Challenging Cases in Head and Neck Surgical Pathology

Robert A. Robinson
Department of Pathology
University of Iowa
American Academy of Oral and Maxillofacial Pathology

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Challenging Cases in Head and Neck Surgical Pathology

Sinonasal tumor in an 18 year old

Thyroid tumor in a 55 year old

52 year old female with a neck mass and a sore throat

Nasal tumor in a 56 year old

Cases will range from one with a very broad differential to cases whose differential is more focused
Challenging Cases in Head and Neck Surgical Pathology

The diagnosis of these cases will variably include the use of:

- Routine H&E stains
- Immunohistochemistry

For some cases we will also discuss evolving NGS use
Case 1

An 18 year old female presented with a short history of headaches and sinus pain. Imaging revealed a mass in the left posterior wall of the maxillary sinus with involvement of the infratemporal fossa and some intracranial extension.
A Caldwell-Luc incision was made in the labio-gingival sulcus and a small opening was made in anterior face of the maxillary sinus. The posterior wall of the maxillary sinus was bulging forward and a biopsy of the mass was obtained from an incision into pterygopalatine fossa.
A sample for frozen section was evaluated and revealed fat.

A second sample sent for frozen section was diagnosed as:

“Small blue cell tumor, defer to permanent sections for final diagnosis”.
H&E stains show a ‘blue cell tumor’

Immunohistochemical stains were performed

What stains would you order?
EWS-PNET

Ewing’s Sarcoma Family of Tumors (ESFT)
Case 1

Round Cell Tumors of the Nasal Cavity, Paranasal Sinus and Skull Base
Objectives for Case 1

✓ Discuss some of the lesions in the differential diagnosis of round cell tumors

✓ Identify hints on H&E slides that might help select the initial antibody panels in round cell tumors

✓ Discuss potential traps in histology and immunohistochemistry of ‘undifferentiated tumors’

✓ Discuss appropriate use of next generation (NGS) ‘fusion panels’ in diagnostic pathology
Objectives for Case 1

✓ Discuss some of the lesions in the differential diagnosis of round cell tumors

Although we are focusing on sinonasal/nasal/skull base location for this case, the workup of round cell tumors anywhere is similar.
Objectives for Case 1

✓ Identify hints on H&E slides that might help select the initial antibody panels in round cell tumors

In my lab, I can choose between ~200 antibodies, but I can’t choose them all!
Objectives for Case 1

✓ Discuss ‘traps’ in histology and immunohistochemistry

Immunohistochemical antibodies can lead us into incorrect diagnoses because the antibodies sometimes bind to antigens that we weren’t expecting to be on that specific tumor type.
Objectives for Case 1

✓ Discuss appropriate use of ‘fusion panels’ and next generation sequencing (NGS) in diagnostic pathology

Molecular testing using NGS is increasing and can be useful in some cases.
Round Cell Tumors of the Nasal Cavity, Paranasal Sinus and Skull Base

Many of these tumors are not seen everyday, yet common enough that you need to have a way to manage their diagnosis.
Round cell tumor differential includes a broad spectrum of tissue types

- Neuroectodermal
- Mesenchymal
- Hematopoietic
- Epithelial
Sinonasal / Skull Base Round Cell Tumors

**Neuroectodermal differentiation**
- Ewing’s sarcoma/PNET (EWS-PNET)
- Olfactory neuroblastoma
- Melanoma
- Neuroendocrine carcinoma
- Pituitary adenoma

**Mesenchymal differentiation**
- Rhabdomyosarcoma
- Synovial sarcoma
- Mesenchymal chondrosarcoma
- Desmoplastic small round cell tumor
- Small cell osteosarcoma

**Hematopoietic differentiation**
- Lymphoma
- Myeloid sarcoma
Sinonasal / Skull Base Round Cell Tumors

Epithelial differentiation

- Adenoid cystic carcinoma
- Lymphoepithelial carcinoma
  - Sinonasal primary vs extension from nasopharynx
- Sinonasal non-keratinizing squamous carcinoma
- Sinonasal basaloid carcinomas
  - Sinonasal undifferentiated carcinoma (SNUC)
- NUT midline carcinoma
- SMARCB1 deficient carcinoma
- HPV-related carcinoma with adenoid cystic carcinoma-like features
Sinonasal / Skull Base Round Cell Tumors

Neuroectodermal differentiation

- Ewing’s sarcoma/PNET (EWS-PNET)
- Olfactory neuroblastoma
- Melanoma
- Neuroendocrine carcinoma
- Pituitary adenoma
Sinonasal / Skull Base Round Cell Tumors

Neuroectodermal differentiation

Ewing’s sarcoma/PNET (EWS-PNET)

Olfactory neuroblastoma
Melanoma
Neuroendocrine carcinoma
Pituitary adenoma
Ewing’s Sarcoma Family of Tumors (ESFT)

All malignant
All aggressive
All histologically similar in appearance
All have similar genetic translocation
Most occur in children and young adults
Ewing's Sarcoma Family of Tumors (ESFT)

✓ PNET
  ✓ (primitive neuroectodermal tumor)
  ✓ (primitive peripheral neuroectodermal tumor)

✓ Ewing's sarcoma

✓ Askin's tumor (Thoraco-pulmonary tumor)

Common term is EWS-PNET
Ewing’s Sarcoma Family of Tumors (ESFT)

- PNET
- Ewing’s sarcoma
- Askin’s tumor (Thoraco-pulmonary tumor)

These tumors are arranged on a spectrum.
Common term is EWS-PNET

PNET
  Classically soft tissue location
Ewing’s sarcoma
  Classically bone location
Askin’s tumor (Thoraco-pulmonary tumor)
  Classically thorax/pulmonary location
The incidence for all ages is one case per 1 million people in the United States.

In patients aged 10 to 19 years, the incidence is between nine and ten cases per 1 million people.
Presentation of EWS/PNET

~40 present in 1st decade

~50% of cases in 2nd decade

Predilection for Caucasians

Slight male predominance
Most common extraosseous primary sites

Trunk (32%)
Extremity (26%)
Head and neck (18%)
  of these, 20% are in sinonasal tract
Retroperitoneum (16%)
Other sites (9%)
EWS/PNET Morphologic Variants

Hyalinized
Spindled
Fasicular

Adamantinoma-like

Recently described
  Squamous differentiation
  Diffuse keratin expression
CD 99

CD 99 is a defining feature of primitive neuroectodermal which is *peripheral*

non- Central Nervous System (CNS)
CD 99

CD99 is a 32kDa glycosylated transmembrane protein encoded by the MIC2 gene, highly expressed in all Ewing's sarcomas (EWS / PNET)

CD99 has been involved in many cellular processes, such as cell adhesion, apoptosis and differentiation and intracellular trafficking
There are two subclassifications of PNET:

**Non-CNS**
- pPNET (peripheral Primitive Neuroectodermal Tumor)

**CNS**
- sPNET (supratentorial Primitive Neuroectodermal Tumor)
<table>
<thead>
<tr>
<th>Peripheral Primitive Neuroectodermal Tumor (pPNET):</th>
<th>Central Nervous System Primitive Neuroectodermal Tumor (sPNET):</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD99 antigen (MIC2 gene expression of MIC2 antigen)</td>
<td><strong>CD99 antigen (MIC2 antigen) is NOT expressed</strong></td>
</tr>
<tr>
<td>FLI-1 (gene fusion product of EWS) is positive in many cases</td>
<td><strong>No FLI-1 expression</strong></td>
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</tbody>
</table>
EWS-PNET result of *EWS – ETS* translocation

*EWS* gene (chromosome 22) encodes a widely-expressed and highly-conserved RNA-binding protein.

