Spooky Spindled Sinonasal Spectres

Learning Objectives

- A presentation of selected spindled cell lesions involving the mucosa and soft tissue of the sinonasal tract and larynx
- Emphasis will be placed on a practical approach to identify important histologic criteria to separate these spindle cell lesions
- Pertinent clinical and immunohistochemical features of diagnostic or prognostic significance will be highlighted
- Select and integrate special studies that aid in diagnosis

Differential Diagnostic Considerations

- Biphenotypic sinonasal sarcoma
- Rhabdomyosarcoma
- Respiratory epithelial adenomatoid hamartoma
- Angiofibroma
- Synovial sarcoma
- Solitary fibrous tumor
- Spindle cell squamous cell carcinoma
- Spindle cell mucosal melanoma
- Mycobacterial spindle cell tumor
- Peritumorous neoplasm (benign or malignant) / PEComa
- Leiomyosarcoma/leiomyoma
- Glomangiopericytoma
- Fibrosarcoma/fibromatosis

Glomangiopericytoma

- A tumor demonstrating perivascular myoid phenotype (myopericyte)
- Sex: Female > Male (1.2:1)
- Age: Peak in the 7th decade
- Symptoms: A short duration of nasal obstruction, mass, and epistaxis
- Rare association with osteomalacia
- Site: Unilaterally in the nasal cavity alone
- May extend into paranasal sinuses
- Surgical excision with excellent outcome
- Recurrence in about 18% of cases

Glomangiopericytoma

- Polypoid tumors
- Size: 3 cm (range up to 8.0 cm)
- Submucosal with intact surface epithelium
- Delineated but unencapsulated cellular tumors
- Diffuse pattern, effacing or surrounding the normal structures
- Short fascicles (storiform, whorled, palisaded)
- Richly vascularized:
  - Vascular channels range from capillary size to large patulous spaces that may have a ramifying “staghorn” or “antler-like” configuration
  - Prominent peritheliomatous hyalinization is classic and characteristic

Pathology Features
Glomangiopericytoma
Microscopic
- Closely packed syncytium of uniform oval to elongate cells
- Indistinct cell borders
- Vesicular to hyperchromatic, round to oval to spindle-shaped nuclei
- Mild nuclear pleomorphism
- Mitotic figures may be present
- Extravasated erythrocytes
- Mast cells and eosinophils usually prominent
- Giant cells and fat are rarely reported
- Rare malignant cases develop
Glomangiopericytoma

**Immunohistochemistry**

- **Positive:** Actins (SMA>MSA), nuclear β-catenin
- **Negative:** CD34, CD31, CD117, STAT6, EMA, keratin, S100 protein, GFAP, FVIIIR-Ag, CD99, desmin

**Genetics:**
- Somatic, single nucleotide substitution heterozygous mutations in CTNNB1 gene encoding β-catenin, specifically in GSK3β region (encoded by exon 3)
- Mutations constitutively active β-catenin with cyclin D1 over expression, and aberrant nuclear accumulation due to nuclear translocation of membrane protein

Rhabdomyosarcoma

**Malignant mesenchymal neoplasm with skeletal muscle differentiation**

- Embryonal rhabdomyosarcoma (botryoid, anaplastic)
- Alveolar rhabdomyosarcoma (anaplastic, botryoid, spindle)
- Incidence
- Most common soft tissue sarcoma in head and neck
- Most common soft tissue sarcoma in children and adolescents
- Embryonal: ear Alveolar: sinonasal tract
- Age: Embryonal (usually < 20 yrs.); Alveolar: Adults
- Sex: Male > Female (1.2:1)
Rhabdomyosarcoma

- Presentation: Unilateral, refractory otitis media, neurologic symptoms, mass, slowly enlarging
- Often misdiagnosed as infection or polyp initially
- Imaging used to delineate extent of disease for staging purposes, with heterogeneous signals (stroma, necrosis, vascularity)
  - Chest and abdomen CT and bone scan for metastatic disease
- As a systemic disease, combination of surgery, multiagent chemotherapy, and radiation (latter not used for stage I disease)
- Treatment complications include facial growth retardation, intellectual retardation, visual changes, dental problems
- ~ 60% 5-year survival, depending on age, stage, anatomic site, and histologic subtype

