells
♦ Rarely, focal to strong, patchy reactions with keratin
  ✔ Especially LMW cytokeratin, Cam 5.2

Olfactory Neuroblastoma
Immunohistochemistry

Negative

♦ Desmin
♦ SMA
♦ MSA
♦ Myogenin
♦ HMB45
♦ Melan A
♦ CD45RB
♦ CD99

Synaptophysin
S100 protein

GFAP

Calretinin

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Olfactory Neuroblastoma

**Immunohistochemistry to Order**

- **Positive**
  - Synaptophysin/CD56/Chromogranin
  - S-100 protein
- **Negative**
  - CK-pan
  - Desmin/Myogenin/MYOD1
  - CD45RB

**Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Tumor</th>
<th>5-yr survival</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Confined to the nasal cavity</td>
<td>75-91%</td>
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<tr>
<td>B</td>
<td>Nasal cavity plus one or more paranasal sinuses</td>
<td>68-71%</td>
</tr>
<tr>
<td>C</td>
<td>Extension of tumor beyond the sinonasal cavities</td>
<td>41-47%</td>
</tr>
</tbody>
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**Management**

- Complete radical surgical eradication
  - Most patients present with Kadish stage C
  - Craniofacial resection including cribiform plate by trephination or by endoscopic approach
  - Biopsy discouraged due to vascularity
- Combined with radiotherapy
- Chemotherapy reserved for advanced or disseminated disease
- Bone marrow transplantation shows promise
Olfactory Neuroblastoma

Outcome

• Outcome:
  ◆ Recurrence rate  15 – 30%
    ✔ Usually within the first 2 years
  ◆ Lymph node metastasis:  10 – 20%
  ◆ Distant metastasis:  10%
    ✔ Lungs and bones
• Overall 5-year survival:  60 – 80%
  (stage & grade dependent)
  ◆ Low grade:  80% 5-year survival
  ◆ High grade:  40% 5-year survival

Differential Diagnosis:
Mucosal Melanoma

• Dysohesive, epithelioid to spindled tumor cells, junctional proliferation, pigmented, intranuclear cytoplasmic inclusions, eccentric nuclei, mitoses, peritheliomatous growth
• Positive:  S100 protein, HMB-45, Melan-A, SOX10
• Negative:  Keratin, neuroendocrine markers, pituitary hormones and transcription factors, CD45RB, muscle markers
• Surgery and radiation therapy
### Differential Diagnosis: Rhabdomyosarcoma

- Looks like a polyp
- Can be embryonal, alveolar, or undifferentiated types
- Small round cells to ribbon or strap shaped cells to large cells
- **Positive:** Desmin, myogenin, MYOD1, myoglobin, SMA, MSA
  - CK-pan (8%); CD56
- **Systemic therapy (chemoradiation)**
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Sinonasal Undifferentiated Carcinoma

*High grade carcinoma without squamous or glandular differentiation*

- **Age:** Older patients
- **Sex:** Men > Women
- **Site:**
  - Extensively infiltrative at presentation
  - Multiple sites: Nasal cavity, paranasal sinuses, orbit, skull base

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**Multiple symptoms including**

- Nasal obstruction, epistaxis, proptosis, visual disturbances (e.g., diplopia)
- Facial pain
- Symptoms of cranial nerve involvement
- Rapidly growing clinically (weeks to months)
- High frequency of metastatic disease
Sinonasal Undifferentiated Carcinoma Pathology

- Midline destructive with bone destruction, necrosis and lymph-vascular invasion
- Hypercellular proliferation with varied growth
  - Lobular (organoid), trabecular, solid, sheet-like
- Surface involvement (dysplasia/carcinoma in situ) usually absent
- Often ulceration
- Polygonal cells of medium to large size with open/vesicular chromatin, variable nucleoli
- Varying amount of eosinophilic appearing cytoplasm with poorly defined cell membranes
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Sinonasal Undifferentiated Carcinoma
Immunohistochemistry

**Positive:** CK-pan, EMA, CK7 (~50%), NSE, Ki-67, p16, CD117

**Sometimes:** Synaptophysin, chromogranin, CD56, p63

**Negative:** CK5/6, desmin, CD34, HPV, S100 protein, HMB45, EBER

*High mitotic index*
Sinonasal Undifferentiated Carcinoma

Treatment

- Sequencing of various therapeutic modalities
- Multimodality approaches to management yields best outcome – but still poor
- Generally, resectable or potentially resectable tumors receive neoadjuvant chemoradiation followed by surgical resection

Outcome and Prognosis

- Highly aggressive neoplasm
- Mean survival of 4 months
  - No disease-free patients reported
- Extent of resection most reliable predictor of tumor control
- Local recurrence common
  - Represents major cause of morbidity and mortality
- Metastatic disease to bone, brain, liver, cervical lymph nodes

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Additional Considerations

• There is abrupt squamous differentiation or keratinization
• Otherwise poorly differentiated
• Negative sarcoma and neuroendocrine markers
• Additional evaluation can be done

• *NUT* midline carcinoma
**NUT Midline Carcinoma**

- NUT midline carcinoma (NMC) is an aggressive subset of squamous cell carcinoma, genetically defined by rearrangement of the NUTM1 gene
  - Nuclear protein in testis (NUT, aka NUTM1) gene
- Most common (70%) rearrangements are BRD4-NUTM1 fusion, although NUT-variant fusions are well recognized
- ~35% affect the head and neck area
  - Most in sinonasal tract > orbit
  - Majority in mediastinum
- Generally younger patients
- Usually midline but can be anywhere
### NUT Midline Carcinoma

- Prognosis is usually poor (median 6.7 months)
  - Gives patient time to put affairs in order
- Diagnosis is only confirmed by nuclear immunoreactivity to NUT protein
  - Specific fusion oncogenes for clinical trials
- Conventional chemotherapeutic regimens are ineffective
  - Molecular targeted therapies (bromodomain inhibitors [BETi] and histone deacetylase inhibitors [HDACi]) may yield growth arrest
  - Don’t cross blood brain barrier
- Targeted therapies increase survival to >18 mo

### Conclusion

- Think very broadly when confronted with Sinonasal Tract “Small Round Blue Cell” tumors (MRS. LEEP)
- H&E features are often characteristic
- Let H&E guide ancillary/pertinent studies
- There will be immunohistochemistry overlap
- Targeted molecular studies as needed

### Take Home Points

- **Always** try to use radiology and/or clinical findings
- Consider what will be done with positive or negative findings when ordering special studies
- Preferentially and sequentially order studies
- Wide differential diagnoses are common, but they can be narrowed significantly with clinical, imaging and laboratory findings

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