ETS (erythroblastosis transforming-virus-1) family of transcription factors which are involved in cell proliferation, development, and tumorigenesis.

- **FLI1**
- **ERG** (*ETS related gene*)
- **ETV1** (*ETS variant gene 1*)
- **ETV4** (*ETS variant gene 4, E1AF*)
- **ETV5** (*5th Ewing sarcoma variant, FEV*)
Chromosomal translocations in EWS-PNET

t(11;22)(q24;q12) FLI1-EWS genes : ~90%

t(21;22)(q12q12) ERG-EWS genes : ~10%

t(7;22)(p22;q12) ETV1-EWS genes : Rare

t(17;22)(q12;q12) ETV4(EIAF)-EWS genes : Rare

t(2;22)(q33;q12) ETV5(FEV)-EWS genes : Rare
$t(11;22)(q24;q12)$

*EWSR1* encodes RNA-binding protein involved in DNA transcription

5’ sequences from the *EWSR1* result in a strong transcriptional regulatory domain

*FLI1* is part of a family DNA transcription factors that contain Ets domain

3’ sequences of *FLI1* (or other Ets gene family member) provide for a DNA binding domain.
Oncogenic potential of EWS-ETS fusion proteins

- EWS-FLI1 functions primarily as a transcription factor to regulate gene expression. EWS-FLI1 may orchestrate multiple oncogenic hits

- Activate human telomerase activity through upregulation of TERT (telomerase reverse transcriptase) gene expression

- Mediation by upregulation of LAMB3 expression, a gene encoding the β3 chain of laminin-5, a protein often expressed in invading tumor cells
EWS-PNET

How do we make the diagnosis?

✓ Correct histologic features on H&E
✓ Supporting immunohistochemistry
✓ Translocation testing:
  ✓ FISH
  ✓ NGS fusion panel
EWS-PNET

How do we make the diagnosis with H&E?
Nuclear features of EWS - PNET

Dispersed chromatin
Micro-nucleoli
No anaplasia

Growth pattern:
Nested or diffuse pattern
Necrosis and dystrophic mineralization
Monotonous monolayer of cells
Atypical / Large cell EWS

Larger cells

Larger nuclei

More pleomorphism

Behavior is the same as ‘typical’ EWS
EWS-PNET

How do we make the diagnosis?

✓ Correct histologic features on H&E
✓ Supporting immunohistochemistry
✓ Translocation testing:
  ✓ FISH
  ✓ RNA based NGS fusion panel
EWS-PNET

Pre-1990’s, the only ‘special techniques’ were to search for glycogen:

1) periodic acid Schiff (PAS) stain

2) Electron microscopy

The clinical and radiologic findings were of upmost importance as well
Antibodies expressed in EWS-PNET
CD99
FLI 1
ERG

NSE
Synaptophysin
CD57
Neurofilament
Vimentin:
  dot like/perinuclear
Keratin (20-25%)
Desmin
S100 (rarely)
Antibodies helpful in diagnosis of EWS-PNET

CD99: Strong diffuse linear membrane pattern

FLI1: Most EWS-PNET also express

ERG: Generally, EWS-ERG fusion cases

EWS-ERG fusion cases also express FLI1 in most cases

FLI1 is not considered specific to rearrangement type cross reactivity with the highly homologous ETS DNA-binding domain present in the C-terminus of both ERG and FLI1
Some other malignancies with CD99 expression:

Small cell melanoma
Neuroendocrine carcinoma
Poorly differentiated carcinomas, multiple types
Prostatic adenocarcinoma
Esophageal adenocarcinoma
Squamous cell carcinomas of multiple sites
Hepatocellular carcinoma
Endometrial carcinoma
Renal cell carcinoma
Urothelial carcinoma
Mucoepidermoid carcinoma
Fli 1 Antibody  
(Friend Leukemia Integration – 1)  
Nuclear staining  
   Endothelial cells  
   Small lymphocytes  

Positive:  
   EWS / PNET  
   Vascular lesions  

Variable:  
   Melanoma  
   Merkel cell  
   Lymphoma (Lymphoblastic, ALC, AITC)  
   Desmoplastic small round cell tumor
EWS-PNET

How do we make the diagnosis?

- Correct histologic features on H&E
- Supporting immunohistochemistry
- **Translocation testing:**
  - FISH
  - Targeted NGS panel
EWS/PNET

FISH

$t(11;22)(q24;q12)$ FLI1-EWS genes: ~90%

Most cytogenetic FISH studies target this translocation

FISH has a relatively fast turn around time

However, since this could underestimate 10% of cases, additional FISH probes or other molecular techniques should be used if the clinical and histologic/immunohistologic findings support EWS/PNET
Even though florescence in situ hybridization (FISH) technique is the current gold standard in fusion detection, it can generally not detect a large number of possible fusions in parallel.

Fusion targets for probe design must be known in FISH. FISH lacks high-resolution evaluation of the molecular identity of these fusion partners.
Fusion panels
Panels are developed to have broad coverage

Identifies both gene partners in a rearrangement

Diagnostic and therapeutic information from a sole sample.

Panels are developed to use formalin fixed paraffin embedded tissue
When should NGS be employed in clinical practice?

Some tumors can have identical H & E morphology with Ewing’s that are not Ewing’s.

IHC or FISH negative for Ewing’s

NGS fusion panels may offer diagnostic help
Potential downsides for NGS

Turn around time is 7-10 days (sometimes in cases of a failed run, 21).

Expensive
Some tumors share “EWS” fusion

These panels can also detect other EWS fusions

Clear cell sarcoma (12;22)

Desmoplastic round cell tumor (11;22)  
\[ t(11;22)(p13;q11.2 \text{ or } q12) \]

Extraskeletal myxoid chondrosarcoma (9;22)
Round cell tumors can share with EWS-PNET:

1) Morphologic similarities
2) Some genetic abnormalities
3) Immunohistochemical studies
Prognosis of EWS/PNET

Patients with Ewing sarcoma in the distal extremities have the best prognosis.

Patients with Ewing sarcoma in the proximal extremities have an intermediate prognosis, followed by patients with central or pelvic sites.