Rhabdomyosarcoma Pathology features

- Polypoid, poorly circumscribed, fleshy mass, often with intact epithelial surface
  - Spindle cell tumors are more fibrous and firm with whorled cut surface
- Usually < 2.5 cm (limited by anatomic site)
- Primitive mesenchymal cells arranged in fascicles and whorls of spindle cells
- Rhabdomyoblasts (eccentric, eosinophilic cytoplasm) may be seen
- Stellate cells with round nuclei
Rhabdomyosarcoma Pathology features

- Cytoplasmic eosinophilia with tadpole, elongated cytoplasmic extensions
- Cross striations are uncommon and difficult to identify
- Multinucleation may be seen
- Myxoid background stroma is common
- Necrosis may be noted
- Botryoid variant has cambium layer
  - Increased cellularity immediately below intact surface
  - Then hypocellular deeper into stroma
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**Special studies**
- **PAS highlights glycogen**
- **Positive:** Muscle markers (desmin, myogenin, MYOD1, SMA, SMA, calponin), CD56, synaptophysin, CK-pan, CAM5.2 (up to 50%)
- **Negative:** S100 protein, SOX10, CK7, TLE1, STAT6
- **Genetics:** FOXO1 gene fusions with PAX3 or PAX7 (gain of function) detected by FISH for alveolar type

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**Mycobacterial Spindle Cell Tumor**
*Pseudoneoplastic spindle cell proliferation caused by M. avium-intracellulare and occurring in immunocompromised patients*
- Almost always found in immunocompromised individuals
  - AIDS/HIV-positive patients
  - Patients receiving immunosuppressive therapy, including steroids
- Age: Wide age range
- Sex: Equal gender distribution
- Site: Lymph nodes > Skin, bone marrow > Nasal cavity
- Treatment: Species susceptibility testing specific
  - Clarithromycin and azithromycin more effective
**Mycobacterial Spindle Cell Tumor**

**Histology**
- Cellular proliferation composed of bland-appearing spindle-shaped cells in storiform pattern
- Spindle cells represent histiocytes
- Absent granuloma formation
- Multinucleated giant cells and foamy histiocytes typically not present
- Necrotic foci may be present
- Associated lymphocytes and plasma cells present
- Partial or complete effacement of nodal or mucosal architecture

**Special Studies**
- Acid-fast bacilli (AFB) or Ziehl-Neelsen stain
  - AFB-positive organisms within cytoplasm of spindle cells
  - Spindle cells engulf (phagocytize) organisms acting as facultative histiocytes
- **Positive:** CD68, lysozyme, vimentin
  - Weakly: S100 protein, desmin, MSA
- **Negative:** CK-pan, HMB45, Melan-A, SMA, SMMHC, myogenin, MYOD1, CD99, TLE1, SOX10, STAT6, CD31, CD34

**Solitary Fibrous Tumor**

Solitary fibrous tumor is a fusion gene-associated tumor of fibroblastic phenotype with a branching vasculature
- Solitary fibrous tumors (SFT) are rare
- Adults without sex predilection
- Pathology:
  - Submucosal, pseudoencapsulated and variably cellular, with bland spindle-shaped cells
  - Haphazard architecture
  - Stellate to staghorn-like vessels
  - Variable collagenous background
- **Positive:** STAT6 (nuclear), CD34, bcl-2, CD99
- **Genetics:** NAB2-STAT6 fusion seems specific
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Synovial sarcoma

Mesenchymal spindled cell neoplasm with variable epithelial differentiation and specific chromosomal translocation: t(X;18)(p11;q11)
- Incidence: ~10% of soft tissue sarcomas
- About 10% develop in head and neck
- Age: Bimodal presentation
  - Young adults (15-35 years)  Older age (around 50 years)
- Sex: Male > Female (3:1)
- Site: Neck, oropharynx and hypopharynx/larynx
- Symptoms: Nonspecific, but usually a mass
- Aggressive local excision with combination therapy is best

