Diagnosing Small Biopsies of the Sinonasal Tract

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Learning Objectives

Following the presentation, participants should be able to:
1. Interpret and incorporating radiology findings into determining the best diagnosis for small biopsies.
2. Create a hierarchy of immunohistochemistry evaluation to achieve the best diagnosis with limited material.
3. Learn which entities can be combined versus separated into groups for management purposes.

Case #1

- 28 year old
- Woman
- Sinus pain with recent onset of diplopia
- Proptosis and exophthalmos
- Headaches
- By computed tomography, there is a 1.8 x 1.1 cm left frontoethmoid sinus mass that involved the medial superior bony orbital wall, and extends to involve the soft tissues of the orbit and maxillary sinus
- Biopsy performed
S100 protein

CK5/6

p63

CD34

CD45RB, Desmin, MSA, Synaptophysin
Additional Considerations

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

**NUT carcinoma**

NUT Carcinoma

* NUT carcinoma is a poorly differentiated carcinoma often with evidence of squamous differentiation, defined by the presence of NUT gene rearrangement
  - Nuclear protein in testis (NUT, aka NUTM1) gene
  - Most common (70%) rearrangements are BRD4-NUTM1 fusion, although NUTM1-variant fusions are well recognized
  - ~35% affect the head and neck area
    - Most in sinonasal tract > orbit, nasopharynx, oropharynx
    - Usually, but not always midline
    - Majority in mediastinum
  - Age: Younger patients (mean 22 years)
  - Sex: Slight female predominance

**Case #2**

- 40 year old
- Man
- Congestion, difficulty breathing
- Epistaxis
- Imaging showed a nasal cavity centered mass
- Biopsy performed

Diagnosis confirmed by immunoreactivity to NUT protein; FISH or RT-PCR when necessary

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
Sinonasal Undifferentiated Carcinoma

Undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable

- Age: Older patients (mean 50-60 years)
- Sex: Men > Women
- Rapidly growing clinically
- Midline destructive with bone destruction, necrosis and lymph-vascular invasion
- High frequency of metastatic disease
- Poor outcome

Sinonasal Undifferentiated Carcinoma

- Sheets, lobules, trabecular, moderately large monotonous cells, round nuclei, vesicular to open chromatin, prominent nucleoli, well defined borders; ± rosettes, high mitotic index
- **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
Sinonasal neuroendocrine carcinoma (SNEC) is a high-grade carcinoma with morphologic and immunohistochemical features of neuroendocrine differentiation (small cell and large cell types)
- Generally no squamous/glandular areas
- Salt-and-pepper nuclear chromatin, crush artifacts, very high mitotic index, including atypical forms
- Lymphovascular invasion, perineural invasion, tumor necrosis
- Positive: AE1/AE3 & CAM5.2: Cytoplasmic dot/punctate

Neuroendocrine markers:
- Synaptophysin, chromogranin
- Non-specific: CD56, NSE, p16
- Negative: HPV, NUT, CD34, pituitary hormones, muscle markers, hematologic, melanoma
Sinonasal Tract Lesions

- CK-pan
- Synaptophysin
- CD56
- CK5/6, S100 protein, Prolactin, Desmin, CD34
Differential Diagnosis: Mucosal Melanoma

A malignant neoplasm arising from melanocytes in the mucosa

- Dyscohesive, 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
Differential Diagnosis: Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant mesenchymal tumor with skeletal muscle differentiation.

- Looks like a polyp
- Embryonal, alveolar, pleomorphic, spindle types
- Alveolar pattern with fibrovascular septa surrounding small round cells to ribbon or strap shaped cells to large cells; dyscohesion at periphery, giving dilapidated appearance

- **Positive:** Desmin, myogenin, MYOD1, myoglobin, SMA, MSA
  - CK-pan (8%); CD56
- Systemic therapy (chemoradiation)

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23rd Seminar in Pathology-Allegheny Health Sinonasal Tract Lesions
CD56

Myogenin

Actin

Desmin

CK-pan
Initial panel for poorly differentiated tumor:
- CK-pan
- Desmin
- CD56
- S100 protein
- CD45RB

Case #3
- 58 year old
- Man
- Congestion, difficulty breathing
- Imaging showed a sphenoid sinus mass
- Biopsy performed

Synaptophysin
The most accurate diagnosis:

1. Neuroendocrine carcinoma
2. Pituitary adenoma
3. Rhabdomyosarcoma
4. Sinonasal undifferentiated carcinoma
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)

Pathogenesis

- Anterior pituitary primordium appears at about 4 weeks of embryogenesis
- During 8th developmental week, pituitary divides into sellar and pharyngeal parts
  - Supradiaphragmatic attachment to pituitary stalk
  - Cephalic invagination of Rathke pouch (intrasellar)
- Migration into sphenoid or pharynx along craniopharyngeal canal
  - Ectopic pituitary adenomas are derived from these embryologic remnants along the migration path
  - Fully functional tissue in these ectopic locations