Infants and younger patients have a better prognosis than do patients aged 15 years and older.
Small Round Blue Cell Tumors in the Sinonasal Region with Neuroectodermal Differentiation

Ewing’s sarcoma/PNET (EWS-PNET)

Olfactory neuroblastoma

Melanoma

Neuroendocrine carcinoma

Pituitary adenoma
Olfactory neuroblastoma

Arises in neuroepithelium in cribriform plate, superior nasal vault/nasal septum

Incidence: ~ 3-5 % of sinonasal tumors
Gender: Essentially equal
Age range: Infancy to 90’s
Most cases occur in 5th and 6th decades
Olfactory neuroblastoma

Frequently ‘over’ diagnosed microscopically

Tumors ‘masquerading’ as ONB

Melanoma
Sinonasal undifferentiated carcinoma
Pituitary adenoma
Olfactory neuroblastoma : Lower Grades

Cytoplasm
- Minimal cytoplasm
- Uniform cells

Nuclei
- Round
- Salt and pepper chromatin
- Small chromocenters/nucleoli
- Mitoses uncommon, can be seen in grade 2

Neurofibrillary matrix
Homer Wright rosettes (‘Pseudorosettes’)

Olfactory neuroblastoma: Higher Grades

Cytoplasm

- Minimal cytoplasm, less than low grade

Pleomorphism of cells

Nuclei

- Round
- Coarse chromatin

Mitoses

- No or minimal neurofibrillary matrix

Flexner-Wintersteiner rosettes (‘true’ rosettes)

Necrosis can be seen
Olfactory neuroblastoma

Nuclear pleomorphism
Fibrillary matrix
Mitoses
Necrosis
Rosettes
Architecture
## Hyams Grading System for Olfactory Neuroblastoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nuclear</th>
<th>Fibrillary Matrix</th>
<th>Rosettes</th>
<th>Necrosis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pleomorphism</td>
<td>HW rosettes</td>
<td>FW rosettes</td>
<td>Rare</td>
</tr>
<tr>
<td>I</td>
<td>None</td>
<td>Prominent</td>
<td>HW rosettes</td>
<td>None</td>
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<tr>
<td>II</td>
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<td>FW rosettes</td>
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<tr>
<td>IV</td>
<td>High</td>
<td>Absent</td>
<td>None</td>
<td>Frequent</td>
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<tr>
<td>Grade</td>
<td>Lobular Architecture</td>
<td>Mitotic Index</td>
<td></td>
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<tr>
<td>I</td>
<td>Present</td>
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<tr>
<td>II</td>
<td>Present</td>
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<tr>
<td>III</td>
<td>May or may not be present</td>
<td>Moderate</td>
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</table>
Olfactory neuroblastoma
Positive Immunohistochemistry

Synaptophysin
Chromogranin
NSE

S-100 (sustentacular cells)
Cytokeratin (some cases)

Calretinin (seen in other tumors in the differential)

Rarely muscle markers if rhabdomyoblastic differentiation (desmin, myogenin)
Olfactory neuroblastoma

Negative Immunohistochemistry

CD 99

FLI-1

CD45

p63
Olfactory neuroblastoma Staging

Morita modification of Kadish staging

A) Tumor confined to nasal cavity
B) Tumor involves nasal cavity and paranasal sinuses
C) Tumor extends beyond the nasal cavity and paranasal sinuses
D) Metastatic disease (regional or distant)
Olfactory neuroblastoma treatment

Surgery with curative intent
Cranial facial resection
Endoscopic sinus surgery

Postoperative radiotherapy combined with adjuvant cisplatin-based chemotherapy.
Olfactory neuroblastoma treatment

Overall survival

85% at 5 years
75% at 10 years.

If recurrence, usually it is within the first 4 years but can occur late
Neuroectodermal differentiation

Ewing’s sarcoma/PNET (EWS-PNET)
Olfactory neuroblastoma

Melanoma

Neuroendocrine carcinoma
Pituitary adenoma
Sinonasal Melanoma

Uncommon in sinonasal regions

Cutaneous > Orbital > Sinonasal

~ 1% of all melanomas

~ 3-5% of sinonasal tumors

Gender: 1:1

Age: Any age but usually 4\textsuperscript{th} to 8\textsuperscript{th} decade

Usual sites: Nasal Cavity [Nasal septum, lateral nasal wall]

Unusual sites: Maxillary sinus and nasopharynx
Sinonasal Melanoma

**BRAF** mutations = < 5% in this location

[~50-60% of cutaneous melanomas]

**NRAS** mutations = 20%

**KIT** mutations/amplification = ~ 25%
Before establishing a diagnosis of primary sinonasal melanoma, we must assure that there are no sites of cutaneous melanoma.

Rarely the sinonasal region can be a site for metastasis.
Sinonasal Melanoma

Gross:
Nasal melanomas are often polypoid.

Microscopic patterns:
- Sheets
- Fascicles
- Organoid
- Solid

Cell appearance:
- epithelioid
- clear
- spindled
- plasmacytoid
- rhabdoid
- small round cell

Many cases may be amelanotic
IHC markers in the diagnosis of Melanoma

S100

HMB45

MITF

MART-1 / Melan A

Sox 10
IHC markers useful for Melanoma

S100
Neural crest (and other diverse cell types)

HMB45 (Human Melanoma Black 45) - monoclonal antibody derived from lymph node tissue containing metastatic pigmented melanoma

MITF- microphthalmia transcription factor (MITF); melanocyte master regulator; DNA-binding nuclear protein that regulates several melanocytic genes that play a central role in the development, differentiation, and survival of melanocytes.

Mart 1 (melanoma antigen recognized by T-cells 1)/Melan A

Sox 10-Sry-related HMG-BOX gene 10 (SOX10); nuclear transcription factor involved in the development of melanocytes and is expressed in all phases of the melanocyte life cycle, from neural crest stem cells to terminally differentiated melanocytes
S100 (Soluble 100% in ammonium sulfate)

Neural crest derived tissue
  Schwann and glial cells, melanocytes

Some breast epithelial cells
Myoepithelial cells, cartilage, adipose
Macrophages, Langerhans cells
Apocrine and eccrine glands
S100 (Soluble 100% in ammonium sulfate)

Neural crest derived tissue
- Schwann and glial cells, melanocytes
- ~ 95% of epithelioid melanoma
- ~ 85% of spindle melanoma
HMB45 (Human Melanoma Black 45) monoclonal antibody derived from lymph node tissue containing metastatic pigmented melanoma

Positive: Melanoma (85-90%)

Negative: Some melanomas (desmoplastic, oral mucosal, spindle cell)
HMB45 Positive staining lesions

PEComa
Adrenal: Pheochromocytoma
Soft tissue: Clear cell sarcoma of soft tissue
[melanoma of soft tissues]
Kidney: Angiomyolipoma
Lung: Lymphangioleiomyomatosis [LAM]
MITF- microphthalmia transcription factor

DNA-binding nuclear protein regulator of melanocytic-related genes

MITF stains a variety of cells and tumors
Beware of MITF

Other cells that are MITF +:
Histiocytes-[a real trap]
  problematic if staining for occult melanoma cells in sentinel lymph nodes

Perivascular epithelioid tumors: Angiomyolipoma
Clear cell sarcoma
Giant cell tumor
Undifferentiated pleomorphic sarcoma
Atypical fibroxanthoma
Melan A

Melan A, a product of the MART-1 gene, is a melanocyte differentiation marker recognized by autologous cytotoxic T lymphocytes.
MART-1 positive lesions

Sex cord stromal tumors
Clear cell sarcoma of soft tissues
Angiomyolipoma
Lymphangioleiomyomatosis
Adrenal cortical adenoma
Adrenal cortical adenocarcinoma
Sox 10-Sry-related HMG-BOX gene 10 (SOX10)

Nuclear transcription factor involved in the development of melanocytes

Found in all phases of the melanocyte life cycle, from neural crest stem cells to terminally differentiated melanocytes
Sox 10 is expressed in normal tissues and a variety of tumors

Breast
- Normal myoepithelial cells
- Basal like/ triple negative carcinomas

Salivary
- Normal: acini and both luminal and abluminal cells of intercalated ducts
- Carcinomas: acinic cell, adenoid cystic, epi-myoepithelial
- Pleomorphic adenoma

Neural
- Malignant peripheral nerve sheath tumor (useful to exclude synovial sarcoma)
- Schwannoma & Neurofibroma
Melanoma IHC markers
Which is the best?
Of these available markers, it is advisable to use at least two or more before diagnosing melanoma in an unusual location, such as the sinonasal region

S100
HMB45
Melan A (MART 1)
Sox 10
Melanoma IHC markers
Which is the best?