Pathology Features

- Macroscopic:
  - Pedunculated or polypoid, usually circumscribed; may be multinodular and cystic
  - Size: Range: 1-12 cm (but usually < 5 cm)
  - Separated into monophasic and biphasic
    - Monophasic: most common in head and neck
    - Densely packed, short fascicles
  - May be marbled: Alternating light and dark areas
  - Spindled cells are uniform with indistinct cell boundaries
  - Hemangiopericytoma-like pattern with rich vascularity
- Biphasic
  - Variable proportions of epithelial and spindled cell components
  - Epithelial cells have abundant cytoplasm, creating glandular appearance
  - Mitotic figures are identified, but usually not increased
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Special Studies

- Immunohistochemistry
  - **Positive**: Epithelial markers (CK-pan, CK7, EMA), TLE1, S100 protein, CD99, bcl-2, SMA
  - **Negative**: p63, SOX10, HMB45, Melan-A, desmin, CD34, STAT6

- Characteristic gene fusion: SSX1/2/4-SYT
  - t(X:18)(p11.2;q11.2)
Spindle cell (sarcomatoid) Squamous Cell Carcinoma

Will be presented by my main man…

BMW

Mucosal Melanoma

Anatomy

- Melanocytes are distributed throughout the upper respiratory tract and oral cavity within many cell types
- Greater degree in African Americans and Japanese
- About 20% of skin melanomas occur in the head and neck
- About 4% of head and neck melanomas are mucosal (most common site)
- Preexisting melanosis (pigment in the mucosa) in the sinonasal tract is uncommon
- Melanoma arises de novo rather than from a preexisting nevus
Mucosal Melanoma

**Etiology**
- Sunlight is a presumed non-factor
- Formaldehyde exposure is a possible etiology
  - Painters, furniture and cabinet makers, laundry, construction, & lab workers
- Geographic place of residence at the time of diagnosis
  - Living in southern latitudes (defined as < 40°N in North America) have increased incidence of melanoma
- Radiation exposure (therapeutic or environmental) does not seem to play an etiologic role

**Clinical**
- Sex: Men = Women
  - Different from M > F in cutaneous
- Age: Mean age: 65 years (older than cutaneous melanomas)
- Site: Nasal cavity alone or combination of nasal cavity with paranasal sinuses
  - Anterior nasal septum > maxillary sinus
- Short duration of non-specific symptoms
  - Epistaxis, mass, obstruction, headache, visual symptoms
  - Melanorrhea: “coal flecked” or brown nasal discharge

**Macroscopic**
- Mean size: 2 — 3 cm
  - >3.0 cm tend to have a worse clinical outcome
- Most are a polypoid, fleshy, bulky mass
- Dark tumors suggest melanin pigment
- Surface ulceration is common
- “Breslow thickness” is meaningless (do not measure)
- “Clark level” cannot be determined

**Microscopic**
- If junctional activity or pagetoid spread is present (surface involvement), it defines primary disease
  - However, stroma involvement alone is common
- Wide histologic spectrum
- Patterns include peritheliomatous (quite distinctive), epithelioid, solid, fascicular, storiform, papillary, alveolar
Mucosal Melanoma
Microscopic

- Tumor cells can be:
  - Undifferentiated
  - Epithelioid
  - Spindled
  - Plasmacytoid
  - Meningothelial
  - Rhabdoid
- Cells usually have a high nuclear to cytoplasmic ratio
- Pleomorphic nuclei
- Prominent, enlarged, magenta, and irregular nucleoli
- Intranuclear cytoplasmic inclusions
Mucosal Melanoma

Special Studies

- **Positive:** S100 protein, SOX10, HMB-45, Tyrosinase, Melan A
- **Negative:** Pancytokeratin, desmin, SMA, CD34, STAT6
- Phenotypic infidelity or anomalous immunoreactivity

