Founders Seminar

Handout material

Challenging Cases in Head and Neck Surgical 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

EWS/PNET

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 subclassificatons of PNET

Non-CNS

pPNET

(peripheral Primitive Neuroectodermal Tumor

CNS

sPNET

(supratentorial Primitive Neuroectodermal Tumor)

Primitive Neuroectodermal Tumor
Peripheral vs. CNS

Peripheral Primitive Neuroectodermal Tumor (pPNET):	Central Nervous System Primitive Neuroectodermal Tumor (sPNET):
CD99 antigen	*CD99 antigen*
(MIC2 gene expression of MIC2 antigen)	*(MIC2 antigen) is NOT expressed*
FLI-1 (gene fusion product of EWS) is positive in many cases	*No FLI-1 expression*

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

FLI 1: Most EWS-PNET also express

ERG: Generally, EWS-ERG fusion cases

EWS-ERG fusion cases also express FLI 1 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 technques 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 or q12)

Extraskeletal myxoid chondrosarcoma (9;22)

Round cell tumors can share with EWS-PNET:

1) Morphologic similarites
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

Grade	Nuclear Pleomorphism	Fibrillary Matrix	Rosettes	Necrosis
I	None	Prominent	HW rosettes	None
II	Low	Present	HW rosettes	None
III	Moderate	Low	FW rosettes	Rare
IV	High	Absent	None	Frequent

Hyams Grading System for Olfactory Neuroblastoma

Grade	Lobular Architecture Preservation	Mitotic Index
I	Present	Zero
II	Present	Low
III	May or may not be present	Moderate
IV	May or may not be present	High

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^{th} to 8^{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%

Sinonasal Melanoma

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

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 diagnosi

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	*Alveolar*
Desmin	Desmin
Myogenin (more variable staining)	*Myogenin (100% of cells, strong)*
Myoglobin	Myoglobin
Muscle specific actin	Muscle specific actin
Smooth 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

Rhabdomyosarcoma

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 *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

Desmoplastic small round cell tumor

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

Lymphoepithelial carcinoma

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Immunohistochemsitry
Solid adenoid cystic carcinoma

Positive	Negative
p63	Synaptophysin
p40	Chromogranin
CK 5/6	p16
CK 7	EBER
34Beta E12	
S100	
Myb	

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

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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, 4th-7th 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	Negative
EBV (EBER, at least in endemic regions)	S100
p63	Synaptophysin
p40	Chromogranin
CK 5/6	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: 3-8th decade; median 5-6th 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, oncocytic 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 *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.

CASG
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; Seromucinous 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

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 seroumucinous 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, oncocytic 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, oncocytic 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