✓ S100
HMB45
Melan A (MART 1)
✓ Sox 10

S100 and Sox 10 are a good combination
IHC markers that can also be positive in melanoma

CD99

CD117

Synaptophysin
Sinonasal Melanoma

Prognosis: Generally poor, 5yr survival <15-20%

Local recurrence is common

Very rarely the sinonasal region may be a site for metastases from melanoma elsewhere
Neuroectodermal differentiation

Ewing’s sarcoma/PNET (EWS-PNET)
Olfactory neuroblastoma
Melanoma

Neuroendocrine carcinoma

Pituitary adenoma
Neuroendocrine carcinoma

Well differentiated [carcinoid]

Moderately differentiated [atypical carcinoid]

Poorly differentiated [small cell carcinoma] [large cell neuroendocrine carcinoma]
Well differentiated [carcinoid]

Moderately differentiated [atypical carcinoid]

Carcinoid and atypical carcinoid are so rare in the sinonasal region as not to generally be considered
High grade neuroendocrine carcinoma

Small cell neuroendocrine carcinoma
- Closely packed small cells with scant cytoplasm, extensive necrosis, and brisk mitotic activity

Large cell neuroendocrine carcinoma
- Cytoplasm is moderate, nuclei are vesicular with prominent nucleoli, moderate pleomorphism is present
Small cell
Histologic features

Crush artefact
Nuclear shapes ranging from angular to round
No prominent nucleoli
‘Azzopardi’ effect
  [staining of blood vessels by tumor cell nuclear material]
High mitotic rate
Large cell neuroendocrine carcinoma

Larger cells with cytoplasm
Nuclei have coarse chromatin with a nucleolus
Organoid / trabecular patterns
Necrosis
High mitotic rate
Sinonasal neuroendocrine carcinoma immunohistochemistry

Positive:
- PanKeratin
- Chromogranin
- Synaptophysin
- Neuron specific enolase
- CD56

TTF-1, very common in high grade neuroendocrine carcinoma of the lung, is not so commonly expressed in sinonasal high grade neuroendocrine tumors.
Chromogranin and Synaptophysin should always be used together in neuroendocrine carcinoma workup, as one can often be positive and the other negative.

Dot-like pankeratin staining in high grade neuroendocrine carcinoma can be very useful to point to the correct diagnosis.
Beware CD 56

Often ordered in the workup of neuroendocrine tumors (neuroendocrine carcinoma, olfactory neuroblastoma)

I try not to order it as a ‘first-line’ antibody

In some cases, CD 56 will be the only antibody that stains a tumor.

That might not ‘prove’ the tumor is neuroendocrine
Beware CD 56

CD 56 can also be positive in:
- Myeloid cells
- T-cytotoxic cells
- Myeloma
- Rhabdomyosarcoma (solid, alveolar)

If CD56 is the only antibody positive in a tumor which I believe may be neuroendocrine, I make a comment in the report noting that other tumors may also stain with this antibody.
Neuroectodermal differentiation

Ewing’s sarcoma/PNET (EWS-PNET)
Olfactory neuroblastoma
Melanoma
Neuroendocrine carcinoma

Pituitary adenoma
Pituitary adenoma

Nested patterns a useful hint

Reticulin stain helpful
Sinonasal / Skull Base Round Cell Tumors

Neuroectodermal differentiation
- Ewing’s sarcoma/PNET (EWS-PNET)
- Olfactory neuroblastoma
- Melanoma
- Neuroendocrine carcinoma
- Pituitary adenoma

Mesenchymal differentiation
- Rhabdomyosarcoma
- Synovial sarcoma
- Mesenchymal chondrosarcoma
- Desmoplastic small round cell tumor
- Small cell osteosarcoma

Hematopoietic differentiation
- Lymphoma
- Myeloid sarcoma
Rhabdomyosarcoma

Alveolar

Embryonal

Pleomorphic

Spindle cell
Rhabdomyosarcoma

Incidence overall: 4-5/1,000,000
Sinonasal incidence: 0.35/1,000,000
Most common sinonasal sarcoma, children and adults
Age: Embryonal <15 years [childhood, classically]
   Alveolar 10-30 years [adult, classically]
Gender: M = F, maybe slightly more M in ERMS
Site: EMRS-orbit and parameningeal
   Alveolar-deeper soft tissues in H&N
   Paranasal sinuses > nasal cavity
Embryonal Rhabdomyosarcoma (EMRS)

Variable histologies

- Cellular with myxoid zones
- Spindle to ovoid cells
- Rhabdomyoblasts

  - Botryoid (exophytic/polypoid)

  - Mixed EMRS/ARMS
Alveolar Rhabdomyosarcoma

Small round blue cells separated by fibrous septa
Minimal cytoplasm
Mitotic figures common
Tumor giant cells present
Rhabdomyosarcoma IHC

Positive
Desmin
Myogenin
MyoD1
Myoglobin

Variable
Vimentin
CD56

Focal
CD99

Occasional
Pankeratin
Rhabdomyosarcoma
IHC markers

Myoglobin

Desmin

Muscle specific actin

Myogenin

MyoD1
Rhabdomyosarcoma
IHC markers

Myogenin & MyoD1

Both more specific than desmin and muscle specific actin

Both more sensitive than myoglobin

MyoD1:

Diffuse cytoplasmic staining and staining of background non-tumor cells can be limiting on a practical basis.

Nuclear staining should only be counted but MyoD1 can also be seen to stain nuclei in a number of tumors
Rhabdomyosarcoma

**Embryonal**
- Desmin
- **Myogenin (more variable staining)**
- Myoglobin
- Muscle specific actin
- Smooth muscle specific actin

**Alveolar**
- Desmin
- **Myogenin (100% of cells, strong)**
- Myoglobin
- Muscle specific actin
- Smooth muscle specific actin
Embryonal Rhabdomyosarcoma (EMRS)

IHC:
- Desmin – positive diffusely
- Myogenin – positive, variable
- MYO-D1– positive, variable
- Smooth muscle actin– positive, variable

Molecular findings:
- Lost of heterozygosity (LOH) at 11p 15.5
- No PAX3 FOXO1 or PAX7 FOXO1 fusions (indicative of ARMS)
Alveolar Rhabdomyosarcoma

IHC
Desmin – positive
Myogenin – positive
MYO-D1– positive

Molecular findings:
PAX3 FOXO1 or PAX7 FOXO1 fusions
Myogenin staining also reported in:

- Synovial sarcoma
- Desmoid
- Non-neoplastic skeletal muscle (~60% in one study)
Rhabdomyosarcoma

Other immunohistochemistry that can be positive:

- CD99
- CD20
- EMA
- Cytokeratin
- Chromogranin
- Synaptophysin
- CD56
We utilize sarcoma fusion panels in the diagnosis and classification of rhabdomyosarcoma when we have insufficient material for FISH testing or if there are equivocal FISH results, the latter often due to insufficient material.
Rhabdomyosarcoma
Embryonal (EMRS) and Alveolar

Clinical course: Alveolar worse prognosis
Desmoplastic small round cell tumor

Peak incidence in young adults, described as between 20 and 24 years (range 10-40), There is a striking male predominance of at least 4:1
Desmoplastic small round cell tumor

Majority present within the abdominal cavity and pelvis.