Comparative genomic hybridization (CGH) show remarkably consistent alterations (gains in chromosome arm 1q, 6p and 8q), distinctly different from cutaneous melanomas

- NRAS and KIT mutations/amplifications much more common than BRAF, distinctly different from cutaneous melanomas

Management

- Surgery with clear margins of resection is the cornerstone of therapy
- Radiotherapy for palliation
  - Radiotherapy does not change the overall patient survival
  - Specific immunologic therapy has shown promise, but remains investigational
- Local recurrence is a major factor in failure of treatment
  - Unstable mucosa (field effect phenomenon)

Prognosis

<table>
<thead>
<tr>
<th>Factor associated with a worse prognosis</th>
<th>Univariate analysis</th>
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</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>p = 0.029</td>
</tr>
<tr>
<td>Symptoms of obstruction or epistaxis</td>
<td>p = 0.020</td>
</tr>
<tr>
<td>Anatomic site (nasopharynx)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Tumor size (cm) ≥ 3.0</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Undifferentiated histology</td>
<td>p = 0.033</td>
</tr>
<tr>
<td>Mitotic index ≥ 10 / 10 HPF</td>
<td>p = 0.026</td>
</tr>
<tr>
<td>Development of recurrence</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Increasing stage</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
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Malignant Peripheral Nerve Sheath Tumor

Malignant tumor of peripheral nerves or having differentiation along the lines of various elements of nerve sheath

- de novo (sporadic), post irradiation or neurofibromatosis type 1 (NF1)
- ~5% of all soft tissue carcinomas, ~20% in head and neck
- Age: 5th decade, but younger if NF1 associated
- Sex: Equal sex distribution
- Site: Neck > sinonasal tract > oral cavity
- Management: Surgery and chemotherapy
Malignant Peripheral Nerve Sheath Tumor
Microscopic Features

- Unencapsulated hypercellular proliferation
- Fascicular growth with long sweeping (herringbone-like) fascicles that swirl or interdigitate with one another
  - Hypercellular (Antoni A) alternating with hypocellular (Antoni B)
- Cells have elongated, tapered nuclei with irregular contour
  - Nuclei appear wavy or buckled
- Nuclear palisading may be seen
- MPNST with rhabdomyosarcoma (malignant Triton tumor)
  - Approximately 60% associated with NF1
  - Rhabdomyoblasts scattered throughout tumor
- Low and high grade (necrosis, mitoses, pleomorphism)

Malignant Peripheral Nerve Sheath Tumor
Immunohistochemistry

- **Positive:** S100 protein (variable), SOX10
- **Negative:** SMA, CK-pan, TLE1, CD34, STAT6, chromogranin, HMB45, Melan-A, β-catenin

S100 protein
PEComa

Distinctive mesenchymal neoplasm arising from perivascular epithelioid cells that usually demonstrates combined myomelanocytic immunophenotype

- Extremely rare in sinonasal tract
- Age: Wide age range (median: 45 years)
- Sex: Marked female predominance
- Site: Nasal cavity and sinuses
- Symptoms: Non-specific
- Good prognosis with excision (targeted therapy if malignant)
- High-risk features:
  - Size > 5 cm, pleomorphism, high cellularity, increased mitoses, infiltrative growth, necrosis, vascular invasion

- Nests, trabeculae, or sheets
- Epithelioid to spindled cells with granular, clear to eosinophilic cytoplasm
- Cytoplasm sometimes described as “moth-eaten” or “stringy”
- Some larger epithelioid cells may appear “spider-like”
- Association with walls of larger vessels in many cases
- Profound pleomorphism may be seen
- Positive: SMA, desmin, caldesmon, HMB45, Melan-A, nuclear TFE3 (subset)
- Negative: cytokeratins, CD34, myogenin, DOG1, STAT6

Fibromatosis

Locally aggressive, intermediate type of non-metastasizing, well-differentiated, unencapsulated monoclonal myofibroblastic proliferation with tendency for local invasion and recurrence