Presentation

- Obstruction, sinusitis, rhinorrhea, discharge
- Headache and pain
- Visual disturbances
  - Diplopia, acuity loss, blurring
- Endocrine syndrome
  - Cushing, acromegaly, impotency, amenorrhea, galactorrhea
- Asymptomatic (10%)

Laboratory Tests

- Hormones can be measured serologically or via stimulation/suppression testing
  - ACTH, GH, TSH, prolactin, cortisol
- Releasing hormones can also be measured

Imaging Findings

- Intraspheonoidal 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
Sphenoid Sinus Pituitary Adenoma
Macroscopic Features

- Polypoid and pedunculated mass within sphenoid sinus
  - May expand bone into adjacent structures
- Size: Range: 0.5 to 8.0 cm
  - Mean: 2.9 cm
- Tumor size does not seem to correlate with symptom severity

Polypoid

- Intact surface epithelium
- Submucosal location, unencapsulated tumor
- Invades into subepithelial stroma and bone
- 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

Pituitary Adenoma

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Sinonasal Tract Lesions
**Histologic Findings**

- Fibrovascular, hemorrhagic to sclerotic background stroma
- Rarely, calcified with psammomatoid bodies
- Extends around minor mucoserous glands
- Somewhat monotonous population of epithelial cells
  - Polygonal, plasmacytoid, cuboidal, spindled
  - Round or oval nuclei
  - “Salt-and-pepper,” clumped chromatin
  - Majority have small nucleoli
  - May see prominent nucleoli (20%)
  - Eosinophilic, granular, amphophilic or clear, eccentrically located cytoplasm
  - Profound pleomorphism (15%)
Immunohistochemistry

Positive Epithelial:
- 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 +

Immunohistochemistry

Positive Hormones:
- Prolactin: 59%
- FSH: 47%
- LH: 37%
- ACTH: 33%
- TSH: 29%
- GH: 26%

Immunohistochemistry

Positive:
- Multiple hormones: 48%
- Single hormone: 33%
- No hormones: 19%*

*Pituitary transcriptions factors can be performed:
- Pit-1, T-pit, SF-1, ER-α, and GATA-2

Immunohistochemistry

Positive:
- Multiple hormones: 48%
- Single hormone: 33%
- No hormones: 19%*

Treatment

- Complete surgical removal is treatment of choice
- Medical/hormonal manipulation
  - Dopamine-agonists (bromocriptine), somatostatin analogs (octreotide), corticosteroids (hydrocortisone, prednisone), thyroxine
- Stereotactic radioablation
  - For larger or incompletely removed tumors
**Prognosis**

- **Excellent prognosis**
  - 96% are Alive or Dead with no evidence of disease (mean follow-up: 10.5 years)
  - 4% died with disease (0.8 years)
  - 14% persistence/recurrence (mean, 2.1 years)
  - Managed with surgery or radiation
- Metastases are not reported

**Case #4**

- 35 year old
- Female
- Unable to breathe through left side of nose, with marked obstructive symptoms
- Large polyp obstructing left nasal cavity.
- The computed tomography scan and the MRI demonstrate a 4.3 x 3.7 x 2.5 cm mass pushing the right frontal brain lobe, extends through the right ethmoid sinus
- Calcifications noted

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**Small Round Blue Cell Tumors**

**Small Blue Round Cell:**
- Melanoma / Mesenchymal Chondrosarcoma / MNTI
- Rhabdomyosarcoma
- Sinonasal undifferentiated carcinoma (SNUC) / Small cell mesothelioma
- Lymphoma / Leukemia
  - Mantle cell, Diffuse large B-cell, Burkitt, Follicular, T-cell
  - Rich large B-cell, Classical Hodgkin lymphoma
- Esthesioneuroblastoma (Olfactory neuroblastoma)
- Ewing sarcoma / Primitive Neuroectodermal tumor
- Pituitary adenoma / Plasmacytoma / Paraganglioma

**Small Round Blue Cell Tumors**

**Small Blue Round Cell:**  
- Melanoma
- Rhabdomyosarcoma
- Sinonasal undifferentiated carcinoma (SNUC)
- Lymphoma
- Esthesioneuroblastoma (Olfactory neuroblastoma)
- Ewing sarcoma
- Pituitary adenoma
Olfactory Neuroblastoma

**Background**

A malignant neuroectodermal neoplasm with neuroblastic differentiation, most often localized to the superior nasal cavity

- Previously called: esthesioneuroblastoma
- Arises from the specialized sensory neuroepithelial (neuroectodermal) olfactory cells
- Distributed in upper part of the nasal cavity
  - Cribriform plate (ethmoid sinus), superior nasal concha, upper half of nasal septum, roof of nose