More rarely as primary disease at other anatomic sites, including the head and neck.

Can also present with nodal and visceral metastases without evidence of a primary site.
Desmoplastic small round cell tumor

Histology:
uniform small round cells in a fibroblastic/desmoplastic stroma,

IHC:
Epithelial, neural and muscle markers can be present.
WT-1 common

However, DSRCT is characterized by a recurrent t(11;22)(p13;q12) translocation, which leads to formation of the \textit{EWSR1-WT1} fusion oncogene
Desmoplastic small round cell tumor
Immunohistochemistry

Epithelial, neural and muscle markers can be present.

- Desmin
- WT-1 (~75% of cases)
- EMA
- Pan Keratin
- NSE
- CD57

Can be seen
- CD99
- CD15
- MOC-31

Not seen
- CK 20
- CK 5/6
Outcome:

Treatment has been along lines of that for Ewing sarcoma.

However, treatment has been seen to work best with de-bulking of as much tumor as possible.

In spite of initial significant response, recurrences are frequent and durable response is infrequent.
Small cell osteosarcoma

Diffuse growth pattern
Uniform, small cells
  Round to spindled

Malignant osteoid, can be very focal
Can be mixed with cartilage
Small cell osteosarcoma

Poor prognosis

Patients given therapy as for other osteosarcoma subtypes
Hematopoietic neoplasms

Diffuse large B cell lymphoma

Extranodal NK / T cell lymphoma

Extramedullary plasmacytoma

Myeloid sarcoma
Diffuse large B cell lymphoma

Most commonly arises in the paranasal sinuses, followed by nasal cavity
Diffuse large B cell lymphoma

Uniform population of cells

Larger than small lymphs

Less angioinvasion than in NK/T cell lymphoma
Diffuse large B cell lymphoma

Uniform population of cells
Larger than small lymphs

CD45, CD20, CD79a

EBV -- negative
Diffuse large B cell lymphoma
IHC and Molecular markers

Positive:
CD45, CD20, CD79a

Negative: CD 3

Note: cytokeratin can be expressed in DLBCL

EBV -- negative

Molecular: IgH gene rearrangement
NK-Cell Tumors

Extra-nodal NK / T cell lymphomas, nasal type

Extra-nodal NK / T cell lymphomas, non- nasal type

NK cell leukemias
Extranodal NK / T cell lymphoma

Angiocentric

Mix of small to large cells

Necrosis

Non-lymphoid inflammatory cells
Extranodal NK / T cell lymphoma

CD2: Positive
CD3 – cytoplasmic positive
  CD3 surface negative (fluorescence)
CD5: Positive
CD56 positive
EBV: Positive
Extramedullary plasmacytoma

Proliferation of monoclonal plasma cells outside of the marrow space and in the absence of multiple myeloma.

Clinical:

Age is usually 6-7th decade
Male predominance 3:1
Nasal cavity and paranasal sinuses, but multiple locations in the head and neck
Extramedullary plasmacytoma

In the head and neck, most tumors are solitary.

May have obstructive symptoms, epistaxis.

Some patients have paraprotein, and if so, it is usually IgA.
Extramedullary plasmacytoma

CD138

CD38

Kappa and lambda light chains

Note: Cytokeratin can be expressed
Myeloid sarcoma

Defined by WHO as a tumor mass consisting of myeloid blasts, with or without maturation, occurring at extramedullary sites.

Leukemic infiltration is considered myeloid sarcoma only if it forms a mass that effaces tissue architecture.

Myeloid sarcoma is diagnostic of acute myeloid leukemia (AML) regardless of bone marrow or peripheral blood involvement.
Myeloid sarcoma

Myeloid sarcoma occurs in 3 settings:

As initial presentation of AML

Most often with concurrent AML, diagnosed by bone marrow biopsy or peripheral blood

Relapsed AML
Myeloid sarcoma

May represent progression from myelodysplastic syndrome (MDS) or MDS / myeloproliferative disorder (MPD) to a "blastic phase" of leukemia

Often [~ 75%] misdiagnosed as large cell lymphoma
Myeloid sarcoma
Presentation as a round cell tumor

Primitive myeloid cells

KP1
CD43
CD79a
CD3
CD34
CD117
Myeloperoxidase
Chloroacetate esterase
Lysozyme
Epithelial differentiation

Adenoid cystic carcinoma

Lymphoepithelial carcinoma
  Sinonasal primary vs extension from nasopharynx

SINonasal basaloid carcinomas

  Sinonasal undifferentiated carcinoma (SNUC)
  NUT midline carcinoma
  SMARCB1 deficient carcinoma
  HPV-related carcinoma with adenoid cystic carcinoma-like features
Some of these tumors are not necessarily ‘round cell’ in morphology, but their light microscopic appearances are in their combined differential diagnosis.

- Adenoid cystic carcinoma
- Lymphoepithelial carcinoma
  - Sinonasal primary vs extension from nasopharynx
- Sinonasal basaloid carcinomas

- Sinonasal undifferentiated carcinoma (SNUC)
- NUT midline carcinoma
- SMARCB1 deficient carcinoma
- HPV-related carcinoma with adenoid cystic carcinoma-like features
Some of these tumors are not necessarily ‘round cell’ in morphology, but their light microscopic appearances are in their combined differential diagnosis.

However, it is not uncommon to be faced with biopsy material that is ‘less than ideal’, i.e. nearly non-existent!
Epithelial differentiation

**Adenoid cystic carcinoma**

Lymphepithelial carcinoma
  - Sinonasal primary vs extension from nasopharynx

**Sinoonasal basaloid carcinomas**

Sinonasal undifferentiated carcinoma (SNUC)
NUT midline carcinoma
SMARCB1 deficient carcinoma
HPV-related carcinoma with adenoid cystic carcinoma- like features
### Immunohistochemistry

**Solid adenoid cystic carcinoma**

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>p63</td>
<td>Synaptophysin</td>
</tr>
<tr>
<td>p40</td>
<td>Chromogranin</td>
</tr>
<tr>
<td>CK 5/6</td>
<td>p16</td>
</tr>
<tr>
<td>CK 7</td>
<td>EBER</td>
</tr>
<tr>
<td>34Beta E12</td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td></td>
</tr>
<tr>
<td>Myb</td>
<td></td>
</tr>
</tbody>
</table>
Solid adenoid cystic carcinoma

Chromosomal rearrangement

t(6;9) (q21-24;p13-23)  
MYB-NFIB  
~ 60 -70 %
Solid adenoid cystic carcinoma

Solid nests of basaloid cells

Small biopsies can be difficult to diagnose without cribriform or tubular patterns

Minimal tissue may be available

Consider NGS testing
Salivary gland NGS panel

Custom made panel

Works well with formalin fixed – paraffin embedded tissue as well as fine needle aspirate specimens

14 genes, 13 targets, 100% coverage

Can reflex to Ion 318 CHIP V2
Salivary gland NGS panel

Useful for cytologic specimens

Cell samples can be removed from the cytology air-dried smears that have been stained with metachromatic stain.
Epithelial differentiation

Adenoid cystic carcinoma

*Lymphoepithelial carcinoma*

*Sinonasal primary vs extension from nasopharynx*

Sinonasal basaloid carcinomas

*Sinonasal undifferentiated carcinoma (SNUC)*

NUT midline carcinoma

SMARCB1 deficient carcinoma

HPV-related carcinoma with adenoid cystic carcinoma- like features
Lymphoepithelial carcinoma

Non-keratinizing squamous carcinoma as a primary tumor in the sinonasal region is rare and usually when found is direct extension from nasopharynx.