- Rare: 0.3/100,000 ~15% within head and neck
- Age: Mean 18 years for head and neck sites
- Sex: Male > female (1.1:1)
- Site: Maxillary sinus, turbinates (mandible highest in H&N)
- Local but complete surgical excision
- There are frequently positive margins, thus a high rate of recurrence (25%)
Fibromatosis

- Infiltrative growth with low to moderate cellularity
- Broad fascicles of bland-looking spindle cells arranged in uniform direction ("purposeful")
- Elongated parallel blood vessels
- Matrix is collagenized to focally myxoid; keloid-like collagen may be present
- **Positive:** β-catenin (nuclear), actins, vimentin; focal desmin

**Somatic** mutations in β-catenin (CTNNB1) gene on 3p21
Fibrosarcoma

Malignant neoplasm with only fibroblastic &/or myofibroblastic differentiation (a diagnosis of exclusion)

- Incidence: Uncommon (~ 3% of sinonasal malignancies)
  - BUT: Many are reclassified into other categories now
- Age: Peak: 5th to 6th decades
- Sex: Female > Male (3:2)
- Site: One or more paranasal sinuses (maxillary, ethmoid)
- Symptoms: Short duration of nasal obstruction, epistaxis
- Treatment: En-bloc resection and radiation yield best outcome (75% 5 year survival)
- High incidence of recurrence (up to 60%)

Fibrosarcoma

- Smooth, nodular, fungating, ulcerated, fleshy mass with a firm, homogenous cut surface
- Size: Range: 2-8 cm
- Unencapsulated, circumscribed, often with bone invasion
  - If surface invaginations, think biphenotypic sinonasal sarcoma
- Cellularity is variable but usually high
- Spindled tumor cells arranged in short, compact fascicles at acute angles:
  - "Herringbone" or "chevron"
  - Vague fasciculation

Fibrosarcoma

- Fusiform syncytial cells with hyperchromatic, needle-like nuclei with tapering cytoplasm
- Mitotic figures: Grade dependent
  - Increasing correlates with grade
- Vascular stroma with delicate to dense collagen
  - Myxoid and edematous change can be seen
- Positive: Vimentin; weak, focal SMA
- Negative: Pancytokeratin, S100 protein, SOX10, HMB45, CD34, TLE1, STAT6, desmin, CD31
Leiomyosarcoma

Malignant tumor of smooth muscle
- Etiology: Irradiation; cyclophosphamide exposure; EBV; immunocompromised patients
- Rare: 4% arise in head and neck
- Age: Wide age range (6th decade)
- Immunocompromise-associated LMS: children/young adults
- Sex: Equal distribution
- Site: Oral cavity > Sinonasal tract > Skin
- Radical surgery is treatment of choice
- Prognosis: Aggressive neoplasm; 70% recurrence; size & stage dependent
  45% die of disease in <2 years

Leiomyosarcoma Pathology Features
- Polypoid or sessile, circumscribed but not encapsulated
- Size: > 5 cm in diameter
- Interlacing fascicular to storiform bundles of spindle-shaped cells
  - Typically intersect at right angles
- Neoplastic cells are elongated (spindle) with centrally located, blunt-ended, cigar-shaped nuclei and eosinophilic cytoplasm
  - Perinuclear vacuole or clear halo may be seen, giving nucleus an indented or concave contour
- Variable pleomorphism, mitotic activity (>4/10 HPF), necrosis
- Stroma tends to be richly vascular
  - Myxomatous stromal changes may be prominent, creating a hypocellular appearance
Leiomyosarcoma

**Special Studies**

- **Positive:** Actins (SMA > MSA), desmin, caldesmon, SMMHC, EBER (subset)
- **Negative:** Epithelial markers, myogenin, MYOD1, HMB45, Melan-A, CD34, STAT6, TLE1
- **Variable:** S100 protein, rare, perinuclear cytokeratin
Respiratory epithelial adenomatoid hamartoma