**Clinical features**

- 3% of all sinonasal tumors
- Age: All ages but with a peak 2nd and 5th – 6th decades
- Sex: Males > Females (1.2:1)
- Non-specific symptoms
  - Nasal obstruction (70%)
  - Epistaxis (50%)
  - Headaches, pain, anosmia, and visual disturbances
  - Anosmia is not a common complaint (5%)
- Non-specific nature of initial presentation, patients often have a long history before diagnosis

**Radiographic findings**

- A “dumbbell-shaped” mass
- Extends across the cribriform plate
- CT may show speckled calcifications and bone erosion of the lamina papyracea, cribriform plate and/or the fovea ethmoidalis
- MRI images with and without contrast show extent of tumor
  - 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; only 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
    ✓ Grade I and II
  • True rosettes (Flexner-Wintersteiner) less common
    ✓ “Gland-like” tight, annular arrangement
    ✓ Grade III and IV
Olfactory Neuroblastoma 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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<td>Mitoses</td>
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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 (suntentacular) cells
- Rarely, focal to strong, patchy reactions with keratin
  - Especially LMW cytokeratin, Cam 5.2

**Negative**
- Desmin
- SMA
- MSA
- Myogenin
- HMB45
- Melan A
- CD45RB
- CD99

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S100 protein

GFAP

Calretinin

Olfactory Neuroblastoma
Immunohistochemistry to Order

- **Positive**
  - Synaptophysin/CD56/Chromogranin
  - S-100 protein

- **Negative**
  - CK-pan
  - Desmin/Myogenin/MYOD1
  - CD45RB

Immunohistochemistry Evaluation

Initial panel for poorly differentiated tumor:
- CK-pan
- Desmin
- CD56
- S100 protein
- CD45RB

Olfactory Neuroblastoma Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Tumor</th>
<th>5-yr survival</th>
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<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>
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Olfactory Neuroblastoma

Management

- Complete radical surgical eradication
  - Most patients present with Kadish stage C
  - Craniofacial resection including cribriform 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

Case #5

- 64 year old
- Man
- History of seasonal allergic rhinitis, with increased facial pain and post-nasal drip
- Endoscopy shows significant crusting

Wegener Granulomatosis

Granulomatosis with Polyangiitis (GPA)

Nonneoplastic, idiopathic aseptic necrotizing disease characterized by vasculitis and destructive properties
- Head and neck, lung and kidney involvement
  - Nasal cavity > Maxillary > Ethmoid sinuses
- Localized or systemic presentation
- Laboratory findings:
  - Elevated antineutrophil cytoplasmic antibody (ANCA)
    - c-ANCA (cytoplasmic) >>> p-ANCA
  - Elevated proteinase 3 (PR3)—most specific for GPA
Granulomatosis with Polyangiitis (GPA)

**Pathology Features**

- Tissue necrosis
  - Biocollagenolytic necrosis (blue, granular)
  - Ischemic and geographic (in stroma)
- Vasculitis
  - Small to medium vessels, angiocentric, with possible thrombus
- Granulomatous inflammation
  - Isolated giant cells but limited or lacking granulomas
- Only about 15% of biopsies will have all 3 features
- Polymorphous infiltrate of lymphocytes, histiocytes, plasma cells and rare eosinophils

**C-ANCA (granular in cytoplasm)**

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Granulomatosis with Polyangiitis (GPA)
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Differential Diagnosis
Common Lesions to Exclude

- **Extranodal NK/T cell lymphoma, sinonasal type**
  - Cytologic atypia, perivascular distribution, geographic necrosis
  - Positive: CD3, CD56, CD138, granzyme, EBER;
    Negative: CD20

- **Sarcoidosis**
  - Epithelioid histiocytes arranged in tight granulomas with giant cells, but without vasculitis

- **Cocaine use**
  - Talc crystals; foreign body giant cells

- **Angiolymphoid hyperplasia with eosinophilia**
  - Epithelioid endothelial cells, eosinophils in both, but no biocollagenolytic necrosis

- **Angiocentric eosinophilic fibrosis (IgG4 sclerosing disease)**
  - Concentric layering of fibrosis with marked eosinophilia

- **Langerhans cell histiocytosis**
  - Classical Langerhans histiocytes (cleaved, coffee bean), eosinophils

- **Infections**
  - Generally to AFB, fungal (PAS/light green) and Warthin Starry
Extranodal NK/T-cell lymphoma, nasal type

CD3

CD56

Extranodal NK/T-cell lymphoma, nasal type

Granzyme

EBER

Cocaine

Extranodal NK/T-cell lymphoma, nasal type

Angiolymphoid hyperplasia with eosinophilia

Cocaine talc crystals
Conclusion

- Think very broadly when confronted with Sinonasal Tract “Small Round Blue Cell” tumors (MR. SLEEP)
- 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 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