Tumor cells grow in a syncytial growth pattern, with indistinct borders, and have markedly vesicular nuclei with prominent nucleoli.
Lymphoepithelial carcinoma

Sinonasal lymphoepithelial carcinoma is rare
Generally men, 4\textsuperscript{th}-7\textsuperscript{th} decades
Most cases are in Asians
Vast majority have EBV

For a lymphoepithelial carcinoma to be considered primary to the sinonasal region, spread from a nearby nasopharyngeal carcinoma must be excluded.
Lymphoepithelial-like carcinoma
Markers

Positive
EBV (EBER, at least in endemic regions)
p63
p40
CK 5/6

Negative
S100
Synaptophysin
Chromogranin
HPV (p16)
Sinonasal basaloid carcinomas

Group of tumors with similar histologies but with evolving separation based on new molecular studies

- Sinonasal undifferentiated carcinoma (SNUC)
- NUT midline carcinoma
- SMARCB1 deficient carcinoma
- HPV-related carcinoma with adenoid cystic carcinoma-like features
Sinonasal Undifferentiated Carcinoma (SNUC)

Incidence: Uncommon; 3-5% of sinonasal carcinomas

Age: 3-8\textsuperscript{th} decade; median 5-6\textsuperscript{th} decade

Gender: More common in men

Site: Paranasal sinuses
  
  Nasal cavity
  
  Invades skull base, brain, orbital apex

Molecular: No specific findings
Sinonasal Undifferentiated Carcinoma (SNUC)

Blue cell tumor, with a variety of cell sizes, not all small

Minimal nuclear pleomorphism

Prominent nucleolus, common

Necrosis

Vascular invasion
Sinonasal Undifferentiated Carcinoma (SNUC)

Sheets, nests or trabeculae of cells

No evidence of squamous or glandular differentiation

No surface precursor; sometimes adjacent carcinoma in situ is seen
Positive in SNUC

Pankeratin, CK7, CAM 5.2

p63 +/-

EMA

NSE

p16: variable results in literature. Some +, some –
Variable expression of HPV
Negative IHC in SNUC

P40 / usually negative

S100 (focally +)

CEA

Chromogranin & Synaptophysin (focally +)

EBV: Usually negative, but + reported in some patients
SNUC

Outcome:

Rapid clinical course with presentation with advanced stage

- Multimodal therapy with surgery, radiation and chemotherapy

5 year survival = ~ 35%
NUT Midline Carcinoma

Incidence: Rare
Age: Usually in 25-30, ranges infancy to 8th decade
Site: Most cases in paranasal sinus and nasal cavity
other sites include nasopharynx, laryngeal structures, orbit, salivary glands
Usually midline
NUT Midline Carcinoma

Rapidly growing mass with nasal obstruction, epistaxis and frequently proptosis

Invades local structures extensively

Often local lymph node and/or distant metastases
NUT Midline Carcinoma

Sheets of monotonous undifferentiated round cells, foci of mature keratinized squamous cells occasionally seen

Always necrosis
NUT Midline Carcinoma

Rearrangements in nuclear protein in testis (NUT) gene (*NUTM1*)

Most cases: *NUTM1* is fused with *BRD4* 
\[ t(15;19) \]

Can also fuse with *BRD3*, *WHSC1L1*

Some cases the fusion partner is not known
NUT Midline Carcinoma

✓ NUT positive by immunohistochemistry
  NUT antibody
  p40
  p63
  CK7

✓ Can also use FISH, PCR or NGS
NUT Midline Carcinoma

Prognosis is poor

Multimodal therapy is attempted
SMARCB1 (INI-1) -deficient sinonasal basaloid carcinoma

Recently a newly described entity of an undifferentiated sinonasal carcinoma characterized by loss of the tumor suppressor SMARCB1 (INI1) encoded by the SMARCB1 gene on chromosome 22q.
SMARCB1 (INI-1) -deficient sinonasal basaloid carcinoma

SMARCB1 is a member of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex.

Group of >20 functionally closely related proteins involved in the regulation of gene expression, cell proliferation and differentiation.
SWI/SNF mutations in cancers of different histological subtypes occurring in different organs

SWI/SNF-deficient neoplasms are generally unified by high frequency of undifferentiated anaplastic and/or rhabdoid cell phenotype
SMARCB1 (INI-1) -deficient sinonasal basaloid carcinoma

Nasal cavity and sinuses

Most tumors are basaloid but other SMARCB1-deficient cases have been found with rhabdoid, squamoid, oncocyctic appearances
SMARCB1 (INI-1) -deficient sinonasal basaloid carcinoma

Basaloid cells
  high N:C ratios

Desmoplastic stroma

Scattered plasmacytoid or rhabdoid-like cells
  Plasmacytoid or rhabdoid can be predominant in the tumor

Occasional sarcomatoid patterns

Can grow in a Pagetoid pattern in the overlying normal epithelium
SMARCB1 (INI-1)-deficient sinonasal basaloid carcinoma: Immunohistochemical findings

- p63: ~50%
- CK7: ~50%
- CK5: ~60%
- Synaptophysin, CD56: < 25%
SMARCB1 (INI-1) -deficient sinonasal basaloid carcinoma

Few cases described but some patients have had responses to multimodal therapies
HPV related carcinoma with adenoid cystic-like carcinoma features

Tumor appears restricted to the sinonasal tract and associated with HPV, particularly type 33

✓ Nested growth pattern
✓ Basaloid component showing myoepithelial differentiation
✓ Microcystic spaces
✓ Squamous differentiation, when present, was restricted to the surface epithelium.
✓ Not associated with the MYB gene
Case 2

55 year old female had been previously diagnosed with a FIGO grade 2, uterine endometrioid adenocarcinoma, T1a (< 50% invasive into the myometrium).

Three years later, she developed a thyroid mass and was subsequently diagnosed with follicular carcinoma of the thyroid. The tumor showed minimal invasion into the capsule, but with focal vascular invasion.
Case 2

She was treated with total thyroidectomy. Five years post-thyroidectomy, she presented with voice alterations.

On exam a large tumor in the neck was present. It was subsequently found to invade the larynx.