- Benign acquired non-neoplastic overgrowth of indigenous glands of sinonasal tract and nasopharynx
- Arising from surface epithelium
- Devoid of ectodermal, neuroectodermal, &/or mesodermal elements
- Related but different:
  - Chondro-osseous and respiratory epithelial (CORE) hamartomas
  - Seromucinous hamartoma
  - Not related: Chondromesenchymal hamartoma

READ Hamartoma

- Incidence: Rare lesions
- Age: Adults (3rd to 9th decades)
- Sex: Equal gender distribution
- Presentation: Nasal obstruction, nasal stuffiness, epistaxis, and chronic (recurrent) rhinosinusitis
- Majority occur in nasal cavity (posterior nasal septum)
- Often associated with inflammatory polyps
- Usually unilateral (rarely, bilateral)
- Complete excision (any method) is curative

- Polypoid or exophytic, up to 6 cm
- Changes dominated by presence of glandular proliferation composed of widely spaced, small to medium-sized glands separated by stromal tissue
  - Glands arise in direct continuity with surface epithelium, which invaginate downward into submucosa
  - Glands are round to oval, composed of multilayered ciliated respiratory epithelium often with goblet cells
  - Stromal hyalinization by thick, eosinophilic basement membrane
  - Atrophic glandular alterations may be seen
Immunohistochemistry not of value, as p63 and other epithelial markers are similar between differential considerations.

Reported to show a mean fractional allelic loss of 31%

- Considered unusually high for non-neoplastic entity
- Suggests possibility that respiratory epithelial adenomatoid hamartoma may be benign neoplasm rather than hamartoma
Biphenotypic Sinonasal Sarcoma

Biphenotypic sinonasal sarcoma (BSNS) is a low grade spindle cell sarcoma with distinctive histologic, immunohistochemical and molecular features, most frequently characterized by a recurrent PAX3-MAML3 gene fusion.

- **Synonym:** Low grade sinonasal sarcoma with neural and myogenic features
- **Sex:** Female > Male (2:1)
- **Age:** Mean: 52 years (range: 24 — 85 years)
- **Site:** Multiple sites, especially superior aspect of the nasal cavity and ethmoid sinus, with extension to orbit or cribriform plate
- **Symptoms:** Nonspecific, but usually a mass

Pathology

- Cellular submucosal spindle cell proliferation
- Unencapsulated and infiltrative, including into bone
- Elongated spindle cells arranged in medium to long intersecting fascicles, sometimes "herringbone" appearance
- Scant, delicate collagen matrix
- Nuclei are uniform and slender
- Few mitoses
- Striking proliferation of the epithelium, with invaginations intimately admixed with neoplastic cells
- Squamous or oncocytic metaplasia resembles sinonasal papilloma
- May show a prominent hemangiopericytoma-like vascular pattern
- Focal rhabdomyoblastic differentiation (11%) is usually associated with an alternate fusion partner
Biphenotypic Sinonasal Sarcoma

Immunohistochemistry

- **Positive:** S100 protein, SMA and/or MSA
  - Staining may be focal, patchy, or diffuse
  - Calponin, β-catenin, factor XIIIA, vimentin

- **Variable:** CD34, desmin, myogenin, EMA, keratin, CD34

- **Negative:** SOX10, TLE1, STAT6, HMB45, ER, PR

S100 protein

SMA
Biphenotypic Sinonasal Sarcoma

- Chromosomal translocation t(2;4)(q35;q31.1)
  - An in-frame fusion of exon 7 of transcription factor PAX3 to exon 2 of MAML3, a co-activator of the Notch signaling pathway
  - PAX3-MAML3 is found in most tumors (highly expressed)
  - A subset harbor the alternate fusion genes including PAX3-FOXO1 and PAX3-NCOA1 (similar to alveolar rhabdomyosarcoma)
- Slow progression with local destruction
- Local recurrences are common (50%)
- Up to 9 years after initial treatment
- Exceptionally rare metastatic disease or death from disease reported