A laryngectomy was performed. The slides presented are from the neck soft tissue and laryngectomy specimen.
Case 2

Thyroid columnar cell carcinoma
Objectives

✓ Recognize an *aggressive* variant of papillary carcinoma that lacks typical morphologic features, particularly nuclear, of papillary carcinoma

✓ Briefly review common primary thyroid carcinomas

✓ Review some of the primary thyroid tumors with uncommon morphology

✓ Review some of the most common tumors metastatic to the thyroid

✓ Discuss some observations about the use of NGS in the diagnosis of thyroid carcinoma
Main objective for this case

Review thyroid tumors that don’t remind you of typical thyroid tumors
Uncommon thyroid tumors

✓ Columnar cell carcinoma
✓ Clear cell carcinoma
✓ Cribriform-morular carcinoma
✓ Intrathyroid thymic carcinoma
✓ (formerly termed carcinoma showing thymus-like differentiation (CASTLE)
✓ Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)

✓ Tumors metastatic to the thyroid
Common thyroid carcinomas

Papillary carcinoma

Follicular carcinoma

Medullary thyroid carcinoma

Anaplastic thyroid carcinoma
Columnar cell carcinoma

Described in 1986 by Evans, as an aggressive form of thyroid carcinoma

Recognized as an unusual variant of papillary thyroid carcinoma by many
Columnar cell carcinoma

Variant of papillary carcinoma?

Paradoxical findings for a thyroid papillary carcinoma
Histologic features *not* present in columnar cell carcinoma, but features that are seen in papillary thyroid carcinoma

- ✓ No intranuclear inclusions
- ✓ No ground glass nuclei
- ✓ No nuclear grooves
Columnar cell carcinoma
Molecular pathology features

Why is columnar cell carcinoma considered a variant of papillary carcinoma?

B-raf (V600E) mutations in some patients
Columnar cell carcinoma

Clinical features

- Female predominant (8-10:1, F:M)
- Age range 30-70
- Size 3-5 cm average (1-10 reported)
Columnar cell carcinoma

- columnar cells
- pseudostratified
- sub and supranuclear vacuoles

appearance similar to early secretory endometrium
Columnar cell carcinoma

Histologic features

Nuclei are elongate
Does not have cleared nuclei or intranuclear inclusions

-additional patterns:
  solid
  trabecular
  papillary
  follicular
Columnar cell carcinoma
Immunohistochemistry

TTF-1 (positive)
Thyroglobulin (variable positive)
CDX-2 can be positive

(antibody generally used to identify cells of gastrointestinal origin)
CDX-2 positive tumors

Gastrointestinal tumors / lesions:
- Esophageal adenocarcinomas and intestinal metaplasia in Barrett’s esophagus
- Colon
  - Polyps
  - Adenocarcinomas
- Gastric carcinoma
- Gastrointestinal neuroendocrine carcinomas
- Small intestinal carcinomas

Lung:
- Mucinous adenocarcinomas

Gynecologic tumors
- Mucinous adenocarcinoma
- Cervical adenocarcinoma
- Endometrioid adenocarcinoma

Testicular teratomas
Columnar cell carcinoma

Differential diagnosis

✓ Follicular carcinoma
✓ Hyalinizing trabecular tumor
✓ Tall cell variant of papillary carcinoma
✓ Poorly differentiated carcinoma  
  (Insular carcinoma)
✓ Metastatic carcinoma to the thyroid
Follicular carcinoma

Vascular invasion in the capsule
Tumor capsule invasion

If cytoplasm exists around the nucleus, it is evenly distributed, not eccentrically placed or elongated.
Hyalinizing Trabecular Tumor

Numerous intranuclear inclusions

Hyalinizing stroma

Trabecular cell arrangement

Cells are palisaded
Poorly differentiated carcinoma

Trabecular pattern

No subnuclear or supranuclear clearing
Papillary carcinoma, tall cell variant

No sub/supranuclear clearing

Has all the nuclear features of usual papillary carcinoma

Nuclear grooves
Nuclear overlapping
Nuclear clearing

Often has oncocytic cytoplasm
Uncommon primary thyroid tumors

Columnar cell carcinoma

- Clear cell carcinoma

Carcinoma showing thymus-like differentiation (CASTLE)

Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)
Clear cell carcinoma of thyroid

Classified as a variant of follicular carcinoma requires capsular &/or capsular vessel invasion to meet diagnostic criteria

Cleared cytoplasm
Cytoplasm contains variable elements of glycogen, lipid, thryoglobulin

No nuclear features of papillary carcinoma
Clear cell carcinoma of thyroid

• Differential always includes clear cell tumors metastatic to the thyroid:
  • Renal cell carcinoma, conventional clear cell type
  • Parathyroid carcinoma
Clear cell carcinoma of thyroid

Immunohistochemistry is positive for

PAX8

TTF-1

The combination of these two antibodies is required to exclude metastatic clear cell renal cell carcinoma which is also PAX8 positive
Uncommon primary thyroid tumors

Columnar cell carcinoma
Clear cell carcinoma
✓ Intrathyroid thymic carcinoma
  [Carcinoma showing thymus-like differentiation (CASTLE)]
Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)
Intrathyroid thymic carcinoma

Carcinoma showing thymus-like differentiation (CASTLE)
Intrathyroid thymic carcinoma

Uncommon tumor with essentially equal female: male ratio

Reported to be more common in Asian patients

Histologic features are that of thymic carcinoma squamous carcinoma appearance with lymphoid associated component
Intrathyroid thymic carcinoma

Immunohistochemistry

CD 5

Bcl 2

p40
Uncommon primary thyroid tumors

Columnar cell carcinoma
Clear cell carcinoma
Carcinoma showing thymus-like differentiation (CASTLE)
✓ Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)
Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)

Uncommon tumor, usually affecting children and young adults (mean age ~ 20)

Slow growing with overall survival at ~85%

Known for very late metastases [25% early, 40% at 10 years]
Spindle Epithelial Tumor with Thymus Like Elements (SETTLE)

✓ Biphasic with glandular structures merging with spindled areas
✓ Usually biphasic but monophasic examples can be seen [differential diagnosis of synovial sarcoma]
✓ Mitoses generally rare
✓ Spindle cells with fine nuclear chromatin
✓ Glandular elements have cuboidal to columnar epithelial cells forming tubules, papillae or glomeruloid structures.
Metastatic tumors to the thyroid

Most common:
- Lung
- Breast
- Melanoma
- Renal cell carcinoma
Columnar cell carcinoma: Therapy

Total thyroidectomy
Lymphadenectomy (ipse-lateral and central compartment neck dissection)
Survey for distant metastasis.
Postoperative radioactive iodine
May be susceptible to treatment targeted against \textit{BRAF} mutation if it exists
External beam irradiation may be used in cases of incomplete resection.
Columnar cell carcinoma
Outcome

For histologically localized/circumscribed tumors:
Good outcome (usually in younger females)

For histologically aggressive tumors (usually in older males) recurrence and local invasion common
Case 3

52 year old female presented to her physician with a neck mass and a sore throat.

Physical exam revealed only a neck mass.

CT imaging revealed a neck mass and a lesion at the base of the tongue.

Biopsy of the lesion at the base of the tongue was performed.
Case 3

Polymorphous Adenocarcinoma

Cribriform Adenocarcinoma of Salivary Gland

(CASG)
Objectives

- Review Polymorphous Adenocarcinoma
  1) Polymorphous low grade adenocarcinoma (PLGA)
  2) CASG (Cribriform adenocarcinoma of salivary gland)

- Identify criteria for the diagnosis

- Consider the differential diagnosis of CASG in neck FNA’s
Polymorphous adenocarcinoma

Polymorphous low grade adenocarcinoma

Cribriform adenocarcinoma of salivary gland
Cribriform Adenocarcinoma of Salivary Gland

Most recent WHO classification suggests PLGA and CASG are best classified as ‘polymorphous adenocarcinoma’ and are related.

Cribriform adenocarcinoma of salivary gland is considered a variant of polymorphous adenocarcinoma.
Cribriform Adenocarcinoma of Salivary Gland

Described in 1999 by Michal et al as *cribriform adenocarcinoma of the tongue*

Probably earlier reports of papillary adenocarcinoma of minor salivary gland or tubular carcinoma of the tongue represented CASG
Cribriform Adenocarcinoma of Salivary Gland

Relatively few cases have still been reported

True incidence is unknown as it is likely under-recognized

Neoplasm often presents with synchronous neck lymph node metastases
Cribriform Adenocarcinoma of Salivary Gland
Sites of occurrence

Base of tongue
Palate
Retromolar trigone
Parotid
Oral cavity (NOS)
Sinonasal
CASG
Histologic findings, low power

Vague, lobular arrangement
Unencapsulated with infiltrative margins
Clefting of epithelial cell nests from dense stroma
Papillary patterns
Hyalinized stroma
Myxoid to mucoid matrix
CASG
Histologic findings, low power

Cribriform and solid growth patterns, sometimes demonstrating
  – peripheral palisading
  – peripheral clefting
  – glomeruloid appearance.
Cytologic findings

- Cytoplasmic variability
- Nuclear overlapping
- Nuclear grooves
- Nuclear membrane irregularity
- Optically clear, ground glass nuclei
Cribriform Adenocarcinoma of Salivary Gland

Vague, lobular arrangement

Unencapsulated with infiltrative margins

Clefting between cells and stroma

Papillary structures

Optically clear, ground glass nuclei
Polymorphous low grade adenocarcinoma

Whirled pattern of cells

Small cribriform structures

Myxoid to hyaline stroma
CASG -

Differential diagnosis

What else?

Papillary thyroid carcinoma
Cytologic findings: CASG vs PTC

CASG
- Nuclear overlap minimal
- Nuclei rounded
- Grooves not prominent
- No bubble gum colloid
- Stroma prominent

PTC
- Nuclear overlap striking
- Nuclei elongate
- Grooves very prominent
- Bubble gum colloid
- Giant cells
Cribriform Adenocarcinoma of Salivary Gland
Immunohistochemistry

Positive:
- Pan keratin
- AE 1/3
- CK7
- S-100
- p63
- CK5/6
- Calponin
- Smooth muscle actin

Negative:
- TTF
- Thyroglobulin
CASG often presents with synchronous neck lymph node metastases

Patients presenting with neck masses are often assessed with fine needle aspiration of the neck lymph node

FNA of these metastases can appear nearly identical to that of papillary thyroid carcinoma metastases
Cribriform Adenocarcinoma of Salivary Gland: Therapy

Primary surgical therapy with negative margins is the goal.

Neck dissection, at least selective for clinically positive neck, is reasonable.
Case 4

56 year old male presented with nasal swelling and was referred to an otolaryngologist. The otolaryngologist discovered a polypoid mass in posterior nasal septum and attempted to excise all of the tumor.
Case 4

Respiratory adenomatoid hamartoma (REAH)
Objectives

Case 4

☑ Describe the clinical findings of Respiratory Adenomatoid Hamartoma (REAH)

☑ Recognize the key histologic findings in REAH

☑ Differentiate REAH from similar lesions (Co-REAH; Seromucinuous hamartoma)

☑ Separate histologically the nasal lesions in the differential diagnosis of REAH
REAH
Clinical Findings
Polypoid mass in the posterior nasal septum

Predominantly males

Inflammatory nasal polyps frequently adjacent to or preceding REAH
Histology

Benign overgrowth of submucosal ciliated respiratory glands

Glands can be back to back

Glandular connection to the polyp surface

Pseudostratified columnar epithelium, some with goblet cells

Periglandular hyalinization
Lesions that are similar to REAH

Seromucinous hamartoma

Chondro-Osseous Respiratory Epithelial Adenomatoid Hamartoma (CO-REAH)
Seromucinous hamartoma

Clinical

Posterior nasal septum and nasopharynx

Polypoid mass

Slight male predominance
Seromucinous hamartoma

**Pathology**

Small tubular glands arranged in lobular as well as in a haphazard pattern

Serous cells that show eosinophilic cytoplasm

Relatively few mucinous cells, despite the name

May have REAH-like areas

- intermixed respiratory glands
- periglandular hyperplasia
Seromucinous hamartoma

Posterior nasal septum and nasopharynx

Polypoid mass

Slight male predominance

Small tubular glands arranged in lobular as well as in a haphazard pattern

Serous cells that show eosinophilic cytoplasm
REAH vs Seromucinous Hamartoma

There is some morphologic overlap between respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma.

Some authorities suggest they are related.
Chondro-Osseous Respiratory Epithelial Adenomatoid Hamartoma (CO-REAH)

All the features of REAH with

Chondroid and Osseous metaplasia
Differentiatial diagnosis of nasal polypoid lesions

- Inflammatory nasal polyps
- Inverted Schneiderian papilloma
- Inverted Oncocytic papilloma
- Adenocarcinomas of the nose and paranasal sinuses
  - Intestinal
  - Non-intestinal types
  - Metastatic (prostate carcinoma most common)
Differentiatial diagnosis of nasal polypoid lesions

✓ Inflammatory nasal polyps

✓ Inverted Schneiderian Papilloma

✓ Oncocytic/Columnar cell Papilloma

✓ Adenocarcinomas of the nose and paranasal sinuses
  - Intestinal type
  - Non-intestinal types
  - Metastatic (prostate carcinoma most common)
Inverted Schneiderian Papilloma

Nests of ‘transitional’ type epithelium

Epithelium connects to the surface

Multiple layers of cells

Neutrophils present
Schneiderian papilloma, oncocyctic type

Synonyms:
Cylindric cell papilloma

Definition:
A histologically distinct Schneiderian papilloma that often has and exophytic and concurrent endophytic growth

Unlike inverted or exophytic papilloma, oncocyctic Schneiderian papillomas have no association with HPV
Schneiderian papilloma, oncocytic type

Clinical findings:

Near 100% on the lateral nasal wall, maxillary sinus or ethmoid sinus

Epistaxis and nasal obstruction

Polypoid growth
Schneiderian papilloma, oncocytic type: Histology

- endophytic as well as exophytic growth

- oncocytic cells

- columnar cells

- cilia can remain

- microabscesses
Intestinal-type adenocarcinoma

Appear identical to those in the intestine, e.g., ‘typical’ colo-rectal primary

Aggressive neoplasms
Non-intestinal type adenocarcinoma
Can be difficult to recognize at first

- Low grade: minimal atypia
- Mitoses often lacking or very minimal
- Papillary projections, tufting
- Cribriform and trabecular patterns

Key to recognition is destructive invasion and back to back glands
Metastases to the nasal region

Metastatic prostate carcinoma

One of the most common metastases to the nasal cavity